***Review Article***

**"In Silico Analysis of Some Medicinal Plants in the Context of COVID-19: Current Evidence and Future Prospectives”**

**ABSTRACT**

The COVID-19 pandemic, caused by SARS-CoV-2, has prompted an urgent need for novel antiviral strategies. Although several therapeutic approaches have been explored, there remains a lack of comprehensive reviews integrating Ayurvedic medicinal knowledge with in silico methodologies. This review addresses this gap by systematically examining computational studies on Ayurvedic herbs for their potential anti-SARS-CoV-2 activity. It highlights the application of molecular docking, molecular dynamics simulations, pharmacokinetic predictions, and network pharmacology in identifying bioactive phytoconstituents, predicting drug targets, and modelling host-pathogen interactions. By combining classical Ayurvedic principles with modern bioinformatics tools, this review supports the scientific validation of traditional remedies and the development of phytopharmaceuticals. The findings underscore the relevance of single-herb in silico investigations in the rational design of plant-based antivirals and offer insights into bridging traditional knowledge with contemporary drug discovery frameworks.

Keywords: Single herbs, Medicinal plants, Covid-19, In-silico study, Anti-viral drugs

**INTRODUCTION**

Coronavirus disease 2019 (COVID-19), which was caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), reveals how new infectious diseases have the power to drastically affect public health systems and affect people's economic and social well-being on a worldwide scale.[[1]](#endnote-1)

A group of enclosed, positive-sense, single-stranded RNA viruses known as coronaviruses infects a wide range of mammals and birds, including humans, hens, civets, and bats. SARS-CoV, MERS-CoV, and the most recent SARS-CoV-2 are linked to more complex and severe clinical signs and symptoms than HCOV-229E, NL63, OC43, and HKU-1, which usually induce the common cold with mild upper respiratory symptoms in humans. People with an acute SARS-CoV-2 infection typically have minor symptoms including fever and cough. The majority of COVID-19 patients experience pneumonia with dyspnoea and hypoxemia following the first 2–14 days of incubation, which can evolve into acute respiratory illness.[[2]](#endnote-2)

Despite the development and clinical application of numerous vaccines, there are currently no completely successful therapeutic medications to treat or prevent COVID-19, highlighting the critical need for alternative strategies, such as the utilization of medicinal plants.[[3]](#endnote-3) Since ancient times, people have traditionally used plants as therapeutic agents. The WHO states that 80% of the world population relies on medicinal plants for treatment, highlighting their importance in traditional herbal medicine systems, which use raw plants for extraction of compounds.[[4]](#endnote-4) Various plant extracts have been the subject of numerous investigations, and the secondary metabolites present in plants may be able to cure SARS-CoV-2.[[5]](#endnote-5) These natural products provide an additional information to unlock several challenges around the illness. The utilization of these natural substances' antiviral actions may provide insight into how they affect the invasion, penetration, reproduction, assembly, release, and life cycle of viruses.

Ayurveda encourages both single-herb and polyherbal compositions. Single-herb studies simplify pharmacological evaluations, promote standardization, minimize potential herb-herb interactions, and enable the identification of certain active molecules responsible for the therapeutic effects.[[6]](#endnote-6)Many herbal substances lack adequate experimental validation due to resource, logistical, or ethical constraints, these studies are highly beneficial. Using In silico techniques provide rapid and cost-effective phytochemical prioritization for experimental validation, which is particularly valuable during pandemics. Before proceeding on to in vitro or in vivo studies, computational techniques can effectively identify active candidates by simulating ligand–protein interactions and facilitating high-throughput screening of individual molecules. It enables feasible for researchers to isolate the role of particular phytoconstituents, which is crucial for the development of drugs and for understanding the molecular mechanism of action. By combining ancient knowledge with contemporary scientific methods, this method also helps to bridge the gap between Ayurveda and current biomedical research.[[7]](#endnote-7)

The aim of this review is to systematically compile and analyse in silico studies conducted on individual medicinal plants for their potential activity against SARS-CoV-2. By highlighting molecular docking, virtual screening, and network pharmacology results from diverse single-herb investigations, the study intends to identify promising phytochemicals, their molecular targets, and pathways involved in antiviral action. This review ultimately aims to support the development of plant-based antiviral agents by offering a consolidated view of computational findings relevant to COVID-19 therapy.

**MATERIAL AND METHODS**

A comprehensive literature search was conducted to identify relevant in silico studies focused on single herbs and their phytoconstituents in the context of antiviral activity, particularly targeting SARS-CoV 2. The search was conducted using electronic databases, including PubMed, Scopus, Web of Science, and Google Scholar, for studies published between January 2020 and May 2025. Only studies that focused on single herbs or their isolated phytoconstituents were included.

**Table 1: Summary of In Silico Studies on Single-Herbs Phytoconstituents Against SARS-CoV-2**

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| --- | --- | --- | --- | --- | --- |
| **Plant** | **Key Phytoconstituents** | **Target Proteins** | **Methods** | **ADMET Data** | **Conclusion** |
| *Aconitum heterophyllum[[8]](#endnote-8)* | Isoatisine | Omicron Spike Glycoprotein (S-protein) | Molecular docking, pharmacokinetic, and global reactivity analysis | good drug-likeness | Isoatisine showed strong binding, high reactivity, and potential antiviral lead compound. |
| *Adhatoda Vasica[[9]](#endnote-9)* | Vasicine, Vasicinone | SARS-CoV-2 Target Proteins | Molecular docking | Vasicine showed better drug-likeness | Vasicine showed superior docking and pharmacological potential over vasicinone |
| *Aerva lanata[[10]](#endnote-10)* | Heptadecanoic acid, methyl ester; Pyridine; 1-Butanol,4-butoxy; Furanone; Propanal oxime | SARS-CoV-2 Main Protease and Papain-like Protease | Molecular docking, binding energy calculation, and interaction analysis | - | A moderate binding affinity indicates a potential candidate for COVID-19. |
| *Albizia lebbeck[[11]](#endnote-11)* | Vicenin 2, Myricetin, Quercetin, Albigenic acid | SARS-CoV-2 main protease (Mpro) | Docking, MD simulation, MM-PBSA, DFT | - | Vicenin 2, Myricetin, and Quercetin showed strong binding, conformational stability, favorable reactivity and potential therapeutics against SARS-CoV-2 |
| *Aloe vera[[12]](#endnote-12)* | 10 Aloe vera compounds tested three potential inhibitors  ( Ligand 6, Ligand 1, Ligand 8) | SARS-CoV-2 Main Protease (3CL<sup>pro</sup>) | Molecular Docking,  Molecular Simulation,  ADMET Analysis | Ligand 6 fully satisfies Lipinski’s rule of five, ADMET profiles support drug-likeness | Ligand 6 identified as the most promising inhibitor with highest binding affinity and drug-like properties |
| *Allium cepa[[13]](#endnote-13)* | Chlorogenic acid, Caffeic acid, Kaempferol | RdRp, Envelope (E) protein | UPLC-MS/MS, Chemometrics, Molecular Docking, MD Simulation, In vitro IC₅₀ assays, Gene downregulation studies | - | Copper-yellow onion had the richest metabolite profile. Key compounds showed strong inhibition of RdRp and E genes (up to 86%). |
| *Allium sativum[[14]](#endnote-14)* | Squalene, 1,4-dihydro-2,3-benzoxathiin 3-oxide, 1,2,3-propanetriyl ester, trans-13-octadecenoic acid, methyl-11-hexadecenoate | SARS-CoV-2 3CL-Pro (main protease) | Molecular docking | - | Five compounds showed good binding affinity, potential therapeutic candidates. |
| *Andrographis paniculata[[15]](#endnote-15)* | 16 Semisynthetic Andrographolide Derivatives (AGP 1–16) | SARS-CoV-2 M<sup>pro</sup>, PL<sup>pro</sup>, Spike, NSP15, RdRp | Molecular Docking against 5 targets, pharmacokinetic and toxicity prediction tools | Computational ADMET screening | Compounds 14 & 15 showed best binding, all better than hydroxychloroquine and promising leads for COVID-19 treatment |
| *Artemisia annua[[16]](#endnote-16)* | Rhamnocitrin, Isokaempferide, Kaempferol, Quercimeritrin, Apigenin, Isorhamnetin, etc. | SARS-CoV-2 Main Protease (M<sup>pro</sup>) | Docking, MD Simulation, MM-GBSA, ADMET, Pharmacophore Modeling | Good drug-likeness and safety profile | Rhamnocitrin and others showed strong binding, stable interactions and potential COVID-19 inhibitors. |
| *Asparagus racemosus[[17]](#endnote-17)* | Asparoside-C, Asparoside-D, Asparoside-F | SARS-CoV-2 NSP15 Endoribonuclease, Spike RBD | Molecular Docking (Schrödinger Glide), Molecular Dynamics Simulation (100 ns), MM-GBSA Binding Energy Calculation | - | Asparoside-C and Asparoside-F showed the most stable and strong binding: −62.61 and −55.19 kcal/mol with spike RBD and NSP15, respectively. |
| *Avicennia officinalis[[18]](#endnote-18)* | Avicennone B, Avicenol A, Flavonoids | SARS-CoV-2 M<sup>pro</sup>, ACE2 receptor | Molecular docking, Molecular dynamics simulation, Biochemical assays (in vitro) | Evaluated using pkCSM and SwissADME | Avicennone B showed strong binding and good drug-likeness and a potential SARS-CoV-2 inhibitor. |
| *Azadirachta indica[[19]](#endnote-19)* | Desacetylgedunin (DCG) | SARS-CoV-2 Papain-like protease (PLpro) | Molecular docking, MD simulation (RMSD, RMSF, SASA) | - | DCG showed highest binding affinity and significant impact on PLpro structure, indicating therapeutic potential against SARS-CoV-2. |
| *Bauhinia variegata[[20]](#endnote-20)* | 2,5-Dimethyl-1H-pyrrole, 2,3-Diphenylcyclopropylmethyl phenyl sulfoxide, Benzonitrile m-phenethyl | SARS-CoV-2 main protease (Mpro) | GC-MS profiling, molecular docking, MD simulation, MM-GBSA | Good pharmacokinetics, drug-likeness, acute oral toxicity | Three compounds showed strong binding (−5.7 kcal/mol), stability, and drug-likeness, potential SARS-CoV-2 inhibitors |
| *Berberis asiatica[[21]](#endnote-21)* | Berbamine, Oxyacanthine, Rutin | SARS-CoV-2 main protease (Mpro) | Molecular docking, Molecular dynamics simulation, MM-PBSA free energy calculations | non-toxic | All three compounds showed strong stable binding, and potential as SARS-CoV-2 Mpro inhibitors. |
| *Boerhavia diffusa[[22]](#endnote-22)* | Liriodenine and others | ACE-II | Molecular docking, ligand-protein interaction analysis | Evaluated physicochemical properties, drug-likeness, water solubility, lipophilicity, pharmacokinetics | Liriodenine showed best drug-likeness and binding affinity and potential to treat COVID-19 and related diseases |
| *Bryophyllum pinnatum[[23]](#endnote-23)* | Bryophyllin B, Bryotoxin A | IL-6, TNF-α, Gly-ACE | Molecular docking | - | Both compounds show potential against cytokine storm in COVID-19. |
| *Calendula officinalis[[24]](#endnote-24)* | Flavonoids: Rutin, Quercetin, Isorhamnetin, Calendoflavoside | SARS-CoV-2 Main Protease (M<sup>pro</sup>) | Molecular docking, Molecular Dynamics Simulation, MM-PBSA binding energy calculation | ADMET analysis via SwissADME and pkCSM | Rutin and Isorhamnetin showed strong and stable binding with M<sup>pro</sup>, suggesting potential as effective inhibitors of SARS-CoV-2 |
| *Calotropis gigantea[[25]](#endnote-25)* | Calotropagenin, Calactin, Uzarigenin, β-Amyrin | Main protease (M<sup>pro</sup>/3CL<sup>pro</sup>) | Molecular docking, ADME/T analysis | Analyzed for drug-likeness and toxicity | Four compounds showed strong binding and potential M<sup>pro</sup> inhibitors |
| *Cannabis sativa L.[[26]](#endnote-26)* | Cannabidiol, Cannabinol, Tetrahydrocannabivarin, Cannabidivarin, Cannabigerol, Cannabichromene, Cannabicyclol | SARS-CoV-2 M<sub>pro</sub>, RdRp, Spike protein, ACE2 recepto | Molecular docking, Binding energy analysis, Drug-likeness screening, ADMET profiling | Good oral bioavailability, low toxicity | Cannabidiol (CBD) and Tetrahydrocannabivarin (THCV) showed strong binding  cannabinoids may serve as COVID-19 inhibitors. |
| *Carica papaya[[27]](#endnote-27)* | Protodioscin, clitorin, glycyrrhizic acid, manghaslin, kaempferol-3-(2g-glucosylrutinoside), rutin, isoquercetrin, acacic acid | SARS-CoV-2 proteins (Nucleocapsid, Mpro, RdRp, Spike variants), human TNF-alpha, alpha-thrombin | Molecular docking, 100 ns molecular dynamics simulation, MM-PBSA binding free energy | - | Protodioscin showed strong binding affinity and stable interactions with all targets, indicating multi-target antiviral and anti-inflammatory potential against COVID-19. |
| *Carthamus tinctorius[[28]](#endnote-28)* | Daphnoretin, Rutin (flavonoids) | TLR4, TLR8, FcγRIIa | Molecular docking (AutoDock), KEGG pathway analysis | - | Daphnoretin shows strong binding affinity to TLR4 (inflammatory receptor), weak to TLR8; Rutin binds best with FcγRIIa. Daphnoretin may inhibit hyperinflammation (cytokine storm) in COVID-19. |
| *Cassia angustifolia[[29]](#endnote-29)* | Sennoside B, Aloe-emodin | SARS-CoV-2 main protease (Mpro) | Molecular docking (AutoDock Vina) | - | Sennoside B showed strong binding (−9.05 kcal/mol), better than drugs like hydroxychloroquine and ribavirin; potential antiviral candidate. |
| *Cinnamon[[30]](#endnote-30)* | Tenufolin, Pavetannin C1, and 7 others | SARS-CoV-2 Main Protease (Mpro) | Molecular docking, MD simulation | Passes Lipinski’s Rule of Five | nine compounds with strong binding  Tenufolin and Pavetannin C1 are promising hits for COVID-19 therapy development |
| *Citrus limetta[[31]](#endnote-31)* | D-limonene, α-pinene, β-pinene, Camphene | SARS-CoV-2 main protease, RdRp, Spike RBD | Molecular docking (AutoDock Vina) | - | Phytochemicals showed good binding affinity, a potential supportive agent against COVID-19. |
| *Citrus macroptera[[32]](#endnote-32)* | Limonene and other GC-MS identified phytochemicals | Inflammatory proteins: COX-2, NMDA receptor, VCAM-1 | In silico molecular docking, MM-GBSA, Lipinski’s rule, VEBER, PAINS analysis | Phytochemicals showed drug-likeness per Lipinski, VEBER, PAINS. | Limonene showed the strongest binding with VCAM-1  all phytocompounds had better binding energies than conventional drugs; potential candidates for post-COVID inflammatory conditions. |
| *Clitoria ternatea[[33]](#endnote-33)* | Clitorin, Delphinidin, Kaempferol, Quercetin | M<sub>pro</sub>, RdRp, ACE2 | Molecular docking, ADMET, Drug-likeness | Good drug-likeness, oral bioavailability | Clitorin and Delphinidin showed strong binding  *C. ternatea* compounds may act as SARS-CoV-2 antagonists. |
| *Cocculus hirsutus[[34]](#endnote-34)* | Betulin, Coclaurine, Quinic acid | SARS-CoV-2 Main Proteases (M<sup>pro</sup>) | Molecular Docking, Molecular Dynamics Simulation, ADMET & Drug-likeness Prediction | Phytoconstituents showed favorable pharmacokinetic properties and drug-likeness profiles; stable protein-ligand interactions in simulations | Betulin, coclaurine, and quinic acid exhibited significant and stable binding to SARS-CoV-2 M<sup>pro</sup> |
| *Commiphora wightii[[35]](#endnote-35)(Guggul)* | Guggulsterone | SARS-CoV-2 ADP Ribose Phosphatase (ARP) | Molecular Docking, Molecular Dynamics Simulation |  | Guggulsterone showed strong binding and high stability within ARP's active site. It is a promising candidate against SARS-CoV-2 |
| *Coriandrum sativum seeds[[36]](#endnote-36)* | Rutin (highest affinity), Chlorogenic acid, Quercetin, Caffeic acid | SARS-CoV-2 Main protease (Mpro) | Molecular docking (PyRx), validation by LigPlot Plus | - | Rutin showed the highest binding affinity (-8.3 kcal/mol), a potential main protease inhibitor. |
| *Curcuma longa[[37]](#endnote-37)* | 30 turmeric compounds (e.g., Compound 4, 6, 23) | SARS-CoV-2 Main Protease, Spike glycoprotein, RNA-dependent RNA polymerase (RdRp) | Molecular docking, MM/GBSA binding energy, 100 ns MD simulation | ADME profiles were within the drug-likeness range | Compounds 4 (M<sup>pro</sup>), 23 (Spike), and 6 (RdRp) showed strong binding and stable interactions. |
| *Cyperus rotundus Linn[[38]](#endnote-38)* | β-amyrin, stigmasta-5,22-dien-3-ol | SARS-CoV-2 Main Protease (Mpro) | Molecular docking (LibDock, CDOCKER), pharmacophore analysis, molecular dynamics simulation | pharmacokinetic properties and safety profile were analyzed and found acceptable | β-amyrin and stigmasta-5,22-dien-3-ol showed best binding and stability with Mpro and potential inhibitors against SARS-CoV-2 Mpro |
| *Garcinia cambogia[[39]](#endnote-39)* | Naringin, Catechin, Gallic acid, Quercetin, Amentoflavone, Vitexin, Rutin, p-Coumaric acid | SARS-CoV-2 3CLpro (main protease) | molecular docking | - | Naringin showed potent inhibition of 3CLpro. |
| *Garcinia mangostana L.[[40]](#endnote-40)* | Xanthone derivatives (especially garcinone B) | ACE2 receptor, SARS-CoV-2 Mpro | Molecular docking, Lipinski’s rule of five drug-likeness screening, | Suitable drug-likeness, pharmacokinetic, and toxicity profile | Garcinone B shows promising potential as a COVID-19 therapeutic targeting ACE2 and Mpro inhibition. |
| *Glycyrrhiza glabra[[41]](#endnote-41)* | Liquiritigenin, Isoliquiritin | SARS-CoV-2 main protease, HMOX1, PLAU, PGR, immune & inflammatory pathways | Network pharmacology, molecular docking, molecular dynamics, | Both compounds had good drug-likeness and interacted with key immune-related genes | Liquiritigenin showed potential as a lead molecule inhibiting SARS-CoV-2 main protease; |
| *Gymnema sylvestre[[42]](#endnote-42)* | Gymnemic acids and derivatives | SARS-CoV-2 main protease (Mpro) | Molecular docking, 100 ns Molecular Dynamics simulation | Drug-likeness assessed | Gymnemic acids showed strong binding affinity and stable interaction, targeting key domains of Mpro, promising therapeutic candidates for COVID-19. |
| *Mentha piperita[[43]](#endnote-43)* | Rutin, Hesperidin, Isorhamnetin | SARS-CoV-2 main protease | In silico screening using YASARA, molecular docking via PLANTS, visualized in PyMol. | - | Rutin, hesperidin, and isorhamentin showed promising inhibitory activity against Mpro; mint compounds are potential antiviral agents against COVID-19. |
| *Mesua ferrea[[44]](#endnote-44)* | Mesuferrol-A, Mesuferrol-B, Mesuaferrone-A, Mesuaferrone-B, Mesuol, Mammaesin, Mesuanic Acid, Euxanthone, Mammeigin, Mesuagin | SARS-CoV-2 Main Protease (M<sup>pro</sup>) | Molecular Docking, MM-GBSA Binding Free Energy Estimation, ADMET & Toxicity Prediction, Molecular Dynamics | Mesuferrol-A, Mesuol, Mesuagin) were non-toxic and non-carcinogenic in silico predictions | Mesuferrol-A showed the most favorable binding energy and stable interactions |
| *Michelia champaca[[45]](#endnote-45)* | Taraxerol, Taraxeron; Ferulic Acid, Gallic Acid (Phenols) | ACE2 | Molecular docking | Gallic acid showed similar residue binding with NAG. | Gallic acid may interact with ACE2. |
| *Mimusops elengi[[46]](#endnote-46)* | Hederagenin, Quercetin (among 36 phytocompounds) | IL6, MMP9 (human receptors related to COVID-19 pathology) | In silico target prediction, gene ontology, OMIM analysis, and molecular docking | - | Hederagenin and quercetin showed strong binding to IL6 and MMP9, suggesting potential therapeutic roles against COVID-19 inflammation. |
| *Moringa oleifera[[47]](#endnote-47)* | Isorhamnetin, Kaempferol, Apigenin | SARS-CoV-2 main protease (Mpro) | Virtual screening, 3 × 100 ns Molecular Dynamics simulations, binding energy analysis | - | Isorhamnetin, kaempferol, and apigenin showed strong binding affinity and stable interactions with Mpro, comparable to the known inhibitor baicalein; *M. oleifera* is a promising antiviral source. |
| *Myristica fragrans[[48]](#endnote-48)* | Malabaricone B, Malabaricone C, Licarin A, Licarin B, Licarin C | SARS-CoV-2 Main Protease (M<sup>pro</sup>), Spike-ACE2 Interaction Complex | Molecular Docking (AutoDock, AutoDock Vina, ArgusLab), Molecular Dynamics Simulation, Solvent screening (COSMOquick) | All five compounds have favorable drug-like properties | Malabaricones and Licarins showed better binding energies compared to the standard (Panduratin A) |
| *Nigella sativa[[49]](#endnote-49)* | Thymoquinone, Nigellidine, Dithymoquinone, α-Hederin | SARS-CoV-2 Spike protein (S), Main Protease (M<sup>pro</sup>), ACE2, GRP78 | Molecular Docking, Molecular Dynamics Simulation (100 ns), MM/GBSA Binding Energy | - | α-Hederin showed the highest binding affinity with Spike and ACE2, with a stable MD profile; a potential inhibitor of viral entry and replication |
| *Nyctanthes arbortristis[[50]](#endnote-50)* | Naringenin, Ursolic acid, Beta-sitosterol, Daucosterol | IL6, MAPK3, MDM2 (inflammatory, immune, and cellular regulation) | Network pharmacology, molecular docking, bioinformatics analysis | - | Compounds showed effective binding to COVID-19-related targets; potential for enhancing immune function, reducing inflammation, and regulating cellular environment. |
| *Ocimum basilicum[[51]](#endnote-51)* | Apigenin-7-glucuronide, Dihydrokaempferol-3-glucoside, Aesculetin | SARS-CoV-2 Mpro | Molecular Docking (AutoDock), ADMET, Lipinski's Rule | All 3 passed ADMET; Apigenin-7-glucuronide & Dihydrokaempferol-3-glucoside had 1 Lipinski violation each; Aesculetin had none | Apigenin-7-glucuronide and Dihydrokaempferol-3-glucoside showed stronger Mpro inhibition than Aesculetin |
| *Ocimum sanctum[[52]](#endnote-52)* | Luteolin-7-O-glucuronide, flavonoids, polyphenols | SARS-CoV-2 Main Protease (Mpro) | Molecular docking, Covalent binding (Cys145), Binding free energy (GBSA) | Low toxicity, good drug-likeness | Potential irreversible Mpro inhibitor via covalent binding |
| *Oroxylum indicum[[53]](#endnote-53)* | Baicalein-7-O-diglucoside, Chrysin-7-O-glucuronide, Oroxindin, Scutellarein | SARS-CoV-2 main protease (Mpro) | Molecular docking and molecular simulation | Chrysin-7-O-glucuronide obeys Lipinski's Rule of Five; favorable | Four compounds identified as potential SARS-CoV-2 Mpro inhibitors, with Chrysin-7-O-glucuronide most promising |
| *Pearl millet[[54]](#endnote-54)* | Luteolin, Apigenin, Quercetin, | SARS-CoV-2 RNA-dependent RNA polymerase (RdRp) | Virtual screening, molecular docking, normal mode analysis, ADMET profiling, chemical-protein network analysis | Luteolin, Apigenin, and Quercetin showed good oral bioavailability and safety. | Luteolin, apigenin, and quercetin are potential RdRp inhibitors; pearl millet compounds may aid COVID-19 management. |
| *Phyllanthus emblica[[55]](#endnote-55)* | Chlorogenic acid, Quercitrin, Myricetin | NSP15 endoribonuclease, Main protease (Mpro), Spike RBD | Molecular docking (Schrödinger Maestro), Molecular dynamics, Network pharmacology analysis | - | These compounds showed the highest binding affinity to SARS-CoV-2 targets; they may modulate immune response, inflammation, and cytokine storm; potential for COVID-19 management |
| *Phyllanthus niruri[[56]](#endnote-56)* | Phyllanthin, hypophyllanthin | SARS-CoV-2 spike glycoprotein, main protease | Molecular docking (Molegro Virtual Docker 6.0) | - | Both compounds showed stronger binding affinity than native ligands, suggesting potential inhibition of viral entry and replication. |
| *Piper longum[[57]](#endnote-57)* | Piperine, Piperlongumine, Sesamin | M<sup>pro</sup>, ACE2 | Docking, MD Simulation, MM-GBSA | pkCSM, SwissADME | Piperine showed stable binding with M<sup>pro</sup>; promising lead for drug design. |
| *Pueraria tuberosa[[58]](#endnote-58)* | Robinin, Daidzin, Hydroxytuberosone, Genistin, Tuberostan, Anhydrotuberosin, Stigmasterol | M<sup>pro</sup>, TMPRSS2 | Molecular docking; MD simulation (for Robinin) | Followed Lipinski’s Rule; safe ADMET profiles | Robinin most potent and stable; PTY-2 phytochemicals are promising inhibitors of COVID-19 targets |
| *Prunella vulgaris[[59]](#endnote-59)* | Quercetin, Luteolin, Kaempferol | ACE2, inflammatory cytokines, renal injury pathways | Network pharmacology, molecular docking, molecular dynamics simulation | - | Quercetin and luteolin showed stable binding to RELA; IL6, VEGFA, and RELA identified as key targets modulating inflammation and kidney injury |
| *Punica granatum[[60]](#endnote-60)* | Punicalin, Quercetin-3-O-rhamnoside, Cyanidin-3-glucoside, etc. | SARS-CoV-2 Mpro | Docking, MD simulation, Binding energy | - | Several polyphenols showed higher binding affinity than N3 and curcumin, stable Mpro complexes suggest strong prophylactic potential. |
| *Rauvolfia tetraphylla[[61]](#endnote-61)* | (E,E,E,E,E,E)-2,6,10,15,19,23-hexamethyltetracosa-1,6,10,14,18,22-hexaen-3-ol, α-Tocospiro A, α-Tocopherol | SARS-CoV-2 3CL<sup>pro</sup> | GC-MS profiling, molecular docking | 8 compounds passed ADMET and mutagenicity filters | Identified compounds showed strong docking; plant holds promise as source for anti-COVID-19 agents |
| *Salvadora persica L.[[62]](#endnote-62)* | Eleven flavonol glycosides (e.g., rutinose-containing flavonoids) | SARS-CoV-2 main protease (Mpro) | Molecular docking, binding stability analysis | - | Flavonoids showed strong binding stability to SARS-CoV-2 Mpro; structural features enhance binding; supports potential antiviral activity |
| *Salvia plebeia R. Br.[[63]](#endnote-63)* | Rutin, Plebeiosides B | Main protease (Mpro) of SARS-CoV-2 | Molecular docking, ADMET, Drug-likeness, Biological activity, Molecular Dynamics, MM-PBSA, Secondary structure analysis | Showed drug-likeness; no toxicity | Rutin (−9.1 kcal/mol) and Plebeiosides B (−8.9 kcal/mol) are stable and potent inhibitors of SARS-CoV-2 Mpro |
| *Solanum torvum[[64]](#endnote-64)* | Torvoside H, A, E, F; Torvonin A; Torvanol A; Jurubine; Chlorogenone spirostane-3,6-dione; others (12 total) | SARS-CoV-2 Main Protease (M<sup>pro</sup> | PubChem compound retrieval, molecular docking (AutoDock Vina), binding site analysis | - | Most compounds showed strong docking scores and stable protein-ligand interactions, promising antiviral agents |
| *Saussurea costus[[65]](#endnote-65)* | 4,8,13-Cyclotetradecatriene-diol, Andrographolide, Δ⁴-Androstene | SARS-CoV-2 M<sup>pro</sup> | GC-MS, docking, pseudovirus assay | Water-soluble, good bioavailability | water-soluble inhibitors with moderate binding energies; aqueous extract inhibited SARS-CoV-2 pseudovirus post-entry |
| *Saussurea lappa[[66]](#endnote-66)* | Ellagic acid, Rutin, and 31 others (polyphenols, terpenoids) | SARS-CoV-2 Mpro, PLpro, Spike glycoprotein | Green extraction (CO₂ and hydroalcoholic), GC-MS, HPLC, Molecular docking (AutoDock Vina) | - | Ellagic acid and rutin showed strong binding, promising multi-target inhibitors |
| *Sesamum indicum[[67]](#endnote-67)* | Sesamin, Sesamolin, Pinoresinol, Hydroxymatairesinol, Spicatolignan, | SARS-CoV-2 M<sup>pro</sup>, PL<sup>pro</sup>, RdRp | Molecular docking and MD simulation | Good ADME, Lipinski rule compliant, stable binding | Hydroxymatairesinol showed the highest affinity, surpassing darunavir; lignans are promising natural COVID-19 leads |
| *Solanum surattense[[68]](#endnote-68)* | 13 phytochemicals (8 strong binders, 4 moderate-strong) | SARS-CoV-2 Main protease (3CLpro, PDB:6LU7) | Molecular docking (AutoDock Vina) | - | Several phytochemicals showed strong binding to 3CLpro at the inhibitor N3 binding site; potential COVID-19 inhibitors |
| *Tephrosia purpurea[[69]](#endnote-69)* | Tephrorin B, Deguelin, Vitamin P, Lanceolarin, 3β-Hydroxy-20(29)-lupene | SARS-CoV-2 Main Protease (M<sup>pro</sup>) | Molecular Docking, MM-GBSA, Drug-likeness prediction, Toxicity prediction, Molecular Dynamics Simulation | 4 out of 5 compounds predicted to be non-mutagenic and non-carcinogenic, top 2 showed good oral bioavailability | Binding of top phytochemicals altered protein conformation and stability, indicating potential as M<sup>pro</sup> inhibitors for COVID-19 therapy |
| *Terminalia chebula[[70]](#endnote-70)* | Daucosterol, Arjunetin, Maslinic acid, Bellericoside | SARS-CoV-2 M<sup>pro</sup> | Molecular docking (22 compounds), MD simulation, MM/PBSA & MM-GBSA analysis | Stable binding, strong H-bonding | Daucosterol and others showed strong, stable M<sup>pro</sup> inhibition; promising anti-COVID-19 leads |
| *Tinospora cordifolia [[71]](#endnote-71)* | Tinosporide, Berberine, Magnoflorine, Cordifolioside A, Tinosporaside, Columbin | SARS-CoV-2 Main Protease, Spike protein, ACE2 | Molecular Docking, Molecular Dynamics Simulation, MM-PBSA binding free energy | Evaluated for drug-likeness, absorption, and toxicity using SwissADME and pkCSM | Tinosporide & Berberine showed strong, stable binding, promising candidates as SARS-CoV-2 inhibitors |
| *Tinospora crispa[[72]](#endnote-72)* | 9 bioactive compounds in which 3 showed strong activity | SARS-CoV-2 Main Protease (M<sup>pro</sup>) | GC-MS Compound Identification, Molecular Docking | - | 3 compounds exhibited strong binding and potential biological activity |
| *Vitex negundo L[[73]](#endnote-73)* | Oleanolic acid, Ursolic acid, 3β-acetoxyolean-12-en-27-oic acid, Isovitexin | PL<sub>pro</sub> (Papain-like protease) of SARS-CoV-2 | Molecular Docking, Molecular Dynamics (MD) Simulation (50 ns), MM-GBSA Binding Free Energy Calculation | - | Oleanolic acid formed the most stable complex with PL<sub>pro</sub>. Other compounds showed moderate stability. All tested phytoconstituents demonstrated potential inhibitory interaction with PL<sub>pro</sub> |
| *Withania somnifera[[74]](#endnote-74)* | Withaferin A (wifA), Withanone (win) | SARS-CoV-2 main protease (Mpro) | CMap analysis, molecular docking, DFT calculations, LC-MS/MS, enzymatic & cell culture assays | - | Withaferin A and Withanone covalently and irreversibly inhibit Mpro, showing stable binding and potential for COVID-19 |
| *Zingiber officinale[[75]](#endnote-75)* | (6)-Gingerdiacetate, zingiberenol, pungent compounds | SARS-CoV-2 Mpro, Spike RBD, Human ACE2 | Network pharmacology, molecular docking, MD simulation, experimental validation | - | (6)-Gingerdiacetate showed strong binding to Mpro, RBD, and ACE2; extract confirmed potent antiviral activity |

**DISCUSSION**

The unprecedented global health crisis caused by SARS-CoV-2 highlighted critical gaps in our antiviral drug arsenal, despite the accelerated development of vaccines. While vaccination played a pivotal role in reducing disease severity and transmission, the lack of effective therapeutic agents remains a pressing concern. In this context, medicinal plants have emerged as valuable candidates for antiviral drug discovery, especially when explored through in silico approaches, which provide rapid, cost-effective screening of bioactive compounds.

This review systematically compiles single-herb in silico studies conducted between 2020 and 2025, emphasizing their molecular interactions with key SARS-CoV-2 proteins such as the main protease (Mpro), RNA-dependent RNA polymerase (RdRp), spike glycoprotein, and host cell receptors like ACE2. Several phytoconstituents including flavonoids (rutin, quercetin, kaempferol, isorhamnetin), alkaloids (berberine, piperine), terpenoids (ursolic acid, oleanolic acid), and glycosides (sennoside B, asparoside C) demonstrated strong binding affinities and favorable pharmacokinetic properties. These findings suggest their potential as multi-target inhibitors with broad-spectrum antiviral activity.

Compounds from *Andrographis paniculata*, *Azadirachta indica*, *Artemisia annua*, and *Withania somnifera* exhibited higher docking scores than standard antivirals such as hydroxychloroquine, indicating their promise as lead molecules. Furthermore, ADMET analyses performed using SwissADME and pkCSM tools revealed that many of these phytochemicals possess favorable oral bioavailability, drug-likeness, and low toxicity—key characteristics for therapeutic development.

A notable strength of in silico studies is their ability to simulate ligand–protein interactions, predict molecular dynamics, and identify active site compatibility with minimal laboratory resources. For example, molecular dynamics simulations (100 ns) confirmed the stability of binding for compounds such as asparoside-F (*Asparagus racemosus*) and cannabidiol (*Cannabis sativa*), reinforcing their structural suitability. Moreover, network pharmacology analyses helped elucidate multi-target mechanisms, such as anti-inflammatory effects and immune modulation, crucial in managing COVID-19 pathophysiology.

Despite these promising insights, in silico studies are inherently predictive and must be complemented by in vitro and in vivo validation. Experimental studies are essential to verify biological activity, bioavailability, and potential side effects. Additionally, viral mutations and emerging variants necessitate adaptable strategies, reinforcing the value of multi-target and synergistic phytochemical combinations.

**Conclusion**: this review highlighting the potential of computational phytochemical screening for the discovery of natural antiviral medicines. Modern bioinformatics technologies combined with traditional medical knowledge provide a scientifically sound and sustainable basis for the development of antiviral drugs in the future. The gap between clinical applications and computational projections must be closed by sustained interdisciplinary efforts, which will ultimately improve preparedness for both present and upcoming pandemics.

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