Unravelling Vitamins as Wonder Molecules for Covid-19 Management via Structure-based Virtual Screening

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Research Article

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Abstract

The emergence situation of coronavirus disease 2019 (COVID-19) pandemic has realised the global scientific communities to develop strategies for immediate priorities and long-term approaches for utilization of existing knowledge and resources which can be diverted to pandemic preparedness planning. Lack of proper vaccine candidate and therapeutic management has accelerated the researchers to repurpose the existing drugs with known preclinical and toxicity profiles, which can easily enter Phase 3 or 4 or can be used directly in clinical settings. We focused to justify even exploration of supplements, nutrients and vitamins to dampen the disease burden of the current pandemic may play a crucial role for its management. We have explored structure based virtual screening of 15 vitamins against non-structural (NSP3, NSP5, ORF7a, NSP12, ORF3a), structural (Spike & Hemagglutinin esterase) and host protein furin. The in silico analysis exhibited that vitamin B12, Vitamin B9, Vitamin D3 determined suitable binding while vitamin B15 manifested remarkable H-bond interactions with all targets. Vitamin B12 bestowed the lowest energies with human furin and SARS-COV-2 RNA dependent RNA polymerase. Furin mediated cleavage of the viral spike glycoprotein is directly related to enhanced virulence of SARS-CoV-2. In contrast to these, vitamin B12 showed zero affinity with SARS-CoV-2 spike protein. These upshots intimate that Vitamin B12 could be the wonder molecule to shrink the virulence by hindering the furin mediated entry of spike to host cell. These identified molecules may effectively assist in SARS-CoV-2 therapeutic management to boost the immunity by inhibiting the virus imparting relief in lung inflammation.

Keywords: Vitamins, Furin, B12, viral drug targets, Covid-19,

1. Introduction

The outbreak of novel coronavirus disease (COVID-19) has been declared as the global pandemic by the world health organization. Currently, the world is facing an awful pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), represents an unprecedented challenge to the medical sciences as the virus is highly contagious [1]. The first case was reported in Wuhan city of China in December 2019 and spread across the globe through human-to-human transmission. Worldwide there are 77,228,903 confirmed cases of COVID-19, including 1,718,470 deaths have been reported for the across 216 countries dated on 24th December 2020 *(https://covid19.who.int/)*. Since last two decades, three outbreaks of coronavirus ensued worldwide: (i) severe acute respiratory syndrome coronavirus (SARS-CoV), (ii) Middle East respiratory syndrome coronavirus (MERS-CoV) and (iii) SARS-CoV-2 [2]. Coronaviruses are single-stranded RNA viruses (+ssRNA) with 26 to 32 kb in size and appear with crown-like structure due to presence of spike glycoproteins on their surface. They are categorized into four genera: Alpha (α), Beta (β), Gamma (γ), and Delta (δ) coronavirus. β-coronavirus include SARS-CoVs, MERS-CoVs, and SARS-CoV-2 and can infect both humans and animals [3]. SARS-CoV and MERS-CoV have developed mechanisms to reduce IFN production ensuing increased inflammatory host responses, which produce powerful inflammatory cytokines (cytokine storm) and severe lung injury [4]. Cytokine storm found in SARS-CoV and MERS-CoV infected patients, would correlate with disease severity and poor prognosis [5].

SARS-CoV-2 also known as novel coronavirus (nCOV-2) encodes for various structural as well as non-structural proteins facilitates viral entry as well as replication inside the host cell. SARS-CoV-2 encodes the envelope spike glycoprotein which binds to its cellular receptor, angiotensin-converting enzyme 2 (ACE2) and stimulates membrane fusion and endorsements of the virus into human cells [6, 7]. The affinity of SARS-CoV-2 towards the ACE-2 is much higher compared to SARS-CoV, may be reason for higher severity in terms of transmission compared to SARS- CoV [8]. Other than S and hemagglutinin-esterases (HE) glycoprotein, SARS-CoV-2 encodes various nonstructural proteins, which include the main protease (Mpro /3CL pro), papain-like protease (PL pro), RNA dependent RNA polymerase (RdRp) and Nsp3 largest protein encoded by coronavirus. Availability of SARS-CoV-2 structural and non-structural proteins has given the opportunity for structure-based screening of existing compounds against them. Various studies have been already done on molecular docking-based screening of existing antiviral, antibacterial and other FDA approved drugs [9].

Although the combat to find a specific therapy for the recent pandemic of COVID-19 is still on the way, clinically approved antiviral drug or vaccine is though developed, the effect is yet to be confirmed against the SARS-CoV-2. Several drugs have been reported for *in vitro* activity against different coronaviruses. Drug repositioning may offer a strategy hence, many drugs have been repurposed, including Remdesivir, Hydroxychloroquine and Chloroquine, Umifenovir (Arbidol), Lopinavir-Ritonavir, Favipiravir (Avigan), Oseltamivir (Tamiflu), Sofosbuvir, galidesivir and tenofovir showed promising results for treatment of newly emerged strain of coronavirus [10, 11]. Other antiviral drugs including ribavirin, zanamivir, acyclovir, peramivir and ganciclovir which are commonly used in clinical practice, are currently not recommended for COVID-19 [12]. Numerous computational theranostic approaches yet developed for the infectious disease [13, 14]. Due to lack of specific vaccines or therapeutic drugs, many supporting agents used as adjunctive therapies for COVID-19 patients which includes Azithromycin, Epoprostenol, Tocilizumab, Sirolimus, Corticosteroids, Sarilumab, Colchicine, Indomethacin, Thiazolidinediones and Ibuprofen [13]. Recently, several possibilities such as targeting viral binding receptors (ACE2) and spike proteins, small-molecule drugs, monoclonal antibodies, stimulating an immune response, peptides, etc. are being discovered against emerging SARS-CoV-2 infection. Lot of research efforts have been carried out to develop vaccines around the globe. Until we have specific vaccines or therapeutic drugs targeting SARS-CoV-2, “repurposed” drugs that have been approved by the FDA in the USA for other indications have been used to treat COVID-19 patients.

Currently, there is no appropriate drug treatment or vaccine against the SARS-CoV-2 virus. Until these become available, one must include suitable and balanced nutrition for appropriate body functioning and enhancing of the immune system especially with the help of various vitamins. Several vitamins, minerals and herbs have a treasured effect on mitochondrial function. Vitamins (Vita.) including B1, C (Ascorbic acid), D, E and Omega-3, minerals such as magnesium and manganese and herb like thyme play an important role on the innate system under the virus infection [15]. The study suggests the need to diet with the higher content of Vitamin C [16] and Vitamin B- Complex micro-nutrients to manage this pandemic successfully [17]**.** Due to anti-inflammatory properties, zinc has been suggested to limit the cytokine storm [18]. Petite study has been reported till date for role of vitamins to treat COVID 19 pandemic. Hence, we, here using in silico study reports the inhibitory effects of different Vitamins on SARS-COV-2 structural and non-structural proteins.

2. Materials and Methods

2.1 Retrieval of vitamin structures

Total of 15 vitamins were retrieved from the PubChem database (Table S1). The three-dimensional structure of the molecules was downloaded in SDF format and the molecules whose only two-dimensional structures were available, were converted into the three-dimensional form using Marvin Sketch and the best confirmation obtained is minimised in semi-empirical PM3 method using Polak-Ribeire algorithm in Hperchem Student evaluation version. The minimised structure is then converted to pdbqt by AutoDockTools [19].

2.2. Protein preparation

The high resolution three dimensional X-ray crystal structures of the target proteins of SARS-CoV-2 retrieved from protein data bank (PDB) ***(http://www.rcsb.org/)*** using their accession IDs 6LU7 (main proteases), 6M71(RdRp), 6vxx (spike protein), 6Y3Y(Hemagglutinin esterase (HE)), 6w6y (NSP3), 4non (NSP10), 6w37(ORF7a),6xdc (ORF3a)and Human proprotein convertase furin (5jxg) respectively.The selected target proteins were prepared for docking using AutoDockTools 1.5.6 [19]. The structures were saved in PDBQT format.

2.3. Molecular docking study

The binding affinity of each vitamin compound with the SARS-Cov-2 structural and non-structural targets was determined by molecular docking method. The molecular docking was performed using blind docking method in Autodock Vina 1.1.2 [20]. The grid box outsized enough to cover the entire protein structure to encounter any probable protein-ligand interactions. The binding poses were clustered and ranked in the order of their binding affinities. The molecular interactions (hydrogen bonds and hydrophobic interactions between the target proteins and compounds were studied using LigPlot + version 1.4.5 [21].

2.4 Molecular dynamics simulation

The 50 ns molecular dynamics (MD) simulation was carried out for complex using Gromacs version 5.1.1. [22] The simulation system was set up using the CHARMM-GUI web-based graphical interface [23]. The CHARMM General Force Field (CGenFF) program (University of Maryland, Baltimore, MD, USA) was used to create ligands and the CHARMM36m force field was used to construct the system. CGenFF is considering a partial atomic charge to create

a ligand parameter (http://docs.silcsbio.com). Charges are set according to the mandatory charge increase scheme [24]. The protein-ligand system was dissolved in the aqueous TIP3P model and ionized with NaCl. After the system is neutralized, energy minimization is carried out to eliminate steric collisions. This minimum energy system is balanced in six steps by gradually reducing the constant and thermal power (in the NVT ensemble) at 500 K and the pressure (in the NPT ensemble) at 1 bar per 1000 ps. Simulation results were first centered and trajectories analyzed with VMD software [25]**.** A variety of analytical methods are used for path analysis, including RMSD calculations, interaction energy calculations and many more.

3. Results and discussion

Vitamins are the essential elements required for cell proliferation, function and development. Moreover, it plays a crucial role against the pathogens via cell-mediated response and increase the immunity. All the vitamins except vitamin C are reported for the antibody production [26]**.**

Till now, there is no specific antiviral therapy for COVID-19. However, drug repurposing has been an approach accepted by scientists to seek effective treatment in a short period [27]**.** Recent studies revealed that vitamins reduce the risk of pneumonia and other viral respiratory tract infections [28]. The vitamins also exhibit direct inhibition of viral replication or with immunomodulatory or anti-inflammatory means [29-31]. The computational approach, molecular docking appears as a tool for screening new antiviral compounds. Anywhere scientists can practice this tool as a complementary approach so the synthesis of new compounds or repositioning of drugs can be assigned.

The present computational study conducted to investigate structural characteristics and molecular details of interactions between the SARS-CoV-2 therapeutic targets and the supplementary drugs vitamins. This is not the first time that vitamins have been considered for a new medical use. Vitamins have been proposed as immunomodulators since time immemorial. Vitamins are essential nutrients as they serve a plethora of important metabolic functions in the body. It has been well documented that the protection provided by vitamins through the natural defence mechanism of the host not only functions against infectious diseases, but also against cancer and other degenerative diseases. The enhancement of host resistance to disease results due to biosynthetic, antioxidant and immunostimulatory activity. Direct antiviral action of some vitamins to protect against viral disease being inactivation of a wide spectrum of viruses as well as suppress viral replication and expression in infected cells.

One mechanism of virus inactivation can be explained that depends on presence of oxygen and production of reactive oxygen species (ROS) through the Nrf 2 pathway [32]. COVID-associated severe cases, the result of complex biological spectacles, such as apoptosis induction, macrophage activation, oxidative tissue damage and higher contents of pro-inflammatory cytokines [33]**.** The superoxide anion-mediated pathways denote severe tissue injury for that drug with antiviral and antioxidant activities may be the choice. Therefore, apart from Vita.C. we selected vitamins with antioxidant properties, Vita.A, Vita. E and Vita.D. Antioxidant properties of vitamin A, C, E and D are being utilized against heightening oxidative stress in COVID reatment [34, 35]**.** Moreover, Vita. D with its ACE2 binding property also being exploited against increased ACE2, resulted from demethylation by the virus activity [36]. Direct antiviral activity by remarkable binding of vitamins as inhibitors to various important proteins of SARS-Cov-2 are suggested in the present report.

3.1. Molecular docking of vitamins with viral targets

In this study, 15 vitamins (see supplementary table S1) were docked against five non-structural proteins (NSP3, NSP5, ORF7a, NSP12 and ORF3a) and two structural proteins (Spike and Hemagglutinin esterase) and on one host protein furin. Since the presence of furin cleavage site (PRRA motif) in the spike has been confirmed [37], researchers are engaged in looking for a satisfactory mechanism to explain the importance of furin activity in spike maturation thus viral infectivity. Furin was shown to facilitate virus entry into the cell after receptor binding for other coronaviruses, e.g., MERS-CoV [38]. Furin is generally membrane bound, but an active isoform has been described that can be secreted, potentially facilitating cleavage of the SARS-CoV-2 S protein in the cellular neighbourhood [39]. Realising the important role of this host protease in spike activation we also targeted the protein for inhibitor binding that resulted with a very exciting outcome. The arrangement of the binding mode of the ligands is considered mainly based on the positions of hydrogen bond interaction with protein and minimum binding energy. Amongst all molecules vitamin B12, vitamin D3 and vitamin B9 exhibited good affinity, and vitamin B15 showed strong interaction in terms of H-bonds. Table1 illustrates of binding energies of all vitamins with target protein of SARS-CoV-2.

Table 1: *Binding energies of Covid-19 targets with Vitamins*.

	Mpro (NSP5)	RDRP (NSP12)	NSP3	ORF7a	ORF3a	Spike protein	HE	Furin
	Binding energy (kcal/mol))							
Vitamin B12	-7.3	-8.3	-6.9	-6.1	-6.9	0	-6.8	-9.2
Vitamin D3	-6.8	-7.4	-7.6	-7.4	-6.3	-7.4	-8.1	-8.2
Vitamin B9	-6.6	-7.6	-7.8	-7.1	-6.6	-7.4	-7	-8.2
Vitamin K1	-6.3	-4.9	-6.9	-7.2	-4.5	-5.3	-6.8	-6.1
Vitamin B1	-5.2	-5.6	-6.4	-5.3	-5.4	0	-5.5	-6.3
Vitamin A	-6	-6.5	-6.5	-6.5	-6.1	-7	-7.3	-7.1
Vitamin B2	-5.8	-6.9	-6.2	-6.1	-5.8	0	-6.3	-6.8
Vitamin B3	-4.2	-4.3	-4.6	-4.2	-4	-4.4	-4.5	-4.8
Vitamin B5	-4.5	-4.9	-5.6	-4.8	-4.6	-5.2	-4.7	-5.7
Vitamin B6	-4.4	-4.8	-5.3	-4.9	-4.6	-4.9	-5	0
Vitamin B7	-4.1	-5.4	-5.5	-4.9	-4.1	-4.5	-5.4	-5.8
Vitamin B15	-5.3	-4.8	-4.8	-4.2	-4.8	-4.6	-5.1	-5.3
Vitamin C	-4.7	-5.6	-4.5	-4.6	-4.3	-5.1	-5.1	-5.2
Vitamin E	-5.4	-6.3	-6.6	-6.5	-5.7	-5.5	-7.2	-7.5
Vitamin K2	-5.9	-6.1	-7.1	-6.5	-6.5	-6.7	-6.6	-7.1

3.1.1 Vitamin B

The group of vitamin B has a prime role for the immune response to antigen as well some of the water-soluble vitamins act as a coenzyme in the body for certain biochemical reaction to enhance the immune system. Thiamine, also called Vitamin B1 has a role in B and T cell production [40]**.** Riboflavin (B2) in combination with UV hinders DNA replication in MERS CoV. Hence it may have a role in SARS- CoV prevention. Nicotinamide (V-B3) is the building block of NAD+, which acts as a coenzyme in various metabolic pathways. Hence, it plays a significant role in the inflammatory response and prevents lung tissue damage. Pyridoxal 5′-phosphate is the active form of vitamin B6 and is involved in carbohydrate, protein and lipid metabolism. BAN (vitamin B6-derived bananin) inhibits the SARS-helicase enzyme, which hinders the viral replication process. Vitamins B6, B12, and B9 (folic acid) proliferate the

activity of natural killer cells, which offers a significant antiviral effect. Vitamin B12 inhibits the RNA-dependent RNA polymerase, which leads to the SARS-CoV-2 viral replication. In a nutshell, vitamin B complexes have the potential to frontier the complications associated with COVID-19 infection [41]**.**

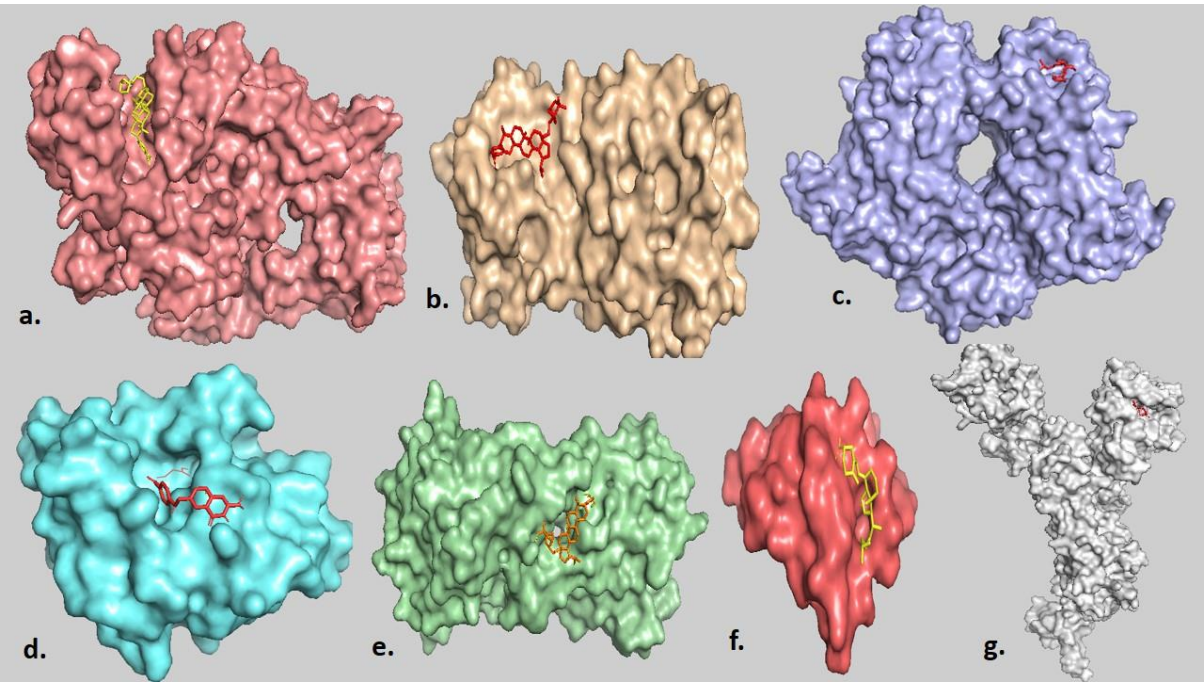

Figure 1: *Top molecular interaction of SARS-CoV-2 Drug targets and vitamin: (a) RdRP-Vita.B12. (b) MPro-Vita.b12. (c) HE-Vita.D3. (d) NSP3-Vita.B9 (e) ORF3a-Vita.B12 (f) ORF7a-Vita.B12. (g) Spike-Vita.D3.*

Our results reveal that vitamin B12 is an efficient nutraceutical for almost all the nCoV-2 drug targets including the host protease furin. Methylcobalamin unveiled high binding affinity with furin (-9.2 kcal/mol), RdRP (-8.0 kcal/mol), HE (-9.0 kcal/mol), NSP5 (-7.3 kcal/mol) NSP3 (-6.9 kcal/mol), ORF7a (-6.1 kcal/mol), ORF3b (-6.9 kcal/mol) proteins. However, the spike protein of nCOV-2 defended and demonstrated zero binding affinity with this vitamin. In this study, Vita.B12 exemplify fair interaction with furin in terms of seven H-bonds and nine hydrophobic interactions. The interacting residues of furin in context to H-bonds and hydrophobic contact are Glu256 (3.11Å), Gly255 (2.90 Å), Ser253 (3.13Å), Ser368(3.20Å), Thr 365(3.0Å), Arg193 (3.21Å), Asp191(2.80Å) and Trp254, Leu 227, Gly 229, Asp154, Asn190, His 364, His 194, Asn295, Asp258 respectively (see figure 2).

Vita.B12 also shows good hydrophobic interactions with 15 amino acids (leu172, phe169, asp170, arg173, arg249, thr319, tyr265, phe321, pro323, arg349, phe396, thr394, leu

460, pro667, pro461) and four H-bonds tyr465 (3.19 Å). Asn459 (3.15 Å), cys395 (2.95 Å), arg415 (2.80Å) with RNA dependant RNA polymerase enzyme. Figure 3 shows that Vita.B12 has decent interactions with all viral targets.

Vitamin B12, cobalamin, is a water-soluble vitamin produced in nature by microorganisms mainly get from animal proteins and deficiency cause with different disease states [42]. It is involved in different pathways as well in hematopoiesis. B12 is an important factor for activation of transcription factors like NF-κB, Myc and Fos [43] and thought to potentiate anti-inflammatory effects. Though Vita.B12 has been used to improve immunity in HIV infected patients, there is no evidence of direct inactivation of any virus by this compound.

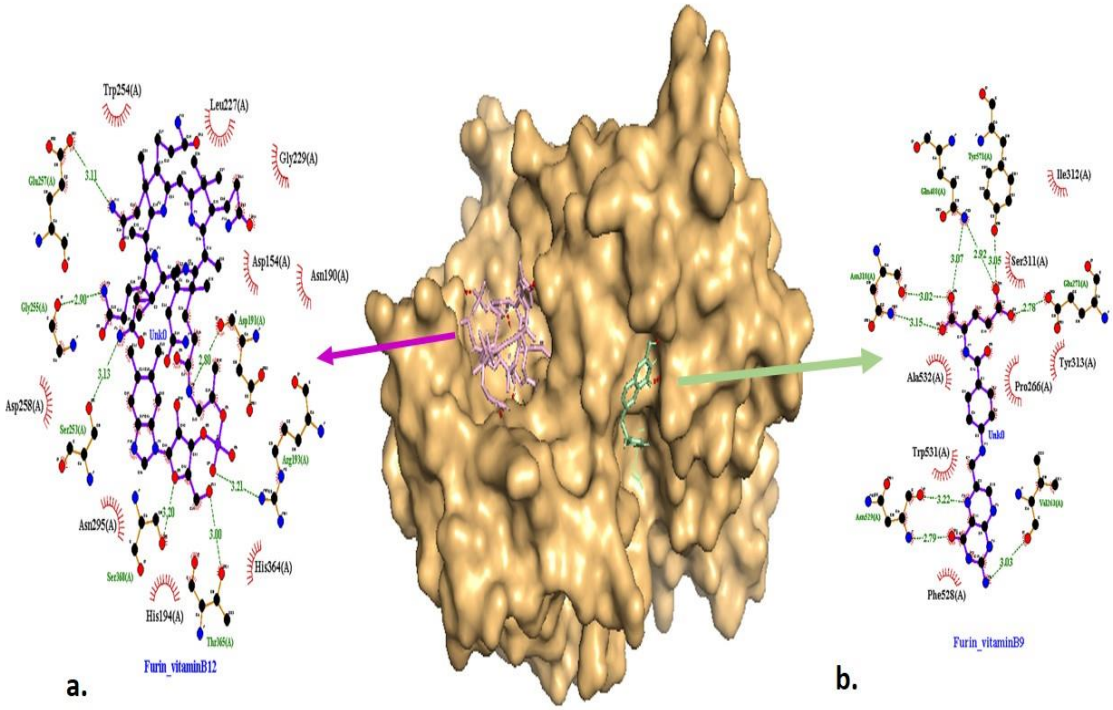

Figure 2: *Interaction of furin residues with (a) vitamin B12 and (b) vitamin B9.*

The insilico analysis explained that vitamin B9 proved one of the best inhibitor for all viral targets. Amongst eight viral targets Vita.B9 illustrates best binding with Furin (-8.2 kcal/mol), spike (-7.4 kcal/mol), RdRp (-7.6 kcal/mol), NSP3 proteins (-7.6 kcal/mol) (See Fig.3.). Our frequent observation denotes (Fig.2.) that amino acids residues of furin interrelates with vitamin B9 and vitamin B12 at distinguished domains. LigPlot exposed two strong H-bonds Asn310 (3.15Å, 3.02Å), Asn529 (3.22Å, 2.79Å), Gln488 (3.07Å, 2.92Å) and single H-bond Val263 (3.03Å), Glu271 (2.78Å), Tyr571 (3.05Å) between furin and this vitamin.

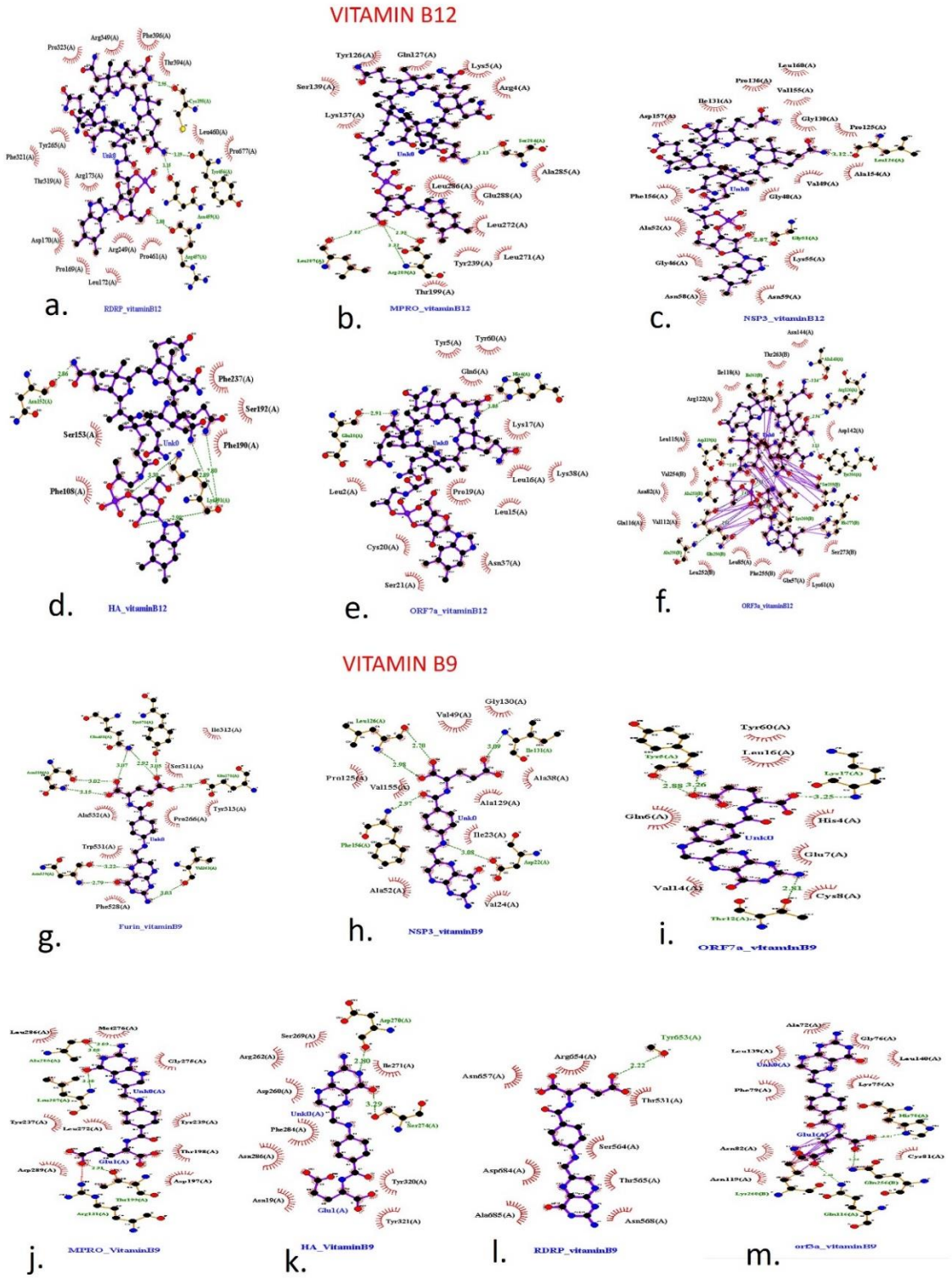

Figure 3*: Interaction plot of vitaminB12 and vitamin B9 with all viral targets. (a) RDRP-Vita.B12. (b) MPRO-Vita.B12. (c) NSP3-Vita.B12. (d) HA-Vita.B12. (e) Orf7a-Vita.B12. (f) Orf3a-Vita.B12. (g) Furin-Vita.B9. (h) NSP3- Vita.B9. (i) Orf7a- Vita.B9. (j) MPRO- Vita.B9. (k) HA- Vita.B9. (l) RDRP- Vita.B9. (m) Orf3a- Vita.B9.*

Vitamin B9, Folic acid is a type of B vitamin normally found in foods rich in iron and dried beans mainly helps the body to produce and maintain new cells, DNA repair mechanism. It is well known that folate intake is essential for human health because it prevents megaloblastic anaemia and neural tube birth defects as well as cardiovascular disease, dementia, cognitive function alterations, osteoporosis and several types of cancer. Recent computer simulation researches on antiviral activity of Vita.B9 have been reported [44, 45] where the authors have suggested that B9 can inactivate the furin endoprotease that is crucial for the SARS-CoV-2 virus to enter its host cell [46, 47]. While another work [48] explained that Vita.B9 inactivates protease $3CL^{pro}$, which is vital in the replication of all coronaviruses.

The structure of the vitamin B15 also known as pangamic acid complexed with HE protein, ORF7a, NSP5 and NSP12 highlighted hydrogen bond interaction to be the main contributor in protein–ligand interaction whereas binding energy contributes moderately (Fig.3.) in this study. This vitamin shows maximum15 H-bond interaction with viral HE protein, 10 H-bonds with ORF7a and 7 with NSP5. It is reported that assorted strong-weak H-bond unions decrease ligand binding affinity and sometimes connects poorly with experimental binding affinity [49]**.** The robust hydrogen bonding and hydrophobic interaction between vitamin with the enzyme infer it may be a potent HE and ORF7a inhibitor.

Laboratory experiments have proven the protective effect of B15 on coronary artery occlusion and myocarditis in animals. Though controversy exists in categorising B15 under vitamin group it has received the most attention for its effect in stress and on athletic and physical effort. Apart from its protective role in hypoxia, another important function of cellular detoxification associated with cytochrome p450, B15 has a protective role in various health conditions like fatty infiltration of liver, atherosclerosis, alcoholism etc [50]. Anticipating its role in covid-19 induced hypoxia the present investigation also focused on its antiviral activity. Amongst Vita.B1 to B6, Vita.B2, B5, and B6 manifest good H-bond networks with all viral targets (Fig.S1 & S2). Our results unveil zero affinity of Vita.B1 and B2 and no interaction with spike protein. In contrast to that, Vita.B3, B5, and B6 have connections with S protein. Vita.B5 shows a maximum of 8 H-bonds with S protein and 7 H-bonds with furin.

3.1.2 Vitamin D3

The authors of the present report are able to find a mechanism through binding of vita. D3 to various proteins of nCov-2. The vitamin D3 displays best dock score with furin (-8.2 kcal/mol), RdRP (-7.4 kcal/mol), HE (-8.1 kcal/mol), NSP3 (-7.6 kacal/mol), spike protein (-

7.4 kcal/mol), ORF7a (-6.1 kcal/mol), ORF3b (-6.9 kcal/mol) proteins. In this study, we observed that all viral targets spectacles (Fig. 4) decent hydrophobic interactions with vitamins. Klebe in 2015 reported that binding affinity of several ligands is very high due to hydrophobic interactions. In hydrophopic intractions, ligand suppresses the lipophilic surface of target protein and dislocates the water.

Vitamin D from diet and dietary supplements is converted to its biologically active form inside the human body. Photo-mediated conversion of 7- dehydrocholesterol in the skin is the primary source of Vita.D inside our body. Thus exposure to sunlight is important to promote vitamin D production in the skin. Major sources of Vita.D include egg yolks, saltwater oily fish and liver as food. Some other foods, like milk and cereal, mushrooms often have added vitamin D. To become biologically active D3, 25-hydroxylation of vitamin D requires in the liver and subsequent 1-hydroxylation in the kidney [51]. The fat soluble Vita.D plays a central role in calcium and phosphate homeostasis that is essential for the proper development and maintenance of bone. It is also involved in cell proliferation, differentiation, and immunomodulation. Vitamin D deficiency is associated with increased risk of viral infections such as influenza, respiratory tract infections, and human immunodeficiency virus (HIV) along with many pathological conditions, including cancer, autoimmune diseases, cardiovascular disease, and diabetes [52,53] reported the reason for antiviral activity of Vita.D3 in HCV to be the increased expression of interferon. In the context of increasing respiratory tract infection cases of COVID-19 patients a host of authors are suggesting the Vita.D to be the wonder drug for cure. However, a proper mechanism to confirm the role of Vita.D is lacking.

3.1.3 Vitamin C

Vitamin C (ascorbic acid) essentially required as a natural antioxidant in the body for correct functioning of the immune system, it's a great immunity booster compare to all vitamins found in nature due to its antioxidative property. Thus, it shows potentiality against various infections, including coronavirus infections [53]. Its role in stress response after administration in critically ill COVID-19 patients is well documented. To understand the mechanism of Vita.C, structural and non-structural n-Cov2 proteins were analysed. The ligand interaction maps of the compound with best dock conformation reported in supplementary figure S3. This computational study ascertains inhibitory effect of ascorbic acid on all viral protein. Vita.C indicates (Supplementary Figure S3) interactions with furin, RdRp, ORF7a and HE proteins.

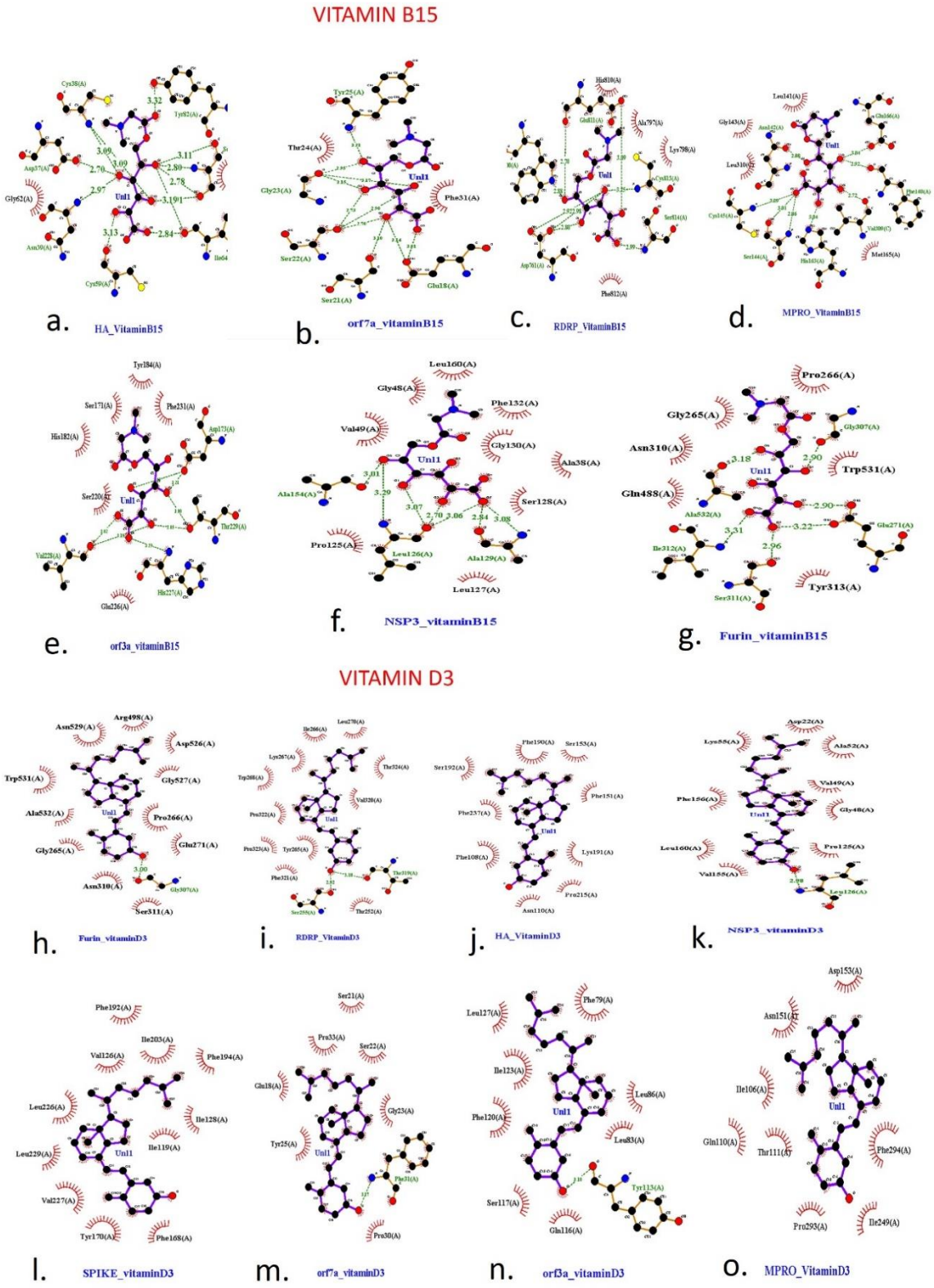

Figure 4: *Interaction plot of vitaminB15 and vitamin D3 with COVID-19 targets. (a) HA-Vita.B15. (b) Orf7a- Vita.B15. (c) RDRP- Vita.B15. (d) MPRO- Vita.B15. (e) Orf3a- Vita.B15. (f) NSP3- Vita.B15. (g) Furin- Vita.B15. (h) Furin-Vita.D3. (i) RDRP-Vita.D3. (j) HA-Vita.D3. (k) NSP3- Vita.D3. (l) SPIKE- Vita.D3. (m) Or7a- Vita.D3. (n) Orf3a- Vita.D3. (o) MPRO- Vita.D3.*

Viral infections generate oxidative stress and certain redox-active substances such as antiviral drug are expected to suppress oxidative stress improve inflammatory symptoms. Influential scavenging and antioxidative property of ascorbic acid have shown protective effect [54]. Both in vitro and in vivo clinical trials with Vita.C treatments showed significant reduction of viral replication without any insight to proper inhibitory mechanisms [55]. The present investigation may be for the first time able to find a plausible mechanism from the observed binding properties to the viral proteins.

3.1.4 Vitamin K

Fat-soluble vitamin K primly affects blood clotting along with wound healing as well as modulate the calcium-binding in bones. Vitamin K deficiency reported a poor outcome of COVID-19 [56]**.** The ligand interaction plot (supplementary Fig.S4.) displays more number of hydrophobic interactions with both vitamin K1 and K2. Vita.K1 shows good docking score with one target ORF7a (-7.2 kcal/mol) and vitamin K2 displays -7.1 kcal/mol affinity with NSP3 and furin.

3.1.5 Vitamin E

Vitamin E deficiency has shown increased levels of the viral (coxsackievirus B3) infection end up with a myocardial injury in mice, due to oxidative stress [57]**.** Likewise, vitamin E deficiency in calves was associated with a high risk of bovine coronavirus infection [31]· Vita.E known as Alpha –tocopherol shows fair score -7.5,-7.2 and -6.6 kcal/mol with furin, HE proteins and NSP3 one-to-one.

3.1.6 Vitamin A

Vitamin A plays a key role for the normal eye vision, functional immune system, and for reproduction. Furthermore, it regulates the antigen-presenting cells and maintains the balance between Th1 and Th2 lymphocytes and produces an antibody response against an antigen [58]**.** Hence, it is the most promising vitamin against lung damage due to COVID-19. The structural protein spike and HE protein of nCOV-2 reveal robust interaction results with Vita.A (Fig.S3.).

3.2 Molecular dynamics simulation of Furin and Vitamin B12

The MD simulation on best docking score complex (Furin-Vitamin B12) for 50 ns measure up to examine the dynamic performance of the protein-ligand complex. The structure experienced initial fluctuation due to the kinetic shock applied during the MD simulation. Figure 5 shows the graphical representation of the root means square deviation (RMSD) and root means square fluctuation (RMSF) of the complex in each amino acid. The amino acid in complex with

vitamin B12 maintains equilibrium throughout the simulation. Around ~0.2 nm RMSD was reported for backbone atoms of the ligand-protein complex. The complex re-equilibrated a few times during the 50 ns simulation. Figure 5a illustrates the retreating of the ligand orientation near~15 ns and ~30 ns. The magnitude of fluctuation and the difference between the average RMSD values recommended that simulation produced stable trajectories.

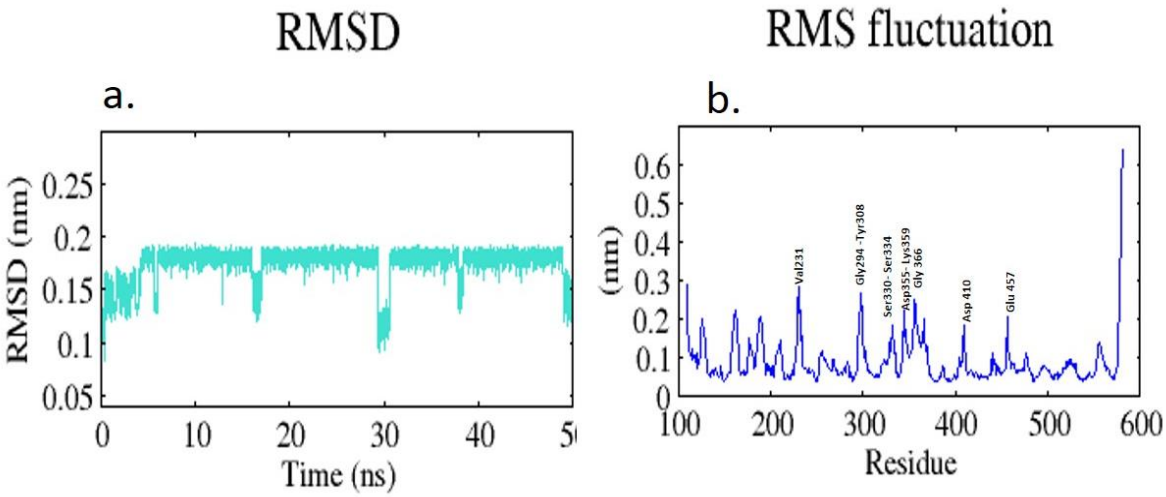

Figure 5: (a.) *RMSD and (b.) RMSF trajectory of Furin-Vitamin B12 complexes obtained from 50 ns MD simulation.*

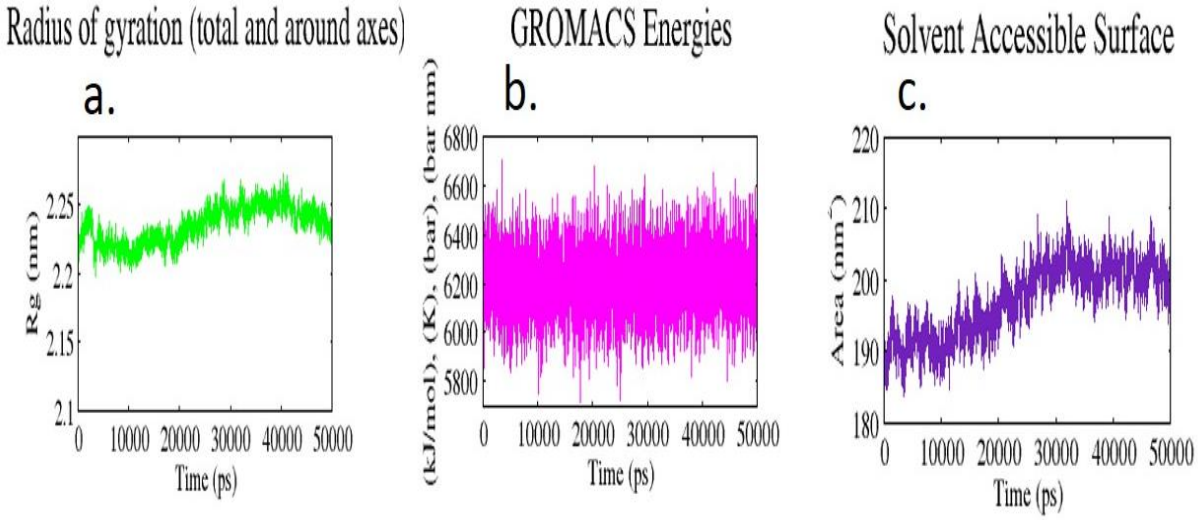

Figure 6: *MD trajectories for (a) Radius of gyration (b) potential energy (C) Solvent accessible surface area.*

The RMSF analysis correlates with the functional analysis and the highest fluctuation in this region. These reported decrease in scores of particular residues proposes their direct participation in enhancing the overall stability of the bound protein complex. The amino acid residues 250, 300, and 350-375 showed high fluctuation. The fluctuation in amino acids is Val 231 (~0.2nm), Gly 294 to Tyr308 (~0.12 - ~0.24 nm). The radius of gyration (Rg) is defined as the circulation of atoms of a protein around its axis. The radius of gyration Furin-Vitamin B12 complex is ~2.2 to ~2.25 nm. The length signifies the distance between the point of rotation and the point where the transfer of energy has the extreme effect gives Rg [59]. The Rg qualifies one to assess the compactness changes of a ligand-protein complex.

The potential energy scrutinized during the 50 ns molecular dynamics simulations is shown in figure 6(b). The potential energy graph shows that all the molecular system stabilized and remained stable throughout the simulations. The variations in the solvent-accessible surface area (SASA) of a protein specifies the change in exposed amino acid residues could affect the tertiary structure of proteins [60]. Protein-ligand complex exhibited SASA ~190–200 nm square in the dynamic period of ~10– 30 ns (Fig.6c.). After the period of 30 ns, the complex exhibited a very high-solvent accessible area. This type of illustration in an experimental setup will be time-consuming, thus creating a method for computational microscope MD to analyze the structural effects [61-63]. The molecular dynamics study of the best ligand-receptor complex also exhibits the stability of the compound during the simulation process, which validates the virtual screening and docking results.

4. Conclusion

In order to tackle the current situation, quick discovery of new antivirals is necessary which may be a resource from the extensive exiting research and development efforts. The present study revealed that the role of vitamins as immunonutritions could be deployed as potential supplements to attenuate the severity of the covid19 infection.

Contribution of authors: The conception and design of study by JD, MP, KJ. Acquisition of data, analysis and interpretation DM, TJ, AP, AG & MP. Drafting and revising article by SS, JD & KJ.

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Figures

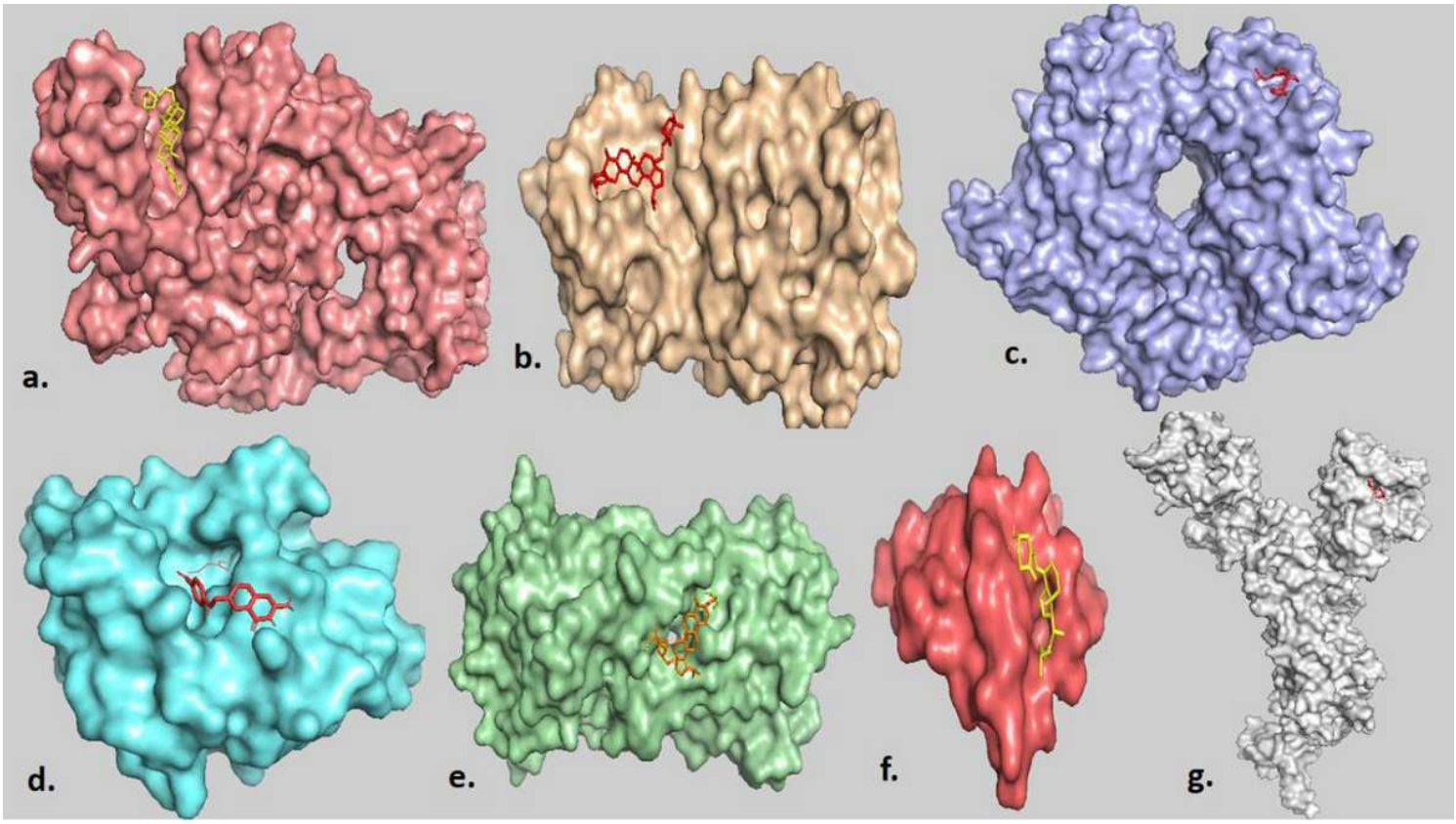

Figure 1

Top molecular interaction of SARS-CoV-2 Drug targets and vitamin: (a) RdRP-Vita.B12. (b) MPro-Vita.b12. (c) HE-Vita.D3. (d) NSP3-Vita.B9 (e) ORF3a-Vita.B12 (f) ORF7a-Vita.B12. (g) Spike-Vita.D3.

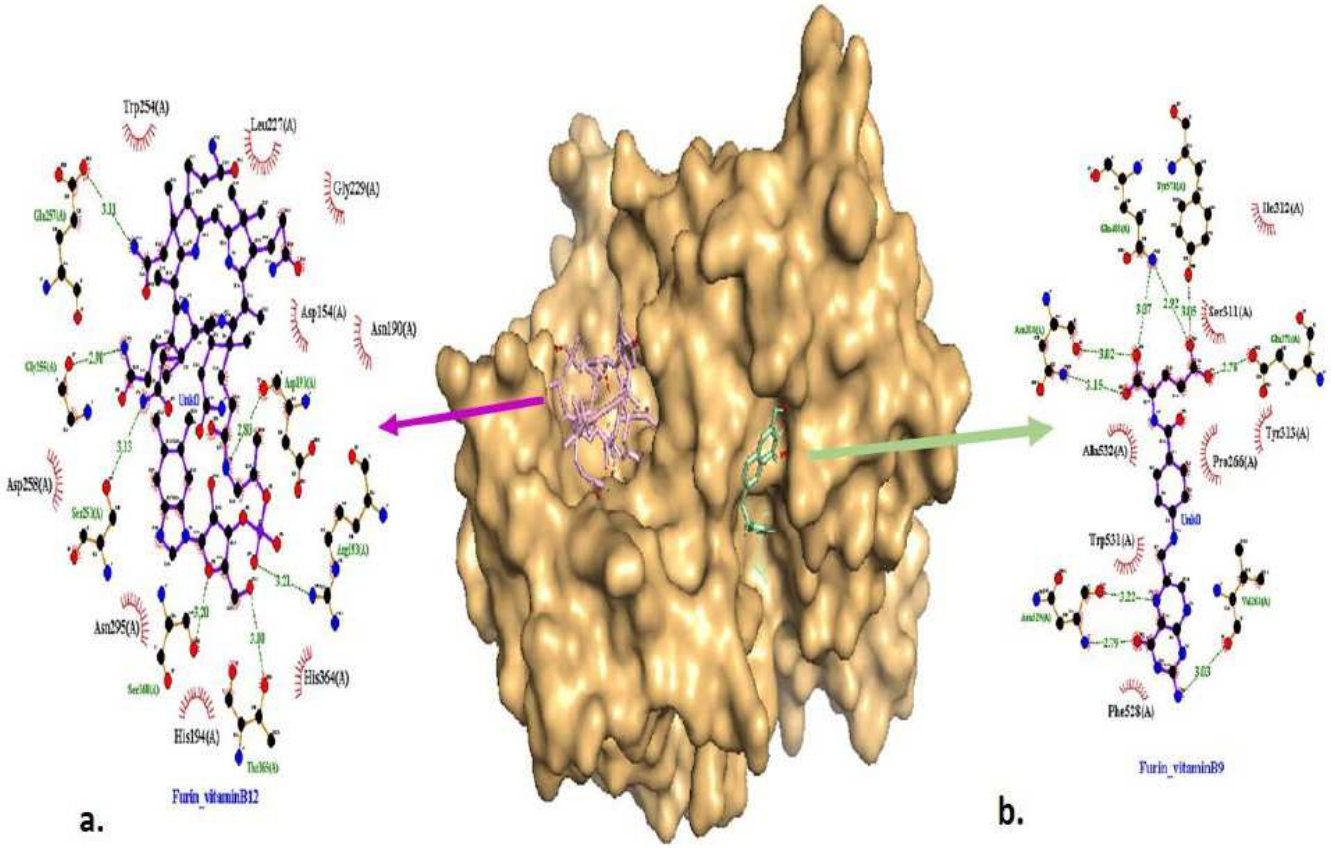

Figure 2

Interaction of furin residues with (a) vitamin B12 and (b) vitamin B9.

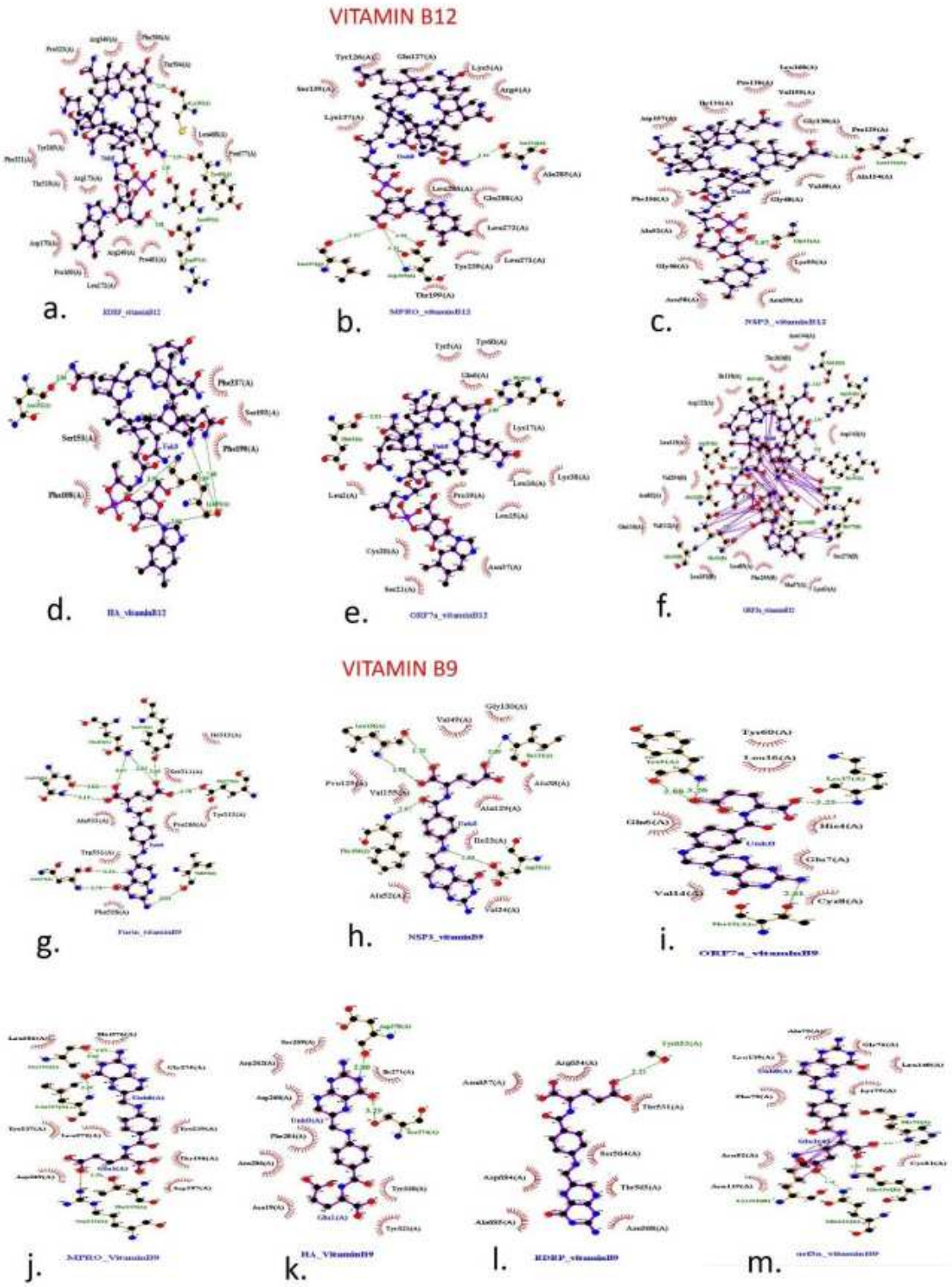

Figure 3

Interaction plot of vitaminB12 and vitamin B9 with all viral targets. (a) RDRP-Vita.B12. (b) MPRO-Vita.B12. (c) NSP3-Vita.B12. (d) HA-Vita.B12. (e) Orf7a-Vita.B12. (f) Orf3a-Vita.B12. (g) Furin-Vita.B9. (h) NSP3- Vita.B9. (i) Orf7a- Vita.B9. (j) MPRO- Vita.B9. (k) HA- Vita.B9. (l) RDRP- Vita.B9. (m) Orf3a- Vita.B9.

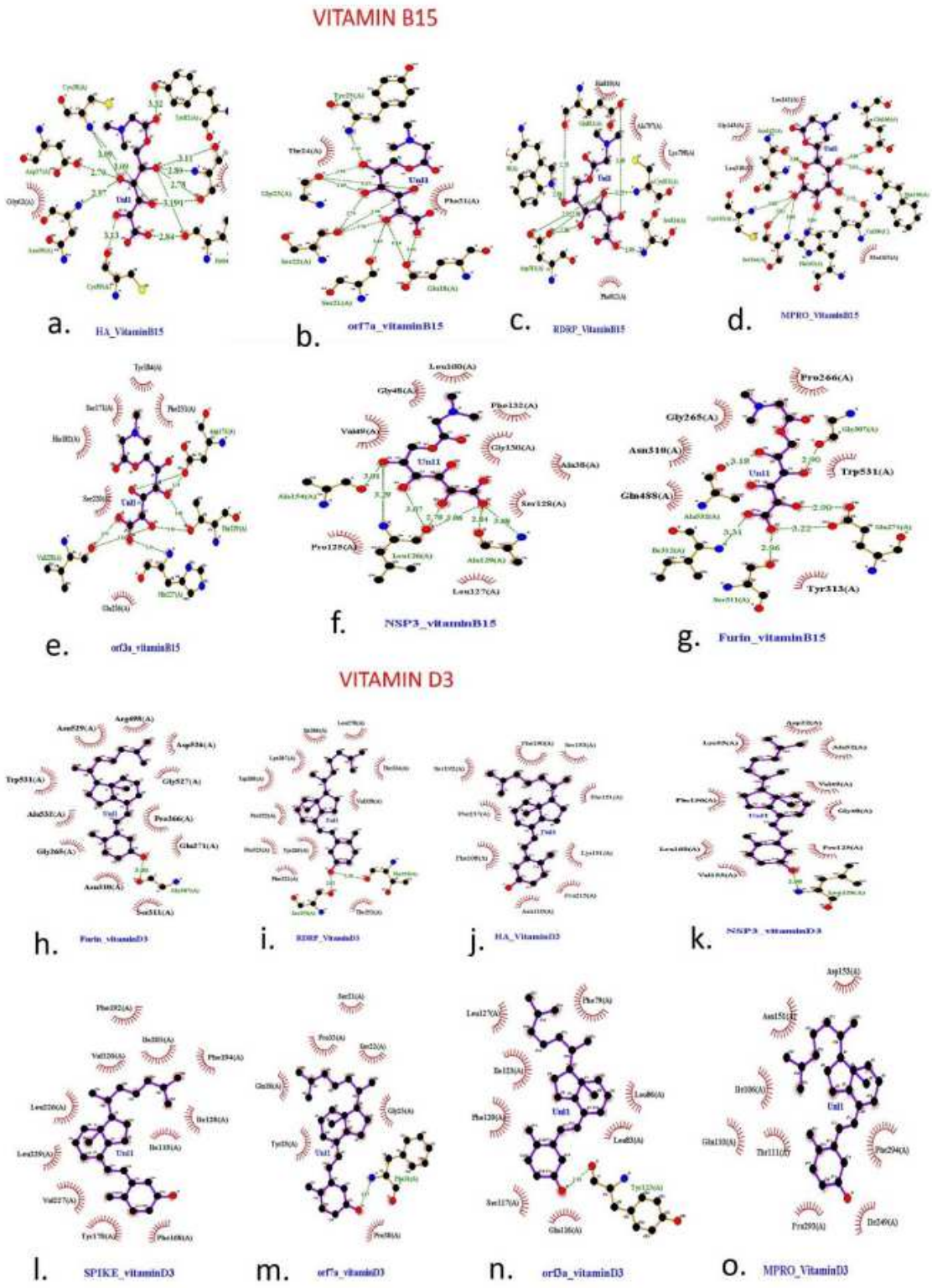

Figure 4

Interaction plot of vitaminB15 and vitamin D3 with COVID-19 targets. (a) HA-Vita.B15. (b) Orf7a- Vita.B15. (c) RDRP- Vita.B15. (d) MPRO- Vita.B15. (e) Orf3a- Vita.B15. (f) NSP3- Vita.B15. (g) Furin- Vita.B15. (h) Furin-Vita.D3. (i) RDRP-Vita.D3. (j) HA- Vita.D3. (k) NSP3- Vita.D3. (l) SPIKE- Vita.D3. (m) Or7a- Vita.D3. (n) Orf3a- Vita.D3. (o) MPRO- Vita.D3.

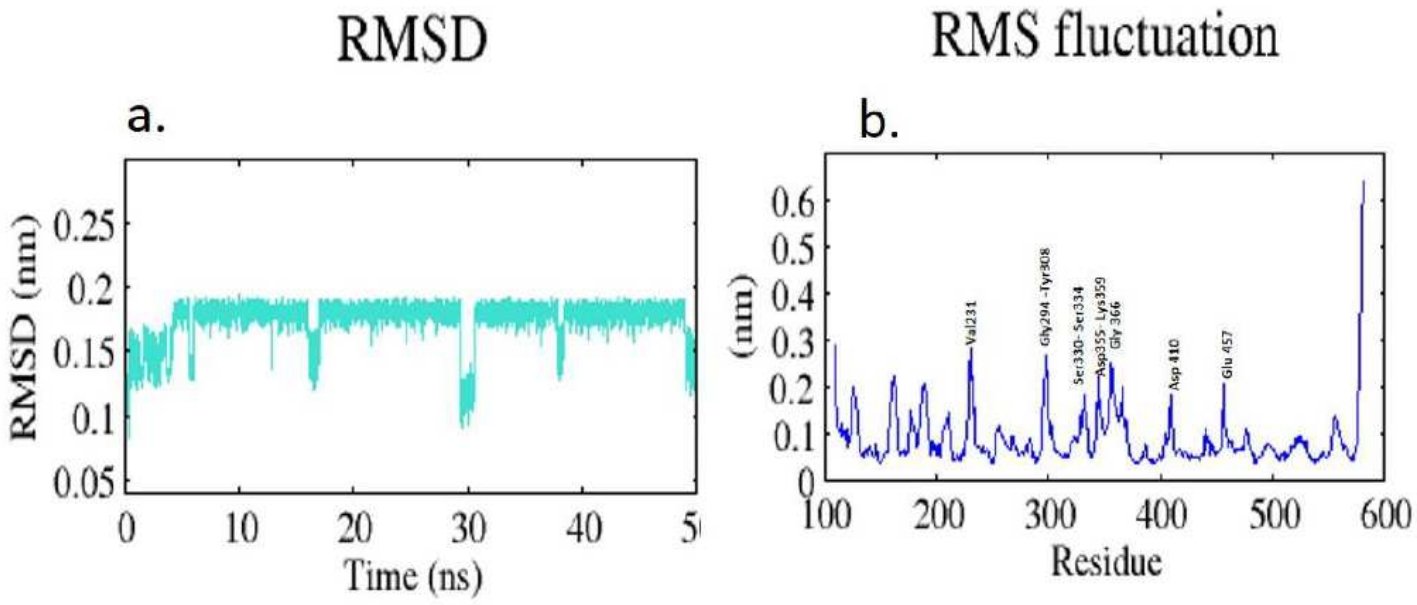

Figure 5

(a.) RMSD and (b.) RMSF trajectory of Furin-Vitamin B12 complexes obtained from 50 ns MD simulation.

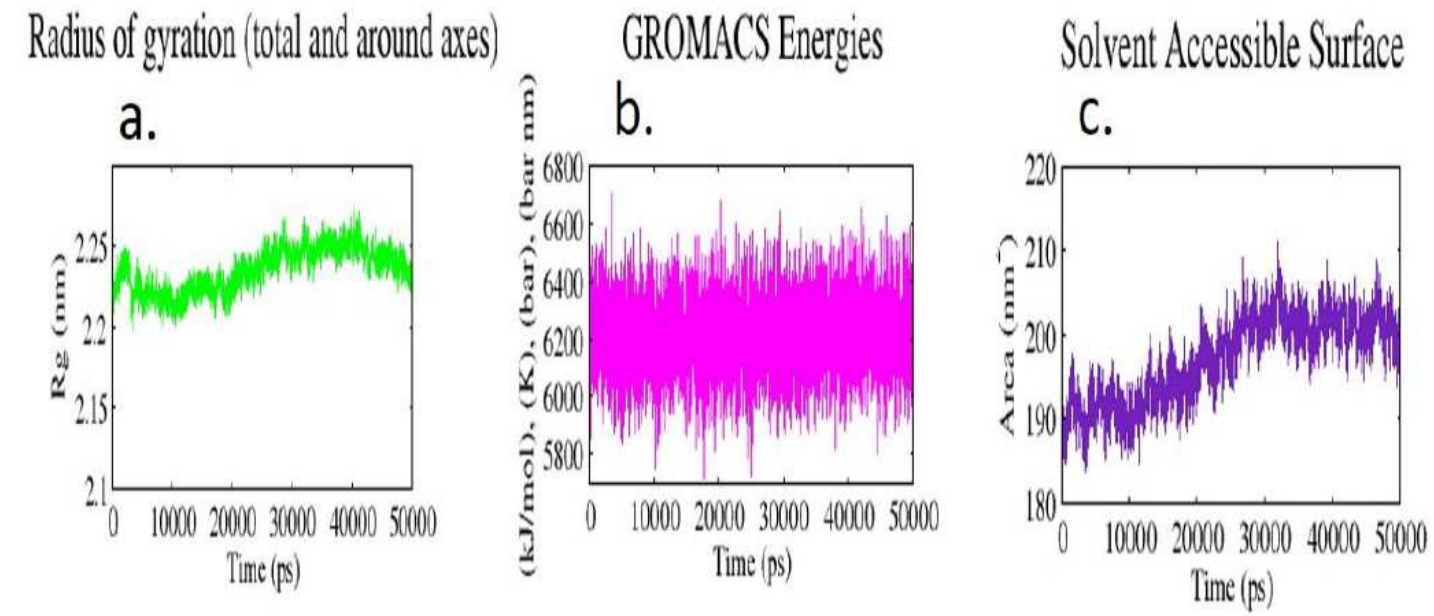

Figure 6

MD trajectories for (a) Radius of gyration (b) potential energy (C) Solvent accessible surface area.

Supplementary Files

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