Received: 9 November 2021 | Revised: 6 May 2022 | Accepted: 10 May 2022

DOI: 10.1111/jfbc.14262

Journal of Food Biochemistry WILEY

ORIGINAL ARTICLE

Structural interactions of phytoconstituent(s) from cinnamon, bay leaf, oregano, and parsley with SARS-CoV-2 nucleocapsid protein: A comparative assessment for development of potential antiviral nutraceuticals

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Abstract

SARS-CoV-2 has been responsible for causing 6,218,308 deaths globally till date and has garnered worldwide attention. The lack of effective preventive and therapeutic drugs against SARS-CoV-2 has further worsened the scenario and has bolstered research in the area. The N-terminal and C-terminal RNA binding domains (NTD and CTD) of SARS-CoV-2 nucleocapsid protein represent attractive therapeutic drug targets. Naturally occurring compounds are an excellent source of novel drug candidates due to their structural diversity and safety. Ten major bioactive compounds were identified in ethanolic extract (s) of *Cinnamomum zeylanicum*, *Cinnamomum tamala*, *Origanum vulgare*, and *Petroselinum crispum* using HPLC and their cytotoxic potential was determined against cancer and normal cell lines by MTT assay to ascertain their biological activity *in vitro*. To evaluate their antiviral potential, the binding efficacy to NTD and CTD of SARS-CoV-2 nucleocapsid protein was determined using *in silico* biology tools. *In silico* assessment of the phytocomponents revealed that most of the phytoconstituents displayed a druglike character with no predicted toxicity. Binding affinities were in the order apigenin > catechin > apiin toward SARS-CoV-2 nucleocapsid NTD. Toward nucleocapsid CTD, the affinity decreased as apigenin > cinnamic acid > catechin. Remdesivir displayed lesser affinity with NTD and CTD of SARS-CoV-2 nucleocapsid proteins than any of the studied phytoconstituents. Molecular dynamics (MD) simulation results revealed that throughout the 100 ns simulation, SARS-CoV-2 nucleocapsid protein NTD-apigenin complex displayed greater stability than SARS-CoV-2 nucleocapsid protein NTD-cinnamic acid complex. Hence, apigenin, catechin, apiin and cinnamic acid might prove as effective prophylactic and therapeutic candidates against SARS-CoV-2, if examined further *in vitro* and *in vivo*.

Practical applications

Ten major bioactive compounds were identified in the extract(s) of four medicinally important plants *viz*. *Cinnamomum zeylanicum*, *Cinnamomum tamala*, *Origanum vulgare* and *Petroselinum crispum* using HPLC and their biological activity was also evaluated against cancer and normal cell lines. Interestingly, while all extract(s) wielded significant cytotoxicity against cancer cells, no significant toxicity was found against normal cells. The outcome of the results prompted evaluation of the antiviral potential of the ten bioactive compounds using *in silico* biology tools. The present study emphasizes on the application of computational approaches to understand the binding interaction and efficacy of the ten bioactive compounds from the above plants with SARS-CoV-2 nucleocapsid protein N-terminal and C-terminal RNA binding domains in preventing and/or treating COVID-19 using *in silico* tools. Druglikeness and toxicity profiles of the compounds were carried out to check the therapeutic application of the components. Additionally, molecular dynamics (MD) simulation was performed to check the stability of ligand-protein complexes. The results provided useful insights into the structural binding interaction(s) that can be exploited for the further development of potential antiviral agents targeting SARS-CoV-2 especially since no specific therapy is still available to combat the rapidly evolving virus and the existing treatment is more or less symptomatic which makes search for novel antiviral agents all the more necessary and crucial.

KEYWORDS
cinnamon, computational analysis, druglikeness, oregano, parsley, SARS-CoV-2 nucleocapsid protein

1 | INTRODUCTION

According to the World Health Organization (WHO), viral diseases are on the rise creating major public health issues. Viruses have been implicated in major biological, clinical cultural, and economic crises around the world since historical times. Human coronaviruses (HCoVs) have been witnessed since the 1960s as a cluster of viruses capable of causing extreme human and animal infections and causal organisms of a number of respiratory, enteric, hepatic, and neurologic diseases (Principi et al., 2010). Several viral outbreaks have been recorded in the previous two decades, including Severe Acute Respiratory Syndrome (SARS) in 2002–2003, H1N1 influenza in 2009, Middle East Respiratory Syndrome (MERS) in 2012 and COVID-19 in 2019.

A total of 503,075,801 confirmed cases of COVID-19 and 6,218,308 deaths have been registered worldwide as of April 15, 2022. The situation is grave in India, too, with as many as 43,039,972 confirmed COVID-19 cases and 521,772 deaths reported as of April 15, 2022 (https://www.worldometers.info/coronavirus/, n.d.).

The Drugs Controller General of India (DCGI) on January 3, 2021, has granted restricted emergency use authorization of Covishield (genetically engineered adenovirus having predicted efficacy rate of 70%–90% in various trials), a vaccine developed by Serum Institute of India (SII), Pune, India, and Covaxin (inactivated SARS-CoV-2 virion having predicted efficacy rate of 81%) developed by Bharat Biotech Hyderabad, India, against COVID-19 (https://www.moneycontrol.com/news/india/coronavirus-news-live-updates-recovery-rate-worldometer-mild-symptoms-covid-19-vaccine-mutant-cases-japan-india-statewise-news-6333021.html) while the third, Russia's Sputnik V, has been approved recently. Lately, India has also fast-tracked approval for foreign vaccines. Though the advent of vaccines against SARS-CoV-2 has raised hopes that the end of the pandemic may be in sight, but it has also sparked some concern about the possibility of side effects and adverse drug reactions in immunized individuals. Additionally, how efficacious are the said vaccines in disease prevention, remains to be seen.

The N-terminal (NTD) and C-terminal (CTD) domains of the nucleocapsid protein are the structural and functional domains that control viral RNA replication and transcription. The most significant function of nucleocapsid protein's NTD is to bind viral RNA, whereas CTD's major function is to dimerize and oligomerize it (Kannan et al., 2020; Walls et al., 2020). SARS-CoV-2 is distinguished from other coronaviruses by the presence of a glycoprotein with acetyl esterase and hemagglutination (HE) characteristics (Prajapat et al., 2020). The open reading frame of SARS-CoV-2 RNA encodes two large polyproteins (PPs) *viz*. PP1a and PP1ab. The digestion of PPs by cysteine proteases results in the production of 16 nonstructural proteins (NSPs). A papain-like protease (PLpro) cleaves the

N-terminal portion of the PPs, generating three NSPs that aid in the assembly of a replicase-transcriptase complex for viral propagation (Munster et al., 2020). Therefore, both nucleocapsid NTD and PLpro are important targets from a drug development perspective.

Till date, researchers have identified over 30 agents, including natural products that could be effective against COVID-19. Though there have been intensive studies on the development and biological characteristics of novel coronaviruses, yet recent efforts to prevent and control spread of coronaviruses especially SARS-CoV-2 have proven to be quite ineffective (Principi et al., 2010). In the revised guidelines for the prevention, diagnosis, and treatment of novel coronavirus-induced pneumonia, the People's Republic of China National Health Commission (NHC) has included antiviral agents such as interferon α, lopinavir/ritonavir, chloroquine phosphate, ribavirin, and arbidol for treatment of COVID-19 (Prajapat et al., 2020). Recently, the detailed mechanism of action of arbidol against SARS-CoV-2 has been demonstrated by molecular dynamics (MD) simulation. Arbidol acts by binding and inhibiting viral binding to host cells at the receptor-binding domain (RBD)/ACE2 interface with an affinity higher than ACE2 and, thus, imparting structural rigidity to the viral glycoprotein preventing it from undergoing conformational rearrangements associated with membrane fusion and virus entry (Padhi et al., 2021). With the possibility of exposure of health care personnel to coronavirus infection looming large, populations are at a significantly higher risk of infection with complications. Age and co-existing disorders (such as diabetes or heart disease) have been proven to exert an adverse effect on the prognosis and outcome of COVID-19 (Báez-Santos et al., 2015).

None of the existing antiviral therapies against SARS-CoV-2 are 100% specific. Therefore, a novel drug that is effective against SARS-CoV-2 and is free of side effects is the need of hour. In the epoch of personalized medicine and cost-effective public health outcomes, information technology has become a fundamental part of drug discovery. Chemoinformatics is employed for reliable target identification and validation together with drug discovery methods to pave the way for an efficient computer-aided drug design (CADD). To this effect, several relatively less explored medicinal plants and their products as well as their phytoconstituents possess vast potential against several diseases in terms of their pharmacological properties. In the present study, ten phytoconstituents from bark of *C. zeylanicum* (CZ) (commonly called as cinnamon); leaves of *C. tamala* (CT) (commonly called as bay leaf); *O. vulgare* (OV) (commonly called as oregano), and *P. crispum* (PC) (commonly called as parsley), were selected as ligands for evaluation of their binding kinetics with NTD and CTD of SARS CoV-2 nucleocapsid protein on the basis of their identification in ethanolic extract(s) by HPLC. As mentioned above, the structural and functional sites of nucleocapsid proteins *viz.*, NTD and CTD, control viral RNA replication and transcription. The nucleocapsid protein's NTD is involved in RNA binding, while the CTD is involved in dimerization (Muhammad & Dewettinck, 2017; Pal & Kerorsa, 2020).

Cinnamon also known as Dalchini (DLC) in India, has recently been the subject of intense research due to its numerous pharmacological properties such as anti-inflammatory, antitumor, anticancer, antidiabetic, antimicrobial, and cardioprotective (Ahmad et al., 2020; Al-Shawabkeh & Al Jamal, 2019; Dugoua et al., 2007; Goswami & Rahman, 2010; Husain et al., 2018; Ranasinghe & Galappaththy, 2016). Cinnamon is generally recognized as safe (GRAS) in the amount normally found in food by the US Food and Drug Administration (FDA). For decades, patients suffering from numerous viral infections have ingested cinnamon. In both developing and developed countries including India, there has been an emerging trend among HIV patients to use cinnamon oil as an antiretroviral medication (Fabros Jr et al., 2018; Premanathan et al., 2000). Consequently, urgent scientific research is required to determine the efficacy level of main constituents of cinnamon oil such as cinnamaldehyde as antiviral antidotes. Antiviral potential of cinnamon/cinnamaldehyde has also been explored against porcine reproductive and respiratory syndrome virus (PRRSV) (Yeh et al., 2013), human respiratory syncytial virus (HRSV) (Fatima et al., 2016), H7N3 Influenza A virus (Tamam et al., 2017), Newcastle disease virus in chickens (Hayashi et al., 2007) as well as influenza A (Rahman et al., 2021), parainfluenza (Sendai), HSV-1 (Fabra et al., 2016; Ovadia, 2016) and enteric viruses (Upadhyay, 2017).

C. tamala leaves also known as Tejpatta (TJP) in India, are widely utilized in the Indian subcontinent to provide a unique flavor to dishes, beverages, and foods. The plant contains a large number of chemical constituents, the majority of which are found in bark essential oil and have biological properties such as anti-diarrheaic, anti-tumor, anti-inflammatory, anti-arthritic, anti-parasitic, gastro-urinary, antitumor, antiparasitic, antioxidant, chemopreventive, and gastroprotective (Bahmani et al., 2018; Dandapat et al., 2014; Husain et al., 2018). There is no reported literature as far as its antiviral potential is concerned and, hence, this plant warrants attention for evaluation of its antiviral efficacy, if any.

Oregano has been used in folk and medicine since time immemorial as an anti-asthmatic, antispasmodic, anticancer, sedative, and in the treatment of gastrointestinal disorders including stomach and intestinal disorders, constipation, and inflation (Gilling et al., 2014; Husain et al., 2018).

Oregano is a common mint family herb that contains chemicals which are known for their therapeutic properties. Murine norovirus (MNV), which is highly contagious and the principal cause of stomach flu in people, has been reported to be inhibited by oregano oil and isolated carvacrol (Pilau et al., 2011). Because human norovirus is difficult to propagate in laboratory settings, it is used in scientific studies. Oregano oil and carvacrol have also been proven to have antiviral properties against HSV-1, rotavirus, a frequent cause of diarrhea in infants and children and respiratory syncytial virus (RSV), which causes respiratory infections (Mediouni et al., 2020; Sharifi-Rad et al., 2017). The antiviral activity of crude oregano oil and its main constituent carvacrol has also been determined against HIV-1 (Gutiérrez-Grijalva et al., 2017). Phytochemical content present in oregano is the principal cause of human health benefits (Blank et al., 2019; Leyva-López et al., 2016; Pascual et al., 2001). A study has reported that antiviral activity of essential oil of oregano against

five DNA viruses *viz*. acyclovir-resistant herpes simplex virus type 1 (ACVR-HHV-1), human herpesvirus type 1 (HHV-1), bovine herpes virus type-1, 2, and 5 (BoHV-1, BoHV-2, BoHV-5) and three RNA viruses *viz*. rotavirus (RV), human respiratory syncytial virus (HRSV) and bovine viral diarrhea virus (BVDV) (Pilau et al., 2011). Antiviral activity of aqueous and ethanolic extracts of *Origanum vulgare* and its phytoconstituents has also been determined against equine arteritis virus (EAV), bovine viral diarrhea virus (BVDV), equine influenza virus (EIV), canine distemper virus (CDV), feline calicivirus (FCV), canine adenovirus (CAV), and canine coronavirus (CCoV) (Zhang, Guo, et al., 2014); Coxsackie virus B3 (CVB3), respiratory syncytial virus (RSV) and herpes simplex virus type 1 (HSV-1) (Lelešius et al., 2019; Santoyo et al., 2014); avian infectious bronchitis coronavirus (IBV) (Brochot et al., 2017), H1N1 and HSV1 viruses (Farzaei et al., 2013).

Parsley or garden parsley is a key source of flavonoids and antioxidants (Ezer & Arisan, 2006; Papuc et al., 2016; Zakaryan et al., 2017). Parsley is a culinary and medicinal herb used to flavor the cuisines of South East Asia, India, South America, China, and Mexico. The aerial parts of PC are used in the traditional medicine system to treat hemorrhoids and the urethral inflammation whereas, the roots are used to pass kidney stones (Adams et al., 2007) and enhance brain function and memory (Butu & Rodino, 2019). Parsley is also used as a demulcent, intestinal tonic, diuretic, anti-dote, anti-urolithiasis, and an anti-inflammatory agent in traditional and folklore medicine for the treatment of dysmenorrhea, amenorrhea, gastrointestinal disorders, high blood pressure, urinary disease, cardiac disease, diabetes, otitis, sniffle, and various dermal diseases (Papuc et al., 2016). Parsley has also been found to display antiviral activity due to its content of flavones apigenin and luteolin and flavanol quercetin (Ezer & Arisan, 2006; Malin et al., 2020).

Remdesivir (RDV) is a nucleotide analog (Gordon et al., 2020) and the triphosphate form of RDV (RDV-TP) is an inhibitor of numerous RNA-dependent RNA polymerases (RdRps) (Gupta et al., 2021; Saha et al., 2020). RDV is a monophosphoramidate which acts by blocking viral RNA production through inhibition of viral RNA polymerase proofreading. For all three coronaviruses *viz*. SARS-CoV-2, SARS-CoV, and MERS-CoV RdRps, it has been demonstrated to block viral RNA synthesis *via* delayed chain termination (Shekhar et al., 2001).

Recently, SARS-CoV-2 proteins have been targeted in many *in silico* based studies which have been provided in supplementary data file (Table S1.1). The table provides an overview of the current state of work being done in this area.

2 | MATERIALS AND METHODS

2.1 | Plant material collection

Dried bark and leaves of *C. zeylanicum* (cinnamon) and *C. tamala* (bay leaves) respectively, that are commonly used as spices and condiments were obtained from a local market in Lucknow, India, whereas fresh leaves of *O. vulgare* (oregano) and *P. crispum* (parsley) were procured from plants growing in Central Institute of Medicinal and Aromatic Plants (CIMAP), Lucknow, India, on payment basis. The plants and their parts thereof were identified by the Department of Pharmacognosy CIMAP, Lucknow and were subsequently shade-dried followed by grinding.

2.2 | Preparation of extract(s)

The dried bark of *C. zeylanicum* and dried leaves of *C. tamala*, *O. vulgare*, and *P. crispum* were weighed and pulverized separately and filtered through a muslin cloth to make a powder. The soluble components present in the coarse powder(s) were extracted with 3 parts of absolute ethanol and 1 part of the respective powder (1:3 ratio, w/v) in a percolator at room temperature for 24 to 48 h. Each extraction was repeated three times and the solvent was evaporated in a Rota vapor. The yields were about 7.5% (w/w) for *C. zeylanicum* and *O. vulgare* extracts and 8.5% and 8% (w/w) for *C. tamala* and *P. crispum* extracts, respectively. Lyophilized crude extract(s) were kept in air-tight and labelled vials. The vials were stored in a desiccator.

2.3 | Phytochemical characterization of extract(s) by HPLC

The plant extracts were characterized using HPLC on an ODS-2 Thermo C18 RP column (250 ×4.6 mm, 5 μm particle size, maintained at 25°C). The mobile phase consisted of water and acetonitrile which was applied as a gradient for 45 min. The extract(s) were dissolved in HPLC grade water and filtered through sterile 0.45 μm Millipore filters prior to injection. The injection volume was 10 μl and the flow rate was set at 0.5 ml/min. The wavelength for absorbance was set at 255 nm.

Eluted peaks from HPLC were recorded at different retention times. The peak fractions were subsequently identified by comparing their retention times on ODS-2 Thermo C18 RP column from review of literature. The phytocomponents showing major abundance in the four plant extracts as evident from the % peak areas were selected for further *in silico* analysis.

2.4 | Biological activity evaluation of ethanolic extract(s) of CZ, CT, OV, and PC

Drug repositioning (also called drug repurposing) involves the investigation of existing agents/drugs for new therapeutic purposes. Keeping in view the extremely limited therapeutic options currently available to effectively combat the ongoing viral pandemic COVID-19, drug repositioning seems to be an attractive therapeutic option in this regard (McLaren & Papac, 1974). Interestingly, since cancer and viral diseases are known to present with similar symptoms and signs (Petersdorf & Larson, 1983; Siddiqui et al., 2020), it was thought that agents/extract(s) having anticancer activity might also behave as potential antiviral agents.

To this effect, the cytotoxic/anticancer potential of CZ, CT, OV, and PC ethanolic extract(s) were evaluated against human breast cancer cell line MCF-7.

2.4.1 | Cell lines

Human breast cancer cell line MCF-7 (ER^+, PR^+, $HER2^-$, tumorigenic, and non-invasive) and human normal kidney epithelial cell line HEK-293 were obtained from the National Centre for Cell Science (NCCS), Pune, India, and as such, were maintained by sub-culturing and passaging as monolayers in 25 and 75 cm^2 cell culture flasks (Nest, Tarsons) at 37°C in Cell and Tissue Culture Lab, Era's Medical College, Lucknow, as reported earlier (Ahmad, 2019).

2.4.2 | Cell culture

For experiments, cells were trypsinized and cultured (0.5×10^5 cells/well) initially for 24 h, in 6-well plates (Linbro, MP Biomedicals) so as to allow the cells to attach. In separate experiments, MDA and HEK-293 cells in culture medium were exposed to 10–100 μg/ml each of the prepared extract(s) in 50% DMSO for the next 48 h. Wells containing equal number of MCF-7 or HEK-293 cells in culture medium containing 50% DMSO (vehicle) served as controls. Results were interpreted as cell viability *versus* time period graph.

2.4.3 | Morphological study

For morphological analysis, cells in 6-well plates were observed under phase-contrast microscope and photographed (Nikon Eclipse Ti, Japan) as reported previously (Ahmad, 2019).

2.5 | Cytotoxicity assays

2.5.1 | (Methyl tetrazolium-MTT assay)

MTT assay provides an indication of mitochondrial integrity and activity, which is interpreted as a measure of percent cell viability and was performed as reported previously (Ahmad, 2019).

2.6 | Comparison of the cytotoxic activity of extracts

The question whether extract mediated cytotoxicity was selective to cancer cells and not to normal cells was addressed by evaluating the effects of the ethanolic extract(s) on normal epithelial cells HEK-293 both morphologically and by MTT assay as reported previously (Husain et al., 2018).

2.7 | Statistical analysis

Cell viability data were expressed as the mean ± *SD* from three independent experiments. Statistical evaluation was determined by one-way ANOVA followed by Dunnett's Multiple Comparison Test using GraphPad Prism software (Version 5.01). A *p*-value less than .05 was considered as statistically significant.

2.8 | PASS analysis and drug-likeness evaluation

To predict the biological activities of chemical compounds, an online web tool known as PASS (Prediction of Activity Spectra for Substances) is used. To predict the pharmacological behavior, mechanism of action, and adverse effects if any, of the selected phytoconstituents *versus* reference drug remdesivir (Lipinski et al., 1997), OSIRIS Property Explorer version 4.51 (http://www.openmolecules.org/propertyexplorer/index.html) was used in this study.

Lipinski's five rule (RO5) was used to determine the druglikeness of the selected phytoconstituents *versus* remdesivir against SARS-CoV-2 (Daina et al., 2017). According to the rule, ligands having good membrane permeability have MW ≤ 500, log*P* ≤ 5, hydrogen bond acceptor sites (NON) ≤ 10, number of hydrogen bond donors (NOHNH) ≤ 5, and topological polar surface area (TPSA) ≤140 $Å^2$. There should be no more than one violation of the criteria for an orally active drug.

2.9 | Pharmacokinetic (PK) parameters prediction

The ADMET features of selected phytoconstituents such as absorption, distribution, metabolism, excretion, and toxicity were calculated using online SwissADME software to determine their pharmacokinetic feasibility as therapeutic candidates. These features were used to predict the biochemical and physiological properties like blood-brain barrier (BBB) permeability, human intestinal absorption (HIA), behavior as P-gp substrate, inhibition of P-glycoprotein, and skin permeability of the selected phytoconstituents *versus* remdesivir (Aniyery et al., 2015; Verma, 2012).

2.10 | Bioactivity score prediction

Molinspiration version 2016.10, a web-based tool was used to determine the drug score values for the selected phytoconstituents *versus* remdesivir. Human receptors *viz*. ion channels, kinases, GPCRs, proteases, nuclear receptors and enzymes are the common protein targets against which the bioactivity scores (BAS) for particular ligands are predicted. A compound is considered to be active if the BAS is greater than 0.0; moderately active if the BAS is between −5.0 and 0.0 and inactive if the BAS is less than −5.0 (Khan et al., 2018; Martin, 2005).

2.11 | Toxicity potential assessment

In order to analyze the toxicity of the selected phytoconstituents *versus* remdesivir, OSIRIS Data Warrior Version 4.5 was used (Lipinski et al., 1997). Assessment of toxicity gives an idea about the possible side effects of chemical compounds in the form of tumorigenic, mutagenic, irritant, and adverse reproductive effects. The process of drug discovery and development involves assessment of toxicity risk as a critical and early step.

2.12 | Principal component analysis (PCA)

PCA was used to define and visualize several multidimensional properties like MW, percent Absorption, and TPSA on the selected phytoconstituents and remdesivir using Osiris Property Explorer 4.5.1. To depict drug-likeness of the phytoconstituents *versus* the remdesivir, bar charts and 3D scatter plots of principal components were created using OSIRIS Property Explorer 4.5.1 (http://www.openmolecules.org/propertyexplorer/index.html) and AccelrysBiovia Discovery Studio version 2017 R2 (Lipinski et al., 1997).

2.13 | Ligand preparation

PubChem and ChEMBL databases were used to retrieve the 3-D structures of the 11 selected active components and downloaded in SDF format. Merck Molecular Force Field (MMFF94) was used for performing energy minimization of components prior to docking (Lipinski et al., 1997).

2.14 | Target protein preparation

Nucleocapsid protein N-terminal domain (PDB ID: 6M3M) and nucleocapsid protein C-terminal domain (PDB ID: 7C22) of SARS-CoV-2 were chosen as prospective viral protein targets and their 3D crystal structures were downloaded in PDB format from protein data bank and their refinement and energy minimization were carried out. AccelrysBiovia Discovery Studio version 2017 R2 was used for the visualization of structures. Chimera 1.12 was used for receptor energy minimization by using a default constraint of 0.3Å root mean square and AMBER force field 14SB following which structural refinement, removal of structural inconsistencies (Lipinski et al., 1997; Pettersen et al., 2004), and energy calculations were done. MMTK was used for performing the minimization routine which is included with Chimera (Srivastava et al., 2020).

2.15 | Molecular docking of selected components with selected targets

The major bioactive components present in ethanolic extract(s) of CZ, CT, OV, and PC (Table 2) and remdesivir were subjected to molecular docking studies with the above protein targets (Ahmad, 2019; Lipinski et al., 1997; Srivastava et al., 2020).

2.15.1 | AutoDock

AutoDock version 4.2.6 was used to measure the binding energies in kcal/mol and K_d values of the active components *versus* remdesivir to each of the selected target proteins. Accelrys Biovia Discovery Studio version 2017 R2 and PyMol were used to analyze the best docking orientations of the active components with the selected proteins (Ahmad, 2019; Lipinski et al., 1997; Srivastava et al., 2020).

2.15.2 | Validation of docking analysis

Two additional docking softwares *viz*. AutoDock Vina (Trott & Olson, 2010) and iGEMDOCK v2.1 (Yang & Chen, 2004) were used to further validate the docking results. AutoDock Vina is two times more accurate and faster than AutoDock 4 and automatically generates grid maps and clusters the results (Trott & Olson, 2010). On the other hand, iGEMDOCK uses a generic evolutionary method (GA) to compute a ligand conformation and orientation relative to the binding site of protein target. Therefore, docking performance is directly related to the selected GA parameters (Yang & Chen, 2004).

A total of 10 best docking poses are generated by AutoDock v4.2.6 and AutoDock Vina on the basis of the 10 best possible orientation(s) of the ligand(s) in the protein binding pocket in terms of lowest binding energy (B.E.) and dissociation constant (K_d). On the other hand, iGEMDOCK generates 70 poses in order to calculate ligand conformation and orientation with respect to the target protein binding site *via* standard docking. Best fit is selected on the basis of total energy *viz*. vdW (van der Waals energy), H-bond (hydrogen bonding energy), and Elect (electrostatic energy) of the predicted pose at the protein binding site.

2.15.3 | Molecular dynamics (MD) simulation

MD simulation was carried out with Desmond module (Schrödinger Release 2020-4) package with apigenin bound with SARS-CoV-2 N-terminal RNA binding domain of nucleocapsid protein (PDB ID: 6M3M) and cinnamic acid bound with SARS-CoV-2 C-terminal domain of nucleocapsid protein (PDB ID: 7C22). The force field used for Molecular dynamics (MD) simulations was OPLS3e.The water-soaked solvated system was created in Desmond using the System Builder tool. The TIP3P model of water was considered for solvating the system. A buffer distance of at least 10 Å from the protein's outer surface was used to construct the orthorhombic box with periodic boundary conditions. Simulations were run with the OPLS-3e force field. An adequate quantity of counter-ions were added to the system to neutralize it. By adding 0.15 M NaCl to the simulation box, the iso-osmotic state was maintained. Before the simulation's production

run, a prescribed equilibration protocol was followed. After equilibration, the unrestrained production phase was run under NPT ensemble for 100 ns at 300 K temperature and 1.01325 bar pressure. A total of 100 nanoseconds of simulation time was used with 1000 frames saved to the trajectory. The simulation interaction diagram was utilized to examine the MD simulation trajectory using RMSD, RMSF, hydrogen bond analysis, and radius of gyration (Rg).

3 | RESULTS

3.1 | HPLC analysis of cinnamon/dalchini (DLC), bay leaf/tejpatta (TJP), oregano (ORG), and parsley (PRL) extract(s)

Retention time (R_t) of compounds contained in the four extract(s) were ascertained. LC chromatogram of cinnamon (Dalchini) extract showed four peaks indicative of presence of three major bioactive components *viz*. cinnamic acid (R_t = 6.450 min), cinnamaldehyde (R_t = 6.786 min), and eugenol (R_t = 7.459 min). Bay leaf extract displayed three major peaks of catechin (R_t = 6.085 min), eugenol (R_t = 7.211 min), and apigenin (R_t = 19.496 min). Oregano extract displayed four major peaks of carvacrol (R_t = 3.825 min), thymol (R_t = 4.259 min), citral (R_t = 6.046 min), and eugenol (R_t = 7.102 min). Parsley extract showed three major bioactive component peaks of apiin (R_t = 3.865 min), limonene (R_t = 6.50 min), and eugenol (R_t = 7.367 min; Figure 1).

Table 1 delineates the molecular formula (MF), molecular weight (MW), chemical structure, PubChem IDs, chemical class, etc. of compounds identified in ethanolic extract(s) of cinnamon bark, bay leaves, oregano and parsley leaves using HPLC.

3.2 | Evaluation of the cytotoxic potential of ethanolic extract(s) of CZ, CT, OV, and PC on MCF-7 cells

Treatment of human breast cancer cell line MCF-7 with ethanolic extract(s) of CZ, CT, OV, and PC in the range 33–100μg/ml yielded IC_{50} values of 47, 110, 230, and 190 μg/ml, respectively, by MTT assay. All extract(s) caused significant alteration in morphology of the cells and the cells assumed a more rounded and spherical appearance in contrast with their epithelial-like morphology (Figure 2). MCF-7 cell line has recently been used as a cell culture model in a number of *in vitro* cytotoxicity studies of ZnO-reduced graphene oxide nanocomposites (ZnO-RGO NCs) using garlic-clove extract (Ahamed et al., 2021a; 2022), bismuth oxide nanoparticles (Bi_2O_3 NPs) (Ahamed et al., 2019) as well as silver-reduced graphene oxide nanocomposites (Ag/RGO NCs) using orange peel extract (Ahamed et al., 2021b). Interestingly, the extract(s) had negligible effect on normal HEK-293 cells (Figure 2). These observations hold great significance in further and future exploration of the potential antiviral effect(s) of the phytoconstituents present in these extract(s). Although their anticancer potential is either known or well-defined (Husain et al., 2018), very little is known about their antiviral efficacy. In the present study, an attempt was made to explore the antiviral potential of these phytocomponents using *in silico* biology tools.

3.3 | Virtual screening of major phytoconstituents present in extract(s) of CZ, CT, OV, and PC on the basis of physicochemical parameters and drug-likeness

Based on the HPLC results, the above phytoconstituents were analyzed for their drug-like characteristics using Lipinski's rule (Table 2). In general, an orally active pharmaceutical drug candidate should not have more than one violation of Lipinski's criteria; otherwise, its bioavailability may be jeopardized (Lipinski et al., 1997).

It is evident from Table 2, that except for apiin, neither of the screened phytoconstituents exhibited any Lipinski's violation. However, remdesivir displayed two violations of Lipinski's rule.

A high MW favors digestion and slower absorption from the gastrointestinal system consequently lowering drug concentration and bioavailability in the bloodstream. In the current study, the MWs of all selected phytoconstituents except apiin and reference drug remdesivir were found to be less than 500, thus favoring rapid GI absorption (Table 2). This was found to be in agreement with the calculated LogP values of the selected phytoconstituents (Table 2). Apart from apiin and the reference drug remdesivir, all phytocomponents were found to be lipophilic in nature, implying that they were well-absorbed across cell membranes.

3.4 | Evaluation of pharmacokinetic parameters of major phytoconstituents from CZ, CT, OV, and PC *versus* reference drug remdesivir using SwissADME

As evident from Table 3, most of the phytoconstituents were found to be capable of crossing the BBB *versus* phytoconstituents apigenin, catechin, apiin, and remdesivir which did not exhibit BBB permeability. Except for catechin, apiin, and reference drug remdesivir, none of the phytoconstituents were found to behave as P-glycoprotein substrates, indicating that they are unlikely to be pushed out of the cell by the glycoprotein reducing the likelihood of cells developing resistance to them. In contrast to the reference drug remdesivir, eugenol, apigenin, carvacrol, and thymol were found to function as CYP1A2 inhibitors, indicating that they were less likely to be metabolized and rendered inactive by the enzyme. On the other hand, none of the phytoconstituents including remdesivir were found to behave as CYP2C19 inhibitors. CYP2C19 is an enzyme that catalyzes the metabolism of a wide range of drugs. Cinnamic acid and limonene were predicted to inhibit CYP2C9, a key enzyme involved in the oxidation of xenobiotic and endogenous molecules, particularly drugs having a limited therapeutic efficacy. Except for apigenin, none of the phytoconstituents were

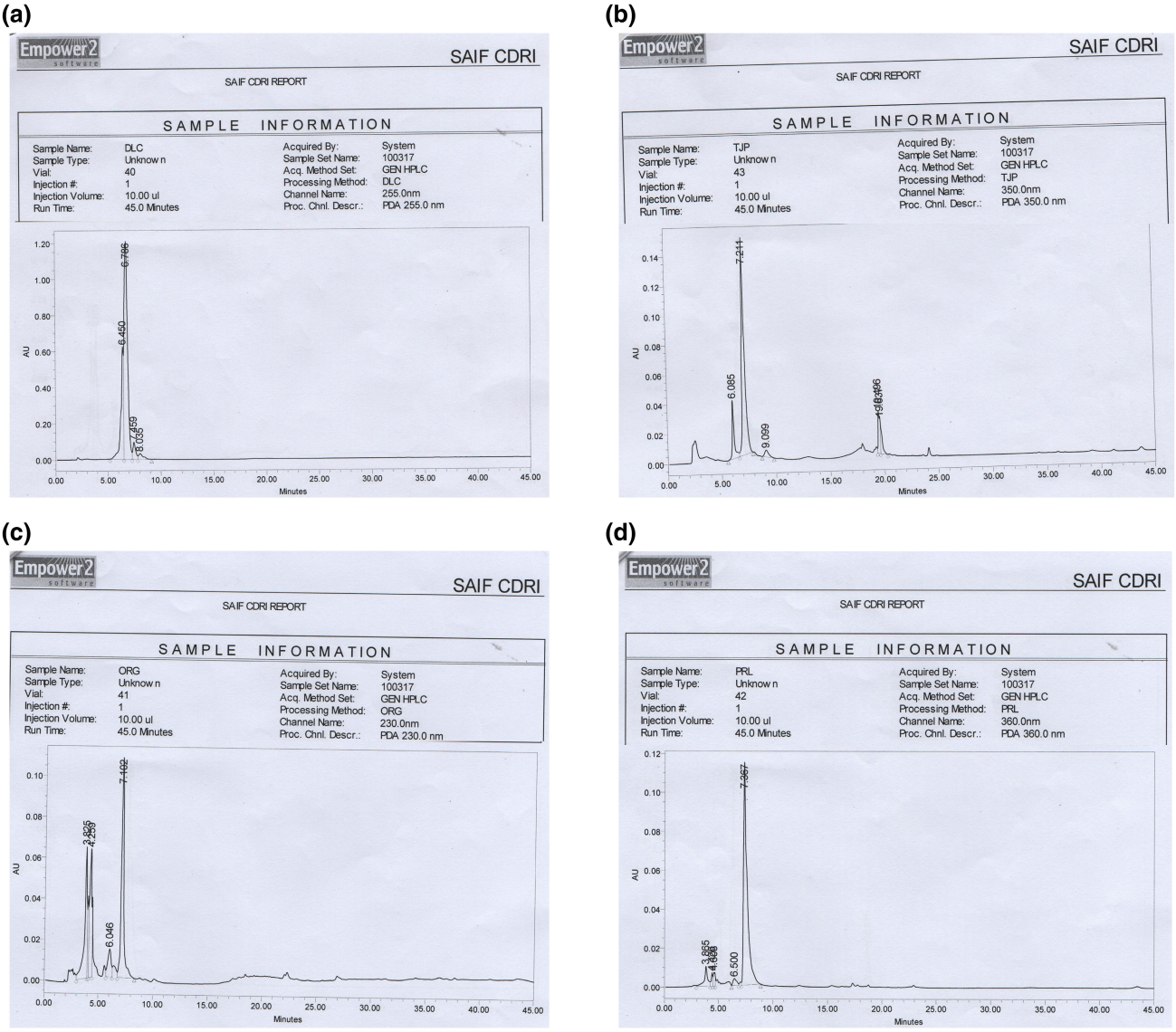


FIGURE 1 HPLC profiling of (a) cinnamon/dalchini (DLC) (b) bay leaf/tejpatta (TJP), (c) oregano (ORG), and (d) parsley (PRL) extract(s).

predicted to behave as CYP2D6 and CYP3A4 inhibitors, indicating their reduced metabolism and elimination by these enzymes, thereby resulting in increased plasma concentrations vis-à-vis other phytoconstituents. Remdesivir was also found to behave as a CYP3A4 inhibitor (Table 3).

The term "skin permeability" (Kp) is commonly used to characterize the rate of chemical penetration through the skin's outermost layer (epidermis). All 10 phytocomponents including the reference drug remdesivir, displayed negative Kp values, indicating that these phytoconstituents are less likely to be absorbed *via* the skin (Potts & Guy, 1992).

3.5 | Bioactivity score (BAS) analysis

Biological targets of potential drug candidates include ion channels, proteases, kinases, G-protein coupled receptors (GPCRs), nuclear receptors, and enzymes. If the BAS is greater than 0.0, the potential drug molecule is pharmacologically active; if it is between −5.0 and 0.0, the drug molecule is moderately active; and if the BAS is less than −5.0, the drug molecule is inactive. In the present study, BAS of major components found in CZ, CT, OV, and PC was determined by Molinspiration (www.molinspiration.com) (Table 4).

As GPCR ligands: Most of the phytoconstituents were predicted to be moderately active except catechin and apiin. Remdesivir too had a positive BAS.

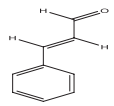
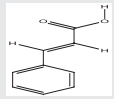
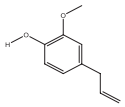
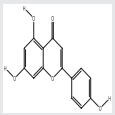
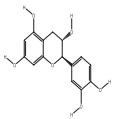
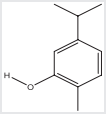
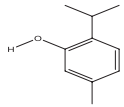
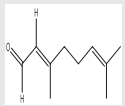
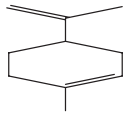
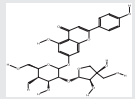
As ICMs: Most of the phytoconstituents including remdesivir had negative BAS scores and were predicted to be moderately active except catechin which had a positive BAS.

As KIs: All phytoconstituents were predicted to behave as moderately active kinase inhibitors except apigenin, catechin, and apiin which had a positive BAS. Remdesivir also had a positive BAS as KI.

As NRLs: Apigenin, catechin, and apiin had positive scores as NRLs.

As PIs: Most of the phytoconstituents possessed negative BAS indicating their moderate activity as PIs except catechin, and apiin. Remdesivir too had a positive BAS as PI.

TABLE 1 Phytoconstituents and their molecular weight (MW), molecular formula (MF), chemical class, retention time (RT), and % Area identified in ethanolic extract(s) of cinnamon bark, bay leaves, oregano, and parsley leaves by HPLC

S.N.	Phytocomponent	Plant source	Part of plant	MF	MW	Chemical structure	PubChem CID	Chemical class	RT	Area (%)
1.	Cinnamaldehyde	Cinnamon	Bark	C_9H_8O	132.16		637511	Phenylpropanoid	6.786	67.22
2.	Cinnamic acid	Cinnamon	Bark	$C_9H_8O_2$	148.16		444539	Unsaturated carboxylic acid	6.450	26.17
3.	Eugenol	Cinnamon, bay leaf, oregano and parsley	Leaves and Bark	$C_{10}H_{12}O_2$	164.2		3314	Phenylpropanoid	7.211	68.45
4.	Apigenin	Bay leaf	Leaves	$C_{15}H_{10}O_5$	270.05		5280443	Flavone	19.496	8.88
5.	Catechin	Bay leaf	Leaves	$C_{15}H_{14}O_6$	290.26		9064	Flavonoid	6.085	13.63
6.	Carvacrol	Oregano	Leaves	$C_{10}H_{14}O$	150.21		10364	Phenol	3.825	25.00
7.	Thymol	Oregano	Leaves	$C_{10}H_{14}O$	150		6989	Monoterpenoid	4.259	23.98
8.	Citral	Oregano	Leaves	$C_{10}H_{16}O$	152.24		638011	Mixture of terpenoids	6.046	7.39
9.	Limonene	Oregano	Leaves	$C_{10}H_{16}$	136.24		22311	Cyclic monoterpene	6.50	2.73
10.	Apiin	Parsley	Leaves	$C_{26}H_{28}O_{14}$	564.5		5280746	Flavonoid	3.865	6.89

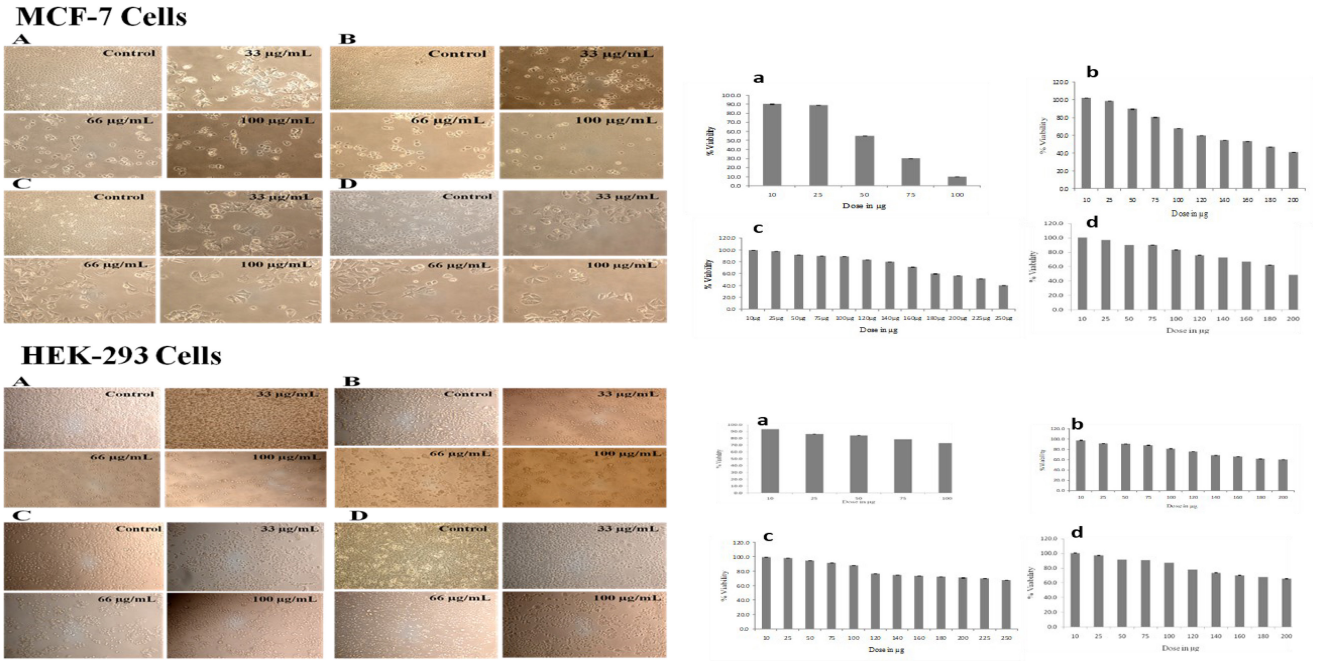


FIGURE 2 (*Left panel*): Morphological and cytotoxic activity analysis of (A) dalchini (DLC) ethanolic extract (Control and experimental [33–100 µg/ml]) (B) tejpatta (TJP) ethanolic extract (Control and experimental[33–100 µg/ml]) (C) oregano (ORG) ethanolic extract Control and experimental [33–100 µg/ml]) and (D) parsley (PRL) ethanolic extract Control and experimental [33–100 µg/ml]) against human MCF-7 and HEK-293 cells, respectively, after 48 hr of incubation (Magnification 10×). The final concentration of DMSO in each well did not exceed 0.5% (v/v). (*Right panel*) Percent cell viability *versus* concentration of (a) DLC (b) TJP (c) ORG, and (d) PRL ethanolic extract(s). Values are expressed as mean ± *SD* of three independent experiments. $^{*}p < 0.05$ as compared to control.

As EIs: Apigenin, catechin, apiin as well as remdesivir possessed positive BAS suggesting that they may act as enzyme inhibitors, whereas other phytoconstituents were predicted to behave as moderate enzyme inhibitors.

3.6 | Druglikeness and toxicity risk analysis using OSIRIS data warrior

A positive druglikeness value for a molecule suggests that it contains fragments that are commonly found in commercial pharmaceuticals (Proudfoot, 2002). Cinnamic acid, apigenin, catechin, and apiin were found to have a druglikeness potential of >0. On the other hand, eugenol, carvacrol, and thymol were found to possess druglikeness potential between −5.0 and 0.0. Interestingly, remdesivir had a negative value of druglikeness less than −5 (Table 5).

In silico prediction of druglike qualities has now become the norm for pharmaceutical firms in order to classify pharmacological compounds and their commercial potential. The unsuitable molecules may have harmful effects on biological systems and, are, thus, removed from drug screening. Tumorigenicity, mutagenicity, irritant, and adverse effects on the reproductive system are some of the parameters for which molecules under study are evaluated. In the present study, catechin and apiin were predicted to have no mutagenic, tumorigenic, anti-reproductive, and irritant effects as compared to other phytoconstituents and remdesivir (Table 5). Interestingly, *in vitro* toxicity assessment of the extract(s) containing the ten bioactive compounds on normal human kidney epithelial cell lines also displayed no toxic effects (Figure 2).

3.7 | Principal component analysis

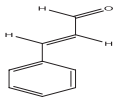
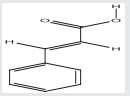
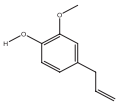
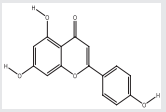
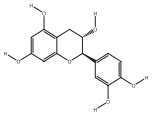
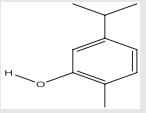
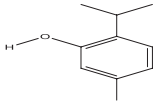
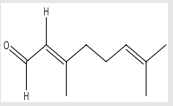
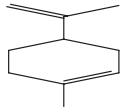
Multivariate analysis was performed using PCA in an attempt to model the overall variance of the data set. PCA was conducted using linear correlation on physicochemical properties like absorption rate, TPSA, MW, clog P, natoms, NOHNH, nON, number of rotatable bonds, and Lipinski's violations (Figure 1a,b).

As seen in Figure 3, most phytoconstituents had similar physicochemical properties in 3D, with the exception of apiin and limonene, which were closer to the antiviral drug remdesivir. Table 6, represents the Bravais-Pearson (linear correlation) coefficients of selected major components in CZ, CT, OV, and PC *versus* remdesivir for physiochemical properties, druglikeness, and bioactivity prediction.

3.8 | Molecular docking studies of major phytoconstituents from CZ, CT, OV, and PC with respect to selected target proteins

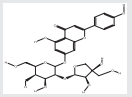
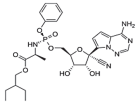
The selected phytoconstituents were docked with N-terminal domain of nucleocapsid protein (PDB ID: 6M3M) and C-terminal domain of nucleocapsid protein (PDB ID: 7C22) of SARS-CoV-2. Three docking programs *viz*. Auto Dock 4.0, AutoDock Vina and iGEMDOCK

TABLE 2 PASS analysis of major phytoconstituents from CZ, CT, OV, and PC *versus* reference drug remdesivir calculated by OSIRIS property explorer

Lipinski's rule of 5 parameters											
S.No.	Phytoconstituent	Molecular structure	% Absorption (>50%)	Topological polar surface area (Å) (TPSA) (160Å)	MW (<500)	c logP (<5)	Heavy atom count (natoms)	Hydrogen bond donors (nOHNH) (≤5)	Hydrogen bond acceptors (nON) (≤10)	Number of rotatable bonds (≤10)	Lipinski's violation
1.	Cinnamaldehyde		103.111	17.07	132.16	2.48	10	0	1	2	0
2.	Cinnamic acid		96.132	37.30	148.16	1.91	11	1	2	2	0
3.	Eugenol		98.837	29.46	164.20	2.10	12	1	2	3	0
4.	Apigenin		77.643	90.89	270.24	2.46	20	3	5	1	0
5.	Catechin		70.923	110.37	290.27	1.37	21	5	6	1	0
6.	Carvacrol		102.021	20.23	150.22	3.81	11	1	1	1	0
7.	Thymol		102.021	20.23	150.22	3.34	11	1	1	1	0
8.	Citral		103.111	17.07	152.24	3.65	11	0	1	4	0
9.	Limonene		109	00.00	136.24	3.62	10	0	0	1	0

(Continues)

TABLE 2 (Continued)

Lipinski's rule of 5 parameters											
S.No.	Phytoconstituent	Molecular structure	% Absorption (>50%)	Topological polar surface area (Å) (TPSA) (160Å)	MW (<500)	c logP (<5)	Heavy atom count (natoms)	Hydrogen bond donors (nOHNH) (≤5)	Hydrogen bond acceptors (nON) (≤10)	Number of rotatable bonds (≤10)	Lipinski's violation
10.	Apiin		30.006	228.97	564.50	−0.74	40	8	14	7	3
11.	Remdesivir		38.758	203.57	602.59	2.82	42	5	14	14	2

Notes: Percentage Absorption was calculated as: % Absorption = 109 − [0.345 × Topological polar surface area]. Topological polar surface area (defined as a sum of surfaces of polar atoms in a molecule). Logarithm of compound partition coefficient between n-octanol and water.

TABLE 3 Calculated ADMET properties of major phytoconstituents from CZ, CT, OV, and PC *versus* reference drug remdesivir using SwissADME

S.N.	Phytoconstituent	Lipophilicity (Consensus Log Po/w)	BBB permeant	P-gp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Log Kp (Skin permeation) (cm/s)
1.	Cinnamaldehyde	1.97	Yes	No	No	No	No	No	No	−5.76
2.	Cinnamic acid	1.79	Yes	No	No	No	Yes	No	No	−5.69
3.	Eugenol	2.25	Yes	No	Yes	No	No	No	No	−5.69
4.	Apigenin	2.11	No	No	Yes	No	No	Yes	Yes	−5.80
5.	Catechin	0.85	No	Yes	No	No	No	No	No	−7.82
6.	Carvacrol	2.82	Yes	No	Yes	No	No	No	No	−4.74
7.	Thymol	2.80	Yes	No	Yes	No	No	No	No	−4.87
8.	Citral	2.71	Yes	No	No	No	No	No	No	−5.08
9.	Limonene	3.37	Yes	No	No	No	Yes	No	No	−3.89
10.	Apiin	−0.72	No	Yes	No	No	No	No	No	−10.00
11.	Remdesivir	1.50	No	Yes	No	No	No	No	Yes	−8.62

TABLE 4 Bioactivity scores of selected phytoconstituents from CZ, CT, OV, and PC *versus* reference drug remdesivir calculated by Molinspiration software

		Bioavtivity score (BAS)					
S.No	Phytoconstituent	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1.	Cinnamaldehyde	−1.09	−0.39	−1.24	−0.96	−0.79	−0.46
2.	Cinnamic acid	−0.74	−0.40	−1.14	−0.47	−0.98	−0.30
3.	Eugenol	−0.86	−0.36	−1.14	−0.78	−1.29	−0.41
4.	Apigenin	−0.07	−0.09	0.18	0.34	−0.25	0.26
5.	Catechin	0.41	0.14	0.09	0.60	0.26	0.47
6.	Carvacrol	−1.02	−0.51	−1.15	−0.70	−1.25	−0.56
7.	Thymol	−1.05	−0.53	−1.29	−0.78	−1.34	−0.57
8.	Citral	−0.86	−0.25	−1.29	−0.42	−0.57	−0.02
9.	Limonene	−0.91	−0.27	−2.01	−0.34	−1.38	−0.21
10.	Apiin	0.18	−0.17	0.09	0.18	0.17	0.42
11.	Remdesivir	0.27	−0.35	0.20	−0.48	0.49	0.38

TABLE 5 Druglikeness and toxicity predictions of major phytoconstituents from CZ, CT, OV, and PC *versus* reference drug remdesivir calculated by OSIRIS property explorer

			Drug-likeness properties				
S.No.	Phytoconstituent	PCID	Drug-likeness	Mutagenic	Tumorigenic	Reproductive effective	Irritant
1.	Cinnamaldehyde	637511	−5.389	High	High	High	High
2.	Cinnamic acid	444539	0.1675	None	None	None	High
4.	Eugenol	3314	−4.6405	High	High	None	High
5.	Apigenin	5280443	0.28194	High	None	None	None
6.	Catechin	9064	0.31525	None	None	None	None
7.	Carvacrol	10364	−2.3359	None	None	None	High
8.	Thymol	6989	−2.3359	High	None	High	None
9.	Citral	638011	−7.3057	Low	High	High	Low
10.	Limonene	22311	−21.855	None	None	None	Low
11.	Apiin	5280746	0.34498	None	None	None	None
12.	Remdesivir	121304016	−21.281	None	High	High	High

predicted the binding energies and dissociation constants (K_d) of selected phytoconstituents with respect to the above protein targets that have been presented in Tables 7 and 8. The prediction of binding sites of the phytoconstituents on the selected target proteins was fairly similar by the three docking softwares (Tables 7 and 8). The common interacting amino acids obtained *via* the three softwares have been written in bold form in Tables 7 and 8. For the sake of reference and comparison, the binding energies and dissociation constants as calculated by AutoDock v4.2.6 have been taken into consideration.

As is evident from Table 7, apigenin displayed the greatest affinity (B.E.−8.11 kcal/mol, K_d1.14 μM) toward SARS-CoV-2 nucleocapsid protein NTD, followed by catechin (B.E. −6.61 kcal/mol, K_d 14.3 μM) and apiin (B.E. −6.10 kcal/mol, K_d 34.0μM) *versus* remdesivir (B.E. −4.61 kcal/mol, K_d 414.94 μM), which showed lesser affinity for nucleocapsid protein than all the three selected phytoconstituents.

With respect to SARS-CoV-2 nucleocapsid protein CTD, the binding efficacies of the top three phytoconstituents decreased in the order apigenin>cinnamic acid>catechin (Table 8) with remdesivir displaying lesser affinity for SARS-CoV-2 nucleocapsid CTD than the above phytoconstituents. The best docking poses of the selected phytoconstituents and remdesivir with respect to the NTD and CTD of SARS-CoV-2 nucleocapsid protein generated by the three docking softwares have been depicted in Tables S1.2 and S1.3.

3.9 | Molecular dynamics simulation

3.9.1 | Stability analysis of complexes by RMSD

Structural variations of the Cα atoms were first computed separately for each time point during the RMSD analysis for MD simulation of

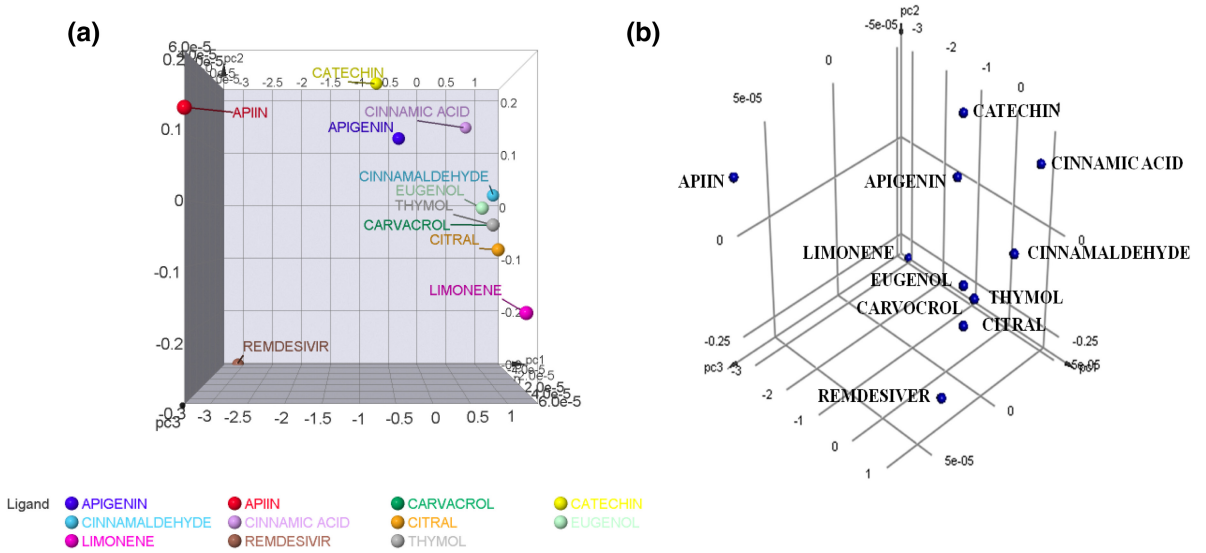


FIGURE 3 Principal component analysis of physicochemical properties of major phytoconstituents from CZ, CT, OV, and PC *versus* reference drug remdesivir (a) Scatter Plot (b) 3D Point Plot.

SARS-CoV-2 nucleocapsid protein NTD (PDB ID: 6M3M)-apigenin complex and SARS-CoV-2 nucleocapsid protein CTD (PDB ID: 7C22)-cinnamic acid complex (Figure 4a,b). The RMSD analysis gave an insight into the rotational displacement of atoms in SARS-CoV-2 NTD and CTD of nucleocapsid protein over the time period of 100 ns. The RMSD analysis of ligands also gave an insight into the stability of the respective ligand with respect to the interacting amino acids of the viral nucleocapsid protein. Figure 4a represents the RMSD graph of SARS-CoV-2 nucleocapsid protein NTD (6M3M) depicting the initial displacement of protein Cα atoms. The equilibrium phase was attained toward the end of simulation with RMSD values between 1.48-5.82Å while the ligand (apigenin) RMSD ranged between 0.95-23.42 Å showing several displacements throughout the 100 ns simulation (Table 9). In MD simulation of 100 ns, apigenin was found to be best stable from 20.6 to 48.5 ns with RMSD values of 8.689-12.622 Å. A detail analysis of ligand fit on protein has been provided in Table 10.

On the other hand, Figure 4b depicts an in-depth analysis of RMSD values of protein Cα atoms of nucleocapsid protein CTD (7C22) showing several time fluctuations over 100 ns MD simulation with RMSD values 1.43-11.72 Å. The ligand (cinnamic acid) position was found to shift from its original position to other positions several times with RMSD values between 0.64-23.24 Å.

3.9.2 | Stability analysis of complexes by RMSF

The RMSF values of Cα atoms of 6M3M and 7C22 were found to range between 0.722-8.52 and 0.84-20.64 Å, respectively, denoting the secondary structural changes in both the proteins (Figure 5a,b). On comparing the RMSF values of both proteins, 6M3M showed lesser structural changes than 7C22. Thus, 7C22 displayed lower stability than 6M3M.In contrast, the RMSF values of 6M3M amino acids that were found to interact with apigenin ranged between 0.764 and 8.76 Å showing stable interaction between apigenin and interacting amino acid in fractions of 100 ns MD simulation. RMSF values of interacting amino acids of 7C22 with cinnamic acid were found to range between 0.95 and 20.78 Å denoting very little stability between ligand and interacting amino acids.

3.9.3 | Protein-ligand contact analysis

Protein-ligand contact analysis histogram of 6M3M revealed B: Arg69 as the best interacting amino acid as it exhibited hydrogen bonds, water bridges, and hydrophobic interactions with apigenin (Figure 6a). Detailed interaction of apigenin with 6M3M at 100 ns with various types of non-covalent interactions *viz*. H-bond, hydrophobic, ionic bond and water bridges have been depicted in histogram (Figure 7a).

On the other hand, A:Thr265, C:Lys257, C:Lys261, and C:Arg262 were found to be the best interacting amino acids in 7C22 with H-bonds, hydrophobic bonds, ionic bonds, and water bridges. Detailed interaction of cinnamic acid with 7C22 over 100 ns with H-bonds, hydrophobic bonds, ionic bonds, and water bridges have been displayed in histogram (Figure 7b).

3.9.4 | Ligand properties

The ligand properties were analyzed with the reference conformation from the first frame during MD simulation of 100 ns. The RMSDs of the ligands apigenin (Figure 8a) and cinnamic acid (Figure 8b) were evaluated with values of 0.094-0.81 and 0.063-0.683 Å, respectively, with reference conformation time $t = 0$. The radius of gyration (rGyr), which allows to assess the compactness

TABLE 6 Bravais-Pearson (linear correlation) coefficient of major phytoconstituents from CZ, CT, OV, and PC *versus* reference drug remdesivir for physicochemical properties

(BRAVAIS- Pearson (correlation of ranks))													
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
% Ab	1		−1	−0.982	0.695	−0.985	−0.958	−0.995	−0.742	−0.9	1	−0.0624	2.71E-05
TPSA	2	−1		0.982	−0.695	0.985	0.958	0.994	0.742	0.9	−1	0.0625	2.71E-05
MW	3	−0.982	0.982		−0.575	1	0.901	0.995	0.836	0.917	−0.992	−0.126	7.59E-09
logP	4	0.695	−0.695	−0.575		−0.586	−0.785	−0.645	−0.222	−0.643	0.657	−0.617	−0.208
natoms	5	−0.985	0.985	1	−0.586		0.907	1	0.826	0.916	−0.994	−0.108	9.52E-04
nOHNH	6	−0.958	0.958	0.901	−0.785	0.907		0.927	0.54	0.825	−0.943	0.273	0.0988
nON	7	−0.995	0.994	0.995	−0.645	1	0.927		0.806	0.914	−1	−0.0327	−0.0198
Rb	8	−0.742	0.742	0.836	−0.222	0.826	0.54	0.806		0.78	−0.777	−0.524	0.156
LV	9	−0.9	0.9	0.917	−0.643	0.916	0.825	0.914	0.78		−0.909	−0.122	0.285
pc1	10	1	−1	−0.992	0.657	−0.994	−0.943	−1	−0.777	−0.909		1.67E-08	2.08E-08
pc2	11	−0.0624	0.0625	−0.126	−0.617	−0.108	0.273	−0.0327	−0.524	−0.122	1.67E-08	–	8.67E-09
pc3	12	2.71E-05	2.71E-05	7.59E-09	−0.208	9.52E-04	0.0988	−0.0198	−0.156	0.285	2.08E-08	8.67E-09	–
(Spearman (correlation of ranks))													
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
% Ab	1		−0.951	−0.797	0.715	−0.884	−0.92	−0.927	−0.323	−0.615	1	−0.417	0.337
TPSA	2	−0.951		0.846	−0.666	0.934	0.97	0.977	0.374	0.687	−0.949	0.467	−0.288
MW	3	−0.797	0.846		−0.371	0.977	0.858	0.87	0.446	0.673	−0.817	0.109	−0.0601
logP	4	0.715	−0.666	−0.371		−0.489	−0.585	−0.677	−0.193	−0.289	0.696	−0.762	0.189
natoms	5	−0.884	0.934	0.977	−0.489		0.927	0.944	0.437	0.688	−0.895	0.23	−0.185
nOHNH	6	−0.92	0.97	0.858	−0.585	0.927		0.92	0.227	0.674	−0.918	0.416	−0.2
nON	7	−0.927	0.977	0.87	−0.677	0.944	0.92		0.486	0.696	−0.925	0.432	−0.313
Rb	8	−0.323	0.374	0.446	−0.193	0.437	0.227	0.486		0.705	−0.334	−0.156	0.0443
LV	9	−0.615	0.687	0.673	−0.289	0.688	0.674	0.696	0.705		−0.614	−0.0552	0.101
pc1	10	1	−0.949	−0.817	0.696	−0.895	−0.918	−0.925	−0.334	−0.614		−0.399	0.314
pc2	11	−0.417	0.467	0.109	−0.762	0.23	0.416	0.432	−0.156	−0.0552	−0.399	–	−0.167
pc3	12	0.337	−0.288	−0.0601	0.189	−0.185	−0.2	−0.313	0.0443	0.101	0.314	−0.167	–

TABLE 7 Binding energies of major phytoconstituents from CZ, CT, OV, and PC with SARS-CoV-2 nucleocapsid protein N-terminal domain (PDB ID: 6M3M) *versus* reference drug remdesivir

		AutoDock V4.2.6			AutoDock Vina			iGEMDOCK V2.1				
S.No.	Phytoconstituent	B. E. (kcal/mol)	K_d (μM)	Interacting amino acids	Affinity	K_d (μM)	Interacting amino acids	Energy	VDW	Hbond	Elec	Interacting amino acids
1.	Cinnamaldehyde	−4.6	428.25	Phe67, Pro68, Arg69, Gln71, Tyr124, Trp133, Val134, Ala135	−5.4	109.04	Trp53, Asn76, Asn127, Ile147, Thr149, Ile158	−60.0158	−53.0158	−7	0	Gly70, Glu137, Leu160, Gln161, Leu162. Pro163, Gln164, Gly165, Thr166,
2.	Cinnamic acid	−5.55	85.51	Lys66, Pro68, Thr92, Arg93, Arg108, Thr167, Leu168, Pro169, Tyr173	−5.7	80.47	Thr50, Trp53, Asn76, Ile147, Asn127, Thr149, Asn155, Ile158	−61.8777	−55.0792	−6.79853	0	Trp53, Asn76, Asn78, Asp83, Gly125, Ala126, Asn127, His146, Ile147,
3.	Eugenol	−5.84	52.52	Pro68, Arg69, Gln70, Gln71, Tyr124, Val134, Trp133, Ala135	−5.5	80.47	Gly70, Thr136, Glu137, Leu160, Gln161, Leu162, Thr166, Leu168, Tyr173	−69.9871	−49.1452	−20.8419	0	Arg69, Gly71, Tyr124, Trp133, Val134, Ala135, Pro168,
4.	Apigenin	−8.11	1.14	Phe67, Pro68, Arg69, Gly70, Gln71, Tyr124, Trp133, Val134, Thr136, Gly138, Ala139	−8.4	1.14	Gly70, Gln71, Thr136, Glu137, Pro163, Gln164, Gln165, Thr166, Leu168, Tyr173	−95.0372	−85.797	−9.24022	0	Trp53, Asn76, Asn78, Ser79, Asp83, Tyr113, Pro123, Tyr124, Gly125, Ala126, Asn127, Ile158,

TABLE 7 (Continued)

S.No.	Phytoconstituent	AutoDock V4.2.6			AutoDock Vina			iGEMDOCK V2.1				
		B. E. (kcal/mol)	K_d (μM)	Interacting amino acids	Affinity	K_d (μM)	Interacting amino acids	Energy	VDW	Hbond	Elec	Interacting amino acids
5.	Catechin	−6.61	14.3	Asn49, Phe67, Pro68, Arg69, Gly70, Gln71, Tyr124, Asn151, Pro152, Ala153, Trp133, Ala135, Thr136	−8.7	1.14	Gly70, Gln71, Gly72, Pro81, Gln84, Thr136, Glu137, Leu162, Pro163, Gly165, Thr166	−97.8386	−63.112	−34.7266	0	Asp64, Arg90, Trp109, Gly125, Ala126, Asn127, Lys128, Asp129, Gly130, Ile131, Ile132, Trp133,
6.	Carvacrol	−5.48	96.48	Phe67, Pro68, Arg69, Gly70, Gln71, Tyr124, Trp133, Val134, Ala135	−5.7	80.47	Leu57, Gly70, Glu137, Leu160, Gln161, Leu162, Thr166, Leu168, Tyr173	−63.6564	−50.6364	−13.02	0	Gly70, Thr136, Glu137, Gln161, Leu162, Pro163, Gln164, Gly165, Thr166,
7.	Thymol	−4.92	247.87	Trp53, Thr116, Gly117, Asp145, Gly148, Asn154, Ala157, Asn155, Ile158	−5.6	85.51	Asn49, Trp53, Asn76, Asn78, Asn127, Ile147, Asn155, Ile158	−59.129	−47.129	−12	0	Asn76, Asn78, Pro123, Tyr124, Gly125, Ala126, Asn127, His146, Ile147
8.	Citral	−4.75	327.39	Glu63, Asp64, Lys66, Pro68, Arg89, Thr92, Thr167, Leu168	−5.2	215.07	Trp53, Asn76, Asn127, Gly148, Thr149, Ala156, Ile158	−50.8053	−47.3053	−3.5	0	Asn78, Asp83, Pro123 Tyr124, Gly125, Ala126, Asn127, His146, Ile147,

(Continues)

TABLE 7 (Continued)

S.No.	Phytoconstituent	AutoDock V4.2.6			AutoDock Vina			iGEMDOCK V2.1				
		B. E. (kcal/mol)	K_d (μM)	Interacting amino acids	Affinity	K_d (μM)	Interacting amino acids	Energy	VDW	Hbond	Elec	Interacting amino acids
9.	Limonene	−4.92	247.04	Thr149, Asn154, Asn155, Ala156, Ala157, Ile158	−5.5	85.51	Leu57, Gly70, Glu137, Leu160, Gln161, Leu162, Thr166, Leu168, Tyr173	−49.8369	−49.8369	0	0	Gly70, Glu137, Thr136, Leu160, Gln161, Leu162, Thr166,
10.	Apiin	−6.10	34.0	Thr50, Ala51, Ser52, Asp64, Lys66, Arg89, Tyr112, Tyr124, Gly125, Ala126, Asn127, Lys128, Ile131, Ile132, Trp133, Val134	−11.0	1.14	Trp53, Asn76, Asn78, Tyr124, Gly125, Asn127, Ile147, Thr149, Asn155, Ala156, Ile158	−116.188	−74.2	−41.9881	0	Thr50, Ala51, Ser52, Glu63, Asp64 Lys66, Asp89, Ala91, Thr92, Arg93, Arg108, Tyr110, Tyr112, Tyr173,
11.	Remdesivir	−4.61	414.94	Asn49, Thr50, Ser52, Lys66, Phe67, Pro68, Arg69, Tyr110, Tyr112, Gly125, Ala126, Asn127, Lys128, Ile131, Trp133, Ala254	−9.7	1.14	Thr55, His60, Arg108, Tyr110, Arg150, Pro152, Ala156, Ala157, Tyr410	−107.519	−79.6085	−27.9101	0	Thr50, Trp53, Gluy63, Asp64, Arg89, Ala91, Thr92, Lys66, Asn127, Ile132, Asn155,

TABLE 8 Binding energies of major phytoconstituents from CZ, CT, OV, and PC with SARS-CoV-2 nucleocapsid protein C-terminal domain (PDB ID: 7C22) *versus* reference drug remdesivir

		AutoDock V4.2.6			AutoDock Vina			iGEMDOCK V2.1				
S.No.	Phytoconstituent	B. E. (kcal/mol)	K_d (μM)	Interacting amino acids	Affinity	K_d (μM)	Interacting amino acids	Energy	VDW	Hbond	Elec	Interacting amino acids
1.	Cinnamaldehyde	−4.68	370.4	Ala254, Lys257, Lys261, Arg262, Thr263, Thr265, Ala267, Tyr268, Lys299, Glu303	−6.3	24.66	Ala267, Gln303, Asn345, Asp348, Gln349, Leu352	−66.5789	−59.5789	−7	0	Lys266, Ala267, Asp297, His300 Gln303, Gln306, Asn345, Asp348, Gln349, Leu352,
2.	Cinnamic acid	−6.29	24.66	Lys257, Lys261, Arg262, Thr263, Thr265, Ala267, Lys299, Pro302, Gln303	−6.5	18.72	Ala267, Asp297, His300, Gln303, Asn345, Asp348, Gln349, Ile351, Leu352, Lys355	−72.1847	−60.7978	−9.62386	−1.76302	Ala267, Asp297, His300, Gln303, Asp348, Leu352, Lys355,
3.	Eugenol	−5.0	215.07	Ala254, Lys257, Arg262, Thr263, Thr265, Ala267, Tyr268, Lys299, His300, Pro302, Gln303	−5.6	85.51	Lys266, Asp297, His300, Gln303, Asp348, Gln349, Ile351, Leu352	−67.884	−55.9385	−11.9455	0	Arg259, Gln260 Arg262, Met317, Trp330, Ala336, Ile337, Lys338
4.	Apigenin	−6.45	18.72	Lys257, Lys261, Thr263, Thr296, Asp297, Tyr298, Lys299, Pro302, Ser310	−8.1	1.14	Lys266, Ala267, Gln294, Asp297, His300, Gln303, Asn345, Asp348, Leu352, Lys355	−98.0032	−87.4404	−10.5628	0	Lys266, Gln294, Asp297, Gln303 Gln306, Asn345, Gln349, Asp348, Ile351, Leu352, Lys355,

(Continues)

TABLE 8 (Continued)

S.No.	Phytoconstituent	AutoDock V4.2.6			AutoDock Vina			iGEMDOCK V2.1				
		B. E. (kcal/mol)	K_d (μM)	Interacting amino acids	Affinity	K_d (μM)	Interacting amino acids	Energy	VDW	Hbond	Elec	Interacting amino acids
5.	Catechin	−6.09	34.29	Thr205, Glu253, Lys256, Arg262, Thr263, Ala264, Thr265, Ala267, Tyr268, Lys299, Pro302, Gln303	−7.4	2.33	Lys266, Thr296, Asp297, Tyr298, Lys299, His300, Asp348, Leu352, Lys355	−92.8237	−63.3254	−29.4983	0	Lys256, Lys257, Pro258, Gln260, Arg262, Gln306, Phe307, Lys338, Leu339, Asp340, Asp343, Gln349
6.	Carvacrol	−4.73	342.16	Ala254, Lys257, Arg262, Thr263, Ala264, Thr265, Tyr268, Lys299, Pro302, Gln303	−6.2	34.0	Lys266, Ala267, Asp297, His300, Gln303, Asp348, Leu352	−60.93	−55.7427	−5.18726	0	Pro258, Arg259, Gln260, Trp330 Ala336, Ile337, Lys338,
7.	Thymol	−4.89	260.75	Lys257, Arg262, Thr263, Ala264, Thr265, Tyr268, Asp297, Tyr298, Lys299, Pro302	−5.8	52.52	Ala254, Lys257, Arg262, Thr263, Thr265, Tyr268, Lys299, Pro302, Gln303	−60.8707	−52.7669	−8.10376	0	Lys266, Ala267, Asp297, His300, Asn345, Asp348, Gln349, Leu352,

TABLE 8 (Continued)

S.No.	Phytoconstituent	AutoDock V4.2.6			AutoDock Vina			iGEMDOCK V2.1				
		B. E. (kcal/mol)	K_d (μM)	Interacting amino acids	Affinity	K_d (μM)	Interacting amino acids	Energy	VDW	Hbond	Elec	Interacting amino acids
8.	Citral	−4.58	442.08	Lys257, Thr263, Thr265, Ala267, Tyr268, Thr296, Asp297, Pro302, Gln303	−5.2	215.07	Gln281, Thr282, Gly335, Ala336,	−51.8508	−46.0249	−5.82587	0	Lys266, Gln294, Asp297, His300, Asp348, Ile351, Leu352,
9.	Limonene	−4.93	244.91	Ala254, Lys257, Arg262, Thr263, Thr265, Ala267, Tyr268, Lys299, Gln303	−6.0	34.0	Lys266, Ala267, Asp297, His300, Gln303, Asn345, Asp348, Leu352	−59.5646	−59.5646	0	0	Lys266, Ala267, Asp297, His300, Gln303, Asp348, Ile351, Leu352
10.	Apiin	−5.41	109.04	Glu253, Ala254, Lys256, Lys257, Lys261, Arg262, Thr263, Asp297, Lys299, Trp301, Pro302	−9.9	1.14	Lys257, Lys261, Thr263, Glu290, Gln294, Thr296, Asp297, Tyr298, Lys299, Trp301, Ala308, Pro309, Ser310, Ala311, Ser316	−130.751	−109.592	−21.1593	0	Lys257, Pro258, Arg259, Gln260, Lys266, Phe307, Trp330, Ala336, Ile337, Lys338, Leu339, Asp340 Asp343

(Continues)

TABLE 8 (Continued)

S.No.	Phytoconstituent	AutoDock V4.2.6			AutoDock Vina			iGEMDOCK V2.1				
		B. E. (kcal/mol)	K_d (μM)	Interacting amino acids	Affinity	K_d (μM)	Interacting amino acids	Energy	VDW	Hbond	Elec	Interacting amino acids
11.	Remdesivir	−5.59	80.47	Lys257, Lys261, Thr263, Glu290, Gln294, Thr296, Asp297, Thr298, Lys299, Trp301, Pro302, Ser310	−9.5	1.14	Lys261, Thr263, Glu290, Gln294, Thr296, Asp297, Lys299, Trp301, Pro302, Ala305, Pro309, Ser310, Ser312	−101.303	−81.4849	−19.8184	0	Lys261, Thr296, Trp301, Pro302, Ala305, Ala308, Pro309, Ala311, Ser312,

fluctuation of a ligand-protein complex was found to have values of 3.56–3.75 Å and 2.76–2.92 Å for apigenin and cinnamic acid, respectively. Intramolecular hydrogen bonds (intraHB) were detected for apigenin in 982 frames whereas for cinnamic acid, no intraHB were detected throughout the 100 ns simulation time. Molecular Surface Area (MolSA) was calculated with 1.4 Å probe radius which is equivalent to a van der Waals surface area and was found to be in the range 236.28–244.26 and 159.01–165.05 $Å^2$ for apigenin and cinnamic acid, respectively. Solvent Accessible Surface Area (SASA) analysis calculates the interaction between a ligand and solvent (water) throughout the 100 ns MD simulation and was found to be in the range of the value of 67.40–456.77 and 21.79–244.48 $Å^2$ for apigenin and cinnamic acid respectively. The Polar Surface Area (PSA) was also evaluated to determine whether solvents could obtain the surface area of the ligands and was found to be in the range 188.8–200.29 and 90.17–96.28 $Å^2$, respectively, for apigenin and cinnamic acid by contributing oxygen and nitrogen atoms.

4 | DISCUSSION

CoVs belonging to the coronaviridae family of enveloped viruses are divided into four genera (α, β, γ, and δ). They are positive-sense single stranded enveloped RNA (ssRNA) viruses with diameter ranging between 60 to 140 nm which can spread from animal to animal, animal to human, and human to human contact. They appear to have multiple spike-like projections on the surface, giving them a crown-like look under the electron microscope, hence the name "coronaviruses" (Trivedi et al., 2021).

Spike (S) protein, membrane (M) protein, envelope (E) protein, and nucleocapsid (N) protein are the four basic structural proteins (Pal & Kerorsa, 2020). The major functions of the coronavirus nucleocapsid (N) protein are interaction and packaging of the viral genome into ribonucleoprotein (RNP) structure (De Haan & Rottier, 2005; Kwarteng et al., 2020; Masters, 2006; Yoshimoto, 2020). Not only this, the N protein has several critical roles to perform throughout the distinct stages of the viral life cycle (McBride et al., 2014) *viz*. viral budding (McBride et al., 2014), viral assembly (De Haan et al., 1998), host cell cycle regulation (Surjit et al., 2005), and viral mRNA replication regulation (Cavanagh, 2004; Van Der Meer et al., 1999). Thus, the N protein could be a suitable target from a pharmacological and immunological perspective owing to the above roles and its high expression during viral infection (Kwarteng et al., 2020). Exploiting N-protein as a target offers opportunities to obstruct and stall coronavirus assembly, protein transcription and genomic replication. As the COVID-19 pandemic rages on, pharmaceutical alternatives are majorly directed toward either novel drug discovery from existing natural products/phytocomponents, or drug repurposing of already known therapeutic entities to reveal their antiviral potential in order to shorten the drug research timeframe (Serafin et al., 2020). To this effect, complementary and alternative medicine therapy includes a number of medicinal plants and their phytoconstituents thereof that might possess antiviral/immunomodulatory activity against

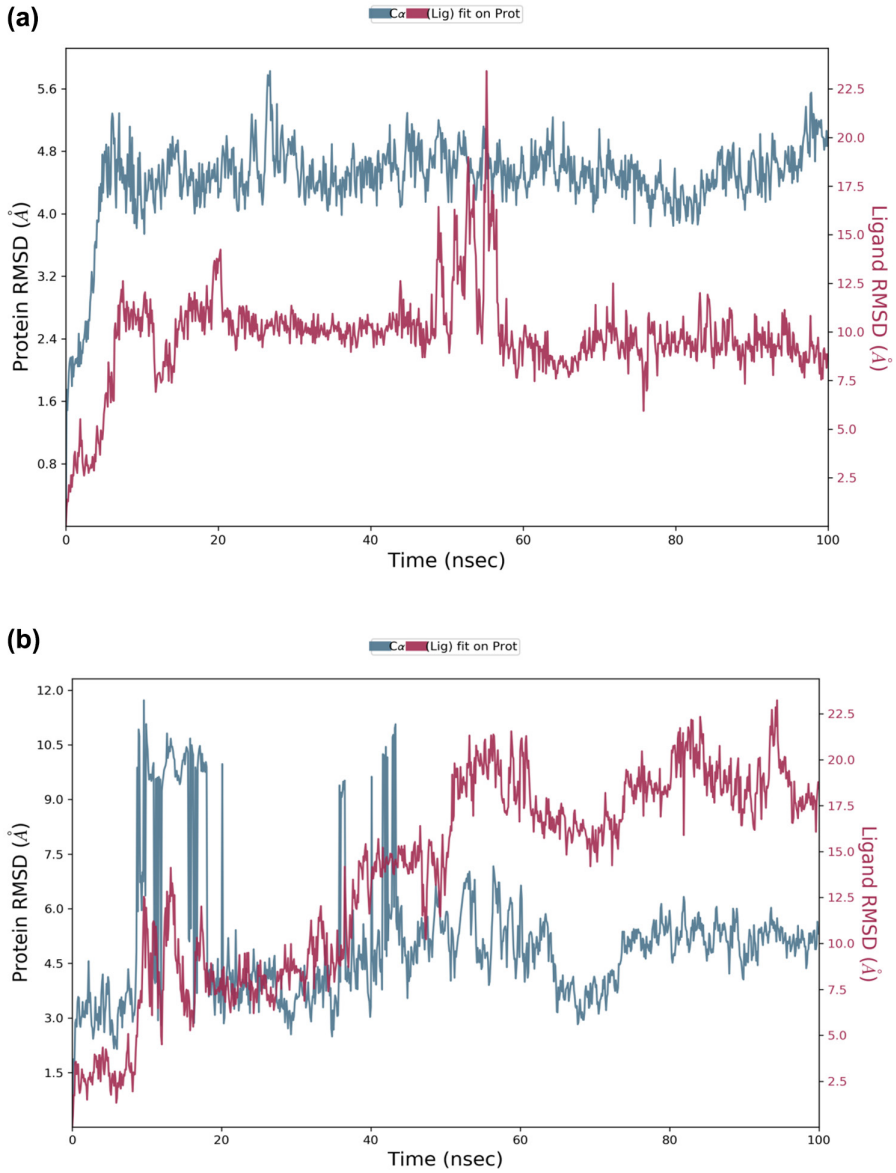


FIGURE 4 RMSD values (Å) of (a) SARS-CoV-2 nucleocapsid protein NTD-apigenin complex and (b) SARS-CoV-2 nucleocapsid protein CTD-cinnamic acid complex *versus* simulation time (100 ns).

TABLE 9 Detailed properties and fluctuations of SARS-CoV-2 nucleocapsid protein NTD (6M3M) and CTD (7C22)

Properties	SARS-CoV-2 nucleocapsid protein NTD (6M3M)	SARS-CoV-2 nucleocapsid protein CTD (7C22)
Protein Cα RMSD	1.48-5.82	1.43-11.72
Ligand write on protein-RMSD	0.95-23.42	0.64-23.24
Protein Cα RMSF	0.722-8.52	0.84-20.64
Ligand RMSF	0.764-8.76	0.95-20.78
Ligand RMSD with reference conformation	0.094-0.81	0.063-0.683
rGyr	3.56-3.75	2.76-2.92
intraHB	982	0
MolSA	236.28-244.26	159.01-165.05
SASA	67.40-456.77	21.79-244-48
PSA	188.8-200.29	90.17-96.28

TABLE 10 Stability of 6M3M-apigenin complex at different time fractions over 100 ns MD simulation

NS	Min	Max	Stability
0–6.3	0.959	8.435	*
6.4–11.5	9.6	12.619	**
11.6–14.3	6.912	9.592	**
14.4–20.5	9.223	14.235	***
20.6–48.5	8.689	12.622	***
48.6–56.7	8.916	23.42	*
56.8–100	5.937	12.495	**

***Most stable.; **Stable.; *Least stable.

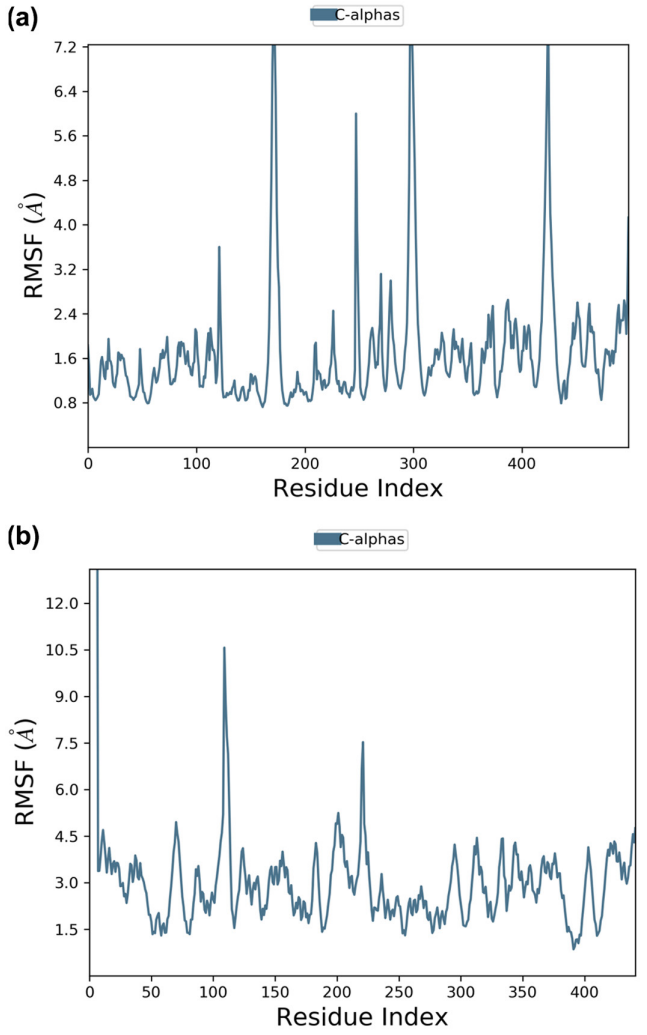


FIGURE 5 RMSF analysis of (a) SARS-CoV-2 nucleocapsid protein NTD-apigenin complex and (b) SARS-CoV-2 nucleocapsid protein CTD-cinnamic acid complex for 100 ns simulation.

SARS-CoV-2 with no serious side effects (Russo et al., 2020; Trivedi et al., 2021). The N-terminal RNA binding of SARS-CoV-2 nucleocapsid protein (PDB ID: 6M3M) has recently been found to be an attractive target for a number of phytoconstituents from *N. sativa* (Siddiqui et al., 2020), *Mentha arvensis*, *Coriandrum sativum*, and *Ocimum sanctum* (Muthumanickam et al., 2021).

The crude extract of cinnamon bark is known to provide relief from several lung conditions, including pneumonia, infectious illness, and malignant pulmonary edema (Lai et al., 2018; Townsend et al., 2013). Since time immemorial, cinnamon bark formulations have been used in the treatment of pyrexia, inflammation, influenza, common cold and cough, dysentery, vomiting and pain (Cheng, 1983). The *in vitro* antiviral effects of *Cinnamon* extract are also known against wild-type SARS infection (Zhuang et al., 2009). Cinnamon essential oil contains about 45%–65% of cinnamaldehyde and cinnamic acid having potent antiviral, antimicrobial, antifungal, anti-atherosclerosis, anti-cancer, anti-inflammatory, anti-ulcer, anti-diabetic, anti-hypertensive, antioxidant and cholesterol and lipid-reducing effects (Connell et al., 2016; Fabros Jr et al., 2018; Rahman et al., 2021). The next important component in cinnamon that contributes to its biological activity is eugenol (Ademiluyi et al., 2020). A number of phytoconstituents from *C. zeylanicum viz.* cinnamyl acetate, caryophyllene oxide, alpha-copaene, camphor, eugenol, cinnamaldehyde, etc., have shown good to moderate binding to SARS-CoV-2 main protease (PDB ID: 6LU7; Mulpuru & Mishra, 2021). Forty-eight compounds from cinnamon have been tested for their binding kinetics to SARS-CoV-2 main protease (PDB ID: 6LU7) and spike receptor domain of SARS-CoV-2 complexed with ACE2 (PDB ID: 6LZG; Prasanth et al., 2020). Another study has reported the *in silico* evaluation of the binding kinetics of major phytoconstituents of essential oils derived from plants belonging to Lamiaceae, Lauraceae, Myrtaceae, Apiaceae, Geraniaceae, and Fabaceae families to the receptor binding domain (RBD) of S1 subunit of SARS-CoV-2 spike glycoprotein (PDB ID: 6M0J; Ghosh, 2020; Kulkarni et al., 2020). The present study is the first of its kind to report the antiviral efficacy of *C. zeylanicum* against NTD and CTD of SARS-CoV-2 nucleocapsid protein. An Ayurvedic formulation/decoction known as "AyushKwath" of which *C. zeylanicum* is a major constituent (Gautam et al., 2020), has been recommended by the Ministry of AYUSH, Government of India, against COVID-19 on account of its immunomodulatory, antiviral, anti-oxidant, anti-inflammatory, anti-platelet, cardioprotective, hepatoprotective and renoprotective properties.

The binding kinetics of *C. tamala*, commonly known as *Laurus nobilis* L. (bay laurel), and its phytoconstituents to the SARS-CoV-2 major protease have been investigated *in silico* (Loizzo et al., 2008; Verma et al., 2020). It has been found recently that lower mortality pertaining to SARS-CoV-2 has been found in forested areas where *C. tamala* grows in abundance, suggesting its antiviral activity (Roviello & Roviello, 2021). The above observations and other studies (Hossain et al., 2020; Orhan & Senol Deniz, 2020; Silveira et al., 2020) prompted testing of *C. tamala* phytoconstituents against NTD and CTD of SARS-CoV-2 nucleocapsid protein in the present study.

Carvacrol ($C_{10}H_{14}O$), a monoterpenoid of the phenolic group [2-methyl-5-(1-methylethyl) phenol] and its isomer thymol is found

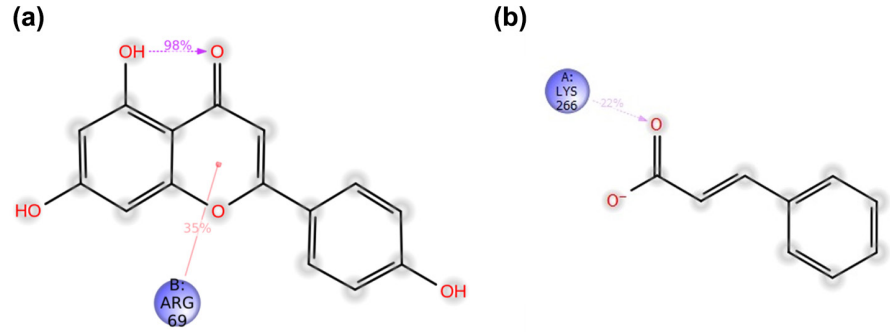


FIGURE 6 Interacting amino acid residues in (a) SARS-CoV-2 nucleocapsid protein NTD-apigenin complex and (b) SARS-CoV-2 nucleocapsid protein CTD-cinnamic acid complex for 100 ns simulation (In case of (a) interactions over 30% of simulation time have been depicted whereas in case of (b) interactions over 20% of simulation time have been shown only).

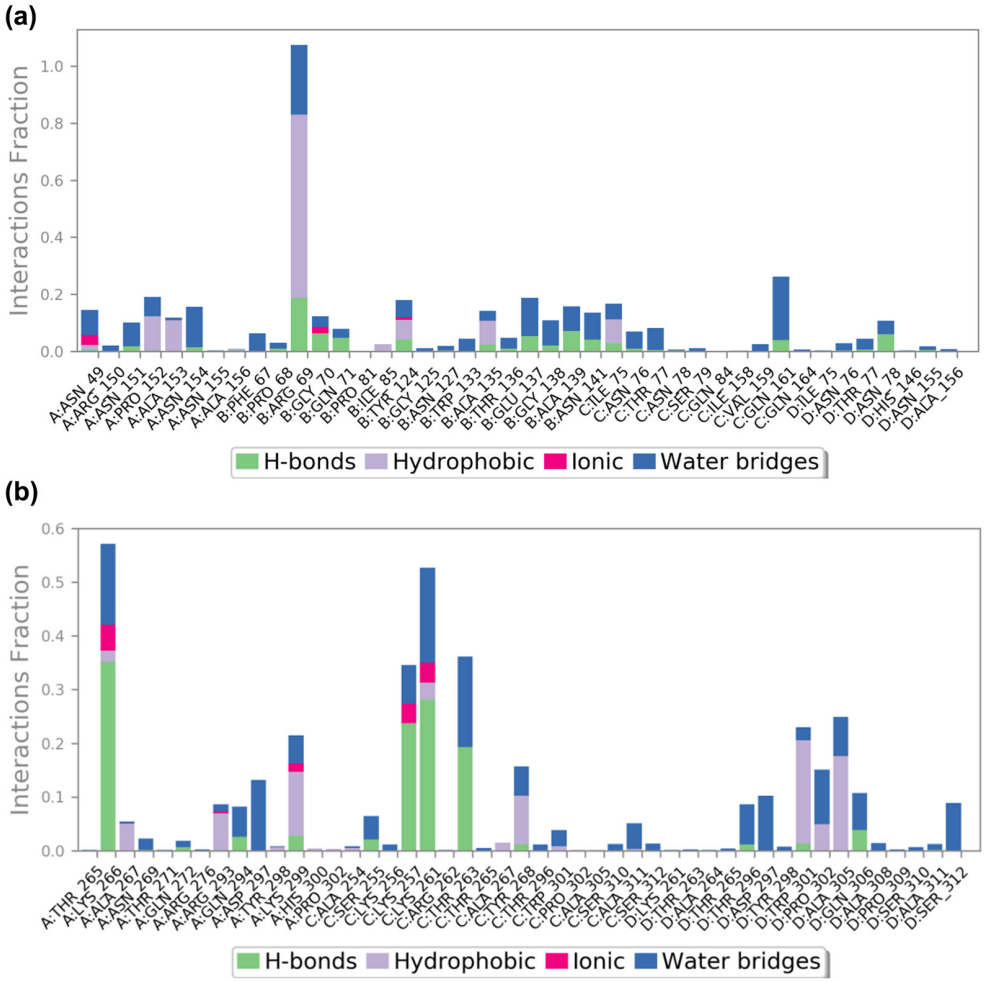


FIGURE 7 Non-covalent interactions in (a) SARS-CoV-2 nucleocapsid protein NTD-apigenin complex and (b) SARS-CoV-2 nucleocapsid protein CTD-cinnamic acid complex for 100 ns simulation.

in essential oils of a variety of fragrant plants including oregano (*Origanum vulgare* L.) and thyme (*Thymus vulgaris* L.). Carvacrol acts as a potential antioxidant and immunomodulatory agent and its derivatives are likely to protect against inflammation, immunological dysfunction, and infection caused by SARS-CoV-2 (Asif et al., 2020; Javed et al., 2020). Although the binding affinity of carvacrol has been reported *in silico* against SARS-CoV-2 main protease (PDB ID: 5R7Y) (Kumar et al., 2020) and S1 subunit of SARS-CoV-2 S protein (Asif et al., 2020; Kulkarni et al., 2020), its binding to NTD and CTD of SARS-CoV-2 nucleocapsid protein has still not been investigated. This has been the criterion for evaluating the anti-SARSCoV-2 efficacy of carvacrol and thymol from *O. vulgare* in the present study.

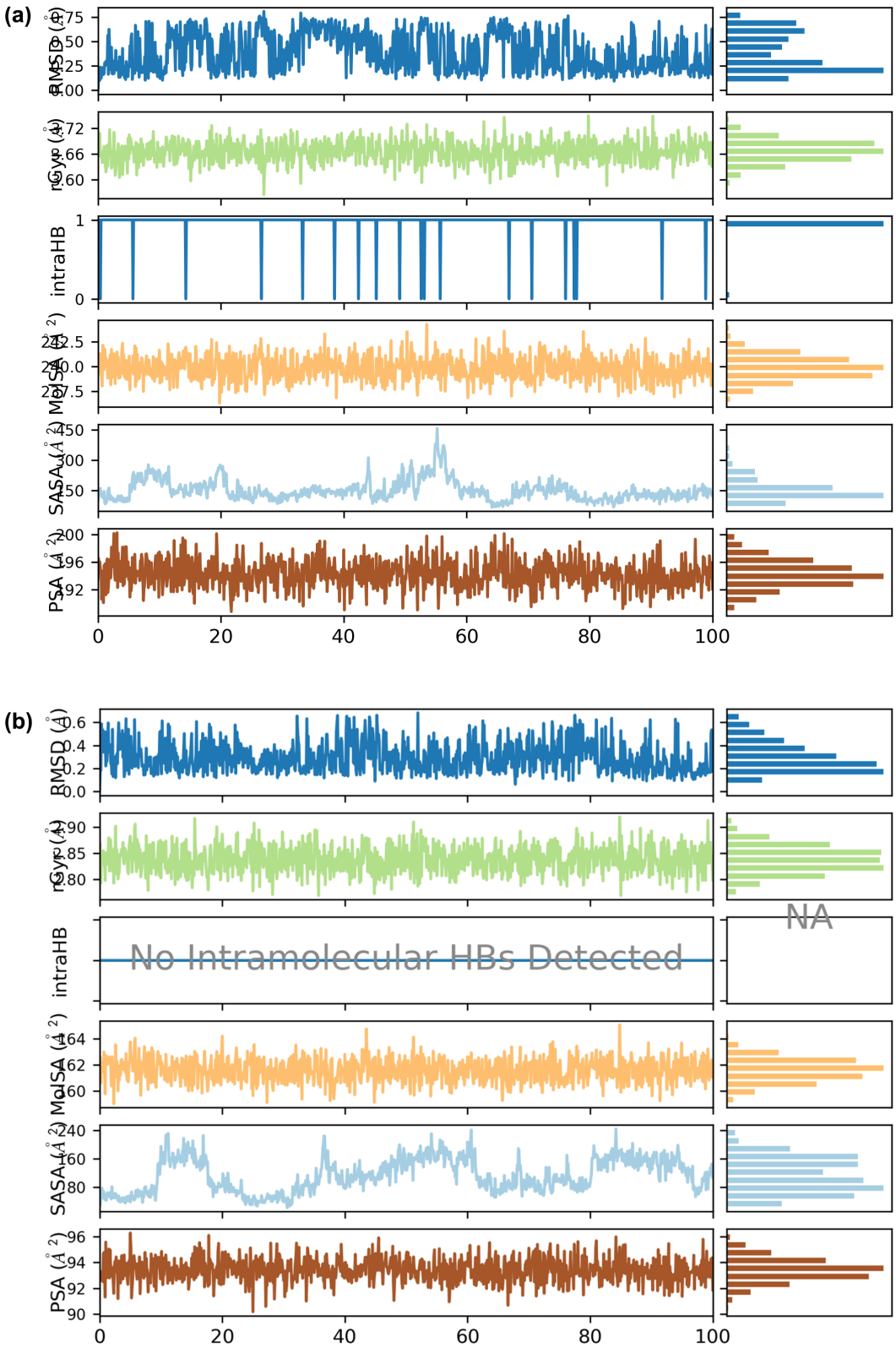


FIGURE 8 Ligand properties demonstrated for (a) Apigenin and (b) Cinnamic acid by RMSD (Blue Line), rGyr (Green Line), MolSA (Orange line), SASA (Cyan blue line), and PSA (Brown line).

An *in vivo* investigation has investigated the effect of carvacrol in mice with lung emphysema induced by elastase (Games et al., 2016). Findings revealed that carvacrol administration reduced alveolar expansion, macrophages infiltration and levels of IL-1β, IL-6, IL-8, and IL-17 in the bronchoalveolar lavage fluid. However, compared to the disease control group, the carvacrol-treated mice had significantly

less lung inflammation and emphysema. Furthermore, as previously stated, carvacrol has antiviral action against various viruses, including HSV-1, acyclovir-resistant herpes simplex virus type 1, human respiratory syncytial virus (HRSV), and human rotavirus (RV; Kamalabadi et al., 2018; Sharifi-Rad et al., 2017).

Moreover, carvacrol, cinnamaldehyde, and thymol have been shown to inhibit S1 subunit of S glycoprotein and cinnamaldehyde has been observed to exhibit better binding kinetics when compared to others (Kulkarni et al., 2020). Cinnamaldehyde has also been found to have a low affinity for SARS-CoV-2 and SARS-CoV RNA-dependent RNA polymerases (RdRps; Elfiky, 2021). On the basis of the above two studies, it can be proposed that cinnamaldehyde has the ability to block SARS-CoV-2 attachment which can be verified using *in vitro* and *in vivo* experimental studies in future. Cinnamaldehyde has been studied in animal models for its protective impact in lowering lung wet/dry ratio and pulmonary edema. Cinnamaldehyde has been found to inhibit neutrophils, macrophages, and total cell number in bronchoalveolar lava. The levels of inflammatory cytokines including TNF-α, IL-6, IL-13, and IL-1β were found to be decreased in the presence of cinnamaldehyde (Huang & Wang, 2017). These findings point toward a possible preventive therapeutic impact of cinnamaldehyde in COVID-19, but to establish its efficacy, detailed *in vitro* and *in vivo* studies need to be carried out.

Similarly, eugenol has been found to have antiviral effects against HSV-1 and HSV-2 (Benencia & Courreges, 2000) and its anti-inflammatory action against lipopolysaccharide-(LPS) induced acute lung damage, restriction of leukocyte recruitment, and down-regulation of pro-inflammatory cytokines IL-6 and TNF-α expression (Barboza et al., 2018).

Apigenin (Khalil & Tazeddinova, 2020), a flavonoid from *P. crispum*, has been shown to block SARS-CoV 3CLpro proteolytic activity. Apigenin intake, whether through a normal diet or supplements, may be useful for chronically infected diseases such as COVID-19 due to its antiviral efficacy, which is thought to be directly linked to suppressing the activity of SARS-CoV 3CLpro (Jo et al., 2019; Khalil & Tazeddinova, 2020). In another *in silico* study, apigenin has shown a B.E. of −7.58 kcal/mol toward SARS-CoV-2 main protease (Mishra et al., 2021; Vijayakumar et al., 2020). Also, apigenin has been shown to be active against foot-and-mouth disease virus (FMDV; Qian et al., 2015) and enterovirus-71 infection (Zhang, et al., 2014). Apiin (Kuete, 2017) has also been recently evaluated for its action against SARS-CoV-2 and has been found to be a potent suppressor of viral main protease by using molecular docking analysis (Adem et al., 2020).

As stated above, though carvacrol, cinnamaldehyde, eugenol, thymol, apigenin, and apiin have been tested *in silico* against a number of SARC-CoV-2 protein targets *viz*. spike (S) protein, main protease (3CLpro), RNA dependent RNA polymerase as well as human ACE2 proteins, none of them have been tested for their interaction with NTD and CTD of SARS-CoV-2 nucleocapsid protein.

A number of recently done studies have focused on the evaluation of binding kinetics of natural products with SARS-CoV-2 proteins *viz*. Verma et al. (2020), Dandapat et al. (2014), Kim (2021), Ao et al. (2021), Jan et al. (2021), Sa-Ngiamsuntorn et al. (2021), etc. Table 11 provides an updated account of the most current literature available in this area.

Three docking softwares *viz*. AutoDock v4.2.6, AutoDock Vina and iGEMDOCK v2.1 were used to analyze and compare docking results of the ten phytoconstituents with NTD and CTD of SARS-CoV-2 nucleocapsid protein. As mentioned earlier in Section 3.8, the binding sites of the phytoconstituents on the viral target protein as well as the interacting amino acids were predicted to be almost the same by the three molecular docking softwares with minor differences (Tables 7 and 8). However, it must be borne in mind that these are just prediction-based softwares and the findings must be validated *in vitro* and *in vivo*.

The present study aimed to examine the druglikeness, pharmacokinetics, bioactivity scores, and binding interactions of 10 major phytoconstituents from four medicinally/nutritionally important plants *viz*. *C. zeylanicum*, *C. tamala*, *P. crispum* and *O. vulgaris* (Table 1), for their various therapeutic properties against the NTD and CTD of nucleocapsid protein of SARS-CoV-2 for lead identification, lead optimization, and drug discovery using *in silico* computational approach. MD simulation was also performed to unravel the dynamic behavior of SARS-CoV-2 nucleocapsid proteins after complexation with the selected phytoconstituents (apigenin and cinnamic acid).

All phytoconstituents except apiin were observed to follow Lipinski's rule-of-five *versus* remdesivir that exhibited two violations of Lipinski's rule. All phytocomponents except apiin, and reference drug remdesivir exhibited lipophilic character and good absorption across cell membranes. Except apigenin, catechin, apiin, and remdesivir, all phytoconstituents exhibited BBB permeability; none of them were found to be P-gp substrates except catechin, apiin, and remdesivir, while all of them including remdesivir exhibited negligible skin permeability. In terms of binding to GPCR, kinases, nuclear receptors, proteins, and enzymes, the majority of phytoconstituents had positive values. Most of the phytoconstituents exhibited good to moderate druglikeness potential whereas catechin and apiin were found to exhibit adverse effects. Apiin and limonene were found to fall closer to remdesivir in 3D projection of chemical space. Molecular docking results revealed that binding affinity of the top three phytoconstituents to SARS-CoV-2 nucleocapsid NTD decreased in the order apigenin>catechin>apiin while for SARS-CoV-2 nucleocapsid CTD, the binding affinity of the top three phytoconstituents decreased in the order apigenin>cinnamic acid>catechin. Remdesivir displayed lesser affinity to both NTD and CTD of SARS-CoV-2 nucleocapsid protein than any of the above mentioned phytoconstituents. MD simulation results revealed that SARS-CoV-2 nucleocapsid protein NTD-apigenin complex had greater stability than SARS-CoV-2 nucleocapsid protein NTD-cinnamic acid complex. Hence, apigenin, catechin, apiin, and cinnamic acid might prove as effective prophylactic and therapeutic agents against SARS-CoV-2 if investigated further *in vitro* and *in vivo*.

TABLE 11 An update on recent work done on SARS-CoV-2

S.No.	Title	Citation	Work summary
1.	Virtual screening of phytoconstituents from miracle herb *Nigella sativa* targeting nucleocapsid protein and papain-like protease of SARS-CoV-2 for COVID-19 treatment	Siddiqui et al. (2020)	Ten phytocomponents from *N. sativa* showed best binding affinity against two viral proteins *viz*. N-terminal RNA binding domain (NRBD; PDB ID: 6M3M) of nucleocapsid protein and papain-like protease (PLpro; PDB ID: 6W9C) of SARS-CoV-2. PASS analyses of all phytocomponents using Lipinski's Rule of five showed promising results. Further, drug likeness and toxicity exhibited the feasibility of phytocomponents as drug candidates with no predicted toxicity. Molecular dynamics simulation study of NRBD of SARS-CoV-2 nucleocapsid protein-alpha-spinasterol complex and PLpro cycloeucalenol complex displayed strong stability at 300 K.
2.	Exploring nature's bounty: identification of *Withania somnifera* as a promising source of therapeutic agents against COVID-19 by virtual screening and *in silico* evaluation	Srivastava et al. (2020)	WS phytoconstituents exhibited potent binding to human ACE2 receptor, SAR-CoV and SARS-CoV-2 spike glycoproteins as well as the two main SARS-CoV-2 proteases. Most of the phytoconstituents displayed good absorption and transport kinetics and were also found to display no associated mutagenic or adverse effect(s).Molecular dynamics simulation analyses of SARS-CoV-2 spike protein and papain-like protease with anolides A and B, respectively, displayed a stability profile at 300 K.
3.	Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods	Wu et al. (2020)	Systematic analysis of all the proteins encoded by SARS-CoV-2 genes, comparison with proteins from other coronaviruses, prediction of their structures, and building of 19 structures homology modeling. Structure and screening results of important targets such as 3-chymotrypsin-like protease (3CLpro), Spike, RNA-dependent RNA polymerase (RdRp), and papain like protease (PLpro) were discussed. The molecular docking results showed that ritonavir's possible target is Nsp3c or E-channel. Lopinavir's possible target(s) are Nsp3b, Nsp3c, helicase, NRBD or E-channel.
4.	Research and development on therapeutic agents and vaccines for COVID-19 and related human coronavirus diseases	Liu et al. (2020)	The drug-repurposing effort documented herein focused primarily on agents known to be effective against other RNA viruses including SARS-CoV and MERS-CoV. The information included in this report provides a strong intellectual groundwork for the ongoing development of therapeutic agents and vaccines.
5.	Anti-SARS-CoV natural products with the potential to inhibit SARS-CoV-2 (COVID-19)	Verma et al. (2020)	The review collates the information regarding the potential of plants and natural products to inhibit coronavirus associated infection in humans and to highlight known drugs which may have potential activity against SARS-CoV-2. Based on current literature, 83 compounds were identified with the potential to inhibit SARS-CoV-2. The most prominent selectivity was found for the alkaloid lycorine, the lignan savinin, and the abietane terpenoid, 8-beta-hydroxyabieta-9(11),13-dien-12-one.
6.	Potential role of medicinal plants and their constituents in the mitigation of SARS-CoV-2: identifying related therapeutic targets using network pharmacology and molecular docking analyses	Shawky et al. (2020)	A database comprising of more than 16 500 compounds was screened against the three SARS-CoV-2 target proteins 3CLpro, PLpro, and RdRp. Several phytoconstituents identified were found to inhibit SARS-CoV-2 activity through inhibition of virus replication. A network pharmacology analysis was performed for all the phytoconstituents which revealed that several compounds possessed multiple targets including cytokine–cytokine receptor interaction, TNF signaling pathway, Toll-like receptor signaling pathway, NF-kappa B signaling pathway, and JAK-STAT3 signaling pathway. These results suggest a potential role of medicinal plants in the management of the current SARS-CoV-2 infection. Meanwhile, the medicinal plants *Glycyrrhiza glabra*, *Hibiscus sabdariffa*, *Cichorium intybus*, *Chrysanthemum coronarium*, *Nigella sativa*, *Anastatica hierochuntica*, *Euphorbia species*, *Psidium guajava* and *Epilobium hirsutum*, were found to be enriched in compounds such as quercetin, ursolic acid, kaempferol, isorhamnetin, luteolin, glycerrhizin, and apigenin.
7.	Flavonol morin targets host ACE2, IMP-α, PARP-1 and viral proteins of SARS-CoV-2, SARS-CoV and MERS-CoV critical for infection and survival: a computational analysis	Gupta et al. (2021)	Flavonol morin displayed potent binding to spike glycoprotein, main protease 3CLpro and papain-like protease PLpro of SARS-CoV-2, SARS-CoV, and MERS-CoV and significant binding to three viral-specific host proteins *viz*. human ACE2, importin-α, and poly (ADP-ribose) polymerase (PARP)-1, further lending support to its antiviral efficacy. Morin displayed potent binding to pro-inflammatory cytokines IL-6, 8 and 10 and strong stability at 300k in Molecular simulation (MD) simulation.

TABLE 11 (Continued)

S.No.	Title	Citation	Work summary
8.	Prophylactic and therapeutic potential of selected immunomodulatory agents from Ayurveda against coronaviruses amidst the current formidable scenario: An *in silico* analysis	Trivedi et al. (2021)	Fifteen phytoconstituents from medicinal plants of Ayurveda against coronaviruses exhibited rapid GI absorption and bioavailability *versus* reference drug Chloroquine. Phytoconstituents displayed significant binding kinetics against SARS-CoV-2 spike protein-human ACE2 complex,ACE2 and main and papain-like proteases than chloroquine. SAR analysis revealed that isomeldenin, tinosporaside, EGCG and ellagic acid bind to viral spike glycoproteins *via* H-bond, Pi-Pi, Pi-sigma and Pi-alkyl type interactions.
9.	Exploration of natural compounds with anti-SARS-CoV-2 activity *via* inhibition of SARS-CoV-2 M^{pro}	Bharadwaj et al. (2021)	Potential compounds *viz.* 2,3-Dihydroamentoflavone, podocarpusflavon-B, rutin and quercimeritrin 6″-O-L-arabinopyranoside exhibited substantial docking energy > −12 kcal/mol and molecular contacts with essential residues including catalytic dyad (His41 and Cys145) and substrate binding residues in the active pocket of SARS-CoV-2 3CLpro (PDB ID:6LU7) against N3 inhibitor.
10.	Natural product remedies for COVID-19: A focus on safety	Omokhua-Uyi and Van Staden (2021)	The review discusses possible natural product remedies and some major conventional treatment options used to manage the infection and safety concerns on the use of unproven or unapproved health products against COVID-19. It suggests that development of safe and effective therapeutics from natural products for the treatment of COVID-19 could be a potential option.
11.	Herbal medicine use for the management of COVID-19: A review article	Demeke et al. (2021)	Herbal medicine can interfere with COVID-19 pathogenesis by inhibiting SARS-CoV-2 replication and entry to host cells. Some of the antiviral medicinal plant species viz. *orange* (*Citrus sinensis*), *Allium sativum*, *Allium cepa*, *Mentha piperita*, and *Nigella sativa* can introduce effective adjuvant components in COVID-19 management.
12.	Chinese herbal medicine: Fighting SARS-CoV-2 infection on all fronts	Wang and Yang (2021)	Chinese herbal medicines have been recognized as very promising anti-SARS-CoV-2 agents, including active ingredients (quercetagetin, osajin, tetrandrine, proscillaridin A, and dihydromyricetin), monomer preparations (xiyanping injection, matrine-sodium chloride injection, diammonium glycyrrhizinate enteric-coated capsules, and sodium aescinate injection), crude extracts (*Scutellariae* radix extract and garlic essential oil), and formulas (QingfeiPaidu decoction, Lianhuaqingwen capsules, and PudilanXiaoyan oral liquid). All these agents showed potential activity against SARS-CoV-2 and have attracted significant attention due to their activities both *in vitro* and in clinical practice.
13.	Use of medicinal plants for COVID-19 prevention and respiratory symptom treatment during the pandemic in Cusco, Peru: A cross-sectional survey	Villena-Tejada et al. (2021)	A web-based cross-sectional study was conducted on 1747 people (20- to 70-year-old). Out of 1747, 80.2% reported that they used medicinal plants as preventives, while 71% reported that they used them to treat respiratory symptoms. At least, 24% of respondents used medicinal plants when presenting with two or more respiratory symptoms, while at least 11% used plants for malaise. For treatment or prevention, the multivariate analysis showed that most respondents used eucalyptus ($p < .001$ for both), ginger ($p < .022$ for both), spiked pepper ($p < .003$ for both), garlic ($p = .023$ for prevention), and chamomile ($p = .011$ for treatment).
14.	Indian medicinal plants and formulations and their potential against COVID-19–preclinical and clinical research	Ahmad et al. (2021)	This communication reviews the AYUSH recommended formulations and their ingredients, routinely used medicinal plants and formulations by Indian population as well as other promising Indian medicinal plants, which can be tested against COVID-19. Special emphasis has been placed on Indian medicinal plants reported for antiviral, immunomodulatory and anti-allergic/anti-inflammatory activities and they are categorized for prioritization in research on the basis of earlier reports. The traditional AYUSH medicines currently under clinical trials against COVID-19 are also discussed.

(Continues)

TABLE 11 (Continued)

S.No.	Title	Citation	Work summary
15.	Therapeutic potential of medicinal plants against COVID-19: The role of antiviral medicinal metabolites	Khan et al. (2021)	Glycyrrhizin from the roots of *Glycyrrhiza glabra* has shown promising potential against the previously epidemic coronavirus, SARS-CoV. Other important plants such as *Artemisia annua*, *Isatis indigotica*, *Lindera aggregate*, *Pelargonium sidoides*, and *Glychirrhiza* sp. have been employed against SARS-CoV. Active ingredients (e.g. emodin, reserpine, aescin, myricetin, scutellarin, apigenin, luteolin, and betulonic acid) have shown promising results against the coronaviruses. Phytochemicals have demonstrated activity against the coronaviruses through mechanisms such as viral entry inhibition, inhibition of replication enzymes and virus release blockage.
16.	Therapeutic opportunities of edible antiviral plants for COVID-19	Patel et al. (2021)	This article attempts to comprehend the information about the edible medicinal plant materials with potential antiviral activity specifically against RNA viruses which additionally possess property to improve immunity along with respiration and exhibit anti-inflammatory properties for the prevention and treatment of the disease.
17.	Phytoconstituents from *Moringa oleifera* fruits target ACE2 and open spike glycoprotein to combat SARS-CoV-2: An integrative phytochemical and computational approach	Siddiqui et al. (2022)	GC-MS analysis of ethanolic extract of *Moringa oleifera* fruits (MOFs) has unveiled the presence of 33 phytocomponents. Eighteen phytocomponents exhibited good binding affinity toward human ACE2 receptor, and 13 phytocomponents had a high affinity with spike glycoprotein through the Maestro software. This finding suggests that the top 11 hits (Docking score ≥ −3.0 kcal/mol) could inhibit SARS-CoV-2 propagation.
18.	Advances in the development of therapeutic strategies against COVID-19 and perspectives in the drug design for emerging SARS-CoV-2 variants	Yin et al. (2022)	The study systematically summarized two main therapeutic strategies against COVID-19, namely drugs targeting the SARS-CoV-2 life cycle and SARS-CoV-2-induced inflammation in host cells. These strategies are implemented by repurposing drugs and exploring potential targets.

5 | CONCLUSION

In conclusion, on the basis of previously done *in silico* studies and the present study, apigenin, catechin, apiin, and cinnamic acid seem to have a potential in the treatment of COVID-19 but further studies are needed to validate the anti-SARS-CoV-2 efficacies of these phytoconstituents *in vitro* and *in vivo* using relevant cell culture and animal models. This would prove to be valuable in establishing the antiviral efficacy of cinnamon, bay leaf, oregano, and parsley against SARS-CoV-2 as a source of antiviral nutraceuticals.

AUTHOR CONTRIBUTIONS

Ishrat Husain: Data curation; investigation; methodology. **Rumana Ahmad:** Conceptualization; data curation; formal analysis; investigation; methodology; software; supervision; validation; visualization; writing – original draft; writing – review and editing. **Sahabjada Siddiqui:** Data curation; formal analysis; investigation; methodology; software; validation. **Anu Chandra:** Formal analysis; project administration; supervision. **Aparna Misra:** Formal analysis; project administration; supervision. **Aditi Srivastava:** Data curation; investigation; methodology. **Tanveer Ahamad:** Investigation; methodology; validation. **Mohd. Faheem Khan:** Investigation; methodology; validation. **Zeba Siddiqi:** Formal analysis; investigation; supervision. **Anchal Trivedi:** Data curation; investigation; methodology. **Shivbrat Upadhyay:** Data curation; investigation; methodology. **Anamika Gupta:** Data curation; investigation; methodology. **Anand N. Srivastava:** Formal analysis; project administration; supervision. **Bilal Ahmad:** Validation. **Sudhir Mehrotra:** Formal analysis; project administration; supervision. **Surya Kant:** Formal analysis; supervision; validation. **Abbas Ali Mahdi:** Formal analysis; supervision. **Farzana Mahdi:** Formal analysis; project administration; resources.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge Dr. Meraj Ahmad, Professor, Dept. of Sociology, University of Lucknow, Lucknow, India, for being the inspiration and motivation behind the present work in view of his exceptional work and contribution in the area of social sciences, social work, humanities, and public health.

FUNDING INFORMATION

The present study did not receive any extramural or intramural grant from funding agencies in the public, commercial, or not-for-profit sectors

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

Data openly available in a public repository that issues datasets with DOIs.

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SUPPORTING INFORMATION

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How to cite this article: Husain, I., Ahmad, R., Siddiqui, S., Chandra, A., Misra, A., Srivastava, A., Ahamad, T., Khan, M. F., Siddiqi, Z., Trivedi, A., Upadhyay, S., Gupta, A., Srivastava, A. N., Ahmad, B., Mehrotra, S., Kant, S., Mahdi, A. A., & Mahdi, F. (2022). Structural interactions of phytoconstituent(s) from cinnamon, bay leaf, oregano, and parsley with SARS-CoV-2 nucleocapsid protein: A comparative assessment for development of potential antiviral nutraceuticals. *Journal of Food Biochemistry*, 00, e14262. https://doi.org/10.1111/jfbc.14262