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Research Article

Nutraceuticals aid in managing COVID-19

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ABSTRACT

In this study authors have investigated some natural compounds derived from common herbs and condiments utilized for prevention and control of cough and cold symptoms. The main chemical constituents of these compounds have been docked to the main protease Mpro active site of SARS-CoV-2 to study its inhibition and hence their utility in controlling cold symptoms associated with COVID-19 infection. Molecular dynamics simulation studies have also been performed to observe the dynamical stability of best pose complexes. Ligand interactions have been analyzed and compared with co-crystallized ligand N3 interactions. Main polar residues involved are gln 189, glu 166 and thr 190. Although all natural compounds investigated show Mpro inhibition capabilities, glabridin and liquiritin which are the main constituents of licorice show best inhibitory property. Therefore, incorporation of licorice in hot beverages like tea is recommended to combat and prevent COVID-19 symptoms.

Keywords: nutraceutical, SARS CoV-2, MPro, curcumin, aloin A, cordioside, nimbin, Liquiritin, glabridin, molecular docking, MD simulations

INTRODUCTION

Scientists across the globe have come forward making all efforts in understanding, managing and combating Coronavirus disease 2019 COVID-19 in their unique ways right from design stage to market and clinical administration. Apart from drugs and vaccines we have forever looked upon nutraceuticals as an easy source of age old medications and preventive measures. COVID-19 patients show symptoms similar to viral fever and pneumonia [1,2]. Therefore, it is only obvious to consider natural compounds used in pneumonia and viral fever. Among the popular choices are aloe vera, basil, neem, licorice, curcumin and giloy [3-8]. We have selected some of the main constituents of these natural compounds and studied their possible inhibitory mode of action on the replication of coronavirus. The coronavirus implicated in COVID-19 is termed as Severe acute respiratory syndrome SARS CoV-2 virus. Its genome houses several proteins involved with its infection and replication process such as spike, main protease Mpro and RNA-dependent RNA

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polymerase [9]. Mpro facilitates the cleavage of viral peptides into smaller functional units involved in replication process [10]. Since coronaviruses were also implicated in Middle east respiratory syndrome (MERS), inhibitors of Mpro are not new. A comprehensive study by Liu et al summarizes Mpro inhibitors [11]. The study summarizes all peptidic and non-peptidic small molecule inhibitors of Mpro. At the same time it also discusses different natural compounds explored for inhibition of Mpro till 2020. It gives a summary of studies performed on flavonoids, chalcones, terpenoid derivatives and isatin derivatives. Here we investigate Mpro inhibitory properties of main constituents of some natural compounds specifically useful in viral fever and infections as mentioned above.

Turmeric is well known for its healing properties which are largely due to its constituent curcumin [12]. One of the main active constituents of aloe vera is a anthraquinone compound Aloin A [13], that of giloy is a terpenoid cordioside [14]. Main constituent of neem is nimbin [15]. The antimicrobial activity of licorice have been mainly attributed to phenolic and flavonoid compounds present such as liquiritin and glabridin [16]. The chemical structures of these constituents are shown in fig. 1.

METHODOLOGY

The selected natural compounds were prepared using the protein preparation wizard of Maestro interface. The X-ray coordinates for the target that is the main protease of SARS-CoV-2 Mpro were taken from pdb file 6LU7 at 2.16 Å resolution without any missing residues [17]. The protein was prepared by adding polar hydrogens using Auto Dock version 4 [18] and Auto Dock Vina Version 1.1.2 [19]. The co-crystallized peptidomimetic ligand N3 was re-docked with RMSD less than 2.0 Å to authenticate grid placement for dockings. The prepared natural compounds or the ligands were then docked one by one in the active site of Mpro and their interactions with the active site residues were analysed in detail. Auto Dock Vina was used to perform flexible ligand docking studies. Best poses obtained were exported to Shaw's Desmond software [20] to perform simulation studies. Standard molecular dynamics protocol was followed on best binding energy complexes to study the dynamical behaviour and stability of complex with time. All atom SPC water was incorporated in a grid of`10 x 10 x 10 Å around the protein and orthorhombic boundary conditions were applied. The minimized complex were subjected to simulated annealing followed by dynamics at 300 K for 25 ns. NPT ensemble was chosen utilizing Martyna-Tobias-Klein barotat method [21]. The RESPA integrator was used with 2 fs time step for near and bonded and 6fs time step for far atoms [22]. Coulombic interaction cutoff was set at 9Å. RMSD analysis has been performed for all heavy atoms together to judge the stability of the system overtime and fluctuations in position of ligand. Deviations have been taken with respect to initial frame for dynamics.

RESULTS AND DISCUSSION

The chemical structures of studied natural compounds are shown in fig. 1. These compounds were prepared as mentioned in the methods section. The choice of these natural compounds is based on the age old ayurvedic Indian tradition of utilizing these natural compounds to cure common cough and cold symptoms. The main protease protein of SARS-CoV-2 Mpro was also prepared using ADT tools associated with Auto Dock software. The center of grid for docking studies was placed at co-crystallized ligand N3 and authenticated by re-docking N3 with a low RMSD as mentioned above. The affinity of N3 is given in table 1 and interactions of re-docked N3 with Mpro active site residues are shown in fig. 2 and listed in table 2. A 2D interaction map is given in fig. 3. After grid authentication prepared compounds were docked one by one. Top nine poses with best docking scores were filtered for each compound. Table 1 lists the best affinities obtained for each compound. As can be seen at least the top three compounds derived from licorice and neem show affinities quite close to the co-crystallized peptidomimetic ligand N3. The detailed interactions of the best affinity compound glabridin are shown in fig. 4. The main electrostatic interactions involved are with gln189, asn 142 and glu 166. There is efficient hydrogen bonding with thr 190, ser 144 and hid 163. Apart from these important hydrophobic interactions are also observed with pro 168 and phe 140. These interactions together hold glabridin in place so as to block the Mpro active site. Similarly, the interactions of other docked natural compounds with good docking score were analyzed. The 2D ligand interaction maps of top 6 docking score compounds are shown in figs. 5 and 6. The main interacting residues are listed out in table 2. Although all compounds dock at the same place in different orientations utilizing the same polar residues (gln 189, glu 166, thr 190 in particular); the ones with lower docking score do not interact very efficiently due to their orientation. The molecular size of glabridin and conformation are most appropriate for MPro inhibition. Although Aloin A, curcumin are lined by many more interacting polar and hydrophobic residues; the

interactions are not optimized and strong enough for efficient Mpro inhibitory property.

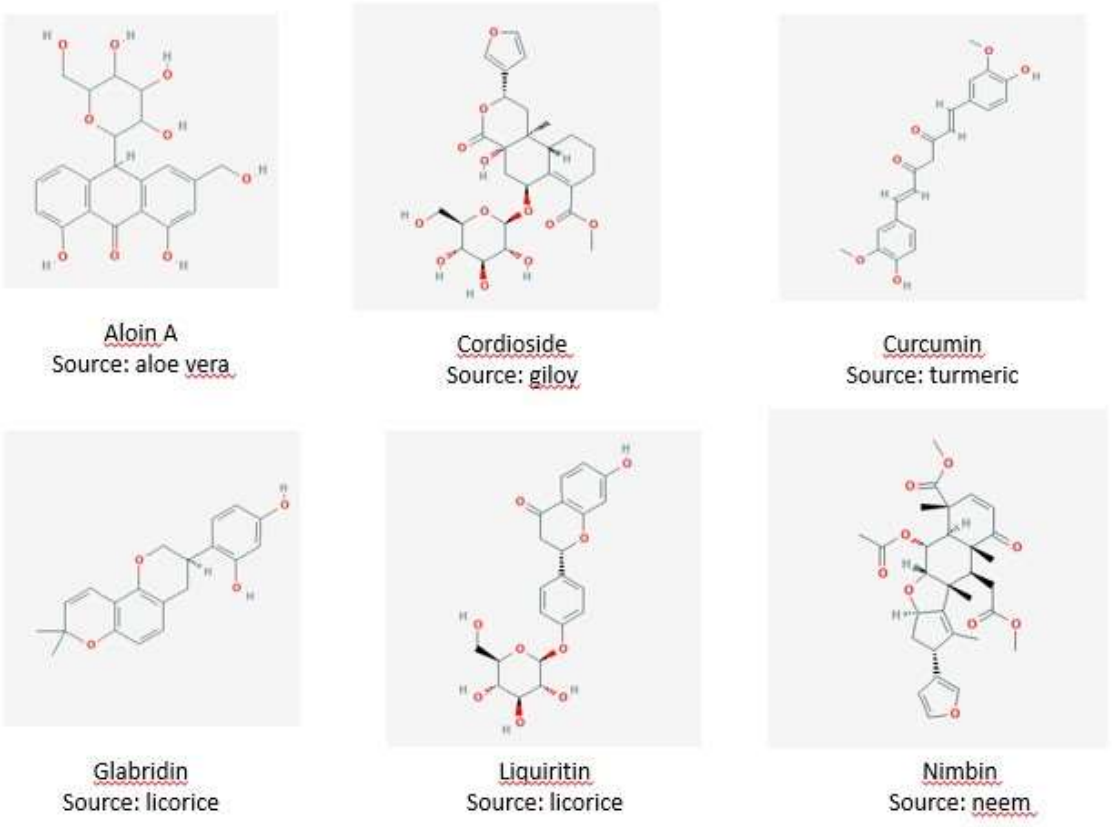

Fig. 1 Chemical structures of some natural compounds useful in cough, cold and fever

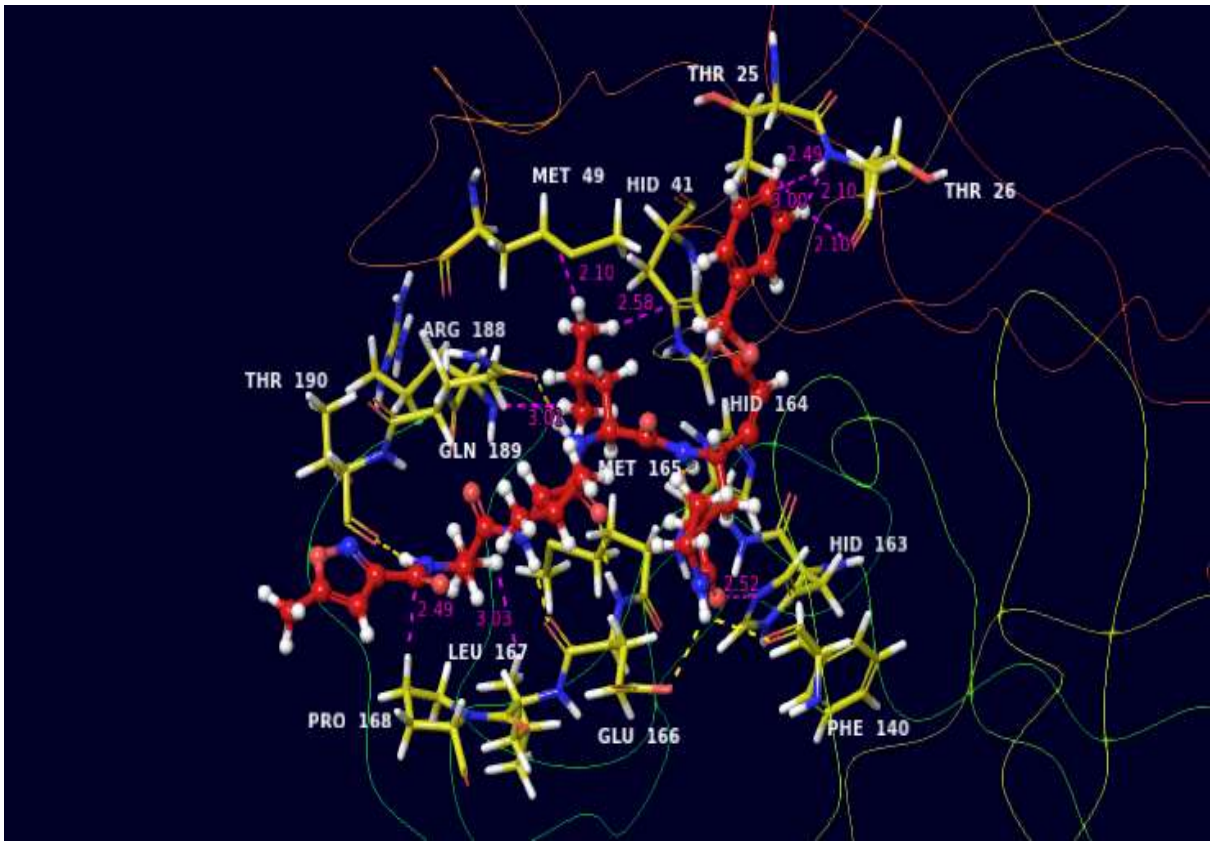

Fig. 2 Interactions of N3 ligand with Mpro active site residues

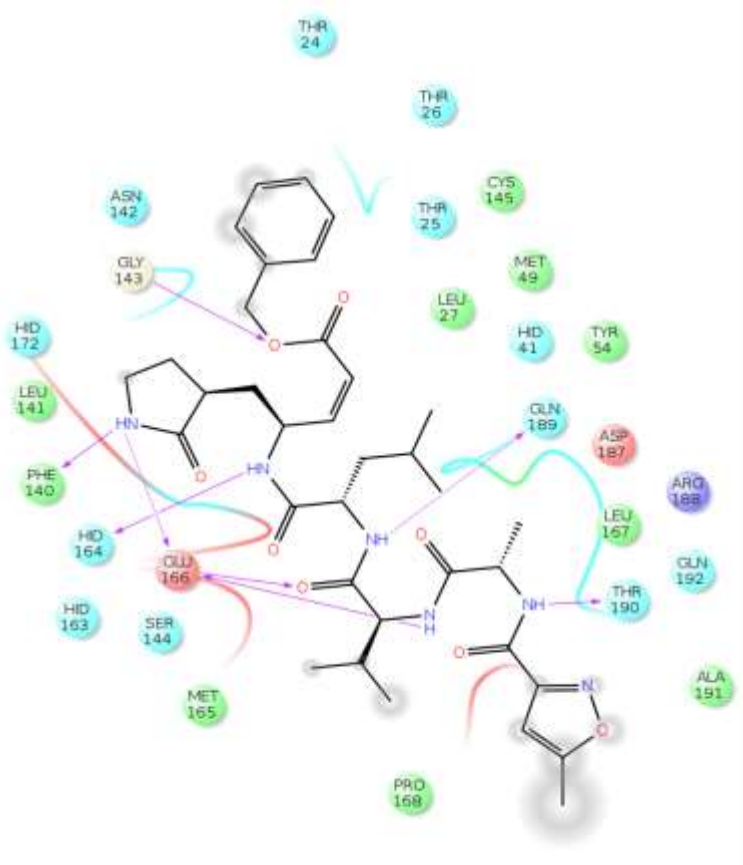

Fig. 3 2D interaction map for N3 with Mpro active site residues

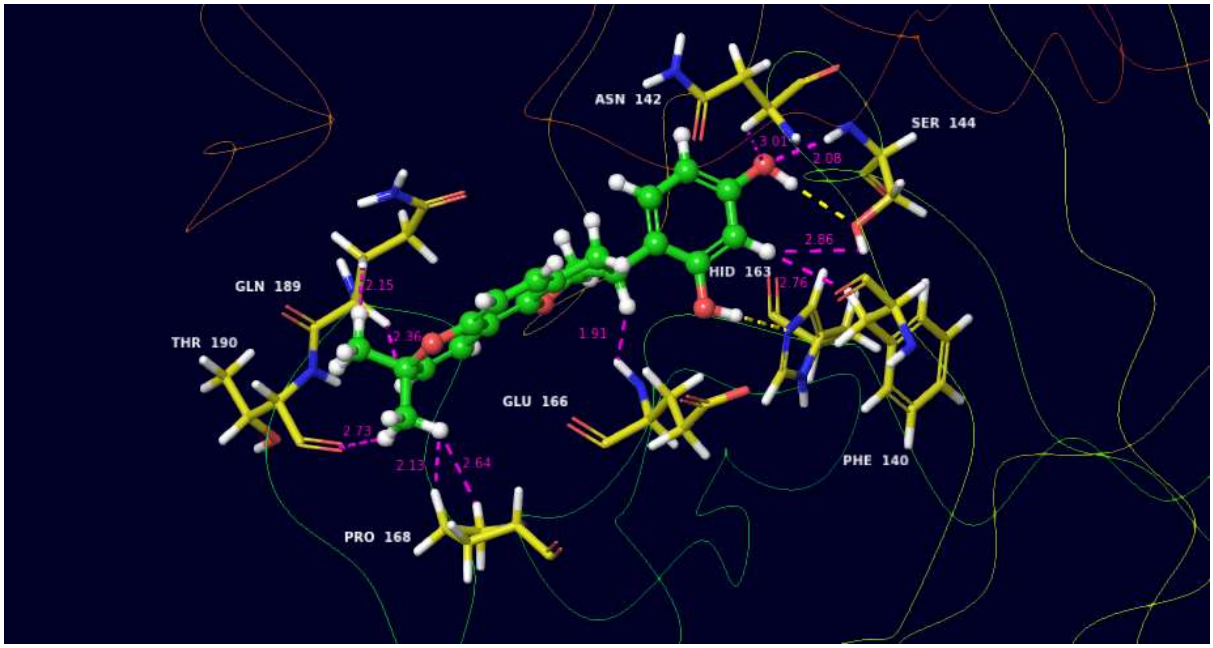

Fig. 4 Interactions of glabridin with Mpro active site residues

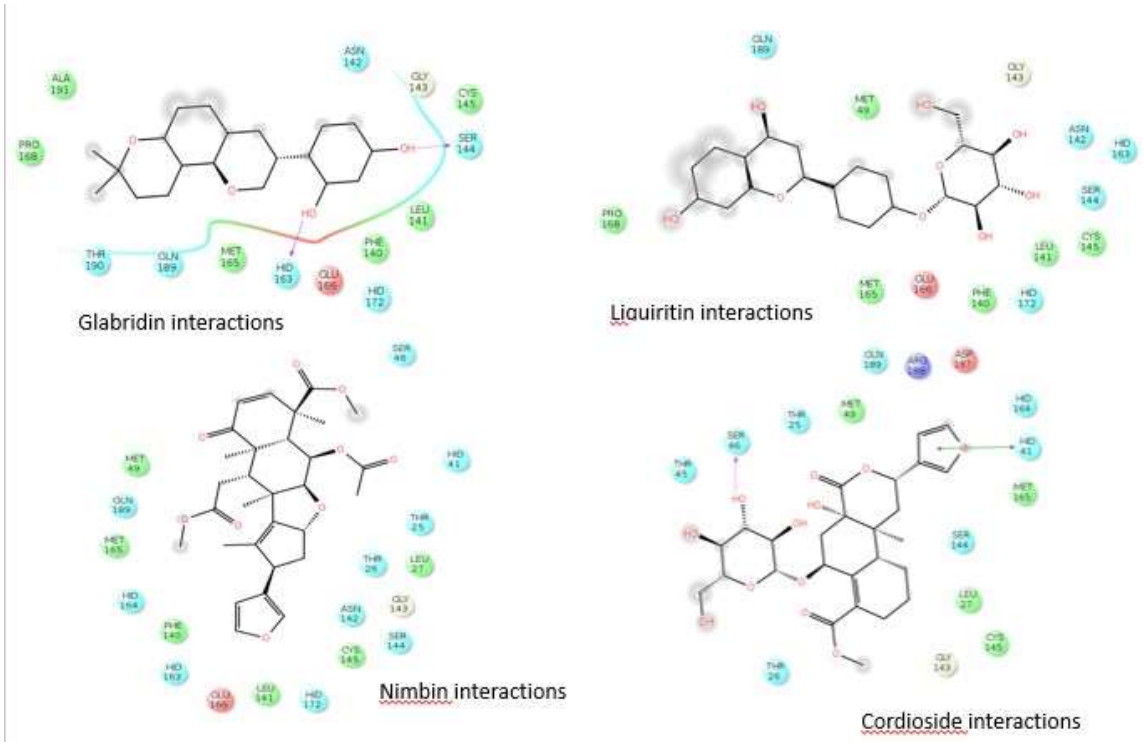

Fig. 5 Ligand interactions with Mpro active site residues

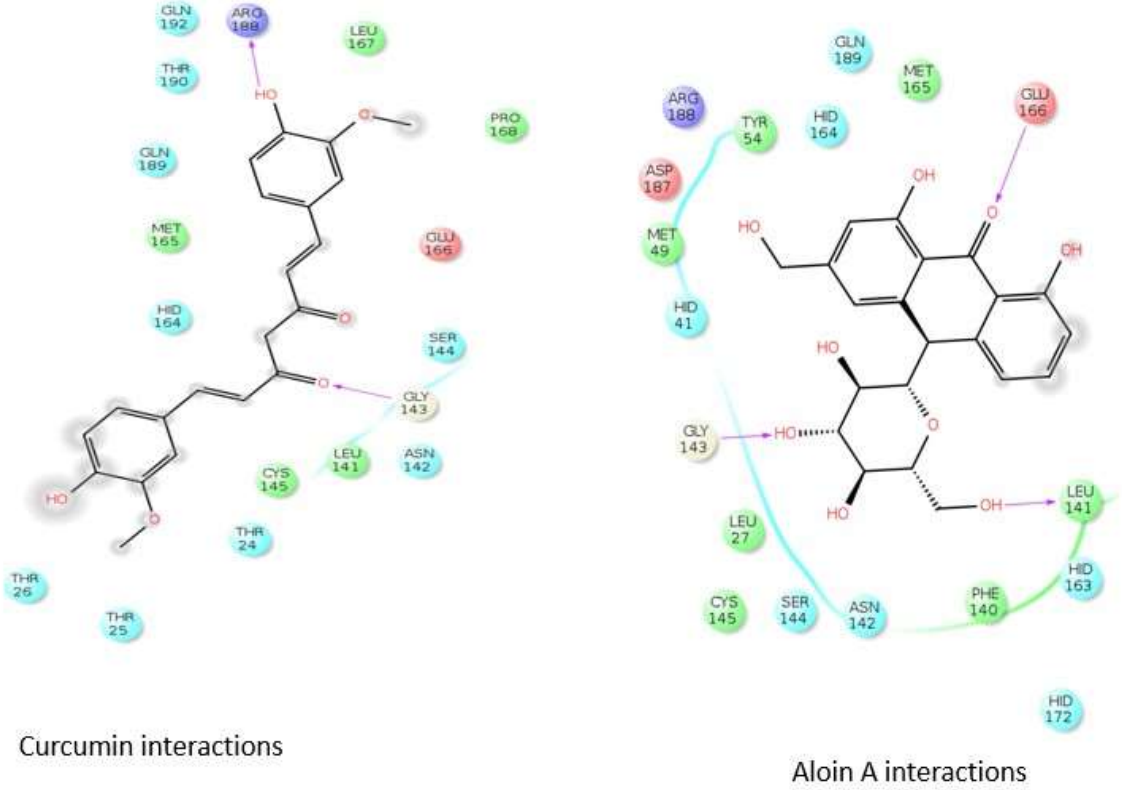

Fig. 6 Ligand interactions with Mpro active site residues

Table 1. Docking results for some natural compounds in Mpro

Compound name	Affinity (kCal/mol)
Redocked N3	-13.6
Glabridin	-9.0
Liquiritin	-9.0
Nimbin	-8.7
Cordioside	-8.5
Curcumin	-8.4
Aloin A	-8.1
Berberine	-7.4
Gingerol	-7.1
Pipernonaline	-6.6
Linalool	-4.8
Nimbin	-8.7
Aloin A	-8.1
Cordioside	-8.5

Table 2. Detailed contact analysis for best pose of different ligands

Ligand	Interacting residues in Mpro active site
N3	Gln189, Thr190, Glu166, Hid164, Phe140, Gly143, Asp187, Arg188
Glabridin	Gln189, Thr190, Glu166, Hid163, Ser144, Gly143
Liquiritin	Gln189, Glu166, Hid163, Ser144, Gly143
Nimbin	Gln189, Glu166, Hid163, Hid164, Phe140, Gly143, Ser144, Hid41
Cordioside	Gln189, Asp 187, Arg188, Hid164, Gly143, Ser144, Hid41, Ser46, Thr26
Curcumin	Arg188, Gln189, Thr190, Glu166, Hid164, Gly143, Ser144, Pro168, thr26
Aloin A	Glu166, Asp187, Arg188, Leu141, Gly143, Phe140, Hid163, Asn142, Hid41, Met49, Tyr54

Docking studies can be deceptive due to their non-dynamical nature and hence lack of stability check over time. We have therefore performed molecular dynamics simulation studies on best docked poses for observing stability of interactions with active site residues over time for the six filtered compounds. 25 ns trajectories have been generated with the exceptions of best and a moderately interacting compound for which longer trajectories of 50 ns have been observed as per the protocol mentioned in methods section. The overall RMSD for all heavy atoms with respect to initial frame are shown in figs. 7 and 8. In general the overall RMSD for all heavy atoms is below 3 Å which indicates low fluctuations in position of ligands and good stability of complexes over time. Molecular dynamics simulation results show that studied natural compounds possess the capability to inhibit Mpro enzyme of SARS-CoV-2 thus retarding the replication of coronavirus responsible for COVID-19 infection. Although all studied compounds show inhibitory property, the phenolic flavonoids glabridin and liquiritin derived from licorice seem to be the best nutraceuticals based on molecular level study in combating and preventing COVID-19 infections. Licorice which is a famous constituent of lozenges consumed during throat irritation and infection is recommended to be incorporated in everyday tea preparations as a preventive measure for common cough and cold infections as well as COVID-19 infections.

Concluding Remarks

In this study we have shown the inhibitory activity of some natural compounds derived from commonly used herbs and spices against cough and cold symptoms induced by SARS-CoV-2 infection. Though all the studied compounds showed activity against main protease enzyme Mpro of SARS-CoV-2 virus involved in its replication; two phenolic flavonoid compounds glabridin and liquiritin which are main constituents of licorice have been recommended as food supplements for protection against COVID-19 infections. This recommendation is based on molecular level docking studies and molecular dynamics simulations on best pose complexes to study their stability in active site over time.

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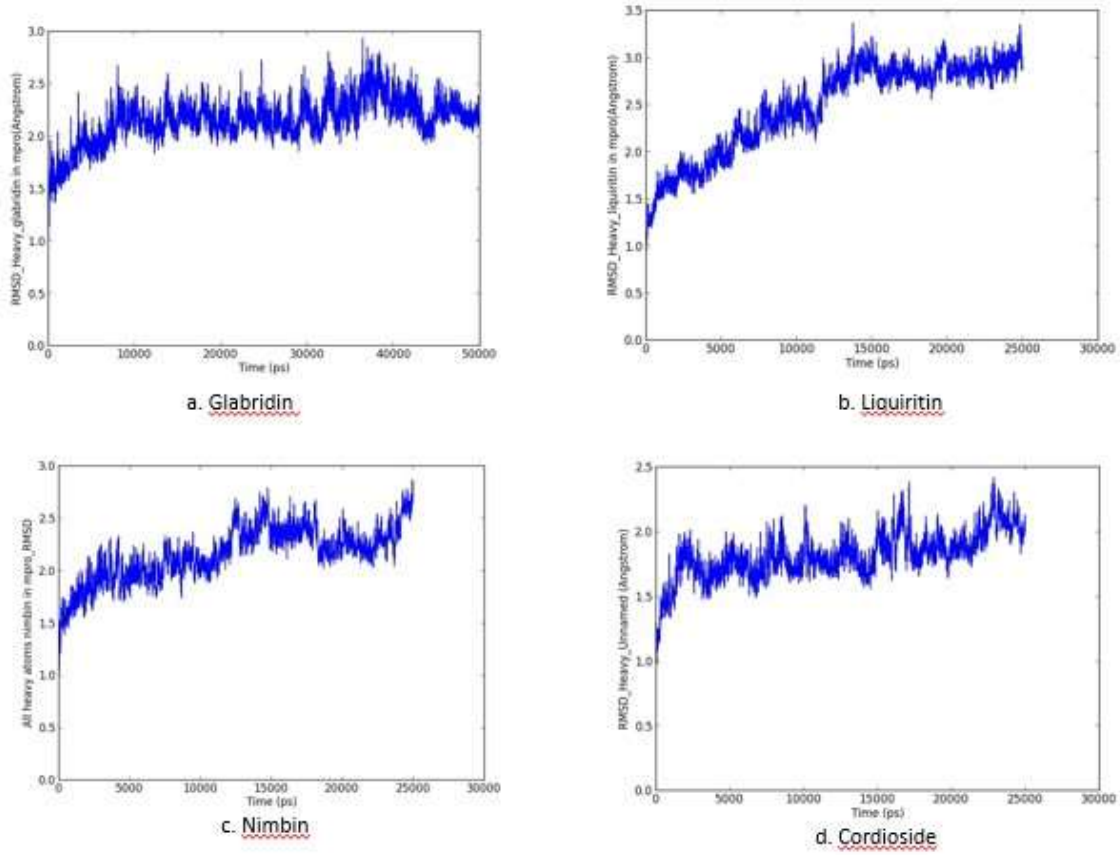

Fig. 7 Root mean square deviation for all heavy atoms with respect to initial frame for best pose complex of different natural compounds in Mpro active site

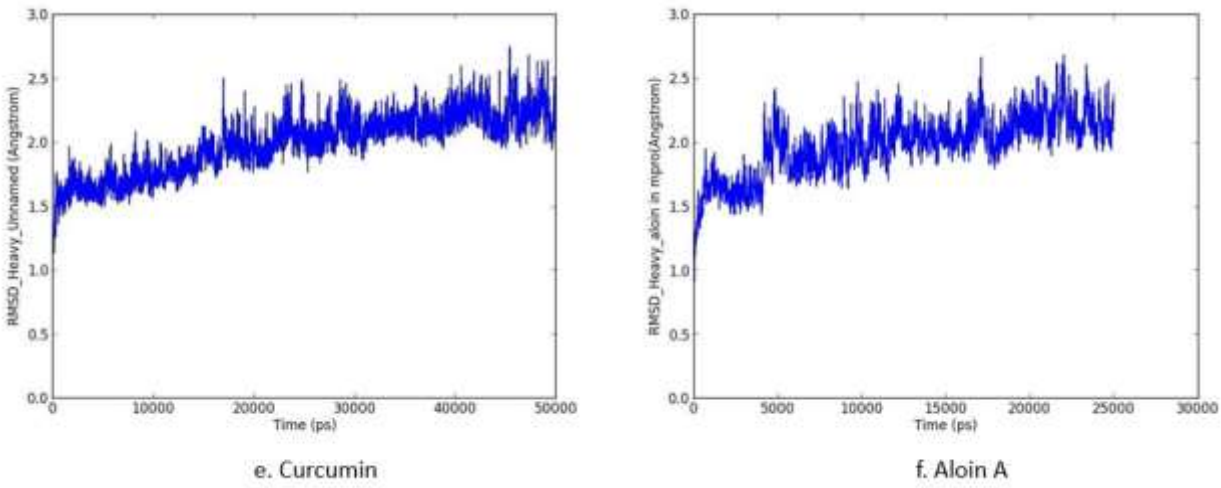

Fig. 8 Root mean square deviation for all heavy atoms with respect to initial frame for best pose complex of different natural compounds in Mpro active site

Conflict of Interests: The authors declare no competing conflicts of interest

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