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EXPRESS COMMUNICATION

Antiviral effects of probiotic metabolites on COVID-19

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ABSTRACT

SARS coronavirus (COVID-19) is a real health challenge of the 21st century for scientists, health workers, politicians, and all humans that has severe cause epidemic worldwide. The virus exerts its pathogenic activity through by mechanism and gains the entry via spike proteins (S) and Angiotensin-Converting Enzyme 2 (ACE2) receptor proteins on host cells. The present work is an effort for a computational target to block the residual binding protein (RBP) on spike proteins (S), Angiotensin-Converting Enzyme 2 (ACE2) receptor proteins by probiotics namely Plantaricin BN, Plantaricin JLA-9, Plantaricin W, Plantaricin D along with RNA-dependent RNA polymerase (RdRp). Docking studies were designed in order to obtain the binding energies for Plantaricin metabolites. The binding energies for Plantaricin W were −14.64, −11.1 and −12.68 for polymerase, RBD and ACE2 respectively comparatively very high with other compounds. Plantaricin W, D, and JLA-9 were able to block the residues (THR556, ALA558) surrounding the deep grove catalytic site (VAL557) of RdRp making them more therapeutically active for COVID-19. Molecular dynamics studies further strengthen stability of the complexes of plantaricin w and SARS-CoV-2 RdRp enzyme, RBD of spike protein, and human ACE2 receptor. The present study present multi-way options either by blocking RBD on S proteins or interaction of S protein with ACE2 receptor proteins or inhibiting RdRp to counter any effect of COVID-19 by Plantaricin molecules paving a way that can be useful in the treatment of COVID-19 until some better option will be available.

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KEYWORDS
COVID-19; spike proteins; RNA dependent RNA polymerase; ACE2; probiotics; plantaricin

Introduction

It is high time since the emergence and spread of Coronavirus (COVID-19) from Wuhan, China has gained much attention without any prophylactic or therapeutic treatment as of now (Huang et al., 2020). The situation has already taken a pandemic form with new cases even after the closing of all the air routes for travelers returning to their native land from China and other countries (World Health Organization (WHO)), 2020). As on date, a total number of cases crossed is approximately. 4.03 million from 195 countries with 278 892 deaths. There are no specific therapeutic agents or vaccines which are available for COVID-19 (WHO, 2020). There are various drugs such as Favipiravir and Remdesivir along with Convalescent plasma are under investigation but antiviral activity on COVID-19 for these drugs is yet to be confirmed (Chen et al., 2020; Enayatkhani et al., 2020; Joshi et al., 2020; Shen et al., 2020; Wahedi et al., 2020). Therefore finding a potent and effective anti-COVID-19 agent to control and prevent further infection has become the need of an hour. Several computational methods (Elfiky, 2020; Elfiky, 2020; Elmezayen et al., 2020; Enmozhi et al., 2020; Islam et al., 2020; Muralidharan et al., 2020, Sinha et al., 2020) have been put forward that could decipher the possible mechanism for COVID-19 treatment (Boopathi et al., 2020; Khan et al., 2020) through drug repositioning targeting at the various active sites of SARS-CoV-2. These targets sites are including protease, (Joshi et al., 2020) different enzymes (Gupta et al., 2020; Khan et al., 2020), protein terminals, (Sarma et al., 2020) proteins including various polymerase (Elfiky & Azzam, 2020) and small peptides (Pant et al., 2020) can be a good option. Probiotics are living organism with health-promoting benefits when consumed adequate amount either in the form of diet or drugs (Novik & Savich, 2020), is beneficial for health. Lactobacillus bacterial species plays a vital role in the treatment of gastrointestinal disorder and are known to possess antibacterial (Di Cerbo et al., 2016) and anti-viral (Sunmola et al., 2019) properties. Inhibition of H1N1, HIV, Gastric Corona and Rotavirus *in vitro* along with a marked reduction in viral (Hasan et al., 2020) load in vivo is well established and documented (Al Kassaa, 2016; Ismail, 2016). Various metabolites of Lactobacillus plantarumsecretes such as Plantaricin, lactic acid, acetic acid, and gamma-aminobutyric acid can enhance the antiviral immunity (Albarracin et al., 2017). In order to infect any host, receptor recognition is the first step by a virus and is a critical aspect

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Table 1. Docking scores and PubChem CIDs of the four Plantaricin compounds.

		RdRp		RBD		ACE2	
Molecule	PubChem CID	S (kcal/mol)	RMSD(Å)	S (kcal/mol)	RMSD(Å)	S (kcal/mol)	RMSD(Å)
Plantaricin W	139586573	−14.7	3.87	−11.1	2.5	−12.7	4.3
Plantaricin JLA-9	132535900	−11.4	4.1	−8.0	1.3	−9.1	2.6
Plantaricin D	139586697	−10.1	1.9	−8.6	1.9	−8.5	3.2
Plantaricin BN	380907	−6.4	1.8	−5.4	2.2	−6.0	1.47

Table 2. Interaction of compounds with RdRp, RBD and ACE2.

			RdRp			RBD			ACE2		
Molecule	PubChem ID	Bond	Residue	AA	Distance (Å)	Residue	AA	Distance (Å)	Residue	AA	Distance (Å)
Plantaricin W	139586573	Hydrogen Bonds	167	GLU	2.26	345	THR	2.74	26	LYS	2.79
			439	HIS	2.72	345	THR	3.28	33	ASN	3.7
			456	TYR	2.32	347	PHE	2.2	37	GLU	1.95
			456	TYR	2.05	441	LEU	2.6	90	ASN	2.7
			457	ARG	2.87	446	GLY	3.14	90	ASN	2.81
			550	ALA	2.38	446	GLY	3.2	319	GLY	2.54
			551	LYS	2.17	446	GLY	2.3	353	LYS	2.9
			553	ARG	2.96	451	TYR	2.58	354	GLY	2.63
			553	ARG	2.34				383	MET	2.28
			621	LYS	1.9				393	ARG	2.47
			623	ASP	3.45				548	THR	2.61
			624	ARG	2.62				26	LYS	2.79
			624	ARG	1.96				33	ASN	3.7
			682	SER	2.27						
			691	ASN	2.58						
			760	ASP	2.9						
			797	ALA	2.74						
			798	LYS	2.67						
		Hydrophobic Interactions	169	PRO	3.77	446	GLY	3.99	29	LEU	3.41
			555	ARG	3.94	447	GLY	3.95	321	PRO	3.81
			558	ALA	3.9				386	ALA	3.91
									389	PRO	3.89
									555	PHE	3.74
		Salt Bridges	623	ASP	4.07				37	GLU	3.86
			760	ASP	3.87						
Plantaricin JLA-9	132535900	Hydrogen Bonds	452	ASP	2.05	446	GLY	3.5	26	LYS	3.07
			452	ASP	2.3	494	SER	2.1	30	ASP	1.89
			497	ASN	2.29	351	TYR	2.59	92	THR	2.75
			500	LYS	2.24	491	GLN	3.50	96	GLN	2.27
			553	ARG	2.14				352	GLY	2.9
			556	THR	2.51				352	GLY	3.03
			619	TYR	2.6				353	LYS	3.07
			621	LYS	3.08				354	GLY	2.32
			623	ASP	2.3				355	ASP	2.91
			624	ARG	2.56				387	ALA	2.19
			680	THR	2.83				388	GLN	2.37
			682	SER	2.05						
			682	SER	2.83						
			688	ALA	2.6						
		Hydrophobic Interactions	455	TYR	3.78	451	TYR	3.60	26	LYS	3.73
			455	TYR	3.47	351	TYR	2.95			
			553	ARG	3.59						
			623	ASP	3.5						
		Salt Bridges	500	LYS	3.36						
			569	ARG	5.01						
		π-Cation Interactions	798	LYS	5.19				26	LYS	3.32
Plantaricin D	139586697	Hydrogen Bonds	500	LYS	3.74	415	THR	3.23	96	GLN	2.45
			553	ARG	2.44	449	TYR	2.1	350	ASP	2.66
			621	LYS	2.83	453	TYR	2.71	353	LYS	2.47
			682	SER	3.11	496	GLY	3.13	354	GLY	3.07
			684	ASP	2.27				383	MET	2.34
			688	ALA	2.86				393	ARG	3.49
			760	ASP	2.27						
		Hydrophobic Interactions	455	TYR	3.75	403	ARG	3.52	386	ALA	3.73
			455	TYR	3.5	421	TYR	3.72			
			624	ARG	3.77	505	TYR	3.62			

of the host cell and tissue tropism. Lie et al. in 2005 gave the concept of binding affinity between SARS-CoV and hACE2 that can correlate the viral transmissibility and disease intensity in humans (Li et al., 2005). COVID-19 entry in a host cell is mediated by transmembrane spike (S) glycoprotein forming homotrimers expressed from a viral surface (Tortorici

& Veesler, 2019; Wan et al., 2020). S glycoprotein binds with high affinity to Angiotensin-Converting Enzyme 2 (ACE2) receptor in humans (Walls et al., 2020). We targeted both spike (S) glycoprotein through blocking of Residual binding domain (RBD) and ACE2 by Plantaricin group of probiotic metabolites to establish the molecular, computational role in inhibiting the entry of COVID-19 by these two mechanisms followed by blocking the RNA dependent RNA polymerase (RdDp) for the virus which might get the entry into the alveolar cell. We selected four metabolic products of *Lactobacillus plantarum* from Plantaricin category viz., Plantaricin BN, Plantaricin JLA-9, Plantaricin W, Plantaricin D to designed computer-based antiviral computational product for COVID-19 that can be consumed as probiotics to retard, inhibit and kill COVID-19 in humans either by blocking or inactivation of RdRp preventing the rise of newly budded progeny virus or by blocking RBD of S protein or interfering with ACE2 receptor proteins and could be useful in the treatment of COVID-19 until some better option is available.

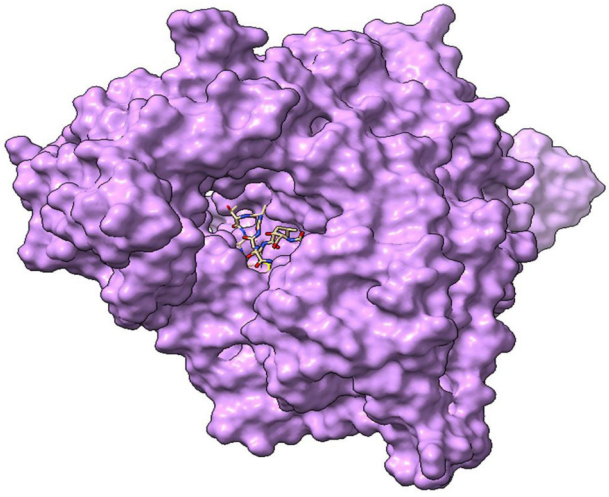

Figure 1. Three-dimensional structure of RNA-dependent-RNA polymerase (RdRp) enzymes with Plantaricin W blocking the active site cavity.

Methods

Protein modelling and quality score

The three-dimensional structure of the SARS-CoV-2 RNA-dependent-RNA polymerase (RdRp) enzyme was built by the Swiss-Model server. Angiotensin-converting enzyme 2 (ACE2) receptor (6VW1) and SARS-CoV-2 spike protein model (6VSB) structures were obtained from the RCSB PDB database (Berman et al., 2002). Ramachandran plots (Furnham et al., 2006) used to assess generated model quality parameters.

Ligands preparation

Four Plantaricin compounds (Plantaricin BN CID:380907, Plantaricin JLA-9 CID_132535900, Plantaricin D CID_139586697, and Plantaricin W CID_139586573) were obtained from PubChem. Compounds energy minimizedand prepared for docking by using Molecular Operating Environment (MOE) software (MOE, 2018).

Docking

Prior docking proteins 3D structure subjected to energy minimization, atoms partially charged and protonated using MOE. Docking software default parameters were used to find the best fit poses in the protein cavities. Chimera software will be used for visualization and calculations of ligands and protein interaction and estimation of H-bonds distances.

Ligand protein interaction and generation of images were rendered using Discovery studio,(Visualizer, 2005) the UCSF Chimera package, (Pettersen et al., 2004) and PLIP webserver

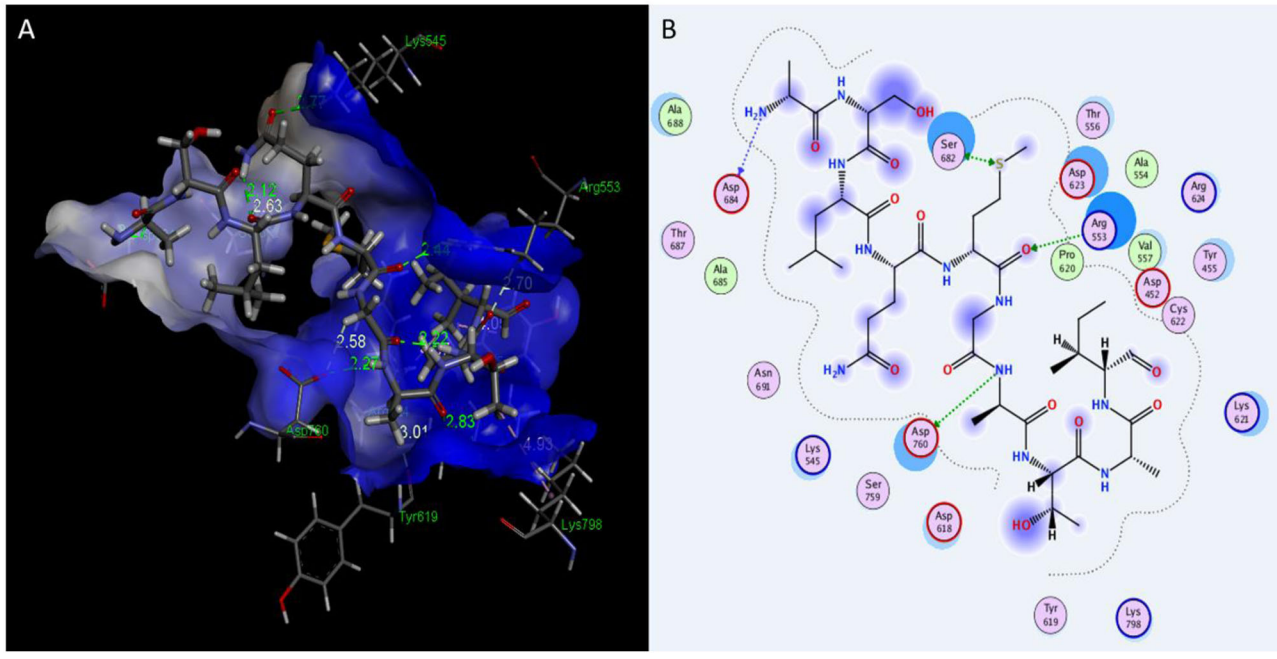

Figure 2. Interaction of Plantaricin D and RNA-dependent-RNA polymerase(RdRp) enzymes. (A) The three-dimensional structure of ligand is surrounded d by the hydrophobic surface of RdRp. (B) Two-dimensional interaction shows hydrogen bonds in green dotted lines.

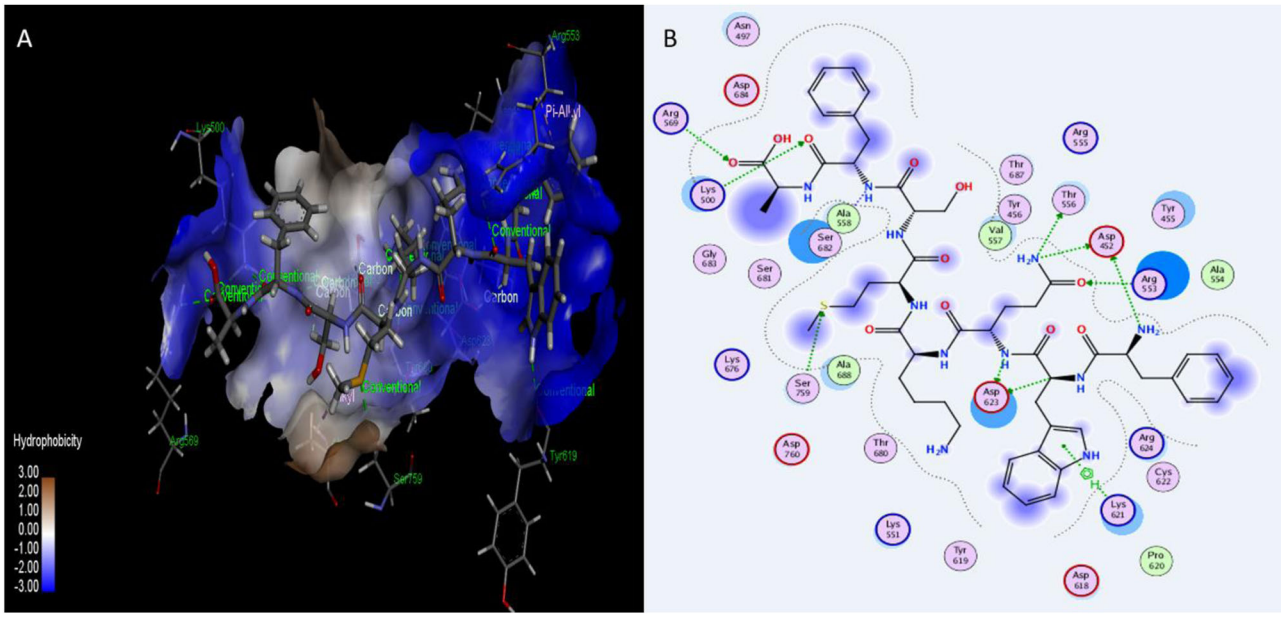

Figure 3. Interaction of Plantaricin JLA and RNA-dependent-RNA polymerase (RdRp) enzymes. (A) The three-dimensional structure of ligand is surrounded d by the hydrophobic surface of RdRp. (B) Two-dimensional interaction shows hydrogen bonds in green dotted lines.

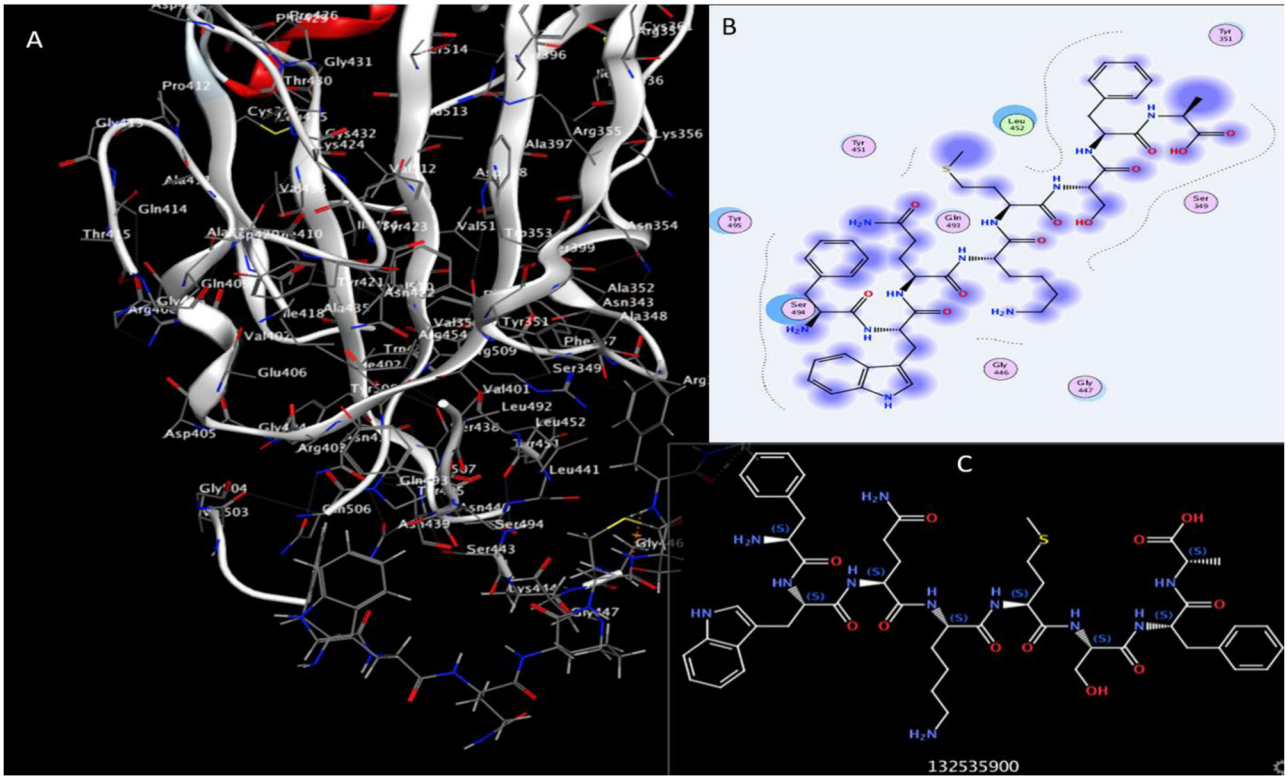

Figure 4. Interaction of Plantaricin JLA and SARS-CoV-2 receptor-binding domain (RBD). (A) The three-dimensional structure of ligand and amino acids, the RBD is coloured white. (B) Two-dimensional interaction shows hydrogen bonds in green dotted lines. (C) Two-dimensional structure and PubChem ID of Plantaricin JLA ligand.

(Salentin et al., 2015). Compounds with docking energy ≤ -6.5 kcal/mol are considered auspicious and proceeded for further analysis (Neira et al., 2017).

Molecular dynamics simulations

By using of Groningen Machine for Chemicals Simulations (GROMACS) 5.1.5 package, time-dependent molecular (MD) simulation was carried out for protein-ligand complexes. Molecules scored the best docking results (plantaricin w) were selected for MD simulation. A water solvation step was carried out by AMBER 18 package, as described by Wang et al. (2019) (Wang et al., 2019). System charges was then neutralized by addition of ions, then the energy minimization step was carried out (nsteps = 50,000) using the steepest descent approach (1,000 ps) with maximum force <

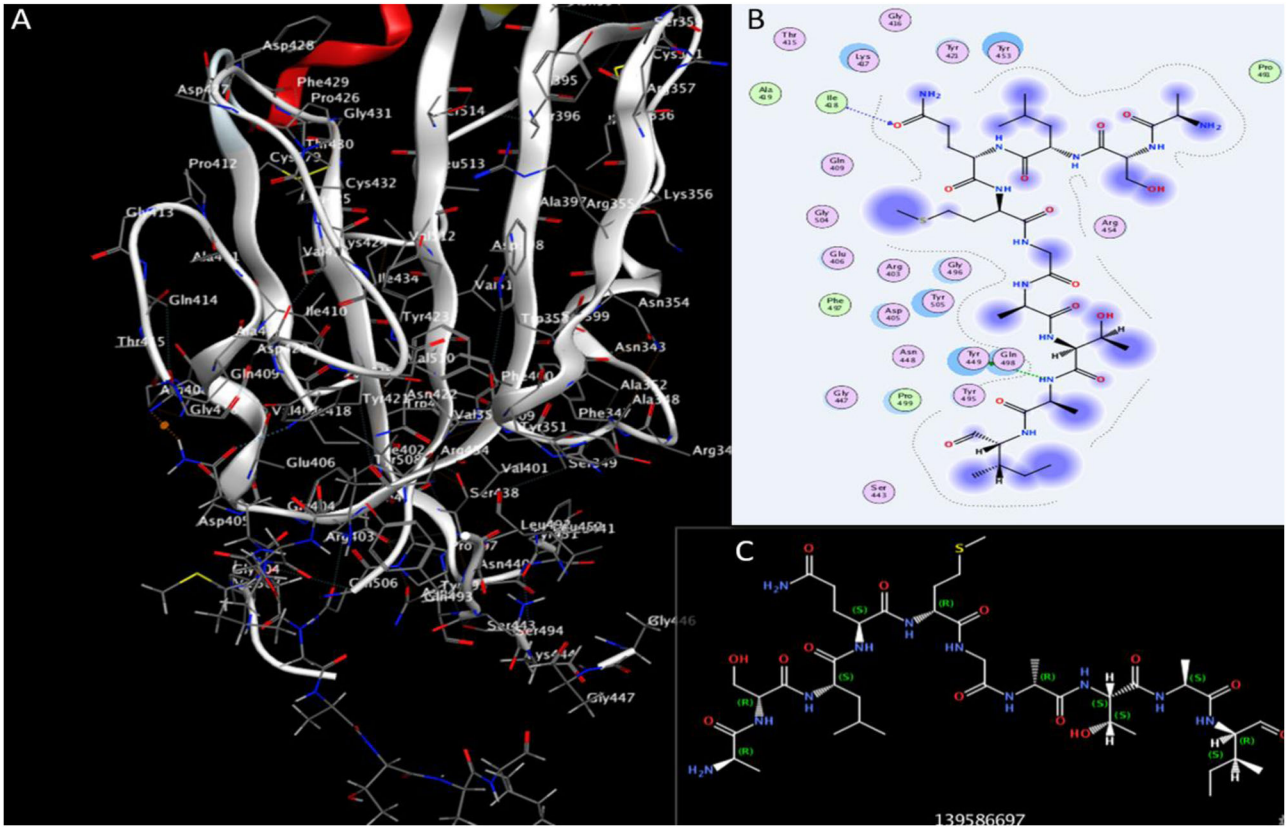

Figure 5. Interaction of Plantaricin D and SARS-CoV-2 receptor-binding domain (RBD). (A) The three-dimensional structure of ligand and amino acids, the RBD is coloured white. (B) Two-dimensional interaction shows hydrogen bonds in green dotted lines. (C) Two-dimensional structure and PubChem ID of Plantaricin D ligand.

1000.0 kJ/mol/nm. Particle Mesh Ewald (PME) method was employed for calculation of electrostatic interaction, then by using of leap-frog integrator system was equilibrated at time step of 2 fs (nsteps= 50,000) using a constant number, pressure and temperature (NPT), and a constant number, volume and temperature (NVT) ensembles. Molecular dynamic simulation finally runs into 10 ns, time step 0.002ps, and 5000,000 steps. Xmgarce (Turner, 2005) was used for visualization of the graphs of Root Mean Square Deviation (RMSD) relative to the structure present in the minimized, equilibrated system (Lu et al., 2010).

Results and discussion

Molecular docking results

Three compounds (Plantaricin W, Plantaricin JLA-9, and Plantaricin D) significantly interacted with RdRp, RBD, and ACE2, scoring the lowest binding energy (≤ -6.5 kcal/mol) (Table 1). Antiviral activity of Lactobacillus plantarum probiotics bacteria has been documented previously on the influenza virus, (Rodrigo-Torres et al., 2019) supports our finding.

Molecular docking of RdRp

Plantaricin W, D, and JLA-9 are able to bind RdRp tightly, with binding energies of −14.7, −11.4, and −10.1ACE2, respectively. The following residues in RpRp active site showed different types of interactions as shown in Table 2: GLU167, PRO169, HIS439, ASP452, TYR455, TYR456, ARG457, ASN497, LYS500, ALA550, LYS551, ARG553, THR556, ALA558, ARG569, TYR619, LYS621, ASP623, ARG624, THR680, SER682, ASP684, ALA688, ASN760, ALA797, and LYS798. These three compounds were able to block the residues (THR556, ALA558) surrounding the deep grove catalytic site (VAL557) of RdRp (Lung et al., 2020).

Plantaricin Winteracted with RdRp active site residues by 18 hydrogen bonds with RdRp enzyme with mean distance 2.7 Å and three hydrophobic bonds, which contribute significantly in binding (Table 2) (Figures 1, 2, and 3). The activity of Plantaricins W, d, and JLA-9 on catalytic site of RdRp is better than the activity of other molecules on RdRp: Lung and his colleagues found thataflavin interacts with RdRp with energy −9.11 (Lung et al., 2020), and (Elfiky, 2020) found IDX-184 interact with binding energy −9.3 to RdRp enzyme.

Molecular docking of RBD

We investigated the potential activity of the four Plantaricinpeptides against RBD of SARS-CoV-2. Plantaricin W, Plantaricin D, and Plantaricin JLA-9 exhibited a strong docking affinity to the RBD, with binding energies −11.1, −8.6, and −8.0 Å respectively (Table 1). They formed different hydrogen, hydrophobic, and salt bridges bonds with the following residues of RBD THR345, PHE347, TYR351, ARG403, THR415, TYR421, LEU441, GLY446, GLY447, TYR449, TYR451, TYR453, GLN491, SER494, GLY496and TYR505 as presented in

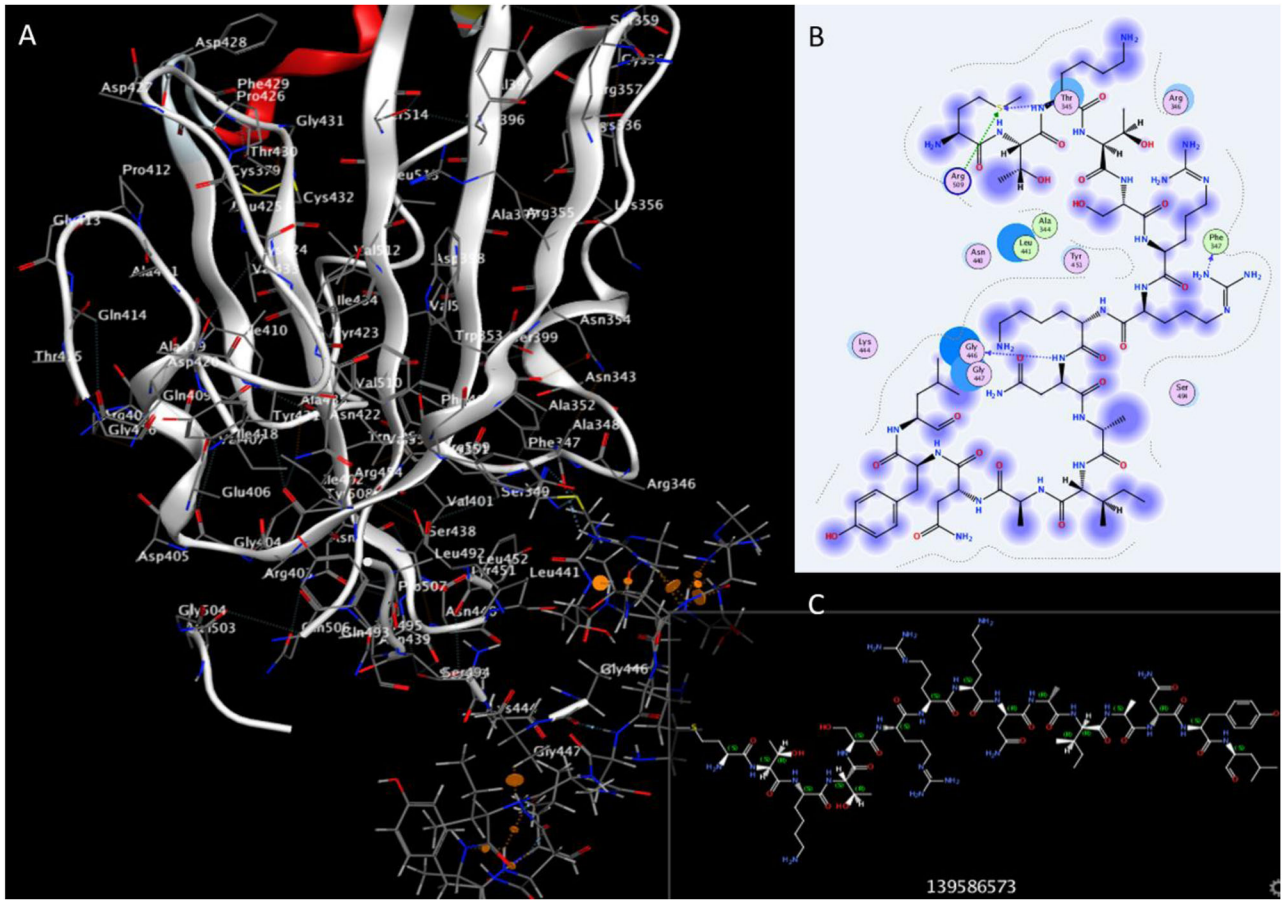

Figure 6. Interaction of Plantaricin W and SARS-CoV-2 receptor-binding domain (RBD). (A) The three-dimensional structure of ligand and amino acids, the RBD is coloured white. (B) Two-dimensional interaction shows hydrogen bonds in green dotted lines. (C) Two-dimensional structure and PubChem ID of Plantaricin W ligand.

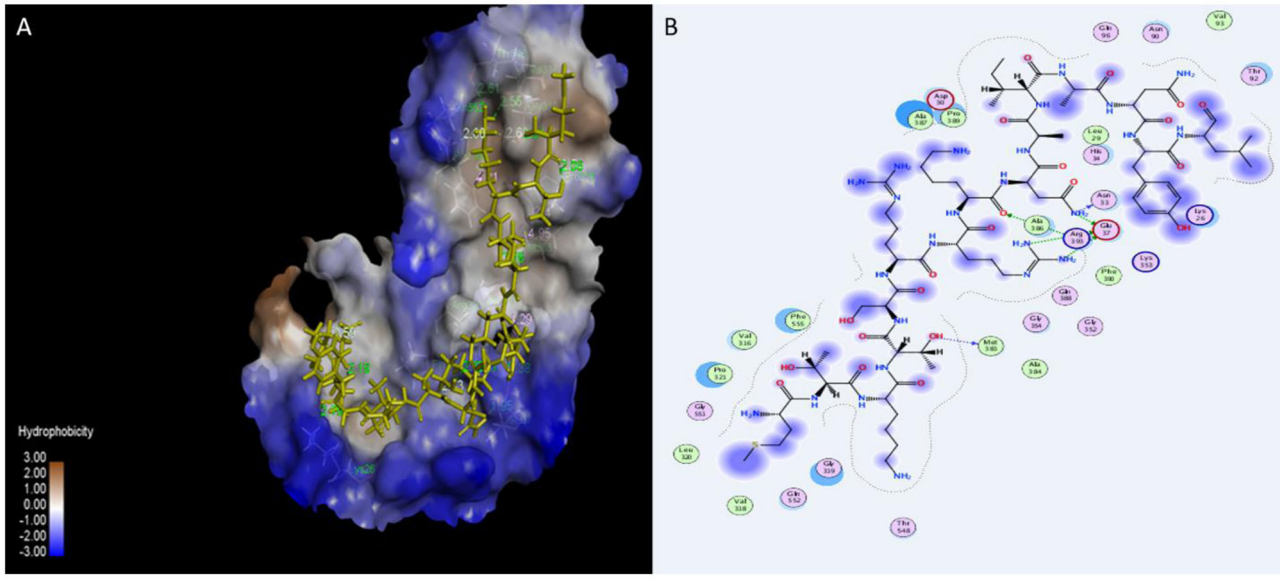

Figure 7. Interaction of Plantaricin W and angiotensin-converting enzyme 2 (ACE2) receptor. (A) The three-dimensional structure of ligand is surrounded d by the hydrophobic surface of ACE2. (B) Two-dimensional interaction shows hydrogen bonds in green dotted lines.

Table 2. These compounds showed strong hydrogen bonds with key residues (GLY446, TYR449, and TYR453) of RBD, that have a role in ACE2 binding (Yan, Zhang, Guo, et al., 2020; Yan, Zhang, Li, et al., 2020) (Figure 4, 5, and 6).

Molecular docking of ACE2

Many published studies suggested that the blocking of viral attachment site in the ACE2 receptor could be useful for patients with COVID-19 (Gurwitz, 2020). In this study, three

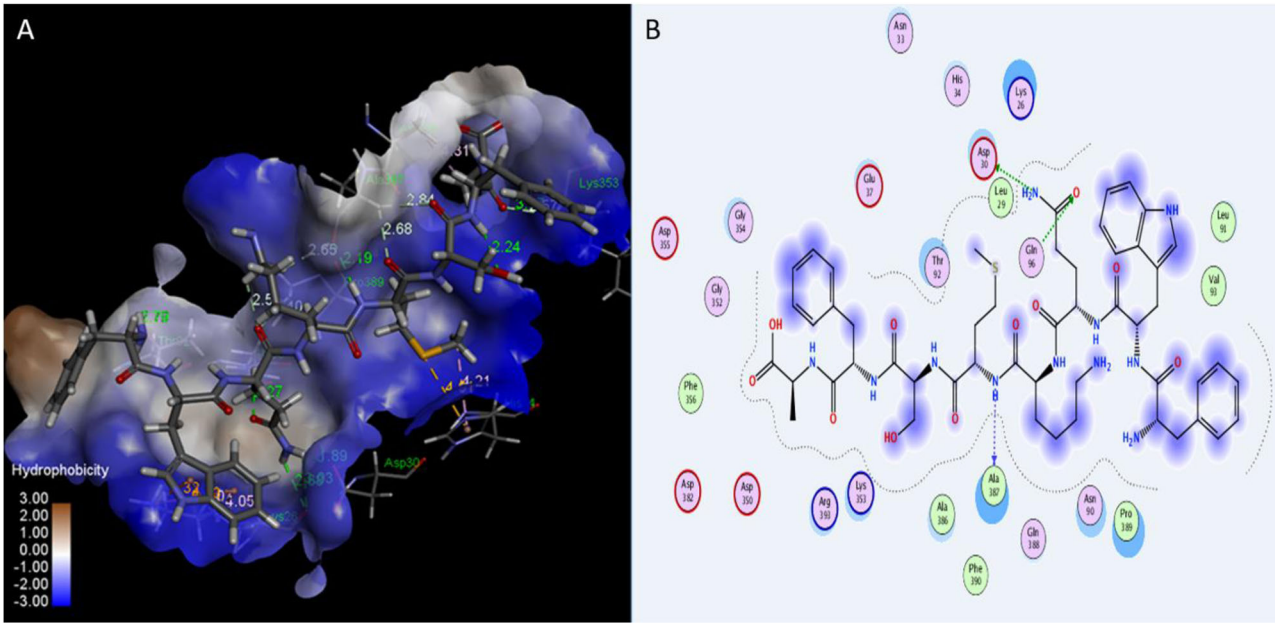

Figure 8. Interaction of Plantaricin JLA-9 and angiotensin-converting enzyme 2 (ACE2) receptor. (A) The three-dimensional structure of ligand is surrounded d by the hydrophobic surface of ACE2 (B) Two-dimensional interaction shows hydrogen bonds in green dotted lines.

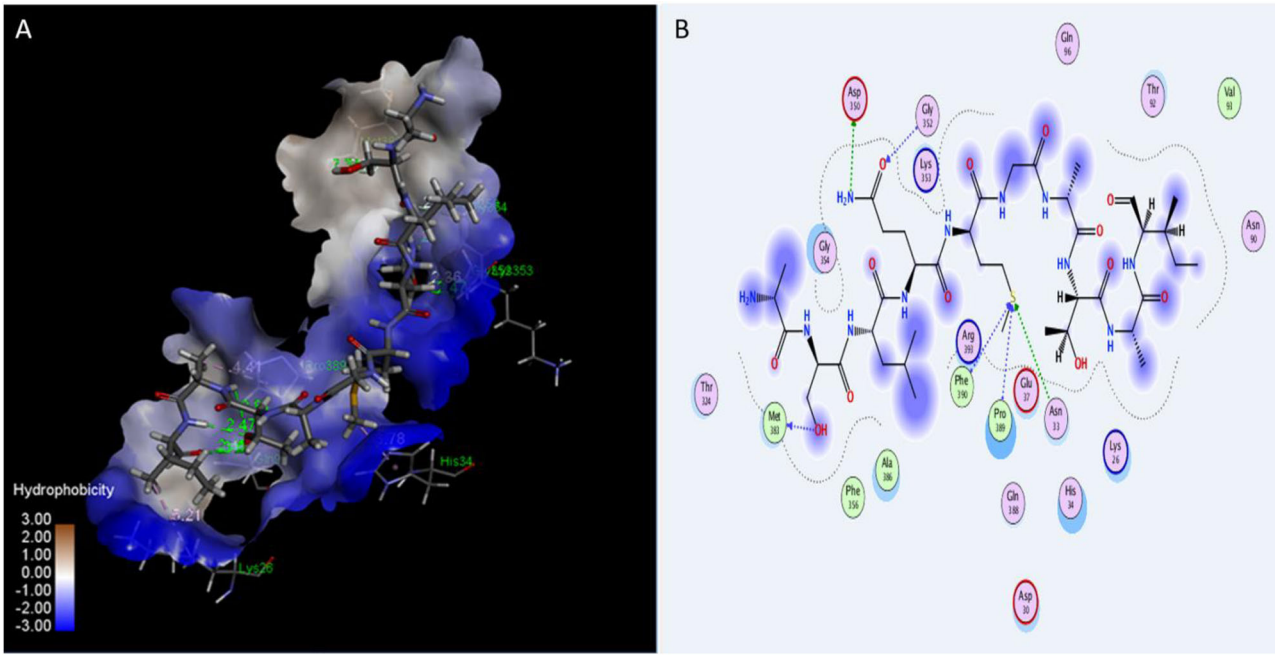

Figure 9. Interaction of Plantaricin D and angiotensin-converting enzyme 2 (ACE2) receptor. (A) The three-dimensional structure of ligand is surrounded d by the hydrophobic surface of ACE2. (B) Two-dimensional interaction shows hydrogen bonds in green dotted lines.

peptides: Plantaricin W, Plantaricin JLA-9, Plantaricin D showed significant activity on human ACE2 receptor, with binding energies −12.7, −9.1, and -8.5 Å respectively (Table 1). The following residues involving in the interaction with ACE2 receptor:LYS26, LEU29, ASP30, ASN33, GLU37, ASN90, THR92, GLN96, GLY319, PRO321, ASP350, GLY352, LYS353, GLY354, MET383, ALA386, ALA387, GLN388, ARG393, THR548, and PHE555 (Table 2).Plantaricin JLA-9 form strong hydrogen bond (with distance 1.89 Å) with ASP30, and Plantaricin W forms another hydrogen bond (2.9 Å) with LYS353 key residues in interaction with RBD of SARS-CoV-2 (Yan, Zhang, Guo, et al., 2020; Yan, Zhang, Li, et al., 2020) (Figures 7, 8, and 9).

Lactobacilli species produce hydrogen peroxide, acides, biosurfactants and bacteriocins giving sufficient protection to host cell (La Fata et al., 2018; Mousavi Khaneghah et al., 2020). Several lactic acid bacteria can synthesize Exopolyscacharides that can modulate the health benefits such as antitumor, antibiofilm and antioxidant activity along with immunomodulatory effects (Silva et al., 2019) such as interference of HIV attachment to target host cells (Martenot et al., 2019).

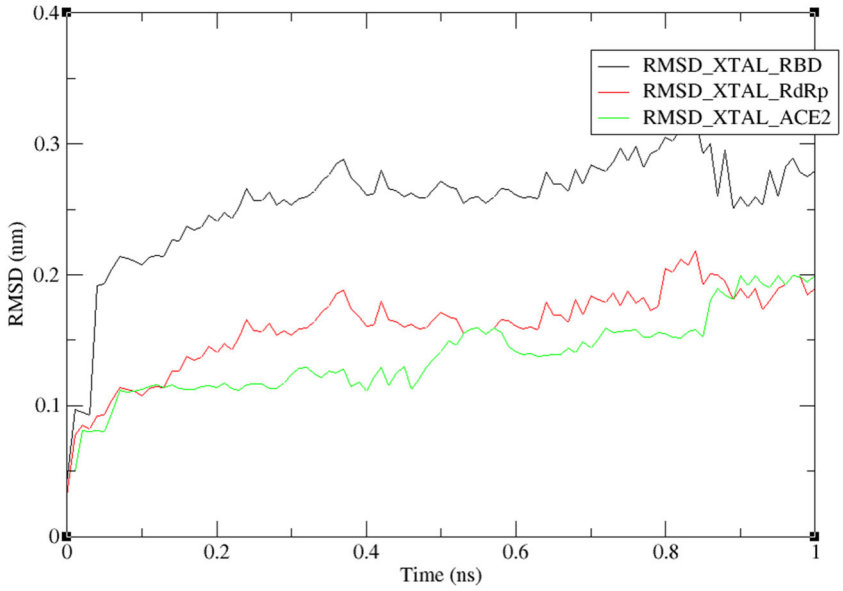

Figure 10. RMSD plot of RBD, RdRp, and ACE2 proteins backbones in complex with plantaricin w, over one nanosecond period.

Lactobacillus plantarum metabolic products established earlier as antiviral metabolites 8 is now computationally proved to inhibit the COVID-19 at various levels. Assessment of our results on COVID-19 through computational studies provides a better glimpse of inhibition, there may be other mechanisms by which these plant products might be working on COVID-19 that need to be deciphered for experiments. Further, these metabolites may also be involved in indirect stimulation of innate and other immunity. Our study can be used as one of the anti-COVID-19 mechanistic approaches through probiotic intake until some effective treatment or vaccine is developed.

Molecular dynamic simulations

The molecular dynamic simulation was used to check the stability of the complexes of plantaricin w and SARS-CoV-2 RdRp enzyme, RBD of spike protein, and human ACE2 receptor. Root-mean-square deviation (RMSD) of the protein backbones was calculated to study the stability of complexes over a period of time. From RMSD trajectories, as shown in Figure 10, all complexes scored values ranged from 1 nm to 3 nm, indicating their high stability. RdRP and ACE2 complexes showed RMSD level near to 0.1 nm (1 Å) after a short period of time (0.1 ns) indicating their best stability (Vyas et al., 2017), this finding agrees with that they have scored the best docking energies (−14.7, and −12.7 respectively) stating their strong interaction.

Conclusion

The present computational representation and molecular dynamics study clearly demonstrates the antiviral activity (Aanouz et al., 2020) of Plantiricin compounds, through multiple mechanistic approach by metabolic product of *Lactobacillus plantarum* blocks the entry by binding with RdRp, RBD, and ACE2. The blocking of main structural protein S is one of the essential accessory protien, playing a vital role in the life cycle of SARS-CoV-2 can prove to be one of the best target for other molecules. The claim is substantiated by Molecular dynamics model that further strengthen stability of the complexes of plantaricin w and SARS-CoV-2 RdRp enzyme, RBD of spike protein, and human ACE2 receptor. Molecular dynamics and computational model are the tools that can precisely predict to reposition the drugs without going in the clinical phase for the effective treatment of COVID-19. Further, it is difficult to find the drug that has a better safety profile than these macrolides, with a cheaper cost, which can be linked with the clinical data for further studies. The present study can state that best possible way about these metabolites that can cease the infection if taken under proper medical supervision. The three antibiotics Azithromycin, Clarithromycin and Erythromycin can be used against new strain of coronavirus with promising result with three way specific target against COVID-19. As of now the plantaricin metabolites can be the alternate till new antiviral drug specific for COVID-19 is discovered.

Disclosure statement

No potential conflict of interest was reported by the authors.

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