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Review Article

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Multi-target therapeutic interventions based on phytochemicals for SARS-CoV-2

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ABSTRACT

COVID-19 has an unprecedented effect on every aspect of human existence. The chief targets for drug design against SARS-CoV-2 are, spike envelope glycoprotein (S), the viral main proteinase Mpro, also referred to as 3CLpro, Angiotensin-converting enzyme 2 (ACE-2), and RNA-dependent RNA polymerase (RdRp). A systematic literature survey was performed extensively from various published sources and peer-reviewed electronic databases such as PubMed, Scielo, Google Scholar, and Science Direct databases to obtain peer-reviewed studies on the chief targets for drug design against SARS-CoV-2 and phytochemicals. Of the 1012 titles identified by the search, 151 were adequate according to the inclusion and exclusion criteria. The promising antibacterial, antioxidant, anti-inflammatory, and antiviral activities of phytochemicals make them an attractive option for drug discovery against SARS-CoV-2. In the quest for finding drug molecules against these targets, ethno-medicinal knowledge is also being explored. In this review, the authors have deduced the available phytochemicals with reported anti-CoV activity. In addition to that, the authors have also briefly thrown light on the etiologic and existing drug targets for SARS-CoV-2. Authors conclude that a multi-target treatment strategy would be the most useful approach against SARS-CoV-2 and phytochemicals can prove to be the gold mine for designing such drugs.

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INTRODUCTION

It has been a test of the ingenuity of scientists to develop a cure for COVID-19 due to its high mortality, extraordinary basic reproduction number, lack of clinically approved drugs and vaccines, and the advent of novel, mutated variants (Kolifarhood *et al.*, 2020). The collaborative efforts for designing a drug for this multi-dimensional problem range from drug repurposing to looking at alternative medicine for inspiration.

Drug repurposing is very beneficial as it decreases the time required to find a new drug but has its limitations, for instance, the repurposed drug can show adverse effects such as cardiotoxicity, hematologic toxicity, hepatotoxicity, hematologic toxicity, and nephrotoxicity (Saini *et al.*, 2022; Saini *et al.*, 2023d). There was so much hype about chloroquine and hydroxychloroquine, the antimalarial drugs for treating COVID-19 but they led to side effects like neuromyopathy, cardiomyopathy, and retinopathy. So much so, that World Health Organisation (WHO) had to notify that HCQ has no benefits if used as a drug against COVID-19 infection (Singh *et al.*, 2020a; Hussain *et al.*, 2021; Kamat & Kumari, 2021; Shah, 2021). Thus, the problem of 'adverse effects' has led researchers to focus their attention on phytochemicals having less toxicity and enhanced bioactivity (Gorlenko *et al.*, 2020). COVID-19 could be managed by various traditional health systems as depicted in Figure 1.

Phytochemicals are a diverse collection of naturally occurring bioactive compounds in plants with excellent therapeutic, pharmacological, and nutritional properties (Anhê *et al.*, 2013; Sharma & Bhatia, 2020a; Saini & Sharma, 2022). They comprise polyphenols, alkaloids, flavonoids, terpenoids, and lignans (Dali *et al.*, 2019; Srivastav *et al.*, 2020), for instance, epigallocatechin gallate (EGCG), curcumin, quercetin, resveratrol, apigenin, anthocyanidins are some of the well-investigated phytocompounds (Saini *et al.*, 2023c). Phytochemicals have excellent anti-inflammatory, anti-amyloidogenic, and antioxidative activities (Davinelli *et al.*, 2012). Also, they have fewer adverse effects,

Figure 1: Traditional Health Systems in COVID-19 Management

show less toxicity, and better tolerance exhibited by patients for drugs based on phytochemicals (Rodrigues *et al.*, 2016; Saini *et al.*, 2023b). These are some of the reasons that researchers are investigating phytochemicals to look for scaffolds/templates for the development of a cure for COVID-19 (Awasthi *et al.*, 2016; Sharma *et al.*, 2022). Various mechanisms have been proposed for the antiviral activity of phytochemicals such as stopping viral assembly and interfering the replication of the virus by targeting DNA/RNA polymerase or post-translational modifications (Swamy, 2020; Barkat *et al.*, 2022).

Literature is rife with examples of phytochemicals being used for treating viral infections. There are various formulations like Ayurvedic concoctions such as *AYUSH Kwath* (Niphade *et al.*, 2009; Alsuhaibani & Khan, 2017; Bhalla *et al.*, 2017; Ghoke *et al.*, 2018), *Samshamani Vati (Guduchighanavati)* (More & Pai, 2011; Sachan *et al.*, 2019), *AYUSH-64* (Sharma *et al.*, 1994; Panda *et al.*, 2017; Win *et al.*, 2019; Woo *et al.*, 2019), *Agasthaya Hareetaki (Avalehakalpana)* (Mouhajir *et al.*, 2001; Balasubramanian *et al.*, 2007; P. Patel & Asdaq, 2010; Lampariello *et al.*, 2012), *Anuthaila* (Patil *et al.*, 2008; Cohen, 2014; Mohanty *et al.*, 2017; Mukta & Neeta, 2017), Unani concoctions like *Triyaq-e-Araba* (Loizzo *et al.*, 2008; Ahmad *et al.*, 2018), *Roghan-e-Baboona* (Srivastava *et al.*, 2010), *Arq-e-Ajeeb* (Lai *et al.*, 2012; Zaia *et al.*, 2016), *Khamira-e-Banafsha* (Gerlach *et al.*, 2019), *AsgandhSafoof (Withania somnifera (L.) Dunal)*, *Habb-e-Bukhar* (Devaux *et al.*, 2020; Rastogi *et al.*, 2020), and Siddha concoctions such as *Nilavembu Kudineer, Ahatodai Manapagu* (Sampath Kumar *et al.*, 2010), *Kabasura Kudineer* (Jin *et al.*, 2011; Chang *et al.*, 2013; Bhattacharya & Paul, 2021; Devi *et al.*, 2022).

In addition to that, Indian medicinal herbs such as *Zingiber officinale* Roscoe (Ginger), *Allium sativum* L. (Garlic), and *Withania somnifera* (L.) Dunal (Ashwagandha), Chyawanprash, *Cinnamomum zeylanicum* Blume (Cinnamon), *Tinospora cordifolia* (Wild.) Miers (Giloe), Sharbat Rooh-Afza, *Curcuma longa* L. (Turmeric), *Piper nigrum* L. (Black Pepper), Triphala, *Linum usitatissimum* L. (Flax Seed), *Phyllanthus emblica* L. (Amla), *Nigella sativa* L. (Black Cumin), and *Ocimum sanctum* L. (Tulsi) are regularly being used as a part of the diet or as spices for flavoring agents in food. Some argue that Indians regularly consume them and the phytochemicals present in these are responsible for the slow death rate in India due to COVID-19 among other factors (Ahmad *et al.*, 2021).

Another major area of phytomedicine that is helping in the management of COVID-19 is Traditional Chinese Medicine (TCM). The main respiratory focus of COVID-19 is the lungs, and TCM targets the lungs (Zhang *et al.*, 2020; Lee *et al.*, 2021). In the initial phase of coronavirus infection, patients display clinical symptoms of sore throat, fever, cough, myalgia, etc. TCM employed in this phase is Maxingshigan (MXSG) decoction (which includes herbs like *Gypsum fibrosum*, *Ephedra sinensis*, *Glycyrrhiza*, and *Semen armeniacae amarum*), and Gancao ganjiang decoction (GCGJ) (which includes herbs like *Rhizoma zingiberis* and *Radix glycyrrhizae*).

The common symptoms of coronavirus infection are diarrhea, fever, chest pain, muscle soreness, vomiting, and cough. The TCM formulations often employed as first-line therapy are: Qingfeipaidu decoction (QFPD) (Chen *et al.*, 2020; Yang *et al.*, 2020) (It includes sheganmahuang decoction, MXSG decoction, xiaochaihu decoction, and wuling powder), Sheganmahuang decoction (SMD) (Eng *et al.*, 2019) (which includes herbs like *Schisandra chinensis seeds*, *Rhizoma Belamcandae*, *Pinelliae Rhizoma Praeparatum Cum Zingibere Ephedra sinensis Rhizoma Zingiberis Recens*, *Ziziphus jujube*, *Asarum sieboldii*, *Flos Farfarae*, and *Radix Asteris*), MXSG decoction, Lianhuaqingwen capsule (LH) (Jia *et al.*, 2015) (which includes herbs like *Fructus Forsythiae*, *Glycyrrhiza*, *Honeysuckle*, *Radix et Rhizoma Rhodiolae Crenulatae*, *Ephedra sinensis*, *Rheum palmatum*, *Agastache rugosa*, *Semen Armeniacae Amarum*, *Herba Houttuyniae*, *Isatis tinctoria*, *Gypsum fibrosum*, and *Rhizoma Dryopteridis Crassi Rhizomatis*), and Jinhuaqinggan granules (JHQG) (Liu *et al.*, 2020; Lee *et al.*, 2021) (which includes herbs like *Honeysuckle*, *Glycyrrhiza*, *Ephedra sinensis*, *Herba Menthae Haplocalycis*, *Gypsum fibrosum*, *Herba Artemisiae Annuae*, *Semen Armeniacae Amarum*, *Rhizoma Anemarrhenae*, *Fructus Arctii*, *Bulbus Fritillariae Thunbergii*, *Scutellaria baicalensis*, and *Fructus Forsythiae*).

Viral diseases such as chikungunya, dengue, HIV/AIDS, Ebola, etc. have all been subject to numerous Ayurvedic and Western natural formulations, which gives hope that they may also prove to be potent against SARS-CoV-2 (Boukhatem & Setzer, 2020; Koulgi *et al.*, 2021). Worldwide, native and aboriginal peoples have relied upon plant-based medicinal strategies, and this approach is also supported by the WHO's call to develop natural product-inspired drug candidates (Yuan *et al.*, 2016; WHO, 2019). At present, 70-80% of commercial drug formulations originate from plant-based compounds (Harrison *et al.*, 2020; Ni *et al.*, 2020; Yanez *et al.*, 2020). Thus, in light of the scarcity of effective medicinal interventions available for SARS-CoV-2, phytochemicals may provide crucial breakthroughs. For instance, the Indian Ministry of AYUSH has initiated clinical trials for the evaluation of four Ayurvedic herbs *viz.* ashwagandha (*Withania somnifera (L.) Dunal*), Guduchi (*Tinospora cordifolia (Willd.) Miers*), yasthimadhu (*Glycyrrhiza glabra L.*), and pipli (*Piper longum L.*) against COVID-19 (Ministry of Ayush, 2020).

In light of the above, the authors have tried to summarize the available studies of phytochemicals with reported anti-CoV activity. Moreover, the authors have also briefly discussed the existing drug targets for SARS-CoV-2 and the mechanism by which phytochemicals act.

METHODOLOGY

Prominent search engines such as Google Scholar, ScienceDirect, Scopus, Web of Science, SpringerLink, PubMed, and BioMed Central were used to search and identify the relevant literature. Extra reading material was retrieved by consulting books and ethnopharmacological. Search terms such as "SARS-CoV-2 and phytochemicals", were used, either alone or along with the terms "spike envelope glycoprotein" and/or the viral main proteinase "Mpro", "3CLpro", "Angiotensin-converting enzyme 2 (ACE-2)" and "RNA-dependent RNA polymerase (RdRp)". Of the 1012 titles identified by the search, 151 were adequate according to the inclusion and exclusion criteria. All of the 151 articles were comprised of only research and review articles Literature search included thesis, book chapters, conference abstracts, encyclopedias, book reviews, and others. Articles excluded from this review are those with incomplete information.

MAIN DRUG TARGETS FOR SARS-COV-2

The potential drug targets, as shown in Figure 2, can be virus-based and host-based, that is, all enzymes and proteins of the SARS-CoV-2 that take part in the replication of the virus and are involved in the control of host cellular machinery. Virus-based proteins of SARS-CoV-2 are structural and non-structural. Structural proteins, as the name suggests, form the structure of the coronavirus, and they include the spike (S) glycoprotein, envelope (E) protein, membrane (M) protein, and the nucleocapsid (N) protein. Out of these, the Spike (S) protein helps in the process of the entry of the virus into the host cell via receptor recognition and membrane fusion; The envelope (E) protein helps in the envelope formation, assembly, and virulence; membrane (M) protein helps in viral assembly and nucleocapsid (N) protein helps in the packaging of the viral RNA genome into nucleocapsid and protects it (Ni *et al.*, 2020).

The 16 non-structural proteins (NSP) have specific roles, in theory, all of them can be used as a drug target but it to be a success, the crystal structure of the target and ligand should be available and they should have a significant role in the process of infection. Keeping these factors in mind, predominantly, the focus has been on the RdRp, the two proteases (3CLpro and PLpro) and helicase (NSP13). Host-based drug targets include angiotensin I converting enzyme 2 (ACE2) receptor, Transmembrane Serine Protease 2 (TMPRSS2), furin, cathepsin L, adaptor-associated Kinase 1 (AAK1) and cyclin G-associated kinase (GAK), phosphatidylinositol 3-phosphate 5-kinase (PIKfyve), and two-pore channel (TPC2). The recognition of the angiotensin-converting enzyme 2 (ACE2) on the surface of the host cell by the S protein of the SARS-CoV-2 and its binding

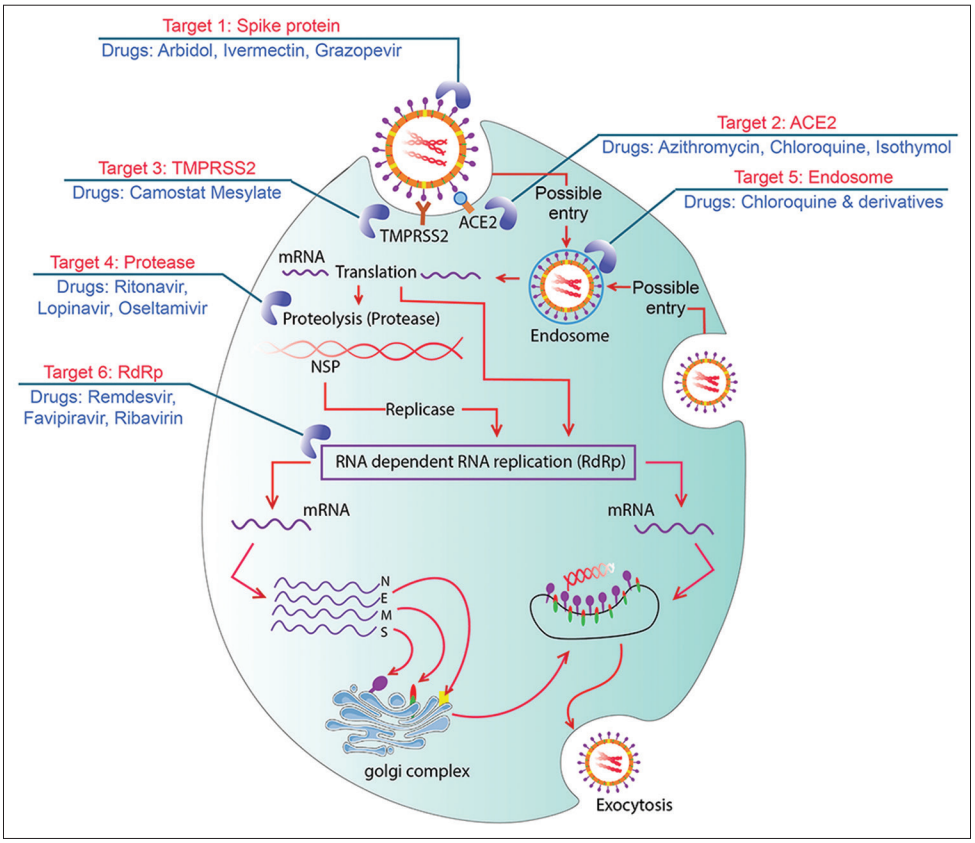

Figure 2: Main drug targets for SARS-CoV-2; Taken from (Sumon *et al.*, 2020) under CC-BY licence

to the membrane by the envelope protein explains the entry of the virus into the host cell. After the introduction of the viral genome into the host cell, transcription and translation of this genome leads to the formation of a polyprotein. This polyprotein is then treated by the protease (3CLpro) into the structural proteins, S, E, M, and N proteins, and NSPs. It is important to note that the human body does not have a 3CLpro homolog, making it a desirable drug target against SARS-CoV-2 (Jo *et al.*, 2020; Singh *et al.*, 2020b; Zhang *et al.*, 2020). Phytochemicals such as carboxylic acid esters, peptides, alkanes, alkenes, quinolines, terpenes, pyrazines, nucleoside analogs, alcohols, flavonoids, and acridones exhibit activity against SARS-CoV-2 (Milugo *et al.*, 2025).

The mechanistic aspects of the action of phytochemicals include interaction with both structural and NSPs of SARS-CoV-2. This involves strong bonding with the active site, leading to large conformational changes. That is why phytochemicals act as inhibitors of these proteins. There are various ways in which they can do so: inhibiting the toll-like receptors (TLRs) and endothelial activation, blocking the ACE-2, inhibiting the entry or replication of the virus, activating the nuclear factor erythroid-derived 2-related factor 2 (Nrf2), blocking the TMPRSS2 and regulating the mediators causing inflammation (Malekmohammad & Rafieian-Kopaei, 2021).

CURRENT STATUS OF PHYTOCHEMICALS FOR TREATING SARS-COV-2 INFECTION

In this section, we have summarized some of the seminal studies that have been done to gauge the potential of phytochemicals against SARS-CoV-2. Most research groups focus their efforts on medicinal plants already documented in the literature.

For instance, six potential inhibitors of the main protease (Mpro or 3Clpro) of SARS-CoV-2 were found through molecular docking and molecular dynamics studies from *Withania somnifera* (Ashwagandha), *Tinospora cordifolia* (Giloy), and *Ocimum sanctum* (Tulsi). The inhibitors identified are *Withanoside V*, *Somniferine*, *Tinocordiside*, *Vicenin*, *Ursolic acid*, and *Isorientin*. The ADMET profile of these inhibitors was very promising (Shree *et al.*, 2022). In another study, a constructed phytochemical library was virtually screened and explored against SARS-CoV-2 papain-like protease, and two potent compounds, broussochalcone A and broussoflavan A, were identified as promising lead compounds against COVID-19 (Wadanambi *et al.*, 2025). India has a long history of using medicinal plants in ayurvedic medications, but the use of phytochemicals is also a global phenomenon. For example, the phytochemicals present in the medicinal plants of the Al-Haouz region, Morocco, were investigated by in-silico methods, and the phytochemicals having potential activity against Mpro were rosmarinic acid, hesperetin, gallocatechin, and cyasterone (Ghanimi *et al.*, 2022). Another study explored the traditional Siddha formulation, Milagai-Kudineer, as an inhibitor of SARS-CoV-2. And it was noted that phytocompounds like Ascorbic acid, Quercetin, Curcumin, and Capsaicin showed considerable binding affinities against the viral target proteins, suggesting their potent role in blocking the viral entry and replication. Also, bioactive natural compounds like Dihydrocapsaicin, Cuminaldehyde, Carvacrol, and Linalool were identified as antiviral agents as they interact with the key amino acid residues of the S protein (Rajamanickam *et al.*, 2025).

Network pharmacology was also employed extensively to find compounds against SARS-CoV-2; for example, 34,472 phytochemicals from 3038 Ayurvedic herbs (AHs) were investigated via network pharmacology and molecular docking. The results highlighted six significant AHs responsible for antiviral immunity. In addition to that, the binding affinities of 292 potentially effective phytochemicals (PEPs) against 24 SARS-CoV-2 proteins were analyzed. This analysis gave forward a bi-regulatory network of 115 PEPs that could help in the regulation of protein targets in the host and the virus. This study was very significant because it also identified 12 PEPs as potential COVID-19 comorbidity regulators (Choudhary & Singh, 2022).

One very interesting trend observed in exploring phytochemicals for treatment against SARS-CoV-2 was the use of secondary data, that is, the use of already published data. This was then coupled with primary data (predominantly in silico studies). For instance, for the medicinal plant Artemisia herba-alba, literature was searched for its phytochemical ingredients, ethnic uses, and pharmacological activities against SARS-CoV-2. The phytochemicals rutin, 4,5-di-O-caffeoylquinic acid, and schaftoside were identified, and they were then investigated using in-silico studies (Hasan *et al.*, 2022).

According to a report, the maximum therapeutic activity is reported from medicinal plants belonging to the Lamiaceae family used in four countries: India, Australia, China, and Morocco. This was followed by Fabaceae, then Asteraceae, Meliaceae, Piperaceae, Zingiberaceae, and Ranunculaceae (Mukherjee *et al.*, 2022). Also, substantial heterogeneity is much more in 3CLpro inhibitors than PLpro inhibitors (Ebenezer *et al.*, 2022). It will be better if the focus is on the recognition of different mechanisms to fight against SARS-CoV-2 infection. That should be the general approach while using phytochemicals for this infection (Soleymani *et al.*, 2022).

Phytochemicals have been screened for their activity against the new delta variant SARS-CoV-2 Indian Delta Variant B.1.617.2. In a recent study, the focus was on inhibition of the S protein Trimer (Bharathi *et al.*, 2022). 603 phytocompounds from 22 plant species were studied and were compared with standard drugs such as ceftriaxone, lopinavir, chloroquine, remdesivir, hydroxychloroquine, and ritonavir. Phytochemicals such as acteoside, verbascoside, kanzonol V, progeldanamycin, and rhodoxanthin were suggested as leads against SARS-CoV-2 infection (Bharathi *et al.*, 2022). Design of inhibitors against the Receptor-Binding domain (RBD) of the S protein of SARS-CoV-2 is a hot area of research now. In one such important study, phytocompounds from two mangrove plants, Pandanus odorifer and Pistacia integerrima, showed activity against the receptor binding domain (RBD) of the S protein of SARS-CoV-2 (Paul *et al.*, 2022). In another computational study, various active sites of the S protein and its

interaction with different conformers of various phytochemicals were examined. The effectiveness of various ethno-medicinal practices were explored to investigate various drug targets to treat COVID-19 infections (Milugo *et al.*, 2025).

Ursolic acid, a pentacyclic terpenoid, is also touted as a potential therapeutic option against SARS-CoV-2 infection (Al-kuraishy *et al.*, 2022). Moreover, the isolation of five abietane-type diterpenes from *Glyptostrobus pensilis* has been reported to be a plausible lead against SARS-CoV-2 (Phong *et al.*, 2022). Similarly, natural biflavones have also been investigated for their inhibition potential against PLpro. The National Compound Library of Traditional Chinese Medicines (NCLTCMs) was searched, and from 9000 TCM-based phytocompounds, nine natural biflavones were selected as potent PLpro inhibitors (Li *et al.*, 2022). And recently, 3 compounds, capparispine, bergenin, and (3*R*)-7,4′-dihydroxy-8-methoxyhomoisoflavane, displayed considerable interaction with key residues of PLpro through hydrophobic interactions and hydrogen bonding, thus highlighting their potency as PLpro inhibitors (Rajchakom *et al.*, 2025).

In addition to that, mannose-specific/mannose-binding lectins (MBL), should also be explored against SARS-CoV-2. Evidence suggests that the glycomimetic approach can be effective in controlling the glycobiological aspects of COVID-19. Plant-based mannose-specific lectins BanLac, FRIL, Lentil, and GRFT from red algae can reduce SARS-CoV-2 infection (S. Sharma & Bhatia, 2020a; Ahmed *et al.*, 2022).

Many medicinal plants have been investigated for possible efficacy against SARS-CoV-2 because for ages they have been used to treat respiratory infections. One such example is *Blumea balsamifera* (L.) DC. Out of 331 phytochemicals investigated, 113 proved to be potent SARS-CoV-2 Mpro inhibitors, with the phenylpropanoid moiety (Ph-C3-) as a possible pharmacophore of the target enzyme (Cayona & Creencia, 2021). In another interesting study, 15 out of 23 active phytochemicals of fingerroot (*Boesenbergia rotunda*) exhibited inhibitory activities against the SARS-CoV-2 main protease enzyme (Gurung *et al.*, 2022). Polycyclic glycoside ouabain is effective for treating COVID-19 patients with cardiovascular morbidity. This was confirmed via in silico methods too (Mithilesh *et al.*, 2022).

In silico investigations confirmed chebulagic acid, chebulinic acid, terflavin A, and chebulinic acid, from *Triphala* formulation as potential inhibitors of SARS-CoV-2 Mpro (Rudrapal *et al.*, 2022). One other class that should be tapped as possible drug leads against SARS-CoV-2 is nucleoside analogs. They are known anticancer and antiviral agents. In fact, in a recent study, Cordycepin (3′-deoxyadenosine) assists greatly in the inhibition of the multiplication of the new resistant strains of SARS-CoV-2. The EC50 of about 2 μM is required, making it better than remdesivir and its active metabolite GS-441524 (Rabie, 2022). This is an interesting finding and paves the way for its preclinical/clinical trials. A TCM Formulation, Jing Si showed inhibition of replication of COVID-19 Variants (Lin *et al.*, 2022). Moreover, forty-six flavonoids were tested in silico against human TMPRSS2 protein, Results seemed promising, with naringin proving to be a better inhibitor for TMPRSS2 and 3CLpro, and hesperidin for Plpro. Glycosylated bioflavonoids were less toxic and had enhanced solubility and bioavailability (Kumar *et al.*, 2022). 50 dietary polyphenols were analyzed computationally for their inhibition potential against Mpro. The analysis revealed some interesting findings. Kievitone and Ellagic acid are promising inhibitors of SARS-CoV-2 main protease as they show effective disruption of the His41 and Cys145 (two crucial residues of Mpro) compared to Remdesivir. Thus, functional foods having kievitone and ellagic acid can be used to manage COVID-19 (Adelusi *et al.*, 2022).

Bitter cola phytochemicals showed promising inhibition against SARS-CoV-2 main protease and RNA dependent-RNA polymerase (Arumugam *et al.*, 2021; Oluyori *et al.*, 2022). Also, Nigella sativa exhibits anti-SARS-CoV activity (Idrees *et al.*, 2021). Computational investigations of fifty-seven phytochemicals against 3CLpro, ACE-2, S protein, and RdRp revealed six phytochemicals showing promise as inhibitors. These were apigenin-o-7-glucuronide and ellagic acid from *Eucalyptus globulus*; eudesmol and viridiflorene from Vitex negundo and; vasicolinone and anisotine from *Justicia adhatoda* when compared with lopinavir and remdesivir, apigenin-o-7-glucuronide appeared to be a remarkable inhibitor of both polymerase and protease (Gowrishankar *et al.*, 2021). In another study, 127 bioactive compounds were screened against the N protein of SARS-CoV-2, nine (eudesmol, linarin, alpha-thujene, kaempferol-3-O-glucuronide, geranyl acetate, cadinene, kaempferide, germacrene A, and baicalin) emerged as potent inhibitors. These phytochemicals come from 3 Indian medicinal plants *Coriandrum sativum*, *Ocimum sanctum*, and *Mentha arvensis* (Muthumanickam *et al.*, 2021). Similar biochemical screening of phytochemicals was done by Bano *et al.* (2025) and Scopoletin was identified as a potent antiviral drug agent against SARS-CoV-2 (Bano *et al.*, 2025).

Gas chromatography was utilized to analyse essential oils from herbal plants of Lebanon viz, *Calamintha origanifolia*, *Pinus pinea*, *Pistacia palaestina*, *Juniperus oxycedrus*, *Juniperus excelsa*, *Cuminum cyminum*, *Pinus brutia*, *Lavandula stoechas*, *Laurus nobilis*, *Origanum syriacum*, *O. ehrenbergi*, *Satureja thymbra*, *Cupressus sempervirens*, *Foeniculum vulgare*, *Mentha longifolia*, *Salvia tribola*, and *Pimpinella anisum* (Muthumanickam *et al.*, 2021). This revealed potential natural compounds against SARS-CoV-2 (Saab *et al.*, 2021). 22 phytochemicals from various Indian medicinal plants were screened against six NSP from SARS-CoV-2. Analysis revealed nine effective phytochemicals, predominantly from *Withania somnifera* (Parida *et al.*, 2021). Exhaustive in silico investigations revealed that Indian medicinal plants *Aegle marmelos*, *Vetiveria zizanoides*, *Moringa oleifera*, and *Punica granatum* have great anti-viral potential (Qazi *et al.*, 2021). Himalayan medicinal plant (HMP) phytochemicals have shown potential inhibition against replication and transmission targets of SARS-CoV-2. About forty-two HMP bioactives were analyzed against these targets for their binding energy, molecular interactions, inhibition constant, and biological pathway enrichment analysis (Natesh *et al.*, 2021). Another similar study postulated the role of HMPs against SARS-CoV-2 (Natesh *et al.*, 2021).

In an important study, 132 phytochemicals from 3 herbal plants conventionally used as antivirals; *Artemisia annua* L. (Asteraceae), *Zingiber officinalis* Roscoe (Zingiberaceae), and *Moringa oleifera* Lam. (Moringaceae), were screened for their inhibition activity against TMPRSS2. Quercetin, niazirin, and moringyne from *Moringa oleifera* exhibited effective inhibition of TMPRSS2 (Oyedara *et al.*, 2021). 605 phytochemicals from 37 plants and 139 antiviral molecules were computationally analyzed in the inhibition of SARS-CoV-2 multiple protein targets. Results revealed the anti-viral properties of traditional "Kabasura kudineer", which is also used in traditional AYUSH medicine (Nallusamy *et al.*, 2021). Phytochemicals isorhamnetin, isorhamnetin 3-*O*-glucoside, astragalin, 3-*O*-caffeoyl quinic acid, and quercetin from *Opuntia ficus-indica* with SARS-CoV-2 Mpro (Vicidomini *et al.*, 2021) with astragalin having a maximum affinity for Mpro and was least toxic. Four phytochemicals were identified from *Nigella sativa*, particularly α-hederin, as RNA-dependent RNA polymerase inhibitors of SARS-CoV-2 (Mir *et al.*, 2022). Alkaloids have also been explored for their antiviral effects against SARS-CoV-2 (Majnooni *et al.*, 2021). Recently, the components of Ligustrum ovalifolium Hassk, which include phenylethanoid/propanoids, iridoids, and triterpenoid derivatives of ursolic acid and oleanolic acid, were also identified as antiviral drug agents against SARS CoV-2 (Afifi *et al.*, 2025). In another study, screening 586 phytochemicals from forty-seven medicinal plants revealed that they could be effective against both the host as well as viral targets (Singh *et al.*, 2021). *Ocimum sanctum*, commonly known as Tulsi was investigated a lot for its possible role against SARS-CoV-2 infection. One such report suggests that flavonoids and polyphenolic compounds of *Tulsi*, especially Luteolin-7-O-glucuronide, after binding to the catalytic residue Cys145 of the main protease, can lead to the irreversible inhibition of the enzyme (Mohapatra *et al.*, 2021). In silico evaluations of the phytochemicals from the plant, *Andrographis paniculata*, led to a promising lead, neoandrographolide (Murugan *et al.*, 2021). Some known antimalarial phytochemicals such as recursive and several shizukaols, have been reported as potential antiviral agents and can be effective against SARS-CoV-2 (Hasan *et al.*, 2021). In another recent study, Beta-Amyrin acetate, 20(29)-Lupenol acetate, 3-Epimoretenol, Lanosterol acetate, and Methyl 3-oxo-12-en-23-oate were identified as the most potent antiviral drug agents against the S protein, RdRp, and SARS-CoV-2 Mpro (Abdullahi *et al.*, 2025).

Chlorogenic acid and hesperidin present in ginger and L-(−)-catechin have been reported to be potential drug leads against Mpro of SARS-CoV-2 (Jahan *et al.*, 2021; Janlou *et al.*, 2025). The concept of chemical space was also invoked for the corroboration of drugs identified from phytochemicals against SARS-CoV-2 (Joshi *et al.*, 2021; Swain *et al.*, 2021). Six phenolic compounds of *Rhus* spp. They were identified for potential inhibition against Mpro of SARS-CoV-2 (Sherif *et al.*, 2021).

In silico investigations revealed that fisetin, quercetin, and kamferol have the potential to disturb the binding of the hACE2-S complex and thus can be explored as possible leads against SARS-CoV-2 (Pandey *et al.*, 2021). In an attempt to identify Mpro inhibitors from a library of bioactives with proven antiviral activities, five active compounds, viz., Withanosides V and VI, Racemosides A and B, and Shatavarin IX, showed promising results, but the best leads were Withanosides V and VI (Patel *et al.*, 2021). One study reported the phytochemicals sarsasapogenin, ursonic acid, curcumin, ajmalicine, novobiocin, silymarin and aranotin, piperine, gingerol, rosmarinic acid, and alpha terpinyl acetate as promising Nsp15 inhibitors (Kumar *et al.*, 2021). In another study, silymarin was identified as a potent drug agent for both omicron and wild-type spikes and human ACE2 protein, which reflects its ability to block the interaction of host-pathogen and avert infection (Dutta *et al.*, 2025). Computational investigations reveal that phytochemicals SilybinC, Isopomiferin, Lycopene, SilydianinB, and Silydianin inhibit the HR1 domain in SARS-CoV-2 S protein (Majeed *et al.*, 2021). In another study, the analysis of 3CLpro and its screening against a medicinal plant library comprising 32,297 probable anti-viral phytochemicals/TCM compounds gave nine possible drug leads against SARS-CoV-2 (Tahir ul Qamar *et al.*, 2020).

In addition to that, Withaferin A from *Withania somnifera*, Silybin, an active constituent found in *Silybum marianum*, phytochemicals from *Tinospora cordiofolia* and *Aloe barbadensis* displayed good binding energetics with the target proteins in SARS-CoV-2 (Pandit & Latha, 2020). Withanolide R and 2,3-Dihydrowithaferin A emerged as potential drug leads from the screening of phytochemicals from *Withania somnifera* and *Azadirachta indica* (Parida *et al.*, 2020b). In another in silico investigation, 92 phytochemicals from medicinal plants of the Andean region were screened against SARS-CoV-2 3CLpro and RdRp. Hesperidin and lupinifolin emerged as potential leads against SARS-CoV-2 infection (Mosquera-Yuqui *et al.*, 2020).

In silico screening of around 1000 phytochemicals derived from traditional Saudi medicinal plants revealed that withanolide A, isocodonocarpine and calonysterone bound tightly to PLpro, luteolin 7-rutinoside, chrysophanol 8-(6-galloylglucoside) and kaempferol 7-(6″-galloylglucoside) effectively bind to RdRp, and chrysophanol 8-(6-galloylglucoside), 3,4,5-tri-O-galloylquinic acid and mulberrofuran G showed strong binding with 3CLpro (Alamri *et al.*, 2020). In another computational investigation, 1916 phytochemicals from fifty-five Indian medicinal plants, were virtually screened on eight structural and non-structural SARS-CoV-2 protein targets. triterpenoids from *Azadirachta indica* and steroidal lactones from *Withania somnifera* emerged as the drug leads (Parida *et al.*, 2020a). 226 phytochemicals from African medicinal plants were virtually screened against RdRp. Alkaloids (strychnopentamine, 10'-hydroxyusambarensine, and cryptospirolepine) and flavonoids (12α-epi-millettosinand usararotenoid A) came out as potential inhibitors of the enzyme (Ogunyemi *et al.*, 2020). The main phytochemicals of the two pulses, *Vigna radiata* and *Vigna mungo*, were virtually screened against C-3, like the main protease of SARS-CoV-2, which showed greater binding of certain phytochemicals with the protease. The authors of this study claim that this could be a cause of the low morbidity of SARS-CoV-2 in India and Bangladesh, as these two pulses are consumed mainly by the populace in these countries (Jannat *et al.*, 2020). Yashtimadhu (*Glycyrrhiza glabra*) was also reported to be effective against

SARS-CoV-2 (Maurya, 2020). Also, phytochemicals from *Solanum surattense* Burm. f. showed potential inhibition against the C-3-like main protease of SARS-CoV-2 (Hasan *et al.*, 2020). An empirical study by Luo *et al.* (2020) saw quicker recovery among patients (n ¼ 54) administered TCM. The Qingfei Paidu decoction used in SARS-CoV-2 treatment (n ¼ 214) produced a significant improvement in patients (60%) after a day regime across 4 provincial-level hospitals in China. 30% of the patients showed stable symptoms without aggravation. This was one of many TCM regimens that have shown effectiveness in screening and clinical trials. It also demonstrates the advantage of using plant secondary metabolites over other natural products, given their lower toxicity, economic costs, and multi-target activities (Andersen *et al.*, 2020; Luo *et al.*, 2020; Zhang, 2020). Zhang *et al.* (2020) used a rational screen approach to conclude that 13 reported TCM derivatives used to fight other viral respiratory infections, such as MERS-CoV/SARSSeCoV, also showed anti-SARS-CoV-2 activity.

Despite the publication of over 5000 reviews in PubMed, since the COVID-19 outbreak, natural product-based strategies have remained neglected. However, literature on various nature-inspired compounds with anti-SARS-CoV and anti-MERS-CoV activity has been of importance as the sequential similarity between the two viruses opens up avenues for computationally supported repurposing of these natural products to tackle SARS-CoV-2 (Andersen *et al.*, 2020). It is a safe and cheap approach to developing anti-COVID-19 drug candidates in shorter periods. The study into phytochemical potential for COVID-19 treatment does not come without its challenges. Knowledge gaps in the mechanism of action of the latent protection against the cytopathic effect of CoV, and crystallographic details of the interaction of phytochemicals with targets on the viral protein remain as obstacles. The inclusion of advanced computational methodologies and machine learning may further strengthen the mission to find potent anti-CoVID drug candidates (Dey *et al.*, 2020; Harrison, 2020; Zhang *et al.*, 2020).

CONCLUSIONS AND FUTURE PERSPECTIVES

As COVID-19 continues to affect millions of people across the globe and exerts overwhelming pressure on national healthcare setups, the search for anti-COVID-19 drugs represents a vital way forward to improve patient outcomes. Since time immemorial, and even in the modern world, especially in aboriginal and tribal communities, substances obtained from medicinal plants have remained a reliable and effective treatment option (Kakkar & Sharma, 2011; Saini *et al.*, 2023a). These include anti-allergic, anti-inflammatory, and anti-viral action.

Apart from their direct anti-viral action on the virus itself, such as 3CLpro, Mpro, and RNA-dependent RNA polymerase inhibition, phytochemicals can also provide other alternative effects to fight SARS-CoV-2. For instance, in cases of COVID-19 with acute respiratory stress disorder, immunomodulatory and anti-inflammatory compounds such as interleukin (IL)-6 antagonists and corticosteroids are employed. *V. amygdala* and *E. longifolia* have both exhibited impedance of the pro-inflammatory cytokines and reduced IL-6 (Asante *et al.*, 2019; Ruan *et al.*, 2019; Zeng *et al.*, 2020). The latter also helps stimulate the immune system in adults, and its ability to control existing cytokine levels needs further validation (George *et al.*, 2016).

The multi-faceted impact of SARS-CoV-2 on patients both during and post-illness through long-term complications such as chronic inflammation, which includes neuropsychiatric and lung fibrosis (Fraser, 2020; Paterson *et al.*, 2020), is a challenge where phytochemicals may be particularly useful. Using the Multi-Target Drug Ligand (MTDL) design, where the computational process focuses on developing ligands that show good binding affinities with multiple targets, has already been used for *in silico* investigation for drug candidates to tackle Alzheimer's Disease, another complex, multifactorial disease (Saini & Sharma, 2024). These molecules are found to have better ADMET properties, can easily cross the blood-brain barrier, and have insignificant side effects. Phytochemicals, by nature, are polypharmacological, less toxic, and have minimal adverse reactions, making them ideal starting candidates for the MTDL approach.

However, phytochemical-based drug design comes with its own set of obstacles. Unlike synthetic drugs, the identification, isolation, and standardization of plant-derived compounds are tedious, slowing down the development of candidates during crises such as the current pandemic (Lim *et al.*, 2021). It also impacts uniformity and effectiveness among batches, which is a major cause of concern. As most medicinal plant usage originates from traditional texts and practices, rigorous scientific validation is necessary. Phytochemicals often consist of harmful chemical moieties which need to be identified and neutralized. Traditionally, plant-derived drug candidates also suffer from poor solubility, low biocompatibility, toxicity, low tissue distribution, etc. which need to be addressed before any effective formulation can be made (Sharma & Bhatia, 2020b; Saini & Sharma, 2023). The reproducibility of experimental findings concerning phytochemicals and their mechanisms of action is often called into question.

Phytochemicals, despite their challenges, represent a vast resource of information that the scientific community should be tapping into to explore potentially revolutionary interventions for COVID-19 management. It combines our traditional knowledge as well as modern technological and scientific advances in a synergistic vehicle that will drive us through not only this pandemic but the pandemics of the future as well.

AUTHORS' CONTRIBUTION

Kunika Saini collected the data, Smriti Sharma did the conception of the paper, Vinayak Bhatia did proof reading, Sheza Zaidi did formatting, and Jayesh Dhalani did reference management.

REFERENCES

Abdullahi, Y., Uthman, U., Shanono, U., Okechukwu, U., Nkechi, O., & Egbe, E. (2025). Molecular docking of SARS - CoV - 2 surface proteins

with some active metabolites from plants used in the therapy of common cold : potential drug identifcation. *Journal of Umm Al-Qura University for Applied Sciences, 2025*, 1-16. https://doi.org/10.1007/s43994-025-00237-2

Adelusi, T. I., Oyedele, A.-Q. K., Monday, O. E., Boyenle, I. D., Idris, M. O., Ogunlana, A. T., Ayoola, A. M., Fatoki, J. O., Kolawole, O. E., David, K. B., & Olayemi, A. A. (2022). Dietary polyphenols mitigate SARS-CoV-2 main protease (Mpro)–Molecular dynamics, molecular mechanics, and density functional theory investigations. *Journal of Molecular Structure, 1250*, 131879. https://doi.org/10.1016/j.molstruc.2021.131879

Afifi, A., Ayoub, M., Kutkat, O., GabAllah, M., & Mohammed, R. (2025). Profiling the phytochemicals and anti-SARS CoV-2 activity of different *Ligustrum ovalifolium* Hassk aerial part extracts: An in vitro-in silico study. *Egyptian Journal of Chemistry, 68*(3), 409-433. https://doi.org/10.21608/ejchem.2024.296342.9836

Ahmad, M., Butt, M. A., Zhang, G., Sultana, S., Tariq, A., & Zafar, M. (2018). *Bergenia ciliata*: A comprehensive review of its traditional uses, phytochemistry, pharmacology and safety. *Biomedicine & Pharmacotherapy, 97*, 708-721. https://doi.org/10.1016/j.biopha.2017.10.141

Ahmad, S., Zahiruddin, S., Parveen, B., Basist, P., Parveen, A., Gaurav, Parveen, R., & Ahmad, M. (2021). Indian Medicinal Plants and Formulations and Their Potential Against COVID-19–Preclinical and Clinical Research. *Frontiers in Pharmacology, 11*, 578970. https://doi.org/10.3389/fphar.2020.578970

Ahmed, M. N., Jahan, R., Nissapatorn, V., Wilairatana, P., & Rahmatullah, M. (2022). Plant lectins as prospective antiviral biomolecules in the search for COVID-19 eradication strategies. *Biomedicine & Pharmacotherapy, 146*, 112507. https://doi.org/10.1016/j.biopha.2021.112507

Alamri, M. A., Altharawi, A., Alabbas, A. B., Alossaimi, M. A., & Alqahtani, S. M. (2020). Structure-based virtual screening and molecular dynamics of phytochemicals derived from Saudi medicinal plants to identify potential COVID-19 therapeutics. *Arabian Journal of Chemistry, 13*(9), 7224-7234. https://doi.org/10.1016/j.arabjc.2020.08.004

Al-kuraishy, H. M., Al-Gareeb, A. I., & El-Saber Batiha, G. (2022). The possible role of Ursolic acid in Covid-19: A real game changer. *Clinical Nutrition ESPEN, 47*, 414-417. https://doi.org/10.1016/j.clnesp.2021.12.030

Alsuhaibani, S., & Khan, M. A. (2017). Immune-stimulatory and therapeutic activity of tinospora cordifolia: Double-edged sword against salmonellosis. *Journal of Immunology Research,* 2017, 1787803. https://doi.org/10.1155/2017/1787803

Andersen, K. G., Rambaut, A., Ian Lipkin, W., Holmes, E. C., & Garry, R. F. (2020). The proximal origin of SARS-CoV-2. *Nature Medicine, 26*, 450-452. https://doi.org/10.1038/s41591-020-0820-9

Anhê, F. F., Desjardins, Y., Pilon, G., Dudonné, S., Genovese, M. I., Lajolo, F. M., & Marette, A. (2013). Polyphenols and type 2 diabetes: A prospective review. *PharmaNutrition, 1*(4), 105-114. https://doi.org/10.1016/j.phanu.2013.07.004

Asante, D.-B., Henneh, I. T., Acheampong, D. O., Kyei, F., Adokoh, C. K., Ofori, E. G., Domey, N. K., Adakudugu, E., Tangella, L. P., & Ameyaw, E. O. (2019). Anti-inflammatory, anti-nociceptive and antipyretic activity of young and old leaves of Vernonia amygdalina. *Biomedicine and Pharmacotherapy, 111*, 1187-1203. https://doi.org/10.1016/j.biopha.2018.12.147

Awasthi, M., Singh, S., Pandey, V. P., & Dwivedi, U. N. (2016). Alzheimer's disease: An overview of amyloid beta dependent pathogenesis and its therapeutic implications along with in silico approaches emphasizing the role of natural products. *Journal of the Neurological Sciences, 361*, 256-271. https://doi.org/10.1016/j.jns.2016.01.008

Balasubramanian, G., Sarathi, M., Kumar, S. R., & Hameed, A. S. S. (2007). Screening the antiviral activity of Indian medicinal plants against white spot syndrome virus in shrimp. *Aquaculture, 263*(1-4), 15-19. https://doi.org/10.1016/j.aquaculture.2006.09.037

Bano, S., Singh, J., Zehra, Z., Sulaimani, M. N., Mohammad, T., Yumlembam, S., Hassan, M. I., Islam, A., & Dey, S. K. (2025). Biochemical Screening of Phytochemicals and Identification of Scopoletin as a Potential Inhibitor of SARS-CoV-2 M^{pro}, Revealing Its Biophysical Impact on Structural Stability. *Viruses, 17*(3), 402. https://doi.org/10.3390/v17030402

Barkat, M. A., Kaushik, P., Barkat, H. A., Khan, M. I., & Hadi, H. A. (2022). Phytoconstituents in the Management of Covid-19: Demystifying the Fact. *Drug Research, 72*(3), 123-130. https://doi.org/10.1055/a-1697-5365

Bhalla, G., Kaur, S., Kaur, J., Kaur, R., & Raina, P. (2017). Antileishmanial and immunomodulatory potential of Ocimum sanctum Linn. and Cocos nucifera Linn. in murine visceral leishmaniasis. *Journal of Parasitic Diseases, 41*, 76-85. https://doi.org/10.1007/s12639-016-0753-x

Bharathi, M., Sivamaruthi, B. S., Kesika, P., Thangaleela, S., & Chaiyasut, C. (2022). In Silico Screening of Potential Phytocompounds from Several Herbs against SARS-CoV-2 Indian Delta Variant B.1.617.2 to Inhibit the Spike Glycoprotein Trimer. *Applied Sciences, 12*(2), 665. https://doi.org/10.3390/app12020665

Bhattacharya, S., & Paul, S. M. N. (2021). Efficacy of phytochemicals as immunomodulators in managing COVID-19: a comprehensive view. *VirusDisease, 32*, 435-445. https://doi.org/10.1007/s13337-021-00706-2

Boukhatem, M. N., & Setzer, W. N. (2020). Aromatic Herbs, Medicinal Plant-Derived Essential Oils, and Phytochemical Extracts as Potential Therapies for Coronaviruses: Future Perspectives. *Plants, 9*(6), 800. https://doi.org/10.3390/plants9060800

Cayona, R., & Creencia, E. (2021). Phytochemical Mining of Potential SARS-CoV-2 Main Protease Inhibitors from Phytochemical Mining of Potential SARS-CoV-2 Main Protease Inhibitors from *Blumea balsamifera* (L.) DC. *Philippine Journal of Science, 151*(1), 235-261.

Chang, J. S., Wang, K. C., Yeh, C. F., Shieh, D. E., & Chiang, L. C. (2013). Fresh ginger (*Zingiber officinale*) has anti-viral activity against human respiratory syncytial virus in human respiratory tract cell lines. *Journal of Ethnopharmacology, 145*(1), 146-151. https://doi.org/10.1016/j.jep.2012.10.043

Chen, J., Wang, Y., Gao, Y., Hu, L.-S., Yang, J., Wang, J., Sun,W., Liang, Z., Cao, Y., Cao, Y. (2020). Protection against COVID-19 injury by qingfei paidu decoction via anti- viral, anti-inflammatory activity and metabolic programming. *Biomedicine & Pharmacotherapy Journal, 129*, 110281. https://doi.org/10.1016/j.biopha.2020.110281

Choudhary, N., & Singh, V. (2022). Multi-scale mechanism of antiviral drug-alike phytoligands from Ayurveda in managing COVID-19 and associated metabolic comorbidities: insights from network pharmacology. *Molecular Diversity, 26*, 2575-2594. https://doi.org/10.1007/s11030-021-10352-x

Cohen, M. M. (2014). Tulsi - Ocimum sanctum: A herb for all reasons. *Journal of Ayurveda and Integrative Medicine, 5*(4), 251-259. https://doi.org/10.4103/0975-9476.146554

Dali, Y., Abbasi, S. M., Khan, S. A. F., Larra, S. A., Rasool, R., Ain, Q. T., & Jafar, T. H. (2019). Computational drug design and exploration of potent phytochemicals against cancer through in silico approaches. *Biomedical Letters, 5*(1), 21-26.

Davinelli, S., Sapere, N., Zella, D., Bracale, R., Intrieri, M., & Scapagnini, G. (2012). Pleiotropic Protective Effects of Phytochemicals in Alzheimer's Disease. *Oxidative Medicine and Cellular Longevity, 2012*, 386527. https://doi.org/10.1155/2012/386527

Devaux, C. A., Rolain, J.-M., Colson, P., & Raoult, D. (2020). New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? *International Journal of Antimicrobial Agents, 55*(5). https://doi.org/10.1016/j.ijantimicag.2020.105938

Devi, M. S. S., Sathiyarajeswaran, P., Kumar, D. T., Kumar, S. U., Siva, R., Doss, G. P., & Kanakavalli, K. (2022). Siddha Medicine and Computer Modeling: A Treasure for SARS-CoV-2 Treatment. In A. T. Azar & A. E. Hassanien (Eds.), *Modeling, Control and Drug Development for COVID-19 Outbreak Prevention* (Vol. 366, pp. 521-541) Cham, Switzerland: Springer. https://doi.org/10.1007/978-3-030-72834-2_15

Dey, L., Chakraborty, S., & Mukhopadhyay, A. (2020). Machine learning techniques for sequence-based prediction of viral–host interactions between SARS-CoV-2 and human proteins. *Biomedical Journal, 43*(5), 438-450. https://doi.org/10.1016/j.bj.2020.08.003

Dutta, S., Pushan, S. S., Ghosh, R., Jose, M., & Pritam, M. (2025). *In silico* Study of Antiviral Phytochemicals for the Potential Drug Development Against Wild-type and Omicron Variants of SARS-CoV-2. *Current Pharmaceutical Biotechnology, 10*, 1-20. https://doi.org/10.2174/0113892010251819241120050831

Ebenezer, O., Bodede, O., Awolade, P., Jordaan, M. A., Ogunsakin, R. E., & Shapi, M. (2022). Medicinal plants with anti-SARS-CoV activity repurposing for treatment of COVID-19 infection: A systematic review and meta-analysis. *Acta Pharmaceutica, 72*(2), 199-224. https://doi.org/10.2478/acph-2022-0021

Eng, Y. S., Lee, C. H., Lee, W. C., Huang, C. C., & Chang, J. S. (2019). Unraveling the molecular mechanism of traditional Chinese medicine: Formulas against acute airway viral infections as examples. *Molecules,*

24(19), 3505. https://doi.org/10.3390/molecules24193505
Fraser, E. (2020). Long term respiratory complications of covid-19. *British Medical Journal, 2020*, 370. https://doi.org/10.1136/bmj.m3001
George, A., Suzuki, N., Abas, A. B., Mohri, K., Utsuyama, M., Hirokawa, K., & Takara, T. (2016). Immunomodulation in middle-aged humans via the ingestion of Physta® standardized root water extract of *Eurycoma longifolia* Jack - A randomized, double-blind, placebo-controlled, parallel study. *Phytotherapy Research, 30*(4), 627-635. https://doi.org/10.1002/ptr.5571
Gerlach, S. L., Chandra, P. K., Roy, U., Gunasekera, S., Göransson, U., Wimley, W. C., Braun, S. E., & Mondal, D. (2019). The Membrane-Active Phytopeptide Cycloviolacin O2 Simultaneously Targets HIV-1-infected Cells and Infectious Viral Particles to Potentiate the Efficacy of Antiretroviral Drugs. *Medicines, 6*(1), 33. https://doi.org/10.3390/medicines6010033
Ghanimi, R., Ouhammou, A., Atki, Y. E., & Cherkaoui, M. (2022). Molecular docking study of the main phytochemicals of some medicinal plants used against COVID-19 by the rural population of Al-Haouz region, Morocco. *Journal of Pharmacy & Pharmacognosy Research, 10*(1), 227-238. https://doi.org/10.56499/jppres21.1200_10.2.227
Ghoke, S. S., Sood, R., Kumar, N., Pateriya, A. K., Bhatia, S., Mishra, A., Dixit, R., Singh, V. K., Desai, D. N., Kulkarni, D. D., Dimri, U., & Singh, V. P. (2018). Evaluation of antiviral activity of *Ocimum sanctum* and *Acacia arabica* leaves extracts against H9N2 virus using embryonated chicken egg model. *BMC Complementary and Alternative Medicine, 18*, 174. https://doi.org/10.1186/s12906-018-2238-1
Gorlenko, C. L., Kiselev, H. Y., Budanova, E. V., Zamyatnin, A. A., & Ikryannikova, L. N. (2020). Plant secondary metabolites in the battle of drugs and drug-resistant bacteria: New heroes or worse clones of antibiotics? *Antibiotics, 9*(4), 170. https://doi.org/10.3390/antibiotics9040170
Gowrishankar, S., Muthumanickam, S., Kamaladevi, A., Karthika, C., Jothi, R., Boomi, P., Maniazhagu, D., & Pandian, S. K. (2021). Promising phytochemicals of traditional Indian herbal steam inhalation therapy to combat COVID-19 – An in silico study. *Food and Chemical Toxicology, 148*, 111966. https://doi.org/10.1016/j.fct.2020.111966
Gurung, A. B., Ali, M. A., Al-Hemaid, F., El-Zaidy, M., & Lee, J. (2022). *In silico* analyses of major active constituents of fingerroot (*Boesenbergia rotunda*) unveils inhibitory activities against SARS-CoV-2 main protease enzyme. *Saudi Journal of Biological Sciences, 29*(1), 65-74. https://doi.org/10.1016/j.sjbs.2021.11.053
Harrison, C. (2020). Coronavirus puts drug repurposing on the fast track. *Nature Biotechnology, 38*, 379-381. https://doi.org/10.1038/d41587-020-00003-1
Harrison, S. L., Fazio-Eynullayeva, E., Lane, D. A., Underhill, P., & Lip,G. Y. H. (2020). Comorbidities associated with mortality in 31,461 adults with COVID-19 in the United States: A federated electronic medical record analysis. *PLoS Medicine, 17*(9), e1003321. https://doi.org/10.1371/journal.pmed.1003321
Hasan, A., Al Mahamud, R., Jannat, K., & Bondhon, T. A., Farzana, B., Fariba, M. H., Jahan, R., & Rahmatullah, M. (2020). Phytochemicals from *Solanum surattense* Burm. f. have high binding affinities for C-3 like main protease of COVID-19 (SARS-CoV-2). *Journal of Medicinal Plants Studies, 8*(4), 20-26.
Hasan, A., Biswas, P., Bondhon, T. A., Jannat, K., Paul, T. K., Paul, A. K., Jahan, R., Nissapatorn, V., Mahboob, T., Wilairatana, P., Hasan, M. N., de Lourdes Pereira, M., Wiart, C., & Rahmatullah, M. (2022). Can *Artemisia herba-alba* Be Useful for Managing COVID-19 and Comorbidities? *Molecules, 27*(2), 492. https://doi.org/10.3390/molecules27020492
Hasan, A., Jannat, K., Bondhon, T. A., Jahan, R., Hossan, M. S., de Lourdes Pereira, M., Nissapatorn, V., Wiart, C., & Rahmatullah, M. (2021). Can Antimalarial Phytochemicals be a Possible Cure for COVID-19? Molecular Docking Studies of Some Phytochemicals to SARS-CoV-2 3C-like Protease. *Infectious Disorders - Drug Targets*, *21*(1), e290721195143. https://doi.org/10.2174/1871526521666210729164054
Hussain, I., Hussain, A., Alajmi, M. F., Rehman, M. T., & Amir, S. (2021). Impact of repurposed drugs on the symptomatic COVID-19 patients. *Journal of Infection and Public Health, 14*(1), 24-38. https://doi.org/10.1016/j.jiph.2020.11.009
Idrees, M., Khan, S., Memon, N. H., & Zhang, Z. (2021). Effect of the Phytochemical Agents against the SARS-CoV and Some of them Selected for Application to COVID-19: A Mini-Review. *Current Pharmaceutical Biotechnology, 22*(4), 444-450.
Jahan, R., Paul, A. K., Bondhon, T. A., Hasan, A., Jannat, K., Mahboob, T., Nissapatorn, V., Pereira, M. de L., Wiart, C., Wilairatana, P., & Rahmatullah, M. (2021). *Zingiber officinale*: Ayurvedic Uses of the Plant and *In Silico* Binding Studies of Selected Phytochemicals With Mpro of SARS-CoV-2. *Natural Product Communications*, *16*(10), 1-13. https://doi.org/10.1177/1934578X211031766
Janlou, M. A. M., Sahebjamee, H., Alaie, H. R., & Heidari, M. (2025). A Virtual Study on the Active Ingredients of *Zingiber officinale* and *Boswellia serrata* as Potential Natural Inhibitors of SARS-COV-2 Main Protease Enzyme. *Journal of Medicinal Plants and By-Products, 14*(2), 137-148. https://doi.org/10.22034/jmpb.2024.365268.1670
Jannat, K., Hasan, A., Al Mahamud, R., Jahan, R., Bondhon, T. A., Rahmatullah, M., Farzana, B., & Rahmatullah, M. (2020). *In silico* screening of *Vigna radiata* and *Vigna mungo* phytochemicals for their binding affinity to SARS-CoV-2 (COVID-19) main protease ($3CL^{pro}$). *Journal of Medicinal Plants Studies, 8*(4), 89-95.
Jia, W., Wang, C., Wang, Y., Pan, G., Jiang, M., Li, Z., & Zhu, Y. (2015). Qualitative and quantitative analysis of the major constituents in Chinese medical preparation lianhua-qingwen capsule by UPLC-DAD-QTOF-MS. *The Scientific World Journal, 2015*, 731765. https://doi.org/10.1155/2015/731765
Jin, J. H., Lee, D.-U., Kim, Y. S., & Kim, H. P. (2011). Anti-allergic activity of sesquiterpenes from the rhizomes of *Cyperus rotundus*. *Archives of Pharmacal Research, 34*, 223-228. https://doi.org/10.1007/s12272-011-0207-z
Jo, S., Kim, S., Shin, D. H., & Kim, M. S. (2020). Inhibition of SARS-CoV 3CL protease by flavonoids. *Journal of Enzyme Inhibition and Medicinal Chemistry, 35*(1), 145-151. https://doi.org/10.1080/14756366.2019.1690480
Joshi, G., Sindhu, J., Thakur, S., Rana, A., Sharma, G., Mayank, & Poduri, R. (2021). Recent efforts for drug identification from phytochemicals against SARS-CoV-2: Exploration of the chemical space to identify druggable leads. *Food and Chemical Toxicology, 152*, 112160. https://doi.org/10.1016/j.fct.2021.112160
Kakkar, R., & Sharma, S. (2011). DFT study of interactions of carbenes with boron nitride nanotubes. *Chemistry Journal, 1*(1), 9-20.
Kamat, S., & Kumari, M. (2021). Repurposing Chloroquine Against Multiple Diseases With Special Attention to SARS-CoV-2 and Associated Toxicity. *Frontiers in Pharmacology, 12*, 576093. https://doi.org/10.3389/fphar.2021.576093
Kolifarhood, G., Aghaali, M., Saadati, H. M., Taherpour, N., Rahimi, S., Izadi, N., & Nazari, S. S. H. (2020). Epidemiological and Clinical Aspects of COVID-19; a Narrative Review. *Archives of Academic Emergency Medicine, 8*(1), e41.
Koulgi, S., Jani, V., Uppuladinne, M., Sonavane, U., Nath, A. K., Darbari, H., & Joshi, R. (2021). Drug repurposing studies targeting SARS-CoV-2: an ensemble docking approach on drug target 3C-like protease (3CLpro). *Journal of Biomolecular Structure and Dynamics, 39*(15), 5735-5755. https://doi.org/10.1080/07391102.2020.1792344
Kumar, S., Kashyap, P., Chowdhury, S., Kumar, S., Panwar, A., & Kumar, A. (2021). Identification of phytochemicals as potential therapeutic agents that binds to Nsp15 protein target of coronavirus (SARS-CoV-2) that are capable of inhibiting virus replication. *Phytomedicine, 85*, 153317. https://doi.org/10.1016/j.phymed.2020.153317
Kumar, S., Paul, P., Yadav, P., Kaul, R., Maitra, S. S., Jha, S. K., & Chaari, A. (2022). A multi-targeted approach to identify potential flavonoids against three targets in the SARS-CoV-2 life cycle. *Computers in Biology and Medicine, 142*, 105231. https://doi.org/10.1016/j.compbiomed.2022.105231
Lai, W.-L., Chuang, H.-S., Lee, M.-H., Wei, C.-L., Lin, C.-F., & Tsai, Y.-C. (2012). Inhibition of herpes simplex virus type 1 by thymol-related mono-terpenoids. *Planta Medica, 78*(15), 1636-1638. https://doi.org/10.1055/s-0032-1315208
Lampariello, L. R., Cortelazzo, A., Guerranti, R., Sticozzi, C., & Valacchi, G. (2012). The magic velvet bean of mucuna pruriens. *Journal of Traditional and Complementary Medicine, 2*(4), 331-339. https://doi.org/10.1016/S2225-4110(16)30119-5
Lee, D. Y. W., Li, Q. Y., Liu, J., & Efferth, T. (2021). Traditional Chinese herbal medicine at the forefront battle against COVID-19: Clinical experience and scientific basis. *Phytomedicine, 80*, 153337. https://doi.org/10.1016/j.phymed.2020.153337
Li, L., Ma, L., Hu, Y., Li, X., Yu, M., Shang, H., & Zou, Z. (2022). Natural

biflavones are potent inhibitors against SARS-CoV-2 papain-like protease. *Phytochemistry, 193*, 112984. https://doi.org/10.1016/j.phytochem.2021.112984

Lim, X. Y., Teh, B. P., & Tan, T. Y. C. (2021). Medicinal Plants in COVID-19: Potential and Limitations. *Frontiers in Pharmacology, 12*, 611408. https://doi.org/10.3389/fphar.2021.611408

Lin, Y., Chiang, C.-Y., Shibu, M. A., Su, S.-H., Dass, K. T. P., Lin, P., Lin, S.-Z., Ho, T.-J., Kuo, W.-W., & Huang, C.-Y. (2022). Novel Herbal Formulation Jing Si Exhibits Multiple Functions to Inhibit Replication Activity and Subsides Viral Load of COVID-19 Variants. *Research Square,* 1-16. https://doi.org/10.21203/rs.3.rs-1122886/v1

Liu, A.-L., & Du, G.-H. (2012). Antiviral Properties of Phytochemicals. In A. K. Patra (Eds), *Dietary Phytochemicals and Microbes* (pp. 93-126) Dordrecht, Netherlands: Springer. https://doi.org/10.1007/978-94-007-3926-0_3

Liu, Z., Li, X., Gou, C., Li, L., Luo, X., Zhang, C., Zhang, Y., Zhang, J., Jin, A., Li, H., Zeng, Y., Li, T., & Wang, X. (2020). Effect of Jinhua Qinggan granules on novel coronavirus pneumonia in patients. *Journal of Traditional Chinese Medicine, 40*(3), 467-472. https://doi.org/10.19852/j.cnki.jtcm.2020.03.016

Loizzo, M. R., Saab, A. M., Tundis, R., Statti, G. A., Menichimi, F., Lampronti, I., Gambari, R., Cinatl, J., & Doerr, H. W. (2008). Phytochemical analysis and *in vitro* antiviral activities of the essential oils of seven Lebanon species. *Chemistry and Biodiversity, 5*(3), 461-470. https://doi.org/10.1002/cbdv.200890045

Luo, E., Zhang, D., Luo, H., Liu, B., Zhao, K., Zhao, Y., Bian, Y., & Wang, Y. (2020). Treatment efficacy analysis of traditional Chinese medicine for novel coronavirus pneumonia (COVID-19): An empirical study from Wuhan, Hubei Province, China. *Chinese Medicine, 15*, 34. https://doi.org/10.1186/s13020-020-00317-x

Majeed, A., Hussain, W., Yasmin, F., Akhtar, A., & Rasool, N. (2021). Virtual Screening of Phytochemicals by Targeting HR1 Domain of SARS-CoV-2 S Protein: Molecular Docking, Molecular Dynamics Simulations, and DFT Studies. *BioMed Research International, 2021*, 6661191. https://doi.org/10.1155/2021/6661191

Majnooni, M. B., Fakhri, S., Bahrami, G., Naseri, M., Farzaei, M. H., & Echeverría, J. (2021). Alkaloids as Potential Phytochemicals against SARS-CoV-2: Approaches to the Associated Pivotal Mechanisms. *Evidence-Based Complementary and Alternative Medicine, 2021*, 6632623. https://doi.org/10.1155/2021/6632623

Malekmohammad, K., & Rafieian-Kopaei, M. (2021). Mechanistic Aspects of Medicinal Plants and Secondary Metabolites against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). *Current Pharmaceutical Design, 27*(38), 3996-4007. https://doi.org/10.2174/1381612827666210705160130

Maurya, D. K. (2020). Evaluation of Yashtimadhu (Glycyrrhiza glabra) active Phytochemicals Against Novel Coronavirus (SARS-CoV-2). *Research Square,* 1-18. https://doi.org/10.21203/rs.3.rs-26480/v1

Milugo, T. K., Owuor, B., Okanya, P. W., Chepukosi, K., & Obiero, G. F. (2025). Natural compounds from ethno-medicinal plants exhibit multiple binding activities on SARS-CoV-2 spike protein receptor-binding domains. *Frontiers in Natural Products, 4*, 1597609. https://doi.org/10.3389/fntpr.2025.1597609

Ministry of Ayush. (2020). *First report and Recommendations: Interdisciplinary Committee for integration of Ayurveda and Yoga Interventions in the 'National Clinical Management Protocol: COVID-19'*.

Mir, S. A., Firoz, A., Alaidarous, M., Alshehri, B., Bin Dukhyil, A. A., Banawas, S., Alsagaby, S. A., Alturaiki, W., Bhat, G. A., Kashoo, F., & Abdel-Hadi, A. M. (2022). Identification of SARS-CoV-2 RNA-dependent RNA polymerase inhibitors from the major phytochemicals of *Nigella sativa*: An *in silico* approach. *Saudi Journal of Biological Sciences, 29*(1), 394-401. https://doi.org/10.1016/j.sjbs.2021.09.002

Mithilesh, S., Raghunandan, D., & Suresh, P. K. (2022). *In-Silico* Identification of Natural Compounds from Traditional Medicine as Potential Drug Leads against SARS-CoV-2 Through Virtual Screening. *Proceedings of the National Academy of Sciences, India Section B: Biological Sciences, 92*, 81-87. https://doi.org/10.1007/s40011-021-01292-5

Mohanty, S. K., Swamy, M. K., Sinniah, U. R., & Anuradha, M. (2017). *Leptadenia reticulata* (Retz.) Wight & Arn. (Jivanti): Botanical, agronomical, phytochemical, pharmacological, and biotechnological aspects. *Molecules, 22*(6), 1019. https://doi.org/10.3390/molecules22061019

Mohapatra, P. K., Chopdar, K. S., Dash, G. C., Mohanty, A. K., & Raval, M. K. (2021). *In silico* screening and covalent binding of phytochemicals of *Ocimum sanctum* against SARS-CoV-2 (COVID 19) main protease. *Journal of Biomolecular Structure and Dynamics, 41*(2), 435-444. https://doi.org/10.1080/07391102.2021.2007170

More, P., & Pai, K. (2011). Immunomodulatory effects of *Tinospora cordifolia* (Guduchi) on macrophage activation. *Biology and Medicine, 3*(2), 134-140.

Mosquera-Yuqui, F., Lopez-Guerra, N., & Moncayo-Palacio, E. A. (2020). Targeting the 3CLpro and RdRp of SARS-CoV-2 with phytochemicals from medicinal plants of the Andean Region: molecular docking and molecular dynamics simulations. *Journal of Biomolecular Structure and Dynamics, 40*(5), 2010-2023. https://doi.org/10.1080/07391102.2020.1835716

Mouhajir, F., Hudson, J. B., Rejdali, M., & Towers, G. H. N. (2001). Multiple antiviral activities of endemic medicinal plants used by Berber peoples of Morocco. *Pharmaceutical Biology, 39*(5), 364-374. https://doi.org/10.1076/phbi.39.5.364.5892

Mukherjee, P. K., Efferth, T., Das, B., Kar, A., Ghosh, S., Singha, S., Debnath, P., Sharma, N., Bhardwaj, P., & Haldar, P. K. (2022). Role of medicinal plants in inhibiting SARS-CoV-2 and in the management of post-COVID-19 complications. *Phytomedicine 98*, 153930. https://doi.org/10.1016/j.phymed.2022.153930

Mukta, N., & Neeta, M. P. (2017). A Review on Sesame - an Ethno Medicinally Significant Oil Crop. *International Journal of Life Science & Pharma Research, 7*(2), 58-63.

Murugan, N. A., Pandian, C. J., & Jeyakanthan, J. (2021). Computational investigation on *Andrographis paniculata* phytochemicals to evaluate their potency against SARS-CoV-2 in comparison to known antiviral compounds in drug trials. *Journal of Biomolecular Structure and Dynamics, 39*(12), 4415-4426. https://doi.org/10.1080/07391102.2020.1777901

Muthumanickam, S., Kamaladevi, A., Boomi, P., Gowrishankar, S., & Pandian, S. K. (2021). Indian Ethnomedicinal Phytochemicals as Promising Inhibitors of RNA-Binding Domain of SARS-CoV-2 Nucleocapsid Phosphoprotein: An *In Silico* Study. *Frontiers in Molecular Biosciences, 8*, 637329. https://doi.org/10.3389/fmolb.2021.637329

Nallusamy, S., Mannu, J., Ravikumar, C., Angamuthu, K., Nathan, B., Nachimuthu, K., Ramasamy, G., Muthurajan, R., Subbarayalu, M., & Neelakandan, K. (2021). Exploring Phytochemicals of Traditional Medicinal Plants Exhibiting Inhibitory Activity Against Main Protease, Spike Glycoprotein, RNA-dependent RNA Polymerase and Non-Structural Proteins of SARS-CoV-2 Through Virtual Screening. *Frontiers in Pharmacology, 12*, 667704. https://doi.org/10.3389/fphar.2021.667704

Natesh, J., Mondal, P., Kaur, B., Salam, A. A. A., Kasilingam, S., & Meeran, S. M. (2021). Promising phytochemicals of traditional Himalayan medicinal plants against putative replication and transmission targets of SARS-CoV-2 by computational investigation. *Computers in Biology and Medicine, 133*, 104383. https://doi.org/10.1016/j.compbiomed.2021.104383

Ni, W., Yang, X., Yang, D., Bao, J., Li, R., Xiao, Y., Hou, C., Wang, H., Liu, J., Yang, D., Xu, Y., Cao, Z., & Gao, Z. (2020). Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. *Critical Care, 24*, 422. https://doi.org/10.1186/s13054-020-03120-0

Niphade, S. R., Asad, M., Chandrakala, G. K., Toppo, E., & Deshmukh, P. (2009). Immunomodulatory activity of *Cinnamomum zeylanicum* bark. *Pharmaceutical Biology, 47*(12), 1168-1173. https://doi.org/10.3109/13880200903019234

Ogunyemi, O. M., Gyebi, G. A., Elfiky, A. A., Afolabi, S. O., Ogunro, O. B., Adegunloye, A. P., & Ibrahim, I. M. (2020). Alkaloids and flavonoids from African phytochemicals as potential inhibitors of SARS-Cov-2 RNA-dependent RNA polymerase: an *in silico* perspective. *Antiviral Chemistry and Chemotherapy, 28*, 1-15. https://doi.org/10.1177/2040206620984076

Oluyori, A. P., Olanipekun, B. E., Adeyemi, O. S., Egharevba, G. O., Adegboyega, A. E., & Oladeji, O. S. (2022). Molecular docking, pharmacophore modelling, MD simulation and in silico ADMET study reveals bitter cola constituents as potential inhibitors of SARS-CoV-2 main protease and RNA dependent-RNA polymerase. *Journal of Biomolecular Structure and Dynamics, 42*(4), 1510-1525. https://doi.org/10.1080/07391102.2021.2024883

Oyedara, O. O., Agbedahunsi, J. M., Adeyemi, F. M., Juárez-Saldivar, A., Fadare, O. A., Adetunji, C. O., & Rivera, G. (2021). Computational

screening of phytochemicals from three medicinal plants as inhibitors of transmembrane protease serine 2 implicated in SARS-CoV-2 infection. *Phytomedicine Plus, 1*(4), 100135. https://doi.org/10.1016/j.phyplu.2021.100135

Panda, S. K., Padhi, L., Leyssen, P., Liu, M., Neyts, J., & Luyten, W. (2017). Antimicrobial, anthelmintic, and antiviral activity of plants traditionally used for treating infectious disease in the Similipal Biosphere Reserve, Odisha, India. *Frontiers in Pharmacology, 8*, 658. https://doi.org/10.3389/fphar.2017.00658

Pandey, P., Rane, J. S., Chatterjee, A., Kumar, A., Khan, R., Prakash, A., & Ray, S. (2021). Targeting SARS-CoV-2 spike protein of COVID-19 with naturally occurring phytochemicals: an *in silico* study for drug development. *Journal of Biomolecular Structure and Dynamics, 39*(16), 6306-6316. https://doi.org/10.1080/07391102.2020.1796811

Pandit, M., & Latha, N. (2020). *In silico* studies reveal potential antiviral activity of phytochemicals from medicinal plants for the treatment of COVID-19 infection. *Research Square,* 1-31. https://doi.org/10.21203/rs.3.rs-22687/v1

Parida, P. K., Paul, D., & Chakravorty, D. (2020a). Nature to Nurture- Identifying phytochemicals from Indian medicinal plants as prophylactic medicine by rational screening to be potent against multiple drug targets of SARS-CoV-2. *ChemRxiv*. https://doi.org/10.26434/chemrxiv.12355937.v1

Parida, P. K., Paul, D., & Chakravorty, D. (2020b). The natural way forward: Molecular dynamics simulation analysis of phytochemicals from Indian medicinal plants as potential inhibitors of SARS-CoV-2 targets. *Phytotherapy Research*, *34*(12), 3420-3433. https://doi.org/10.1002/ptr.6868

Parida, P. K., Paul, D., & Chakravorty, D. (2021). Nature's therapy for COVID-19: Targeting the vital non-structural proteins (NSP) from SARS-CoV-2 with phytochemicals from Indian medicinal plants. *Phytomedicine Plus, 1*(1), 100002. https://doi.org/10.1016/j.phyplu.2020.100002

Patel, C. N., Jani, S. P., Jaiswal, D. G., Kumar, S. P., Mangukia, N., Parmar, R. M., Rawal, R. M., & Pandya, H. A. (2021). Identification of antiviral phytochemicals as a potential SARS-CoV-2 main protease (M^{pro}) inhibitor using docking and molecular dynamics simulations. *Scientific Reports, 11*, 20295. https://doi.org/10.1038/s41598-021-99165-4

Patel, P., & Asdaq, S. M. B. (2010). Immunomodulatory activity of methanolic fruit extract of *Aegle marmelos* in experimental animals. *Saudi Pharmaceutical Journal, 18*(3), 161-165. https://doi.org/10.1016/j.jsps.2010.05.006

Paterson, R. W., Brown, R. L., Benjamin, L., Nortley, R., Wiethoff, S., Bharucha, T., Jayaseelan, D. L., Kumar, G., Raftopoulos, R. E., Zambreanu, L., Vivekanandam, V., Khoo, A., Geraldes, R., Chinthapalli, K., Boyd, E., Tuzlali, H., Price, G., Christofi, G., Morrow,J.,... Zandi, M. S. (2020). The emerging spectrum of COVID-19 neurology: Clinical, radiological and laboratory findings. *Brain, 143*(10), 3104-3120. https://doi.org/10.1093/brain/awaa240

Patil, G. G., Mali, P. Y., & Bhadane, V. V. (2008). Folk remedies used against respiratory disorders in Jalgaon district, Maharashtra. *Natural Product Radiance, 7*(4), 354-358.

Paul, G. K., Mahmud, S., Aldahish, A. A., Afroze, M., Biswas, S., Gupta, S. B. R., Razu, M. H., Zaman, S., Uddin, M. S., Nahari, M. H., Alshahrani, M. M., Alshahrani, M. A. R., Khan, M., & Saleh, M. A. (2022). Computational screening and biochemical analysis of *Pistacia integerrima* and *Pandanus odorifer* plants to find effective inhibitors against Receptor- Binding domain (RBD) of the spike protein of. *Arabian Journal of Chemistry, 15*(2), 103600. https://doi.org/10.1016/j.arabjc.2021.103600

Phong, N. V., Trang, N. M., Quyen, C. T., Anh, H. L. T., & Vinh, L. B. (2022). SARS-CoV-2 main protease and papain-like protease inhibition by abietane-type diterpenes isolated from the branches of *Glyptostrobus pensilis* using molecular docking studies. *Natural Product Research, 36*(24), 6336-6343. https://doi.org/10.1080/14786419.2022.2025801

Qazi, S., Das, S., Khuntia, B. K., Sharma, V., Sharma, S., Sharma, G., & Raza, K. (2021). In Silico Molecular Docking and Molecular Dynamic Simulation Analysis of Phytochemicals From Indian Foods as Potential Inhibitors of SARS-CoV-2 RdRp and 3CLpro. *Natural Product Communications, 16*(9), 1-12. https://doi.org/10.1177/1934578X211031707

Rabie, A. M. (2022). Potent Inhibitory Activities of the Adenosine Analogue Cordycepin on SARS-CoV-2 Replication. *ACS Omega, 7*(3), 2960-2969. https://doi.org/10.1021/acsomega.1c05998

Rajamanickam, B., Balasubramanian, R., Rajammal, M. Y., Govindaraju, B., Selvaraaju, S. S., Thangarasu, H., & Kadarkarai, K. (2025). Exploring the Potential of Siddha Formulation MilagaiKudineer-Derived Exploring the Potential of Siddha Formulation MilagaiKudineer-Derived Phytotherapeutics Against SARS-CoV-2 : An In-Silico Investigation for Antiviral Intervention. *Journal of Pharmacy and Pharmacology Research, 9*(2), 17-27. https://doi.org/10.26502/fjppr.0105

Rajchakom, C., Darai, N., Boonma, T., Sungthong, B., Puthongking, P., Nualkaew, S., Sripadung, P., Rungrotmongkol, T., & Nunthaboot, N. (2025). Molecular insights into natural product compounds targeting papain protease of SARS-CoV-2 through molecular dynamics simulation. *Monatshefte Fur Chemie - Chemical Monthly, 156*, 219-232. https://doi.org/10.1007/s00706-024-03271-8

Rastogi, S., Pandey, D. N., & Singh, R. H. (2020). COVID-19 pandemic: A pragmatic plan for ayurveda intervention. *Journal of Ayurveda and Integrative Medicine, 13*(1), 100312. https://doi.org/10.1016/j.jaim.2020.04.002

Rodrigues, T., Reker, D., Schneider, P., & Schneider, G. (2016). Counting on natural products for drug design. *Nature Chemistry, 8*, 531-541. https://doi.org/10.1038/nchem.2479

Ruan, J., Li, Z., Zhang, Y., Chen, Y., Liu, M., Han, L., Zhang, Y., & Wang, T. (2019). Bioactive Constituents from the Roots of *Eurycoma longifolia*. *Molecules, 24*(17), 3157. https://doi.org/10.3390/molecules24173157

Rudrapal, M., Celik, I., Khan, J., Ansari, M. A., Alomary, M. N., Alatawi, F.A., Yadav, R., Sharma, T., Tallei, T. E., Pasala, P. K., Sahoo, R. K., Khairnar, S. J., Bendale, A. R., Zothantluanga, J. H., Chetia, D., & Walode, S. G. (2022). Identification of bioactive molecules from *Triphala* (Ayurvedic herbal formulation) as potential inhibitors of SARS-CoV-2 main protease (Mpro) through computational investigations. *Journal of King Saud University – Science, 34*(3), 101826. https://doi.org/10.1016/j.jksus.2022.101826

Saab, A. M., Tacchini, M., Sacchetti, G., Contini, C., Schulz, H., Lampronti, I., Gambari, R., Makhlouf, H., Tannoury, M., Venditti, A., Bianco, A., & Racagni, G. (2021). Phytochemical analysis and potential natural compounds against SARS-CoV-2/COVID-19 in essential oils derived from medicinal plants originating from Lebanon. An information note. *Plant Biosystems, 156*(4), 855-864. https://doi.org/10.1080/11263504.2021.1932629

Sachan, S., Dhama, K., Latheef, S. K., Samad, H. A., Mariappan, A. K., Munuswamy, P., Singh, R., Singh, K. P., Malik, Y. S., & Singh, R. K. (2019). Immunomodulatory potential of *Tinospora cordifolia* and CpG ODN (TLR21 agonist) against the very virulent, infectious bursal disease virus in SPF chicks. *Vaccines, 7*(3), 106. https://doi.org/10.3390/vaccines7030106

Saini, K., & Sharma, S. (2022). Use of Tyrosine Kinase Inhibitors for treating Type 2 Diabetes Mellitus: An appraisal. *Chemical Biology Letters, 9*(3), 320.

Saini, K., & Sharma, S. (2023). Nanomedicine's transformative impact on anti-diabetic drug discovery: an appraisal. *Journal of Nanoparticle Research, 25*, 227. https://doi.org/10.1007/s11051-023-05870-8

Saini, K., & Sharma, S. (2024). QSAR Studies of Sodium/Glucose Co-Transporter 2 Inhibitors as Potent Anti-Diabetic Drug Agents. *Theoretical Foundations of Chemical Engineering, 57*, S51-S56. https://doi.org/10.1134/S004057952307014X

Saini, K., Khan, Y., & Sharma, S. (2023a). How Effective are Gliflozins as DPP-4 Inhibitors? A Computational Study. *Theoretical Foundations of Chemical Engineering, 57*, 403-410. https://doi.org/10.1134/S0040579523030168

Saini, K., Sharma, S., & Bhatia, V. (2022). Drug Repurposing and Computational Drug Discovery for Diabetes. *Futuristic Trends in Biotechnology, 2*, 103-130.

Saini, K., Sharma, S., & Khan, Y. (2023d). DPP-4 inhibitors for treating T2DM - hype or hope? an analysis based on the current literature. *Frontiers in Molecular Biosciences, 10*, 1130625. https://doi.org/10.3389/fmolb.2023.1130625

Saini, K., Sharma, S., Bhatia, V., & Zaidi, S. (2023c). Recent advances in Mass Spectrometry : An appraisal of fundamentals and applications. *Journal of Molecular Chemistry, 3*(1), 584.

Saini, K., Sharma, S., Bhatia, V., Khan, Y., & Etters, L. (2023b). Dietary Polyphenolics : Mechanistic role in control management of Diabetes and Metabolic Syndrome. *Chemical Biology Letters, 10*(3), 1-16.

Sampath Kumar, K. P., Bhowmik, D., Chiranjib, Tiwari, P., & Kharel, R. (2010). Indian traditional herbs Adhatoda vasica and its Medicinal application. *Journal of Chemical and Pharmaceutical Research, 2*(1), 240-245.

Shah, R. R. (2021). Chloroquine and hydroxychloroquine for COVID-19: Perspectives on their failure in repurposing. *Journal of Clinical Pharmacy and Therapeutics, 46*(1), 17-27. https://doi.org/10.1111/jcpt.13267

Sharma, M. L., Rao, C. S., & Duda, P. L. (1994). Immunostimulatory activity of *Picrorhiza kurroa* leaf extract. *Journal of Ethnopharmacology, 41*(3), 185-192. https://doi.org/10.1016/0378-8741(94)90031-0

Sharma, S., & Bhatia, V. (2020a). Drug Design of GLP-1 Receptor Agonists: Importance of *In Silico* Methods. *Current Pharmaceutical Design, 27*(8), 1015-1024. https://doi.org/10.2174/1381612826666201118094502

Sharma, S., & Bhatia, V. (2020b). Phytochemicals for Drug Discovery in Alzheimer's Disease: *In Silico* Advances. *Current Pharmaceutical Design, 27*(25), 2848-2860. https://doi.org/10.2174/1381612826666200928161721

Sharma, S., Khan, Y., & Saini, K. (2022). Role of QSAR in filling in the gaps of COVID 19 therapeutics. *Pharma Focus Europe*.

Sherif, Y. E., Gabr, S. A., Hosny, N. M., Alghadir, A. H., & Alansari, R. (2021). Phytochemicals of *Rhus* spp. as Potential Inhibitors of the SARS-CoV-2 Main Protease: Molecular Docking and Drug-Likeness Study. *Evidence-Based Complementary and Alternative Medicine, 2021*, 8814890. https://doi.org/10.1155/2021/8814890

Shree, P., Mishra, P., Selvaraj, C., Singh, S. K., Chaube, R., Garg, N., & Tripathi, Y. B. (2022). Targeting COVID-19 (SARS-CoV-2) main protease through active phytochemicals of ayurvedic medicinal plants–*Withania somnifera* (Ashwagandha), *Tinospora cordifolia* (Giloy) and *Ocimum sanctum* (Tulsi)–a molecular docking study. *Journal of Biomolecular Structure and Dynamics, 40*(1), 190-203. https://doi.org/10.1080/07391102.2020.1810778

Singh, A. K., Singh, A., Shaikh, A., Singh, R., & Misra, A. (2020a). Chloroquine and hydroxychloroquine in the treatment of COVID-19 with or without diabetes: A systematic search and a narrative review with a special reference to India and other developing countries. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 14*(3), 241-246. https://doi.org/10.1016/j.dsx.2020.03.011

Singh, E., Khan, R. J., Jha, R. K., Amera, G. M., Jain, M., Singh, R. P., Muthukumaran, J., & Singh, A. K. (2020b). A comprehensive review on promising anti-viral therapeutic candidates identified against main protease from SARS-CoV-2 through various computational methods. *Journal of Genetic Engineering and Biotechnology, 18*(1), 69. https://doi.org/10.1186/s43141-020-00085-z

Singh, P., Chauhan, S. S., Pandit, S., Sinha, M., Gupta, S., Gupta, A., & Parthasarathi, R. (2021). The dual role of phytochemicals on SARS-CoV-2 inhibition by targeting host and viral proteins. *Journal of Traditional and Complementary Medicine, 12*(1), 90-99. https://doi.org/10.1016/j.jtcme.2021.09.001

Soleymani, S., Naghizadeh, A., Karimi, M., Zarei, A., Mardi, R., Kordafshari, G., Esmaealzadeh, N., & Zargaran, A. (2022). COVID-19: General Strategies for Herbal Therapies. *Journal of Evidence-Based Integrative Medicine, 27*, 1-18. https://doi.org/10.1177/2515690x211053641

Srivastav, V. K., Egbuna, C., & Tiwari, M. (2020). Plant secondary metabolites as lead compounds for the production of potent drugs. In C. Egbuna, S. Kumar, J. C. Ifemeje, S. M. Ezzat & S. Kaliyaperumal (Eds.), *Phytochemicals as Lead Compounds for New Drug Discovery* (pp. 3-14) Amsterdam, Netherlands: Elsevier Inc. https://doi.org/10.1016/B978-0-12-817890-4.00001-9

Srivastava, J. K., Shankar, E., & Gupta, S. (2010). Chamomile: A herbal medicine of the past with a bright future (review). *Molecular Medicine Reports, 3*(6), 895-901. https://doi.org/10.3892/mmr.2010.377

Sumon, T. A., Hussain, M. A., Hasan, M. T., Hasan, M., Jang, W. J., Bhuiya, E. H., Chowdhury, A. A. M., Sharifuzzaman, S. M., Brown, C. L., Kwon, H.-J., & Lee, E.-W. (2020). A revisit to the research updates of drugs, vaccines and bioinformatics approaches in combating COVID-19 pandemic. *Frontiers in Molecular Biosciences, 7*, 585899. https://doi.org/10.3389/fmolb.2020.585899

Swain, S. S., Panda, S. K., & Luyten, W. (2021). Phytochemicals against SARS-CoV as potential drug leads. *Biomedical Journal, 44*(1), 74-85. https://doi.org/10.1016/j.bj.2020.12.002

Swamy, M. K. (2020). *Plant-derived Bioactives: Production, Properties and Therapeutic Applications*. Singapore: Springer. https://doi.org/10.1007/978-981-15-1761-7

Tahir ul Qamar, M., Alqahtani, S. M., Alamri, M. A., & Chen, L. L. (2020). Structural basis of SARS-CoV-2 $3CL^{pro}$ and anti-COVID-19 drug discovery from medicinal plants. *Journal of Pharmaceutical Analysis, 10*(4), 313-319. https://doi.org/10.1016/j.jpha.2020.03.009

Vicidomini, C., Roviello, V., & Roviello, G. N. (2021). In silico investigation on the interaction of chiral phytochemicals from *Opuntia ficus-indica* with SARS-CoV-2 M^{pro}. *Symmetry, 13*(6), 1041. https://doi.org/10.3390/sym13061041

Wadanambi, P. M., Mannapperuma, U., & Jayathilaka, N. (2025). Evaluating phytochemicals as SARS-CoV-2 papain-like protease inhibitors: a docking, ADMET and molecular dynamics investigation. *Chemical Papers, 79*, 2801-2821. https://doi.org/10.1007/s11696-025-03968-y

WHO. (2019). WHO global report on traditional and complementary medicine 2019. Retrieved from https://apps.who.int/iris/bitstream/handle/10665/312342/9789241515436-eng.pdf?ua=1

Win, N. N., Kodama, T., Lae, K. Z. W., Win, Y. Y., Ngwe, H., Abe, I., & Morita,H. (2019). Bis-iridoid and iridoid glycosides: Viral protein R inhibitors from *Picrorhiza kurroa* collected in Myanmar. *Fitoterapia, 134*, 101-107. https://doi.org/10.1016/j.fitote.2019.02.016

Woo, S.-Y., Win, N. N., Noe Oo, W. M., Ngwe, H., Ito, T., Abe, I., & Morita, H. (2019). Viral protein R inhibitors from *Swertia chirata* of Myanmar. *Journal of Bioscience and Bioengineering*, *128*(4), 445-449. https://doi.org/10.1016/j.jbiosc.2019.04.006

Yanez, N. D., Weiss, N. S., Romand, J.-A., & Treggiari, M. M. (2020). COVID-19 mortality risk for older men and women. *BMC Public Health*, *20*, 1742. https://doi.org/10.1186/s12889-020-09826-8

Yang, R., Liu, H., Bai, C., Wang, Y., Zhang, X., Guo, R., Wu, S., Wang, J., Leung, E., Chang, H., Li, P., Liu, T., & Wang, Y. (2020). Chemical composition and pharmacological mechanism of Qingfei Paidu Decoction and Ma Xing Shi Gan Decoction against Coronavirus Disease 2019 (COVID-19): *In silico* and experimental study. *Pharmacological Research, 157*, 104820. https://doi.org/10.1016/j.phrs.2020.104820

Yuan, H., Ma, Q., Ye, L., & Piao, G. (2016). The traditional medicine and modern medicine from natural products. *Molecules, 21*(5), 559. https://doi.org/10.3390/molecules21050559

Zaia, M. G., Cagnazzo, T. di O., Feitosa, K. A., Soares, E. G., Faccioli, L. H., Allegretti, S. M., Afonso, A., & Anibal, F. de F. (2016). Anti-inflammatory properties of menthol and menthone in Schistosoma mansoni infection. *Frontiers in Pharmacology, 7*, 170. https://doi.org/10.3389/fphar.2016.00170

Zeng, F., Huang, Y., Guo, Y., Yin, M., Chen, X., Xiao, L., & Deng, G. (2020). Association of inflammatory markers with the severity of COVID-19: A meta-analysis. *International Journal of Infectious Diseases, 96*, 467-474. https://doi.org/10.1016/j.ijid.2020.05.055

Zhang, D., Wu, K., Zhang, X., Deng, S., & Peng, B. (2020). *In silico* screening of Chinese herbal medicines with the potential to directly inhibit 2019 novel coronavirus. *Journal of Integrative Medicine, 18*(2), 152-158. https://doi.org/10.1016/j.joim.2020.02.005

Zhang, K. (2020). Is traditional Chinese medicine useful in the treatment of COVID-19? *The American Journal of Emergency Medicine, 38*(10), 2238. https://doi.org/10.1016/j.ajem.2020.03.046

Zhang, L., Lin, D., Sun, X., Curth, U., Drosten, C., Sauerhering, L., Becker, S., Rox, K., & Hilgenfelld, R. (2020). Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved α-ketoamide inhibitors. *Science, 368*(6489), 409-412. https://doi.org/10.1126/science.abb3405

Zhang, Y., Wang, Z., Zhang, Y., Tong, H., Zhang, Y., & Lu, T. (2020). Potential Mechanisms for Traditional Chinese Medicine in Treating Airway Mucus Hypersecretion Associated With Coronavirus Disease 2019. *Frontiers in Molecular Biosciences, 7*, 577285. https://doi.org/10.3389/fmolb.2020.577285