ORIGINAL ARTICLE

Inhibitory effect of anti-HIV compounds extracted from Indian medicinal plants to retard the replication and transcription process of SARS-CoV-2: an insight from molecular docking and MD-simulation studies
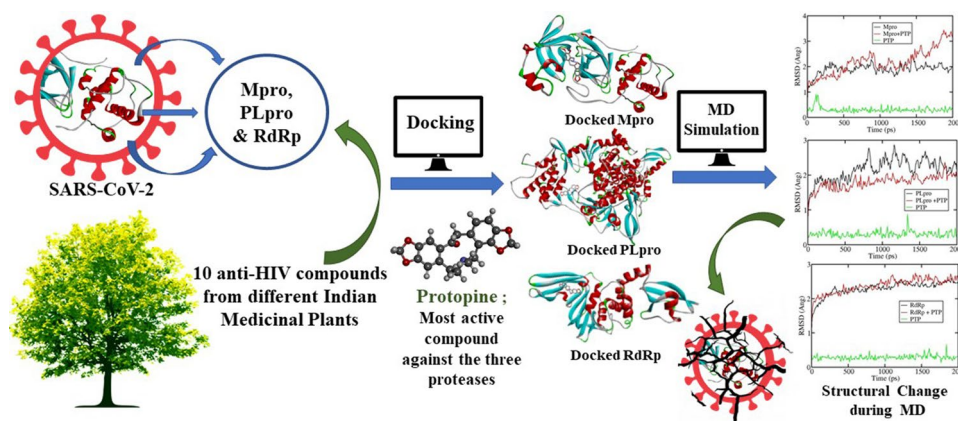
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Abstract

Outbreak of Coronavirus (SARS-CoV-2) has thrown a big challenge to the globe by snatching millions of human lives from the world. In this study, inhibitory efficiency of ten anti-HIV compounds from different Indian medicinal plant parts have been virtually screened against Mpro, PLpro and RdRp proteins of SARS-CoV-2. The molecular docking study reflected that among these compounds, Proptine (PTP) has the highest binding affinity for the three cases. Introduction of PTP molecules within the binding pocket of these proteins showed a large structural and conformational changes on the structure of proteins which is revealed from molecular dynamics (MD) simulation studies. RMSD, RMSF and analysis of thermodynamic parameters also revealed that PTP makes a huge impact on the structures of the respective proteins which will pave an opportunity for doing advanced experimental research to evaluate the potential drug to combat COVID-19.

Graphic abstract

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1 Introduction

In late December 2019, a new strain of Coronavirus (SARS-CoV-2) has spread swiftly around the globe. WHO declared a pandemic situation within 3 months of its initial screening in Wuhan, China (Wang et al. 2020; Lu et al. 2020; Jiang et al. 2020). Hundreds of millions lives of approximately 188 countries are affected with this highly transmissible disease (Shekerdemian et al. 2020; Baildya et al. 2020). This pandemic efficiently strikes the national healthcare systems and global economy. While the year of 2020 was a challenging one, 2021 looks to be more difficult with the appearance of multiple variants SARS-CoV-2 (Fontanet et al. 2021). A new variant can emerge through numerous rounds of viral replication. The variant is co-termed as a strain if the sequence variation shows a distinctly different phenotypic characteristics (Mascola et al. 2021). In December, 2020, there was an unexpected rise of the COVID-19 cases due to the emergence of the new SARS-CoV-2 variants 501Y.V2 (B.1.351) in South Africa and 501Y.V1 (B.1.1.7) in the UK (Fontanet et al. 2021; Tegally et al. 2020; Volz et al. 2021; Davies et al. 2021; Xie et al. 2021). New strains are more transmissible than the previously one (Kirby 2021). Cold, flu, dihedra, headache, lymphopenia, etc. are the common symptoms of COVID-19 but it is not clear new strain-affected patients are sowing the same symptoms or not (Sahin et al. 2020; Graham et al. 2021). SARS-CoV-2, the single-stranded positive-sense RNA virus is included in β-coronavirus genus, closely related to the genomic organization of SARS-CoV identified in 2003 (Pal et al. 2020). With the interaction of angiotensin converting enzyme 2 of Human cell, spike protein of SARS-CoV-2 helps the virus to enter the human cell (Zhang et al. 2020). After entering into the cell, immediately viral replication and transcription are started with the functional proteins like main protease (Mpro), papain-like protease (PLpro), RNA-dependent RNA polymerase (RdRp) (Indwiani Astuti 2020). It is reported that in the new strains, mutation (N501Y) occurred in the receptor-binding domain of the spike protein, responsible for increased transmission (Davies et al. 2021).

With the heavy toll of the pandemic, scientists are actively checking various strategies either new or repurposed drugs as well as vaccines (Kandeel and Al-Nazawi 2020) but till now there is no potentially active drug available in the market which may effectively combat SARS-CoV-2. 2020 saw the development and testing of some COVID-19 vaccines (Fontanet et al. 2021; Baden et al. 2021; Polack et al. 2020). Till now, it is not clear that whether these COVID-19 vaccines can protect against the infection from these new SARS-CoV-2 variants or not (Fontanet et al. 2021; Mascola et al. 2021). Recently, name of the few drugs e.g., Remdesivir, Hydroxychloroquine, Chloroquine are the topic of discussion to researchers but none of these are potentially efficient against this deadly virus (Baildya et al. 2020, 2021a; Elfiky 2020; Khan et al. 2021; Mandal et al. 2021).

Secondary metabolites from different tropical plants are greatly influenced by environmental factors. These secondary metabolites have already drawn the attention for developing medicine against different antiviral diseases (Guerriero et al. 2018; Yang et al. 2018). According to the previous reports, extracts from various medicinal plant parts or plant-derived natural products have shown anti-HIV activity and they are under different stages of clinical development in different parts of the globe (Bedoya et al. 2001; Min et al. 1999, 2001). Different attempts also have been made to search the natural products which can inhibit different proteins of SARS-CoV-2 (Dutta et al. 2021). Few scientists claimed that the leave extracts of *Azadirachta indica* and *Ocimum sanctum* showed significant inhibitory activity against SARS-CoV-2 (Baildya et al. 2021b; Varshney et al. 2020). In-silico-based screening is an effective tool to meet the challenges of antiviral drug discovery. Computational screening of natural compounds as docking followed by molecular dynamics saves resources in terms of money and time (Murgueitio et al. 2012). Generally, the active compounds from one plant were considered in the previous studies (Borkotoky and Banerjee 2020), but in our study, we have considered the most active anti-HIV compounds of different plants with the explanation of the effectiveness against new SARS-CoV-2 variants.

In this study, we have chosen ten highly active compounds (available in traditionally used medicinal plants of India) against HIV (Sabde et al. 2011) and virtually screened their inhibitory activity against Mpro, PLpro and RdRp protein of SARS-CoV-2. Molecular dynamics simulation also performed to check the stability of Mpro, PLpro and RdRp with the compound having the highest Molecular Docking score. These findings will provide valuable information to other researchers to identify the right drug to combat COVID-19.

2 Methodology

2.1 Docking of potentially active anti-HIV compounds with Mpro, PLpro and RdRp of SARS-CoV-2

Structures of Mpro (PDB ID: 6LU7), PLpro (PDB ID: 6W9C) and RdRp (PDB ID: 6M71) were downloaded from Protein Data Bank (http://www.rcsb.org). The "sdf" files of the ten anti-HIV compounds were downloaded from the PubChem (National Library of Medicine) and was converted

to respective pdb files. All the structures of proteins were cleaned by removing hetero-atoms and water molecules using UCSF Chimera (Pettersen et al. 2004). Autodock Vina package (Trott and Olson 2010) was used for docking between the compounds and the best binding sites of the proteins. Autodock Tools was used for the preparation of pre-docking necessary files.

2.2 Molecular dynamics (MD) simulation of protein–protopine complex

MD studies using GROMACS (5.0) (Berendsen et al. 1995) were performed with the minimum energy conformer obtained after docking between proteins and protopine (PTP) by applying CHARMM36-mar2019 force-field (Lee et al. 2014) using TIP3P solvation model (Boonstra et al. 2016). CHARMM General Force Field server for was used the generation of topology and parameter files of the respective drug. Periodic boundary conditions were applied by generating a cubical box of 1-nm length by keeping 2-nm distance between two successive images. All the protein moieties were neutralized by adding adequate number of ions. Using steepest descent algorithm and conjugate gradient protocol, energy minimization was performed until the maximum force of at least 10 kJ mol^{-1} nm^{-1}. Isochoric-isothermal (NVT) and isothermal-isobaric (NPT) ensembles were applied on the system for 100 ps for equilibration at 300 K by keeping 2-fs time step and 1-nm electrostatic and van der Waal cut-offs. Particle mesh Ewald (PME) (Abraham and

Gready 2011) method was used for long range interaction calculations. Finally, 2000-ps MD simulation were subjected to the equilibrated ensembles with the same cut-offs. In all cases, snapshots of the trajectory were saved for each ns.

2.3 Binding free energy calculation

Binding energies between the proteins and PTP were calculated by molecular mechanics Poison–Boltzmann surface area (MM-PBSA) method, implemented on Gromacs tool (g_mmpbsa) (Baker et al. 2001; Kumari et al. 2014). The following formulae was used for binding energy calculation:

$$\Delta G_{bind} = G_{w\text{-}complex} - G_{w\text{-}protein} - G_{w\text{-}PTP}, \tag{1}$$

where $G_{w\text{-}complex}$ is the total free energy of the proteins and PTP complex, $G_{w\text{-}protein}$, $G_{w\text{-}PTP}$ are the free energies of the protein and PTP, respectively.

2.4 MD simulation result analysis

Using trjconv implemented on GROMACS, structural trajectories were calculated for protein and PTP complexes. To re-centre the proteins, PTP, ions and water molecules within the cubical box the same tool was used. gmx energy tool of GROMACS was applied for calculation of van der Waals interaction, electrostatic energy, interaction energy values, etc. With the help of xmgrace plotting tool RMSD


Fig. 1 Docking score of anti-HIV compounds against SARS-CoV-2 proteins
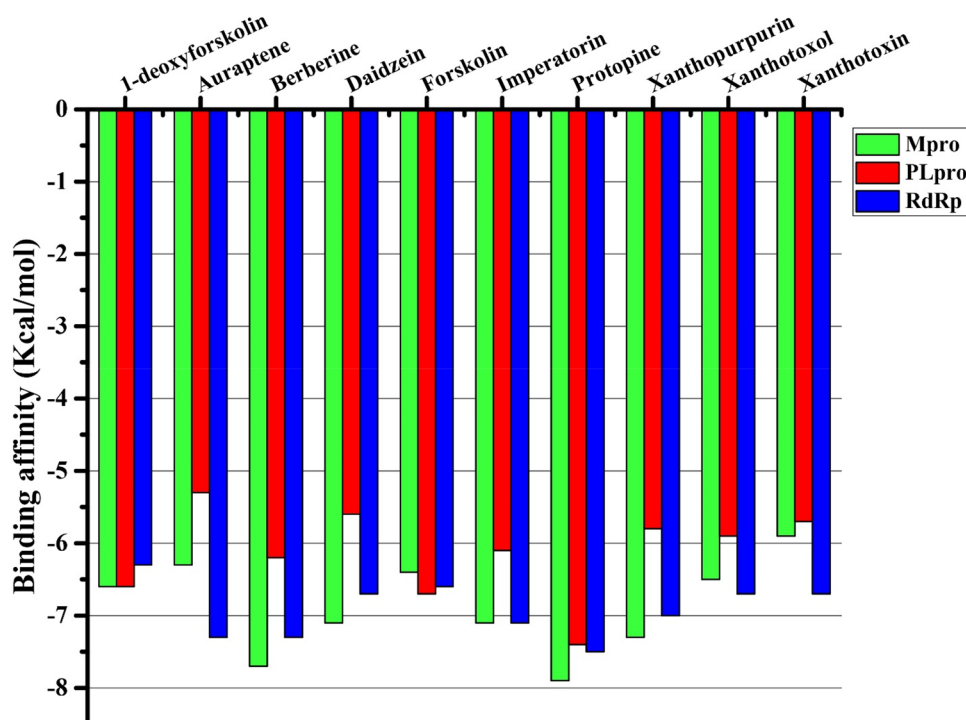
Table 1 Toxicity prediction of different anti-HIV compounds extracted from different Indian medicinal plants

| Name of the compounds	AMES toxicity	Max. tolerated dose (human)	hERG I inhibitor	hERG II inhibitor	Oral rat acute toxicity (LD50) (mol/kg)	Oral rat chronic toxicity (LOAEL) (log mg/kg_bw/day)	Hepato-toxicity	Skin Sensi-tisation	T.Pyriformis toxicity (log ug/L)	Minnow toxicity (log mM)
1-Deoxyforskolin	N	− 0.233	N	N	2.365	2.231	N	N	0.336	2.095
Auraptene	N	0.384	N	N	2.274	2.221	Y	N	1.893	− 0.223
Berberine	Y	0.144	N	N	2.571	1.89	Y	N	0.354	− 0.277
Daidzein	N	0.187	N	N	2.164	1.187	N	N	0.693	1.035
Forskolin	N	0.099	N	N	2.543	2.49	N	N	0.288	3.659
Imperatorin	Y	− 0.593	N	N	2.2	1.794	N	N	0.614	0.25
Protopine	N	− 0.446	N	N	2.993	1.93	N	N	0.64	1.237
Xanthopurpurin	Y	0.136	N	N	2.251	2.083	N	N	0.792	1.463
Xanthotoxol	Y	− 0.317	N	N	2.07	1.112	N	N	0.599	1.777
Xanthotoxin	Y	− 0.62	N	N	2.172	1.674	N	N	0.408	1.065

Y Yes, *N* No
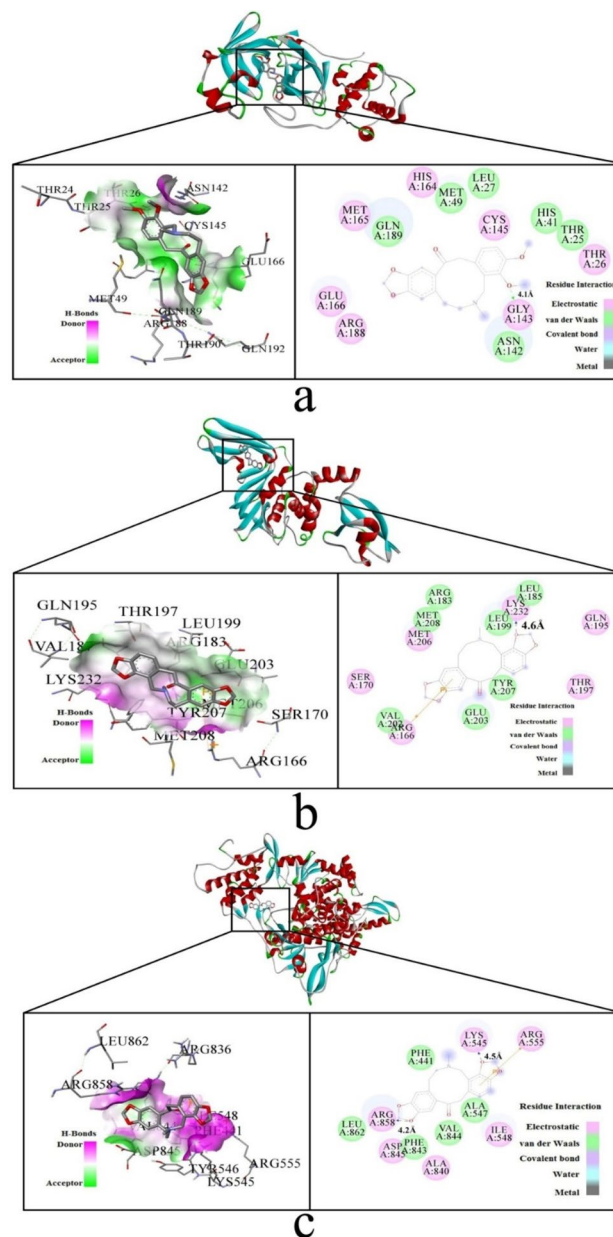
Fig. 2 Docked structure of PTP and SARS-CoV-2 proteins

plots, RMSF plot, Radius of gyration and SASA plots were generated.

3 Results and discussion

The binding affinities of the ten anti-HIV compounds against Mpro, PLpro and RdRp are shown in Fig. 1. Highest binding affinity of − 7.9, − 7.4 and − 7.5 kcal/mol is achieved by protopine (PTP) against Mpro, PLpro and RdRp, respectively. This signifies that among these compounds PTP is strongly binds with these proteins.
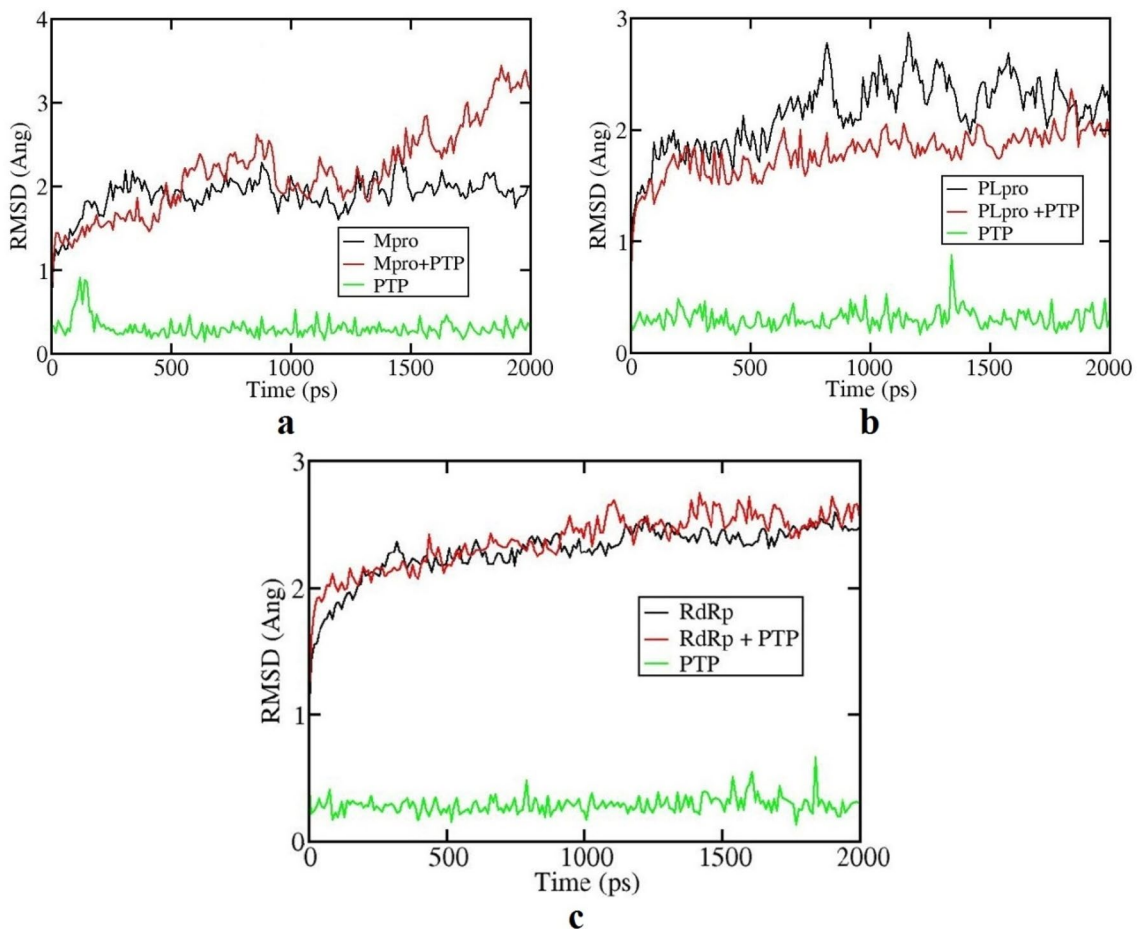
Fig. 3 Root mean square deviation of docked **a** Mpro **b** PLpro and **c** RdRp during MD simulation

Moreover, to determine the level of toxicity of the selected anti-HIV compounds, we have examined out ADME toxicity analyzed by pkCSM online server (Pires et al. 2015).

3.1 Prediction of ADMET

Evaluation of pharmacokinetic properties of the studied anti-HIV compounds suggested that they were effectively absorbed by the gastro-intestinal part with low blood–brain-barrier (BBB) permeability value and these drugs do not affect CYP2D6, CYP2C9 and CYP2D6 cytochromes. Skin permeability for these compounds was found to be in between − 3.078 and 1.089 units. The toxicity table is shown in Table S1.

3.2 Prediction of toxicity

All compounds show negative hERGI inhibition activity. The LD50 values of the examined anti-HIV compounds fall in between 2.0 and 2.993 (mol/kg), while the chronic oral rat toxicity (LOAEL) values fall in between 1.112 and 2.49 (log mg/kg_bw/day). Most of the compounds do not show AMES toxicity and hepatotoxicity. None of the compounds show skin sensitization. *T. pyriformis* and minnow toxicity values are tabulated in Table 1.

From the above analysis, it is clear that the studied drugs showed a descent toxicity level. From the binding affinity and toxicity level analysis, we have selected PTP to carry out further analysis.

The binding interactions of PTP on the binding pockets of Mpro, PLpro and RdRp are shown in Fig. 2a–c. The major interactions that contributes to the binding of the corresponding proteins are electrostatic and Van der Waal types. The donor and acceptor sites that are engaged in H-bonding are shown 3D-contour in the left panel of Fig. 2a–c. The residues corresponding proteins that are involved to the binding of active compound PTP molecule are shown on the right panel of Fig. 2a–c.

To analyze the stability of the PTP–protein complexes, we have performed MD simulation. The root mean square deviation (RMSD) plots of corresponding complexes are
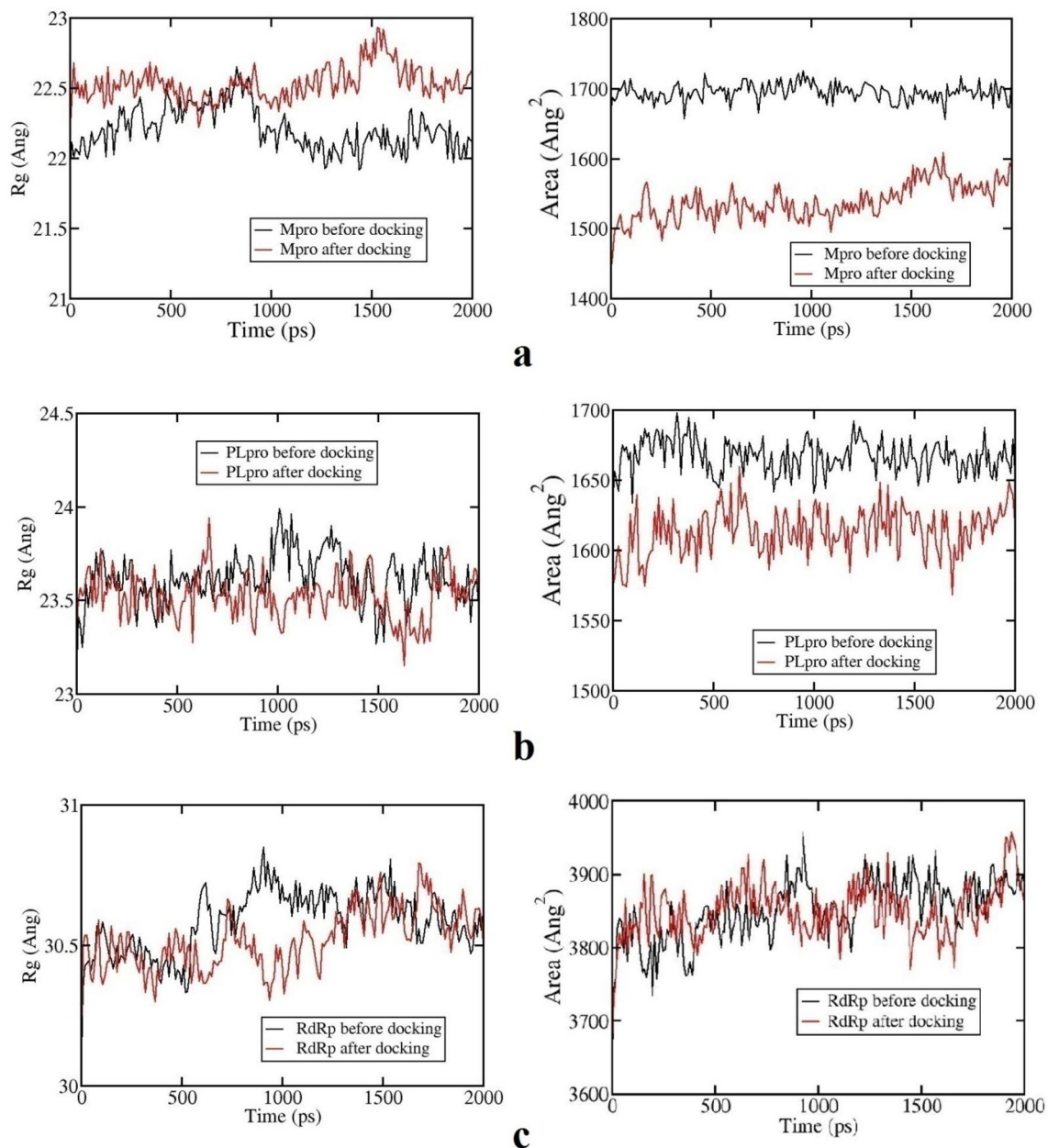
Fig. 4 Radius of gyration (left) and SASA plot (right) of **a** Mpro, **b** PLpro and **c** RdRp during MD simulation

shown in Fig. 3a–c. It is clear from Fig. 3 that Mpro–PTP, PLpro–PTP and RdRp achieved an equilibrium for about 500, 250 and 500 ps with an RMSD value around 2.2, 1.9 and 2.2 Å, respectively.

We found the RMSD fluctuation of the docked PLpro–PTP complex accounts lower RMSD fluctuation with respect to undocked one confirming introduction of PTP in the binding cavity of PLpro stabilizes the corresponding complex.

Figure 4a–c illustrates the radius of gyration (R_g) plot (left panel) and solvent accessible surface area (SASA) plot (right panel). R_g measures the compactness of a system. Except Mpro–PTP complex the docked PLpro and RdRp corresponds lower R_g value compare to undocked one revealing that these complexes are much compact. Higher value indicates lower fluctuation of proteins with time. Figure 4 (left panel) shows that all the docked structure has lower SASA value compare to undocked one which reveals the lower fluctuation of the docked structure. To further assess the flexibility and local motion of the drug–protein complexes, we have further analyzed root mean square fluctuation (RMSF) as shown in Fig. 5a–c.
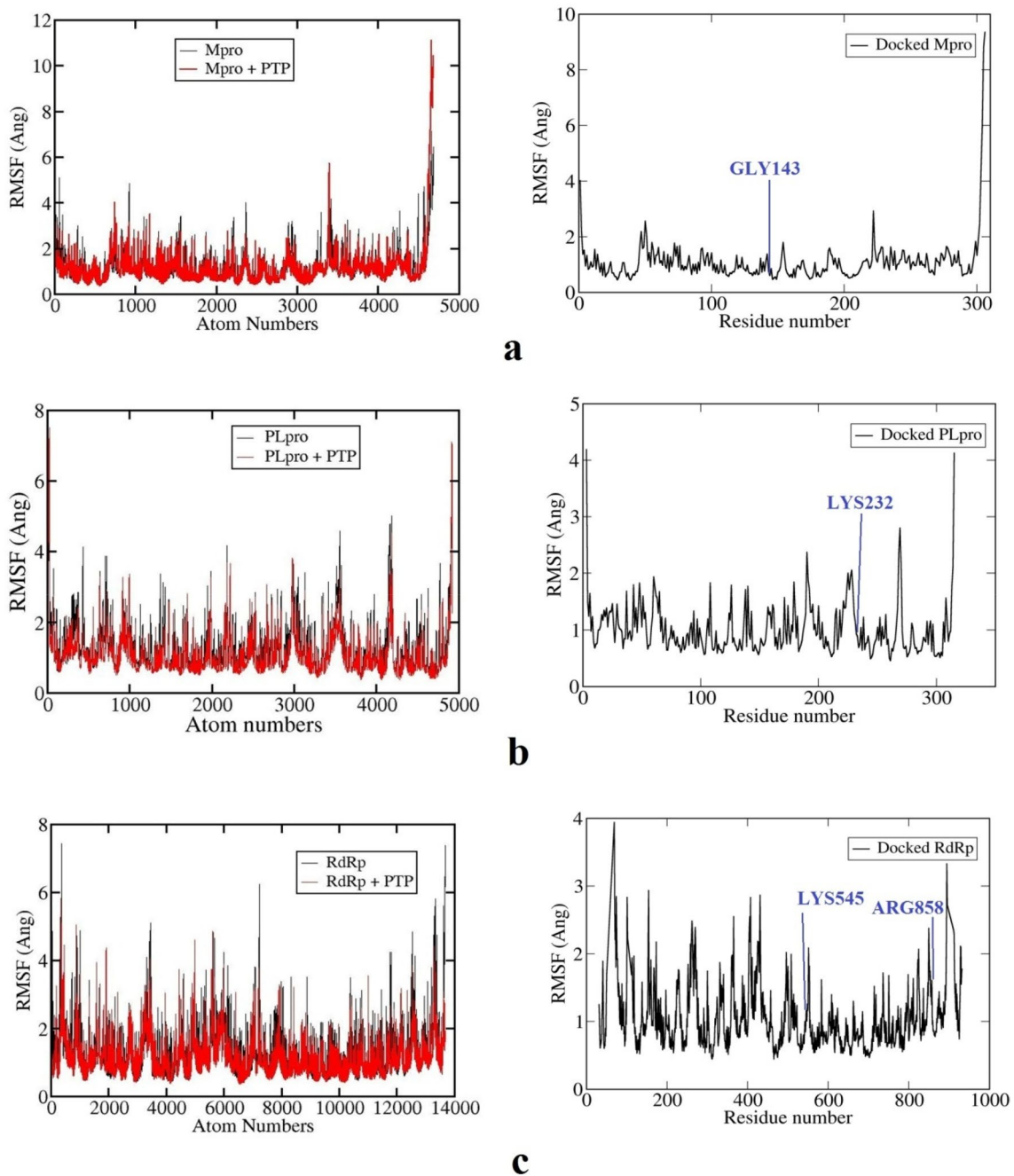
Fig. 5 Root mean square fluctuation of before and after docking of **a** Mpro, **b** PLpro and **c** RdRp

The lower fluctuation of the PTP-protein as compare to the protein clearly reveals that PTP moiety strongly interacts with the protein residues establishing stability of the complexes. We further noted that RMS fluctuation for the residue GLY143 for Mpro, LYS232 for PLpro and LYS545 and ARG858 for RdRp experienced lower fluctuation revealing that they are involved in interaction with the drug and located at the binding loop of the corresponding complexes. Furthermore, we have performed g_MMPBSA

energy analysis. By applying the said tool, we have analyzed the contribution energy of each residue as shown in Fig. 6a–c.

Both the RMSF and the contribution energy graph showed the residues which directly interacts with the PTP moiety expose their highest energy contributions as indicated by the residue numbers in corresponding RMSF graphs (left panel Fig. 5). Different free energy parameters that contribute to the binding energy are plotted in Fig. 7.
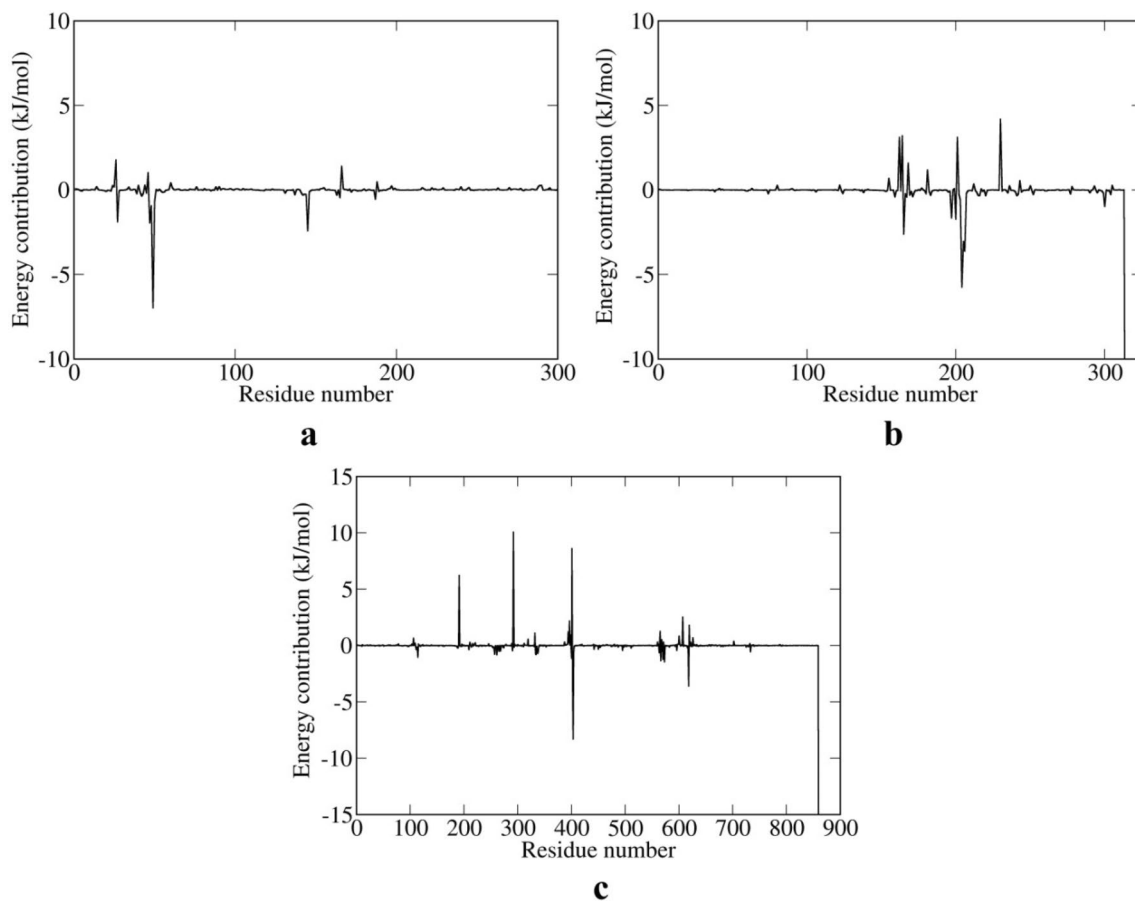
Fig. 6 Contribution energy of different residues of **a** Mpro, **b** PLpro and **c** RdRp
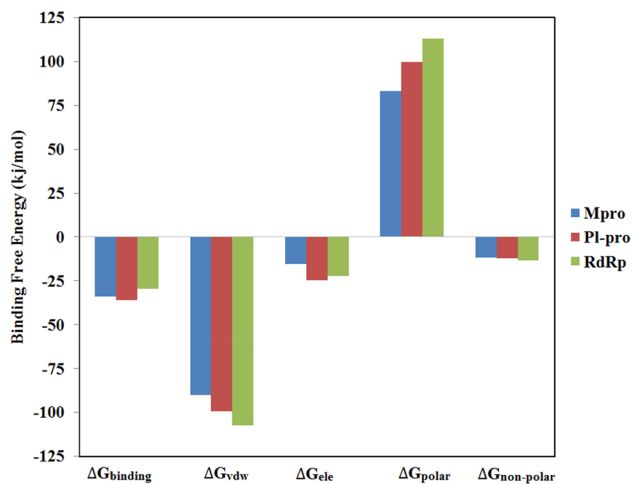
**Fig. 7** Different types of free energies of the PTP docked proteins

It is clear from the figure that none of the parameter has its contribution to the overall binding. Highest Van der Waal interaction is achieved by RdRp, while least is seen by Mpro. Same trend is followed in case of non-polar energy term.

Gibb's free energy change for binding is highest with PLpro, while least is experienced by RdRp.

Furthermore, to analyze the effect of entry of drug to the binding pocket of the corresponding complexes, we have plotted the snapshots after every 1000 ps. We note that there is a huge conformational change experienced by the corresponding proteins at 2000 ps, 1000 ps and 2000 ps for Mpro, PLpro and RdRp, respectively. The snapshots at 0 ps and 2000 ps clearly raised the profound structural changes for stronger binding interactions between drug and proteins during the trajectory.

As per the report, the new variants of SARS-CoV-2 [i.e., 501Y.V1 (B.1.1.7), 501Y.V2 (B.1.351)] carry a mutation in spike protein and for that reason, the transmission rate is increased upto 70% (Xie et al. 2021; Gu et al. 2020; Tang et al. 2020). Our study shows that PTP has potential inhibitory activities against Mpro, PLpro and RdRp proteins of SARS-CoV-2. Hence, there is a chance of PTP to show the effectiveness against the new variants of SARS-CoV-2 (Fig. 8).
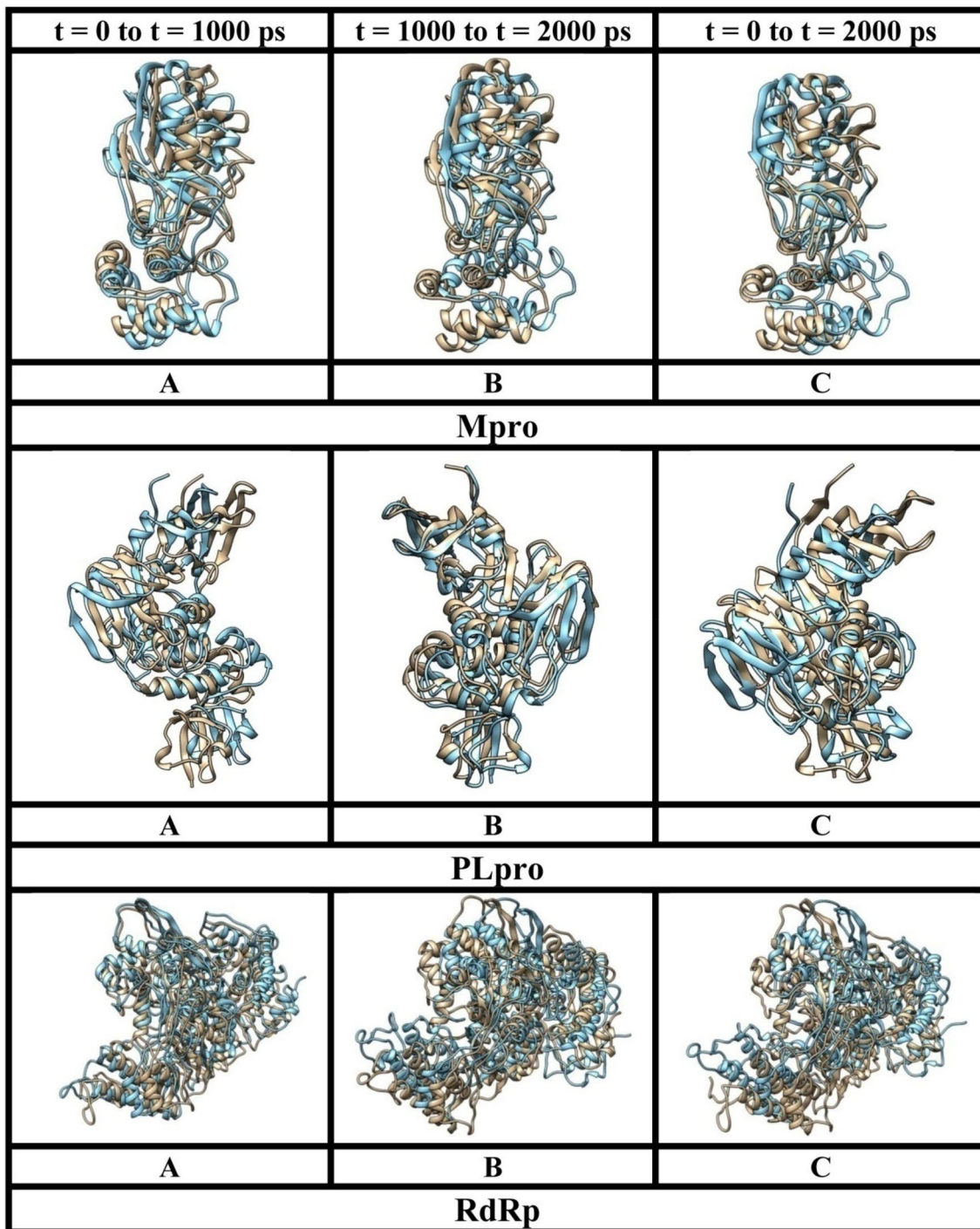
Fig. 8 Structural changes of Mpro, PLpro and RdRp during MD simulation

4 Conclusions

The present work deals with the virtual screening of ten anti-HIV compounds which are extracted from various Indian medicinal plants to retard the overall replication and transmission process associated with SARS-CoV-2. Molecular docking studies revealed that out of ten compounds highest binding affinity is found with PTP against Mpro, PLpro and RdRp. Furthermore, molecular dynamics simulation and evaluation of different parameters such as RMSD, RMSF, Rg, SASA and thermodynamic parameters revealed that introduction PTP moiety to the binding loop of the

corresponding proteins has a huge impact on overall structural and conformational changes. Analysis of the results revealed that PTP could be a potential therapeutic drug to combat the replication and transcription process of SARS-CoV-2. It is expected that PTP will be effective against the new strains of SARS-CoV-2 but more research is required for a proper understanding of the continuous mutation process of the SRAS-CoV-2 such that PTP can be converted from an experimental level to a conclusion.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13721-021-00309-3.

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