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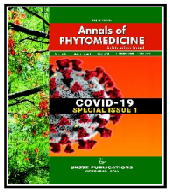

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Potential herbs as therapeutic agents for COVID-19: *In silico* studies

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Abstract

Across 218 countries, since March 2020, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been a reason for concern. Doctors as well as researchers, stand together to find a treatment for this pandemic. The virus attaches to the host cells *via* transmembrane spike glycoprotein. The glycoprotein has affinity for human angiotensin-converting enzyme 2 and is dimeric. Thus, the virus attaches to the ACE receptors through the receptor-binding domain (SARS-CoV-2 RBD Spro). Further, the main protease (Mpro), a chymotrypsin-like protease (3CLpro), plays a critical role in post-translational modifications, thereby affecting viral survival. Thus, targeting these viral markers can not only block the fusion with host cells, but also affect replication of the virus. Ancient civilizations have been using plants, herbs as well as spices for their medicinal values as antiviral, anti-inflammatory, antipyretic, antimicrobial and many more. The rich array of phytochemicals in these spices endows them with these beneficial properties, and hence they are largely being looked as agents for therapeutic use. However, the journey from laboratory for drug development is a time-consuming process as it starts from trying to identify the major therapeutic component to its pre-clinical studies, clinical and then its marketing as a drug. In the current pandemic where loss of human life has been in millions, a faster and more efficient modality like *in silico* studies can help escalate this search for a therapy thereby saving mankind. This study is a comprehensive review on results of *in silico* approaches conducted in near future in an attempt to evolve an ideal therapeutic candidate for ending the pandemic. Results of research conducted on phytochemicals from medicinal and aromatic plants as potential therapeutic candidates using tools of bioinformatics and computational modelling are hereby discussed.

1. Introduction

Till December 2021, SARS-CoV-2, the causal agent of COVID-19 has inflicted more than 27.8 crores people worldwide, leading to the fatality of more than 53.9 lakhs people globally. WHO has declared COVID-19 as the Public Health Emergency of International Concern (PHEIC) signifying the fact that this pandemic seeks harmonized comprehensive retort in all therapeutic facets (Gowrishankar *et al.*, 2021). This pandemic hasled to a global socio-economic catastrophe. Till today, there are no active therapeutic treatments, and the planning for vaccine distribution still embodies a major contest for developing countries, contributed by the specific requirements of vaccine transportation and storage (Nadia *et al.*, 2021). Presently, the different vaccines developed include the one developed by Pfizer (New York, NY, USA), University of Oxford and Astra Zeneca's AZD1222; BNT162, BioNTech (Mainz, Germany), and mRNA-1273, developed by Moderna Inc. (Cambridge, MA, USA).

Recently established biotechnological tools as monoclonal antibodies and recombinant proteins are also under investigation as therapeutic agents (Jahanshahlu and Rezaei, 2020). As per Twomey *et al.* (2020), the most appropriate approach to combat COVID-19 is to redesign the available pharmacological modalities. This is an effective strategy that saves time, money and lives and investigators throughout the world are at work towards the development of effective therapeutic strategies (Sankar *et al.*, 2021). According to the study of Benarba and Pandiella (2020), many of the botanical plants found in Indian subcontinent have been found to exhibit antiviral and anti-inflammatory properties. Some of these phytocompounds have been investigated to be effective against COVID-19 as well (Murugan *et al.*, 2020).

The main reason for disorders related to SARS-CoV2 leading to COVID-19 being declared a pandemic is its contagious nature with mortality rates being high (Coronavirus Update, https://www.worldometers.info/coronavirus/, 2021). With treatment modalities being limited even 1.5 years into the pandemic, the need of the hour is to try to find out tactics that are effective for the viral outbreak. Drug discovery involves handling and interpretation of huge and complex data and so the journey from the bench to the market is a long-drawn process of 12-15 years, besides being an expensive one. The need for elucidating newer therapeutic options which are a reliable and effective, has led to the application of databases to identify active pharmaceutical components. This fast-track modality needs to be adopted so as to hasten the process of identifying possible remedies which can be used as targets to proceed to the clinic and finally reach the customers at large. Here comes the utility of computational modelling for ligand-receptor

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interactions, for drug discovery and development. The use of these tools has been employed over the years to hasten and augment the pharmacologic discovery progression (Yang *et al.*, 2012).

Drug designing owes its origin to the understanding of pharmacokinetics and pharmacodynamics of a molecule being affected by its structure. One of the earliest studies on establishing this relationship was put forward by Meyer (1899) and Overton (1901), who suggested the Lipoid theory to explain cellular depression, which related depressant action with lipid solubility. Hansch (1964, 1972, 2002) made pioneering efforts in using mathematics and statistics to draw quantitative relations between structure and activity. This lead to the birth of the field of quantitative structure-activity relationships (QSARs), progressing to the use of computer graphics for molecular modelling. In the last few decades, computer scientists have evolved as major contributors towards drug discovery and pharmacology. In current times, chemistry-biology-informatics have evolved and contributed to enriching the field of pharmacology. Thus, computational pharmacology or *in silico* methods have not only improved the drug discovery procedure and put it on a fast-track saving both time and money too (Swaan and Ekins, 2005).

The targets on the causative agent can be any of the biomolecules on or within the agent like the nuclear material as DNA or RNA or an array of proteins comprising enzymes, receptors or even transporters. Such targets need further validation, either at cellular or molecular levels so as to delineate their relevance to the known disease with sufficient level of 'confidence' (Taft *et al*., 2008). Next the validation of the target is facilitated through identification of modulators, inhibitors, or antagonists and this process is termed lead identification. This is mediated through designing and development of suitable assay procedures to complete the study for target identification and its validation. With the target validated, complementary molecules, which could be natural or synthetic are identified as per their structure, with the potential of binding to the target, thereby completing the process of lead identification. Progressing further the lead molecule is optimized**,** through studies as physiochemical characterization. Techniques as quantitative structure activity relationships (QSARs) and high throughput screening (HTS) coupled with combinatorial chemistry lead to generation of multiple new chemical entities (NCEs). These processes are not quite viable due to the cost being high as the process involves expensive instrumentation and costly reagents. The utility of computer assisted techniques or *in silico* studies provides not only pace to the drug discovery process but is economical along with being quite viable. Thus, through *in silico* studies an array of molecules along with their analogues can be designed to suit the target specificities and hasten the early stages post which preclinical and clinical phases only need to be conducted for the drug to be marketed (Smith, 2003; Green and Segal, 2014; Etkins *et al.*, 2014).

2. Methods for *in silico* studies

The field of drug discovery *via in silico* drug design is extensive and has multiple approaches modern tools as QSAR structure-based design, bioinformatics, cheminformatics, combinatorial library design, biological and chemical databases (Figure 1).

Homology modelling

Homology modelling, or comparative modelling uses the amino acid sequence and generates an atomic resolution model of the 'target' protein which complements an investigational 3D structure of an associated homologous protein or 'template' (Marti *et al.*, 2000). Thus, it identifies structures from its database and maps for resemblance with the query sequence. It has been observed that even during evolution the protein structure has remained largely conserved over DNA sequences (Park *et al.*, 2008). Software tools create 3D structure based on the known template's 3D structures. Amongst the popular tools used in homology modelling are the modeller along with the SWISS-model repository, the database of protein structures (Richard, 2005).

Virtual high-throughput screening (VS)

The computational approach of virtual screening requires utilization of chemical structures libraries, which are assessed for binding potential of target molecules-largely protein receptors and enzymes (Wadood *et al*., 2013). Its focus is thus to resolve the query of screening amongst 10^{16} possible compounds and short-listing the ones that can be synthesised and evaluated. VS centres on designing and boosting targeted combinatorial libraries and enriching the from compound repositories. It is not only cost-effective than high-throughput screening but also time saving.

Molecular docking

Interaction networks or molecular modelling docking envisages the favoured orientation between a ligand and a receptor or target protein that forms a stable complex on binding to each other (Soloman, 2008). It thus facilitates the recognition and optimization of potential candidates for drugs by studying the possible molecular interactive binding between the ligand and the target. Thus, virtual high-throughput screening (HTS) studies involves generation of several ligand conformations and orientations and the ones with most efficient binding are selected (Perdo, 2010). Widely used tools include DOCK, Auto Dock, ArgusDock, FTDock, FRED and eHITS.

Hologram quantitative structure activity relationship (HQSAR)

QSAR methods depict the association of structural and biological activity. In Hologram QSAR, correct 3D information of ligands is not a pre-requisite and the molecule is split into molecular finger prints and the frequency of occurrence of such molecular fragments is observed. The size of the fragment decides the upper and lower limit of the fragments, though the general length is 4 to 7 atoms (Cramer *et al.*, 1988).

Comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA)

A constructive new tool for QSAR studies is CoMFA or 3D QSAR method. C log *p* values of the ligands are obtained through this technique which give an insight into steric as well as electrostatic hindrances along with the solvent repellent constraints (Cramer *et al.*, 1988). CoMSIA is generally used to pinpoint the shared characteristics between ligand and receptor for proper binding. Besides the steric and electrostatic characteristics, it also gives insight into hydrogen bond donor and acceptors donor groups and hydrophobic interactions present (Kurogi and Guner, 2001).

3D pharmacophore mapping

A pharmacophore is the 3D arrangement of functional groups on a lead molecule which is the active site of an enzyme or ligand. This leads to rapid identification of lead compounds for a chosen target and also accelerates the knowledge on ligand-receptor interaction. With identification of the pharmacophore, *via* database search tools, other novel compounds having structure similar to the pharmacophore are identified. Currently, used search algorithms are advanced to ascertain and optimize efficiently the lead target from combinatorial libraries using virtual high-throughput screening (Meyer *et al.*, 2000).

Microarray analysis

DNA technology or DNA microarrays are prepared on chips/slides having many markings and each comprises of a gene with known DNA sequence. These DNA sequences function as probes to detect gene expression. Effective analysis of transcriptome or the mRNA transcripts expressed by a gene, is thus completed. This facilitates making the appropriate choice of the lead molecule for drug development (Du *et al.*, 2021).

Conformational analysis

Such tools facilitate evolving 3D structures *via* use of calculation on the basis that the molecule should be in a stable conformation with minimum energy configurations. The study involves use of interaction networks to compare the complementarity between the ligand and the receptor such that the association is most energetically favourable (Yang *et al.*, 2021).

Monte Carlo simulation

Statistical mechanics is used in Monte Carlo simulation which gives an output of multiple conformations through computer simulation and suggests the ideal one considering the structure and thermodynamics. Another modification of the technique makes use of variable temperatures to simulate annealing which enhances ligand binding to receptor (Tuckerman and Martyna, 2000).

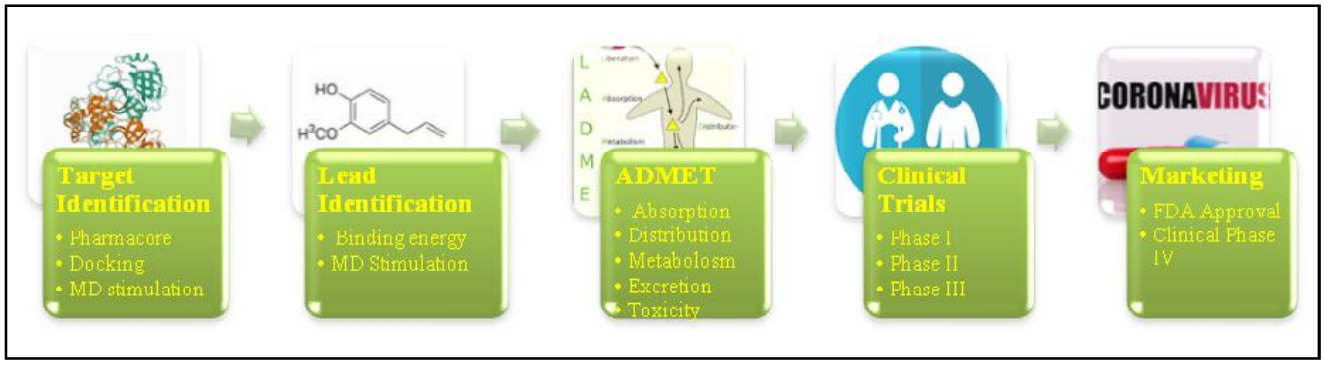


Figure 1: Drug discovery mediated by *in silico* studies.

This current study is focussed on use of *in silico* tools to facilitate the discovery of lead targets and lead molecules from natural plant resources and nutraceuticals with the potential of being developed as remedies for the SARS-CoV-2.

3. Potential herbs

3.1 *Allium sativum* (Garlic)

Allium sativum (Garlic) belongs to the Liliaceae family. It has been used as a therapeutic agent since time immemorial (Singh *et al.*, 2020). Garlic has a high nutritive value and is known to have extensive health benefits (Alam *et al.*, 2016). Garlic is rich in sulphur containing compounds, namely allicin, allinin and its derivatives and derived organosulfur compounds. To name a few important phyto-constituents, S-allyl cysteine sulfoxide (alliin), ajoenes (E- and Z-ajoene), vinyldithiins (2-vinyl-(4H) -1,3-dithiin, 3-vinyl-(4H)-1,2-dithiin), and diallyl (di and tri) sulfide S-allyl-cysteine, S-ally-mercapto cysteine, and nacetylcysteine (El-Saber Batiha *et al.*, 2020).

One of the phytocompound present in *A. sativum* is allicin (diallyl-dithiosulfinate) that has antifungal and antiviral activities. According to the study of Gebreyohannes and Gebreyohannes (2013), the increasing order of virucidal activity of garlic phytoconstituents was due to methyl allyl thiosulfanate, allicin and ajoene. The extract has been observed to be active against the H1NI cell culture of influenza virus A, by inhibiting virus attachment and proliferation in cell culture (Mehrbod *et al.*, 2009). The extract also demonstrates effectiveness against infectious bronchitis virus (IBV-a coronavirus) (Shojai *et al.*, 2016).

Amongst the phytochemicals in garlic, 7 compounds showing decreasing order of binding energies with major protease 6LU7 were S-allylcysteine sulfoxide (Alliin) > S-propyl L-cysteine, >S-allylcysteine> S-ethylcysteine> S-allylmercaptocysteine S-methylcysteine> S-propyl cysteine (Pandey *et al.*, 2021). Thuy *et al.* (2020), characterised the essential oils, namely; allyl- disulfide, and trisulfide, diallyl trisulfide and tetrasulfide and 2-propenyl propyl, and these showed high binding affinity towards Mpro as well as towards the ACE2 receptor with low docking score energies. Thus, these essential oils can be promising candidates as they not only prevent infection as the virus cannot bind to the ACE receptors on the host cells but it also inhibits the molecular mechanisms of DNA replication and RNA transcription through Mpro. Mahmoud *et al.* (2020), too studied sulphur containing phytochemicals in garlic and have found docking scores ranging from –4.4 to –3.4. They found that the binding sites with Mpro were mainly, Arg188 (2.14 α), Thr190 (1.92 α), Gln192 (2.34 α), and Glu166 (1.85).

Garlic can slow the development of cytokine storm as it downregulates close to 36 genes that mediate transcription of a majority of inflammatory cytokines, as the essential oils activate Nrf2 which facilitates the decrease in secretion of cytokines (McCord *et al.*, 2020).

Another factor contributing to allicin being an inhibitor of Mpro in SARS-CoV-2, is that it causes dual S-thioallylation of Cys-85/ Cys-156 residue in Mpro and Cys-145 of the compound (Shekh *et al*., 2020).

3.2 *Azadirachta indica (*Neem)

Neem belongs to a family Meliaceae found in Africa and Asia. Neem is considered to be a medicinal plant as it exhibits properties for treating diverse infectious and chronic diseases (Oladela *et al*., 2020). Each part of this plant, *viz*., seeds, leaves, bark and roots possesses medicinal potential. As per the findings (Yerima *et al*., 2012; Akin-Osanaiya *et al*., 2013; Naik *et al*., 2014; Basir and Shailey, 2012; Singh *et al.,* 2014) and Shrivastava and Swarnkar (2014) bioactive compounds in neem have proven to exhibit anticarcinogenic, antidiabetic, antiplasmodial, antimicrobial, antifungal, anti-inflammatory, and antiviral (Tiwari *et al*., 2010; Sher *et al.,* 2018). Ethanolic extracts of azadirachta have exhibited antimicrobial properties along with free radical scavenging potential (Alzohairy, 2016). According to the studies done by Tiwari *et al.* (2010), 50 to 100 µg/ml of neem bark exhibits inhibitory activity on HSV-1. Inhibition of glycoprotein mediated cell-to-cell fusion of HSV-1 demonstrated the potential antiviral activity of neem bark. Also leaf extract of neem has been selected as virucidal agent against coxackievirus B-4 by interfering in early stages of replication (Badam *et al.,* 1999).

Phytochemicals which hold analogy to limonoids and triterpenoids were found to possess activity against SARS-CoV 2 protein targets, *viz*., 3CLpro, PLpro, SGp-RBD, RdRp and ACE2 (Vardhan and Sahoo, 2020). The relative binding free energy of azadirachtin H with S-RBD-ACE2 and S-RBD was calculated and found to be 129 ± 19 and 152 ± 29 kJ mol 1, respectively (Daniel *et al.*, 2021). Nimbolin A, nimocin, and cycloartanols, from neem effectively bind to envelope as well as the membrane glycoproteins of SARS-CoV-2, and thus inhibits its docking to host cells (Borkotoky and Banerjee, 2020). Further, Aljindil (2012) and Venugopalan *et al*. (2011), observed immunomodulatory effects by enhancing the immune cells from components from neem seeds and leaves. Molecular docking of neem compound with SARS-CoV-2 proteins M and E suggested that these components have ability to prevent viral assembly leading to reduced propagation of viruses. This finding could propose that combination (Lim *et al*., 2021) of viral replication and assembly inhibitors would be better regimen for treatment modality.

3.3 *Curcuma longa* (Turmeric)

A member of the Zingiberacea family, turmeric (*Curcuma longa*) is found to be present naturally in India and Southeast Asia (Singh *et al*., 2021). As reported by Omosa *et al*. (2017), rhizomes of *C. longa* are rich in many secondary metabolites, which includes steroids, curcuminoids, polyphenols and sesquiterpenes as the predominant active therapeutic components. Since ancient times, the polyphenol of turmeric, curcumin has been exploited. Several studies have reported the anticancerous and anti-inflammatory properties of curcumin. The added advantage associated with curcumin is that there are no adverse effects associated with its administration and the US regulatory body, FDA has categorized curcumin as "Generally Recognized as Safe." Wen *et al.* (2017) reported that curcumin inhibits the replication of SARS-CoV-2 by exhibiting its protease inhibitory activity. Curcumin functions as an active antiviral agent in diseases like chikingunya, HIV, hepatitis C by foiling the access of the virus particle into the host cell. This in turn reduces viral replication. Also, curcumin is able to modulate the activity of certain molecular events as well in the virus lifecycle, which includes gene expression inhibition as observed in herpes virus and HPV (Joe *et al*., 2004).

Curcumin's ability to target different virus replication pathways, thus impeding viral growth and multiplication makes it a model candidate for an antiviral drug. Based on their molecular docking study, Utomo *et al*. (2020), reported that curcumin binds and inhibits SARS-CoV-2 protease, spike glycoprotein RBD, and PD-ACE2 receptors which are essentially involved in virus infection. According to Liu *et al*. (2017) curcumin has an antagonistic effect on the pro-inflammatory action of angiotensin II-AT1R, thus causing a decline in the level of proinflammatory cytokines and free radicals. *In silico* research conducted by Khaerunnisa *et al*. (2020), elucidated that demethoxy curcumin and curcumin may inhibit COVID-19 main protease (Mpro). The proteolytic activity of Mpro plays a significant role in the activation of helicase and RNA-dependent RNA polymerase (Rut *et al.,* 2020). Compounds eliciting an Mpro inhibitory effect are potential agents for COVID-19 treatment (Zhang *et al.,* 2020).

Jena *et al*. (2021) used Auto dock Vina 1.1.2. to study the binding modes of curcumin with coronavirus spike (S) protein and ACE2. The binding energy and affinity were documented to be –7.9 kcal/ mol and –7.8 kcal/mol, respectively. The values are suggestive of the fact that curcumin exhibits a strong binding affinity with S-protein as well as ACE2. According to the *in silico* study by Maurya *et al*. (2020), curcumin demonstrated a high-affinity for the S glycoprotein by forming six hydrogen bonds (Maurya *et al.,* 2020). Moreover, docking results have demonstrated that by forming two hydrogen bonds, curcumin interacted with the proteins active site (Maurya *et al.,* 2020). The entry of SARS-CoV-2 through the S protein is facilitated by the transmembrane protein serine protease 2 (TMPRSS2) (Hoffmann *et al.,* 2020). *In silico* analyses focusing on TMPRSS2 showed that curcumin forms four hydrophobic interactions and an H-bond with TMPRSS2 (Motohashi *et al.*, 2020). The results of studies on curcumin as prospective remedy for COVID-19 are encouraging. Curcumin can be effectively administered as part of a combinatorial therapy (Rattis *et al.*, 2021)

3.4 *Piper nigrum* (Black Pepper)

The king of spices or pepper is a member of family Piperaceae. It finds extensive use as a medicine, in perfumery and preservative. The major alkaloid in pepper is piperine (1-peperoyl piperidine), which has been in use as a medicine not only by Indian allied sciences as Ayurveda, Unani and Siddha but also by Chinese and Tibetans. The utility of piperine extends from its use as an anti-microbial, antiasthmatic, antidepressant, analgesic, antihypertensive, anti-inflammatory, antioxidant, antipyretic as well as antitumor (Damanhouri and Ahmad, 2014; Yoo *et al.,* 2019; Jafri *et al.,* 2019; Tiwari *et al.,* 2020).

The binding between piperine and 3CL-protease of COVID-19 is very strong, in fact even better than hydroxychloroquine and

chloroquinein. This binding promotes protein folding, thus causing structural changes in the main 3CL-protease of SARS-CoV-2 (Lenin *et al.,* 2020).

In silico studies by Rajagopal *et al.* (2020) suggest that piperine can be used against COVID-19 as it works in a manner similar to hydroxychloroquine. They suggested that not only piperine but piperdardiine and piperanine, too possess remedial possibilities. Piperine has been found, *via in silico* studies to inhibit not only the spike proteins in SARS-CoV-2, but is effective against mutated forms (S, 12 mutations) of the spike protein and was found to dislocate complex with ACE2 receptor (Nag *et al*., 2021). Shekh *et al*. (2020) recorded that piperine associates with the amino acids 166-Gly and 177-Gly of SARS-CoV-2 RBD Spro motifs and is stabilized by weak interactions as hydrogen bonds and van der Waals interactions with good binding scores. Piperine, was found to have a docking score prediction –6.8 kcal/mol and it leads to H-bonds with Thr25, Ser144 and Cys145 residues Mpro. Roat *et al.* (2020), in a MD simulation study observed stable interactions between piperine and both proteases RBD Spro and Mpro of SARS-Cov-2 based on PCA and binding free energy results. This binding facilitates the inhibition of replication as well as translation of viral proteins, effectively due to specific hindrances caused due to mutarotation. Thus, piperine evolves as a lead molecule for the treatment of SARS-CoV-2.

3.5 *Syzygium aromaticum* (Clove)

Clove is an evergreen tree from Myrtaceae family, growing in tropical climates. For over 2000 years, its use has been widespread across the globe in traditional medicine as well as for culinary purposes. The dried clove buds are largely used and eugenol is the primary essential oil (70-90%). Other important phytochemicals include β-caryophyllene, eugenyl acetate, and several sesquiterpenes (Zheng *et al.,* 1992; Chaieb *et al.,* 2007). It is endowed with medicinal properties and is used as an anti-inflammatory, immunostimulatory, antithrombotic as well as antibacterial, suggesting it as an important candidate in fight against the COVID-19 disease, especially for patients with comorbidities to prevent secondary infections (Bahramsoltani and Rahimi, 2020) .

Eugenol has shown to possess antiviral properties and is effective against HSV-1 and HSV-2, respectively (Benencia and Courrèges 2000). Its anti-inflammatory properties help protect the lungs as it recovers lipopolysaccharide-induced injury. It also inhibits leukocytes recruitment and downregulates the IL-6 and TNF-expression (Barboza *et al.,* 2018).

Eugenol, is reported to associate with spike S1, and thus prevents its interaction with ACE2, thereby inhibiting the entry of SARS-CoV-2 into host cells. It affects the immune system as it reduces the virus induced activation of NF-κB as well as the cytokine storm as it downregulated expression of IL-6, IL-1β and TNFα. Further, this facilitates lowering the inflammation in lungs, fever and improves cardiac function (Paidi *et al*., 2021).

Silva *et al*. (2020), studied the efficacy of aromatic oils including eugenol, carvacrol and menthol, using molecular docking techniques against SARC-CoV-2. The docking scores inferred that eugenol has an affinity towards the main protease (Mpro) on the spike.

3.6 *Tinospora cordifolia* (Giloy)

Tinospora cordifolia (Giloy) belongs to the Menispermaceae family and is indigenous to Asian counties like Myanmar, India, Sri Lanka and China. In India, this plant is commonly referred to as Guduchi and has extensive applications in Ayurvedic medicine (Singh *et al.,* 2020). Giloy is employed as a treatment modality against various inflammatory and allergic condions (Kumar, 2020). According to the study conducted by Pruthvish and Gopinatha (2018), the crude stem extract of giloy exhibited antiviral properties against herpes simplex virus.

The key COVID-19 protease Mpro or 3CLpro is an important target of antiviral approaches as it plays a key role in the virus infectious process. According to the molecular docking study of Shree *et al.* (2020), one of the phytoconstituents, tinocordiside, has been found to inhibit the Mpro of SARS-COVID-19. It revealed highest binding affinity compared to built-in ligand N3 for SARS-CoV-2 Mpro as per YASARA scoring and binding energy of 8.10 kcal/mol. Also, different compounds isolated from giloy like magnoflorine, berberine and isocolumbin presented high binding efficacy against the major surface proteins of SARS-CoV-2. This indicates that giloy has the potential to interfere with virus replication and infection (Sagar and Kumar, 2020).

The *in silico* study conducted by Chowdhury (2020) using tools of molecular docking and molecular dynamics have suggested that of all the phytoconstituents present in *Tinospora cordifolia*, berberine can effectively inhibit 3CLpro. However, according to the docking study of Krupanidhi *et al*. (2020), it was suggested that tinosponone is a potent inhibitor of the 3CL main protease of SARS-CoV-2 and was shown to exhibit a binding affinity of –7.7 kcal/mol. Among 28 active phytochemicals from *T. cordifolia* (giloy), only one compound, namely; tinocordiside (CID_177384) showed highest binding affinity as compared to built-in ligand N3 for SARS-CoV-2 Mpro as per YASARA scoring. Tinocordiside has binding energy of 8.10 kcal/mol. According to the results of docking analysis and ADMET studies conducted by Jena *et al*. (2021) a total five phytoconstituents of *T.cordiofolia* are promising therapeutic agents for COVID-19. These include alkaloids, steroids, terepenoids, octacosanol and heptacosanol.

3.7 *Zingiber officinale* (Ginger)

Ginger (*Zingiber officinale*) is a key medicinal plant. It is rich in many phytochemicals having therapeutic properties, prominent being steroids, phenols and alkaloids (Singh *et al.,* 2021). It is reported that these compounds of ginger exhibit anti-inflammatory, antipyretic, analgesic, antiemetic and antiarthritic properties. Researchers have also found ginger to be an effective therapy in many viral infections as Chikungunya, Herpes simplex, SARS-CoV-2 and Influenza to name a few (Admas, 2020; Sulochana *et al.,* 2020). In a molecular docking study conducted by Ahkam *et al.* (2020), ginger bioactive compounds were found to inhibit anti-SARS-CoV-2 activity by interacting with the main spike protein, S. This impeded virus binding with angiotensin-converting enzyme 2 (ACE2) receptor. The S protein plays a crucial role in the entry of SARS-CoV-2 during infection as it binds with hosts ACE2 receptor leading to a fitting environment for the virus to replicate (Walls *et al.,* 2020). The main protease (MPro) is responsible for processing the poly-proteins, *viz*., pp1a and pp1ab during the replication

phase of the virus (Hilgen Feld, 2014). According to the study conducted by Haridas *et al.* (2021), the *in silico* target binding behaviour of the major phytochemical components of ginger suggested that it may have neutralising effect on SARS-CoV-2 by inhibiting the spike glycoprotein in the virus and the enzyme ACE-2 in the host, both being critical for virus entry into the host cell.

Also, the activity of PLpro (SARS-CoV-2-related papain-like protease) cleaves polyprotein a/b (PP a/b), and thus is an important requirement for SARS-COVID-19 replication and survival (Dibakar *et al.,* 2020). This makes PL pro a noteworthy target of anti-SARS-CoV-2 pharmacological approach (Al Ajmi *et al.,* 2020). Molecular docking studies suggested that 6-gingerol reveals high binding affinity for different viral proteins that are vital for viral replication and survival like the S protein and several RNA binding proteins. Docking studies have also revealed that ginger and its derivatives like gingerol and zingiberenol, to name a few, interact with key residues in the catalytic domain of Mpro. Joshi *et al.* (2020) conducted a computational study which suggested that sesquiphellandrene, a ginger-derived terpene binds to S protein, thus impeding the S protein-ACE2 interaction (Joshi *et al.,* 2020; Jafarzadehab *et al.,* 2021). According to the study of Wijaya *et al.* (2021), 4-gingerol was elucidated to have the lowest binding energy against SARS-CoV-2 Mpro, and is thus proven to be a potent inhibitor of SARS-CoV-2.

3.8 Capsaicin

Capsaicin, chemically known as trans-8-methyl-N-vanillyl-6-nonenamide is the main component in varieties of spices like red chilli, hot peppers, *etc.* (Ann Bode *et al.,* 2011). It possesses natural antioxidant and pharmacological properties (Pandey and Rizvi, 2009; Pathak *et al.*, 2014; Rosa *et al.*, 2002). Capsaicin is a general trigger to cough as it activates of TRPV1 (Khalid *et al.*, 2014) although antagonists of TRPV1 are not effective. According to Ternesten-Hasseus *et al.* (2014), when capsaicin was administered orally for one month, showed improvement in cough through putative desensitization mechanism. As per the directives of U.S. FDA, it has been in use as a principal component for various pharma formulations as a line of treatment of several human diseases (Kraft *et al.,* 2013). Bourne *et al.* (1999) and Steiner *et al.* (2007) reported antiviral properties of capsaicin which helped in reduction of recurrent HSV infection and *Varicella zoster* infection.

As per Moldock molecular docking, algorithm capsaicin has binding potential with ASP 153 and lysin 102 with docking energy of – 54 kcal/mol. According to Anish Nag *et al.* (2021), capsaicin was found to have binding potential with mutated S proteins with binding energy as –7.867 kcal/mol and also with S-hACE2 (Angiotensin-converting enzyme 2) protein complex with docking energy as –9.385 kcal/mol (Lenin Gonzalez-Paz *et al.*, 2020). It has been reported that capsaicin has a potential of binding strongly to 3CL-protease enzyme of coronavirus as compared to antimalarial drugs. This promotes structural changes in viral protease enzyme that includes folding enzyme as well (Lenin Gonzalez-Paz *et al.*, 2020). Another study on molecular docking have reported docking energy of capsaicin with COVID-19 MPro and RNA dependent RNA polymerase (RdRp) as –6.2 and –7.3 kcal/mol, respectively (Brahmaiah Pendyala *et al.*, 2020).

3.9 Catechin

Natural polyphenols present in plants are well-documented as therapeutic and modulatory agents. They are also known to exhibit antiviral properties. Catechins exhibit antiviral activity against a wide range of human viruses including influenza, hepatitis B, hepatitis C, herpes simplex virus and HIV (Call and *et al.,* 2012; Ide *et al.*, 2016). Ganeshpurkar and Saluja (2017) studied the immunomodulatory targets of catechins by analysing *in silico* interactions. The docking scores revealed the ability of catechin to interact with TNFα, IL1β to name a few. Ghosh and coworkers (2020), reported that gallocatechin-3-gallate, a compound derived from *Camellia sinensis* (Green tea), showed significantly more activity (–9.0 kcal/mol) to the COVID-19 Mpro amino acids of E166, F140, H163, S144, C145, G113 (H-bond) and M49, L141, M165, E166, R188 (Hydrophobic interactions). Many phytoactive components present in *C. sinensis* act as effective SARS CoV-2 Mpro inhibitors (Bhardwaj *et al.,* 2020).

According to molecular docking study of Ghosh *et al.* (2020), the three catechins found in tea, *viz.*, EGCG, ECG and GCG interact with the residues of MPro. The affinity with which these three polyphenols bind, ranges between –7.6 and –9.0 kcal/mol with the lowest affinity for GCG and the highest affinity for EGCG. Binding free energy estimations using the MM-GBSA method also reveals that Mpro-GCG complex (–53.54 kcal/mol) is relatively more stable than Mpro-ECG (–48.92 kcal/mol) and Mpro-EGCG complex (–43.56 kcal/mol). These findings strongly support that catechins can be a promising anti-COVID-19 drug candidates.

Epigallocatechin gallate demonstrated the lowest binding energy with the COVID-19 spike protein (–130.566 kcal/mol). Low binding energy values indicate high protein-ligand binding affinity. The affinity value for EGCG, obtained from Auto DockVina, was observed to be –9.2 kcal/mol (Subbaiyan *et al.,* 2020).

Hewan *et al.* (2020) demonstrated catechins to be chiral compounds. To study the same, they employed the MOE software. The catechins were resolved and identified according to their chirality.

3.10 Kaempferol

Kaempferol (3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one) is a flavonoid present in several plants which are edible, *e.g.*, broccoli, kale, tea, beans, tomato, grapes, *etc.* It is also found and used as medicine, *e.g.*, Tilia spp, Moringa spp. *Moringa oleifera, etc.*, (Calderon-Montano *et al.,* 2011). Chemically, kaempferol is tetrahydroxy flavone (Li *et al.,* 2015). Numerous studies have proven kaempferol as anticancer, antimicrobial, antioxidant, and antiviral in action (Devi *et al.*, 2015). It also possesses antidiabetic, cardioprotective, analgesic, neuroprotective, anti-osteoporotic, and antiallergic activities (Lei *et al.,* 2019; Sharma *et al.,* 2007). Based on the research by Jeong *et al.* (2009), kaempferol is shown to inhibit H1N1 along with H9N2. *In vitro* analysis showed the inhibitory activity of it against hepatitis B virus (Li *et al.*, 2008). Kaempferol was found to inhibit viral replication leading to act as antiviral agent against Japanese encephalitis virus (Zhang *et al.*, 2012).

Auto Dock Vina docking was carried out between kaempferol and main protease (3CLpro) which revealed 10 different conformations

of kaempferol found to be antiviral (Trott and Olson, 2010). These docking predictions significantly approve that kaempferol is potent agent to interact with 3CLpro. Molecular docking analysis in 2021 by Laleh Babaeekhou *et al*. (2021), indicated a high affinity of kaempferol 3-O-rutinoside, querciturone and neodiosmin against CoV-2-SP with docking score values of –10.575, –9.904 and –10.208 kcal/mol with ki values of 0.016606, 0.051749 and 0.030921, respectively. Additionally, the total binding energy for 1st conformation calculated by MM GBSA module was found out to be –25.67 kcal/mol, whereas for second and third it was –17.21 kcal/mol and –26.81 kcal/mol, respectively (Genheden and Ryde, 2015). Cytopathic effect (CPE) inhibition assay was performed on Vero E6 cells to investigate inhibitory activity of kaempferol (Ma *et al*., 2020; Sebaugh, 2011). As per the report, SARS-CoV-2 causes cell detachment, rounding and death in infected Vero E6 cells. On incubation of these cells with kaempferol at concentration (62.50-125.00 µg/ml) showed significant decrease in CPE of Vero E6 cells. These discoveries have proven the promising antiviral effect of kaempferol against SARS-CoV-2.

3.11 Quercetin

Among numerous natural products, a dietary flavonoid quercetin is recognized to possess potential to treat chronic diseases and ageing processes in human beings. It is also known to hold antiviral properties (Pawan *et al*., 2020; Zeng *et al*., 2020). Quercetin is mostly found in vegetables and fruits including capers, broccoli, onions, grapes, onions, berries, tea, wine along with nuts, barks, leaves, flowers and spices (Russo *et al.*, 2010; Terahara *et al.*, 2015; Kyle *et al*., 2006). It is found to inhibit production of NLRP3 inflammasome mediated IL-1β (Tőzsér *et al.*, 2016). Lee *et al.* (2017) confirmed a dose-dependent antiviral activity of quercetin against HSV-1 and HSV-2, in cell cultures. It is also reported by Debiaggi *et al.* (1990) that quercetin can inhibit viruses of respiratory origin in cell culture. Quercetin inhibits the cytopathic effects triggered by rhinovirus, type 7, 11, 12, 19 echovirus and A21, B1 coxsackievirus along with type 1 Sabin poliovirus (Ishitsuka, 1992.) In 2018, it was demonstrated by González-Búrquez *et al.* (2018) that quercetin shows antiviral activity by decreasing viral expression and improving cellular viability. Supplementation of quercetin can encourage antioxidant activity (Xu *et al.*, 2019), immunoprotective, anti-inflammatory activities (Saeedi-Boroujeni and Mahmoudian-Sani, 2021), along with antidiabetic and anticarcinogenic potential (Rauf *et al.*, 2018; Carullo *et al.*, 2017; Carrasco-Pozo *et al.*, 2016). Also, it exhibits ability to prevent peroxidation of lipid, aggregation of platelets and permeability of capillary.

In silico as well as *in vitro* studies by Agrawal *et al*. (2020), demonstrated that quercetin can restrict several stages of replication cycle of the coronavirus like 3CLpro, NTPase/helicase and PL pro subsequently preventing its entry into host. Liu *et al.* (2016) through an *in silico* study explained that quercetin can be a potent inhibitor of influenza A H7N9 and H1N1. Docking analysis by Auto Dock 4.2 demonstrated quercetin as inhibitor of NS2 protease in HCV with binding energy of –7.95 kcal/mol. (Sajitha *et al.*, 2015). Molecular docking examination also proved that it may cause interaction with replication machinery like NS5B polymerase, HCV NS3 helicase and p7 proteins (Fatima *et al.*, 2014; Mathew *et al*., 2015). *In vitro* studies by Yi *et al*. (2004), also demonstrated that quercetin has a potential to block entry of SARS-coronavirus into Vero E6 cells with a EC_{50} of 83.4 µM along with low cytotoxicity (CC_{50} 3.32 mM). Docking studies of quercetin to 3CLpro, recommended that it can bind to each target firmly with energy of binding –5.6 kcal/mol to 3CLpro (Smith *et al.,* 2020). They identified quercetin as one of the 5 top most potent compounds amongst the drugs, natural products and metabolites having binding capacity to the interface site and ability to disrupt infection process. This study revealed the interaction between viral spike protein of SARS-CoV-2 and ACE2 protein. It is well known that proteases play vital roles in replication of virus, and SARS-CoV-2 specifically has 6LU7 to be the main protease (Mpro). *In vitro* molecular docking analysis of interaction between quercetin and viral protease demonstrates hydrogen bonding capacity of quercetin with amino acids His164, Glu166, Asp187, Gln192, and Thr190 of 6LU7 at active site (Khaerunnisa *et al.*, 2020). According to the study, the binding energies obtained from docking 6LU7 quercetin is –8.17 kcal/mol. Molecular docking studies by Auto Dock Vina discovered that quercetin-3-O-rhamnoside shows highest binding affinity with energy of –9.7 kcal/mol. These analysis also revealed that flavonoids in glycosylated form are potential inhibitors for protease of SARS-CoV-2 (Cherrak *et al.*, 2020). Docking studies by Bhowmik *et al.* (2019) confirmed the potential interaction of quercetin with ASP38 amino acid residue of ACE2 receptor which could help in preventing the attachment of coronavirus to the host cell.

4. Conclusion

Therapy against SARS-CoV-2, the causative agent of COVID-19, still continues to evade mankind. Drugs to curb infection have been successful but these are mostly antiviral effective against many other viruses. There still is no drug approved directed against the virus in question. This study is an attempt to evaluate medicinal and aromatic plants and nutraceuticals though *in silico* studies for their properties to inhibit the attack and replication of the virus (Figure 2). Table 1 compared the various plants studied. Amongst all the phytochemicals reviewed, allicin and piperine appears to be most promising, besides curcumin, quercitin and tinocordiside. *In silico* studies are suggestive of time-saving drug development as the initial steps are fast-tracked. These perspective candidates have good binding energies and can prove to be potential molecules to develop anti-COVID-19 drugs.

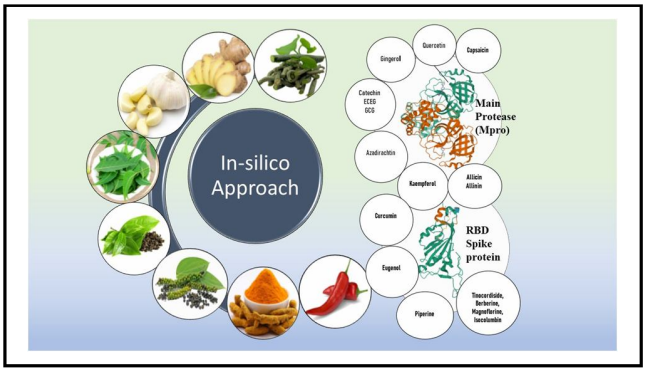
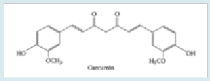
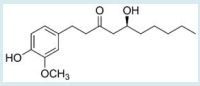
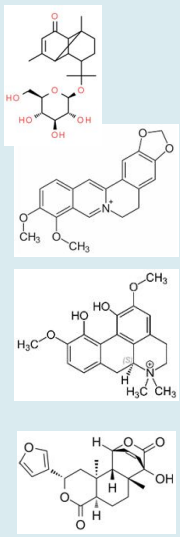
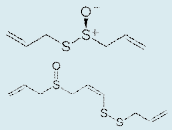
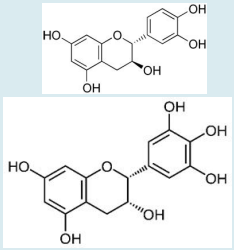
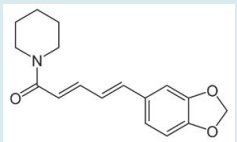
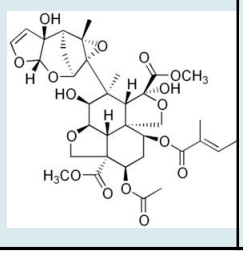
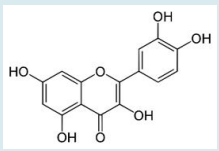
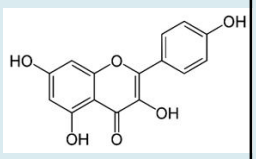
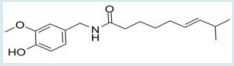


Figure 2: *In silico* approach to drug development for COVID-19.

Table 1: Summary of prospective candidates for COVID-19 therapy

Name of the compound	Active component	Structure	Binding energy in Kcal/mol	References
Curcuma longa	Curcumin		S protein: - 7.9ACE2: - 7.8	Jena *et al.* (2021)
Zingiber officinale	Gingerol		S Protein: - 38.60ACE2:46.85	Haridas *et al.* (2021)
Tinospora cordifolia	Tinocordiside, Berberine, Magnoflorine, Isocolumbin		3CL MPro: -7.7N3 MPro: -8.10	Krupanidhi *et al.* (2020)
Allium sativum	Allicin ajoene		MPro: -4.4 to -3.4.	Mahmoud *etal.* (2020)
Camellia sinesis	Catechin, EGCGE CGGCG		MPro: -53.54, -48.92, -43.56 S protein: -130.566	Subbaiyan *et al.* (2020)
Piper nigrum	Piperine		RBD sPro: -6.8	Shekh *et al.* (2020)
Azadirachta indica	Azadirachtin		S-RBD–ACE2 –129 ± 19S-RBD –152 ± 29 kJ mol”	Daniel *et al.* (2021)

Quercetin			3CL Pro: –5.6 6LU7: –8.17, –9.17	Smith, *et al.* (2020) Cherrak *et al.* (2020)
Kaempferol			3CLPro- –10.575	Laleh Babaeekhou *et al.* (2021)
Capsaicin			S-hACE2: –9.385Mutated s protein: –7.867	Gonzalez-Paz *et al.* (2021) Anish Nag *et al.* (2021)

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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