South African Journal of Botany 184 (2025) 167–181

Contents lists available at ScienceDirect

South African Journal of Botany

journal homepage: www.elsevier.com/locate/sajb

A review of the world's response to COVID-19 and the potential of medicinal plants for future pandemics

Brandon Alston[a], Jacqueline Maphutha[a], Jessica Ackron[a], Anna-Mari Kok[a,b], Namrita Lall[a,c,d,e,*]

[a] Department of Plant and Soil Sciences, University of Pretoria, Pretoria, Gauteng, South Africa
[b] Research Fellow, South African International Maritime Institute (SAIMI), Nelson Mandela University, Gqeberha, 6019, South Africa
[c] School of Natural Resources, University of Missouri, Columbia, MO, United States
[d] College of Pharmacy, JSS Academy of Higher Education and Research, Mysuru, Karnataka, India
[e] Senior Research fellow, Bio-Tech R&D Institute, University of the West Indies, Kingston, Jamaica

ARTICLE INFO

Article History:
Received 28 February 2024
Revised 27 May 2025
Accepted 27 May 2025
Available online xxx

Edited by: Dr. J.S. Boatwright

Keywords:
COVID-19
Government
Lockdown
Medicinal plants
SARS-CoV-2

ABSTRACT

Coronavirus pandemics such as Spanish influenza, severe acute respiratory syndrome-coronavirus (SARS-CoV), middle east respiratory syndrome-coronavirus (MERS-CoV) and severe acute respiratory syndrome-coronavirus (SARS-CoV-2) have displayed high incidence and mortality rates prompting the need for repurposing of drugs, vaccine development and the investigation of medicinal plants. Research on previous coronaviruses has served as the foundation for COVID-19 (arising from SARS-CoV-2) research. Various medicinal plants such as *Glycyrrhiza glabra, Ginkgo biloba, Curcuma longa* and *Artemisia annua* have displayed favorable results against SARS-CoV-2. Medicinal plants as well as bioactive compounds derived from medicinal plants have been investigated in clinical trials to elucidate the effect on SARS-CoV-2. Several clinical trials evaluate the effect of the medicinal plant and bioactive compounds derived thereof on symptoms arising due to SARS-CoV-2 thus, the main aim of this review article is to highlight the gap in the investigation of the effect of medicinal plants and bioactive compounds on the specific mechanisms of COVID-19 in clinical trials. The review also highlights challenges pertaining to the standardization and quality control of medicinal plants as well as bioactive compounds derived from medicinal plants which may impede the feasibility of using medicinal plants in the clinical regimen for COVID-19 or future coronavirus pandemics.

1. Introduction

In 2019 an increasing number of acute pneumonia cases first appeared in Wuhan, China and the series of symptoms were further identified and linked to a novel enveloped RNA beta coronavirus subsequently named as the severe acute respiratory syndrome coronavirus-2 (SARS- CoV- 2) (Guan et al., 2020). This initial outbreak, also known as the coronavirus disease 2019 (COVID-19) emerged as a severe pandemic claiming several lives between December 2019 and August 2020 (Yesudhas et al., 2021). The COVID-19 outbreak was declared by the World Health Organization (WHO) to be a Public Health Emergency of International Concern (PHEIC) in January 2020 (Li et al., 2020).The inception of the COVID-19 outbreak was by zoonotic transmission within the Huanan seafood market in Wuhan with the initial viral vectors suspected to be bats based on the viral genome sequencing showing a 96.2 % homology between the bat-

Abbreviations: 3CLpro, 3-chymotrypsin-like protease; ACE-2, angiotensin-converting enzyme 2; ADMET, absorption, distribution, metabolism, and excretion–toxicity; ARDS, acute respiratory distress syndrome; ASP, alkaline phosphatase; AYUSH, Ayurveda, yoga, unani, siddha and homeopathy; Calu-3, human lung epithelial cells; CC_{50}, half maximal cytotoxic concentration; CD40L, cluster of differentiation 40 ligand; CNS, central nervous system; CVD, cardiovascular disease; CXC-10, C-X-C motif ligand 10; CXC-9, C-X-C motif chemokine ligand 9; EMMPRIN, extracellular matrix metalloproteinase inducer; GM-CSF, granulocyte-macrophage colony-stimulating factor; hACE, human angiotensin converting enzyme 2; HCOV- NL63, human coronavirus; IC_{50}, 50 % minimum inhibitory concentration; IFN, interferon; IL, interleukin; iNOS, inducible nitric oxide synthase; IP-10, interferon gamma-induced protein 10; LDH, lactate dehydrogenase; LQC, lianhua Qingwen capsule; MCP-1, chemoattractant protein; Me-23, curcuminoid; MERS-CoV, Middle East respiratory syndrome coronavirus; NBE, neem bark extract; NFK-ß, nuclear factor-kappa ß; NPI, non-pharmaceutical interventions; NRP, neuropilin; NSO, nigella sativa oil; nsp2, non-structural protein 2; NTD, N-terminal domain; PAMPs, pathogen associated molecular patterns; PD, peptidase domain; PDGF, platelet derived growth factor; PGE, prostaglandin E; PHEIC, public health emergency of international concern; PR8, mouse adapted H1N1 influenza virus); q-CRP, q-C-reactive protein; RBD, receptor-binding domain; RNA, ribonucleic acid; SARS-CoV, severe acute respiratory syndrome coronavirus; SARS- CoV- 2, severe acute respiratory syndrome coronavirus-2; SH-SY5Y, human neuroblastoma cells; SWHD, San Wu Huangqin Decoction; TCM, traditional Chinese medicine; Th17, T-helper 17 cells; Th2, T-helper 2 cells; TMPRSS2, transmembrane serine protease 2; TNF-a, tumor necrosis factor alpha; VEGF, vascular endothelial growth factor; VTE, Venus's thromboembolism; WHO, world health organization; YG, yinhuapinggan granule

* Corresponding author at: Department of Plant and Soil Sciences, University of Pretoria, Pretoria, Gauteng, South Africa.
E-mail address: namrita.lall@up.ac.za (N. Lall).

https://doi.org/10.1016/j.sajb.2025.05.053

CoV and SARS-CoV-2 (Guo et al., 2020; Li et al., 2020; Sun et al., 2020). Through further phylogenetic analysis and protein sequencing it was observed that there may have been other intermediate hosts such as pangolins and civets (Mishra et al., 2021). Human to human contact also played a pivotal role during the outbreak, with the virus shown to have a reproductive number (R_0) of 2.20, indicating that for every individual that is infected by COVID-19, a further 2.20 people are expected to contract the virus (Li et al., 2020; Liu et al., 2020). An epidemic is considered likely to expand when its R_0 is greater than 1 and upon further investigation it was noted that without intervention SARS-CoV-2 would likely have an R_0 of 2.30–3.70 (Sun et al., 2020). As reported by Donnat and Holmes (2023), there is variation between the R_0 values across numerous studies (Donnat and Holmes, 2023). In India the R_0 value was reported to be 2.56 while in China it was reported to be 2.40 and in Italy, 2.40–3.10 (Achaiah et al., 2020; D'arienzo and Coniglio, 2020). Control measures are normally put in place to contain a pandemic and reduce the R_0 to less than 1 suggesting that the measures implemented within various regions may have been a factor in the rate at which the virus spread. The COVID-19 outbreak was declared a pandemic by the WHO on the 11th of March 2020 and was reported in over 200 countries around the world (Balkhair, 2020; Zhang et al., 2020; Zheng et al., 2020).

1.1. Structure

Coronaviruses are enveloped, positive-stranded RNA viruses that contain a nucleocapsid. Their genomic structure is arranged in a single stranded RNA (+ssRNA) of approximately 30 kilobases in length with a 5′-cap structure and 3′-poly-A tail, making them the largest RNA viruses (Fehr and Perlman, 2015). The virus belongs to the order *Nidovirales* and can be classified into four different genera: Alpha (α), Beta (β), Gamma(γ) and Delta (δ). Mammals are only infected by α- and β-Coronavirus while birds are primarily infected by γ- and δ-coronavirus (Van Boheemen et al., 2012). The SARS-Cov-2 virus (Fig. 1) is structurally and phylogenetically identical to both SARS-coronavirus and MERS-coronavirus and consists of four major structural proteins, namely, the spike (S) protein, envelope (E) glycoprotein, nucleocapsid (N), and membrane (M) protein, together with 16 non-structural proteins as well as 5 to 8 auxiliary proteins (Brian and Baric, 2005). The surface spike (S) glycoprotein, which resembles a crown, is located on the outer surface of the virion and undergoes cleavage into an amino (N)-terminal S1 subunit, which facilitates the virus' incorporation into the host cell. Other units include the carboxy (C)-terminal S2 subunit containing a fusion peptide, a transmembrane domain, and a cytoplasmic domain, which is responsible for virus-cell membrane fusion (Du et al., 2009; Jiang et al., 2020).

Through attachment of the SARS-Cov-2 spike or S protein (S1) to the numerous ACE-2 receptors on the respiratory epithelium such as type II alveolar epithelial cells, SARS-CoV-2 obtains access to the host cell ACE-2 receptors which are expressed by the upper esophagus, enterocytes from the ileum, cardiac cells, proximal tubular cells of the kidney, and urothelial cells of the bladder, in addition to the respiratory epithelium (Hu et al., 2021). The process of viral attachment is followed by the priming of the spike protein S2 component by the host transmembrane serine protease 2 (TMPRSS2), which enables cell entrance, viral replication, endocytosis, and the formation of virions (Hoffmann et al., 2020). The S1 subunit is further subdivided into a receptor-binding domain (RBD) and an N-terminal domain (NTD), which enhances viral entrance into the host cell and is a potential target for neutralization by antisera or vaccinations. As a binding site for the human angiotensin-converting enzyme 2 (ACE-2) receptors, the RBD is a crucial peptide domain in the pathogenesis of infection (Song et al., 2018).

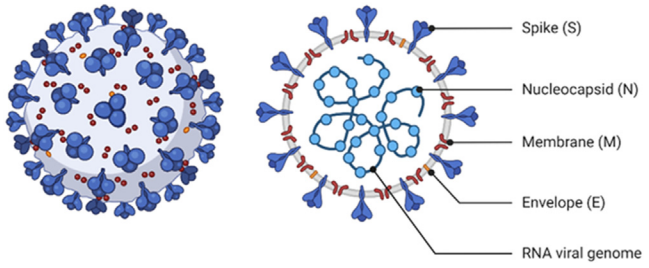

Fig. 1. A model of the structure of the SARS-CoV-2 virus.

1.2. Mechanism of SARS-CoV-2

In laboratory tests, most infected patients exhibited a marked decrease in their total number of lymphocytes, particularly T-lymphocytes, suggesting that they are likely a target of the SARS-CoV-2 virus (Seyed Hosseini et al., 2020). During Covid- 19 infection, viral particles spread in the respiratory tract and infect surrounding cells, this initiates the cytokine storm in which high levels of various pro-inflammatory cytokines including IL-1, IL-2, IL-6, TNF-α, IFN-γ, IP-10, GM-CSF, MCP-1, and IL-10 are expressed (Zanza et al., 2022). The initiation of the cytokine storm consequently triggers severe immune responses which result in changes to immune cells, particularly the lymphocytes causing immune stress and dysfunction (Li et al., 2020; Seyed Hosseini et al., 2020). In addition, new putative receptors have emerged elucidating their probable function in viral entrance (Mayi et al., 2021). Neuropilins are transmembrane glycoproteins that are mostly found in developing neurons and contribute to neuron development. Neuropilin 1 (NRP1) and neuropilin 2 (NRP2) are receptors of class III semaphorin receptors and are also targeted by several ligands accountable for angiogenesis (Lin et al., 2021). A neuropathological study of COVID-19 corpses has shown that cleaved S protein interacts with NRP1 and NRP2, assisting in the infection of the neurological system by the virus (Cantuti-Castelvetri et al., 2020; Daly et al., 2020). The immunoglobulin superfamily member, CD147, also known as basigin or extracellular matrix metalloproteinase inducer (EMMPRIN), is a transmembrane glycoprotein that has been identified as an alternate SARS-CoV-2 entry facilitator within the host cell. Anti-CD147 antibody was found to effectively prevent SARS-CoV-2 entry (Wang et al., 2020a). An intriguing study revealed that keto acid sugars may play a crucial role in the entrance of SARS-CoV-2 and the ensuing "cytokine storm" (Hatmal et al., 2020; Wielgat et al., 2020). The mechanism of entry plays an important role in identifying possible targets for the inhibition of COVID-19 (Fig. 2). Human angiotensin-converting enzyme 2 (ACE-2), expressed on the surface of cells, is the major receptor for SARS-CoV-2. The S1 domain of the spike (S) protein of SARS-CoV-2 interacts with the ACE-2 receptor via the receptor-binding domain (RBD) (Huang et al., 2020). The S2 domain undergoes a conformational change entering a post fusion state in which its buried hydrophobic fusion peptides become exposed and inserted into the target host membrane. This process results in the fusion of the viral and host membrane (Yesudhas et al., 2021).

Notably, SARS-CoV-2 has a higher affinity for human ACE-2 than SARS-CoV. The ectodomain of the SARS-CoV-2 spike protein binds to the peptidase domain (PD) of ACE-2 (Yesudhas et al., 2021). Transmembrane serine proteases 2 (TMPRSS 2) and Furin play a major part in this process. Furin cleaves at the S1/S2 cleavage site, which facilitates RBD-ACE-2 interaction by exposing the RBD. On the other hand, TMPRSS 2 facilitates viral glycoprotein contact and membrane fusion with the host cell membrane (Luan et al., 2020). Generally, SARS-CoV enters host cells through endocytosis, where its spike protein is processed by cathepsin L and cathepsin B lysosomal proteases (Jackson et al., 2022). Further extracellular proteases such as elastase in the respiratory tract and TMPRSS2 on the surface of lung cells are also known to activate spike membrane fusion (Yesudhas et al., 2021).

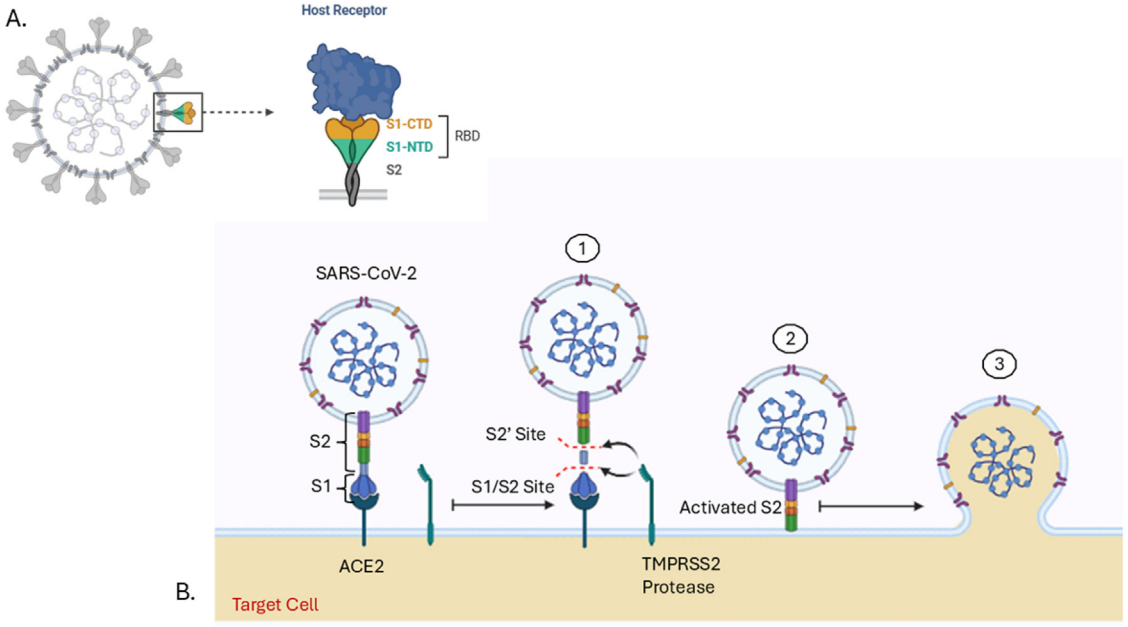

Fig. 2. (A) SARS-CoV-2 Spike binding receptor. (B) Mechanism of SARS-CoV-2 viral entry into target cell membrane where 1- is the cleavage of the SARS-CoV-2 S protein., 2- The activation of the S domain and 3- The fusion of the viral and host membranes.

1.3. Symptoms

The mean incubation period of SARS-Cov-2 is 5.2 days (Li et al., 2020). Infection starts with the initial onset of flu-like symptoms including fever, dry cough and fatigue, additionally the respiratory, gastrointestinal, musculoskeletal and nervous systems may also be affected (Calica Utku et al., 2020). Less common symptoms such as dizziness, headaches, stomach pains, nausea, and vomiting may also be observed (Sun et al., 2020; Wang et al., 2020b). Additionally, patients may experience a loss of smell (anosmia) and loss of taste (dysgeusia) as precursors to fever. It is noteworthy to add that although fever is an important indicator of infection, it may not always be present (Gallo Marin et al., 2021).The severity of a COVID-19 infection can range from mild to critical, with most infections being milder, however, some patients may initially present with mild symptoms but further progress to more severe symptoms after a few days (Guan et al., 2020). Of the patients exhibiting milder symptoms approximately 15 % were shown to progress to severe pneumonia and an additional 5 % further develop acute respiratory distress syndrome (ARDS), septic shock and potentially multiple organ failure (Cao, 2020). COVID-19 infects people of all age groups, but individuals above the age of 60 years and those possessing comorbidities are at a much higher risk of infection (WHO, 2020). Several metabolic and infectious diseases have been shown to impact the severity of Covid- 19 and play a role in the formation of complex symptoms (Ejaz et al., 2020). People suffering from diabetes are at a higher risk of developing infection due to the impaired capabilities of their phagocytic cells. Additionally, elevated levels of the ACE-2 receptors observed to be related to diabetes may therefore increase the likelihood of infection (Rao et al., 2020). In various studies performed in China it was observed that 11 % of patients suffering from COVID-19 infection had diabetes, with one study in Wuhan, China, specifically found an increase in the viral clearance time in patients who also suffered from diabetes (Chen et al., 2020; Singh et al., 2020). Several factors are reported to be responsible for the increased severity of COVID-19 in patients with diabetes, including an increase in ACE-2 expression, an increase in furin, a type 1 membrane-bound protease which was found to impair T-cell function, and an increase in several inflammatory cytokines including interleukin IL-6 (Singh et al., 2020).

Reports have also linked hypertension with a high case fatality rate (CFR) being reported in COVID-19 patients. Singh et al. (2020) highlighted multiple studies showing the strong correlation between COVID-19 patients and hypertension (Singh et al., 2020). In multiple studies conducted in China, it was found that 21 % of COVID-19 patients also suffered from hypertension, with a study by Yang et al. (2020) reporting a 17 % correlation (Chen et al., 2020; Singh et al., 2020; Yang et al., 2022). However, roughly 25 % of the global population suffer from hypertension and thus it could be argued that the correlation between hypertension and COVID-19 does not suggest a causal relationship (Gallo et al., 2022).

Cardiovascular disease (CVD) displayed an increased prevalence in patients suffering from COVID-19, most notably in more severe cases of infection (Ejaz et al., 2020). Studies conducted in Wuhan, China, noted that 6.8 % of those who died from COVID-19 infection suffered from CVD while another study observed 17 % of Covid related deaths to have suffered from CVD (Zheng et al., 2020; Zhou et al., 2020). Infection with COVID-19 triggers an immune response through Toll-like receptors (TLRs) which play an important role in the regulation of cytokine expression and indirectly play a role in the activation of the adaptive immune system and the recognition of pathogen associated molecular patterns (PAMPs) (Birra et al., 2020). Several studies have shown that most Covid −19 patients suffer from lymphopenia (shortage of lymphocytes in the blood) and have elevated levels of various pro-inflammatory cytokines such as Tumour Necrosis Factor alpha (TNF-α) and Interleukin 6 (IL −6) (Khanmohammadi and Rezaei, 2021). Further studies have shown that the immunopathological reason for deaths attributed to COVID-19 infection was due to the interaction of TLRs with viral particles (Patra et al., 2021).

Venous thromboembolism (VTE) is highly prevalent in critically ill patients suffering from COVID-19 (Waite et al., 2020). The percentage of VTE complications recorded in COVID-19 patients varied from 1.7 to 16.5 % in observational studies from around the world (Kunutsor and Laukkanen, 2020). It has been suggested that the severe anti-inflammatory response to COVID-19 infection causes thrombo-inflammation through various mechanisms such as the cytokine storm, complement activation and endotheliosis (Lee et al., 2022). Studies have shown that the SARS-CoV-2 virus induces a particular anti-inflammatory signature that is characterized by a reduction in

multiple interferons (IFN-I and IFN-III) and an increase in antiviral proteins produced in response to pathogens or various pro-inflammatory cytokines. This highlights the effectiveness of the SARS-CoV-2 virus in counteracting the antiviral effects of IFN-I and IFN-III and promoting an inflammatory response through the induction of cytokines needed to recruit cells responsible for adaptive immunity (García, 2020).

Post-acute symptoms of COVID-19 described by the persistence of symptoms and their development up to 4 weeks after the onset of initial COVID-19 infection, are of additional clinical importance (Nalbandian et al., 2021). Patients suffering from post-acute COVID-19, also termed "long Covid" present with persistent neurological, respiratory, or cardiovascular symptoms that could potentially last for months (Montani et al., 2022). At the beginning of the outbreak, cases of COVID-19 infection were largely observed among the elderly, however, as the outbreak continued, the cases in individuals over 65 years of age continued to increase but there was also an observed increase in children under the age of 18 (Chen et al., 2020; Yuki et al., 2020). Initially, the number of cases among males was higher, however, as the case numbers increased no significant gender preference was shown (Yuki et al., 2020).

1.4. World response to COVID-19

The considerable variations in policy response to the COVID-19 pandemic observed among different nations may predominantly be due to a lack of experience in managing pandemics of such magnitude. The global outbreak of COVID-19 led to the implementation of diverse non-pharmaceutical interventions (NPIs) by numerous countries as a means of community mitigation techniques (Redlin, 2022). Non-pharmaceutical interventions (NPIs) encompass a range of measures implemented to mitigate the spread of diseases, to reduce the transmission curve, in addition to medical treatments and vaccinations. Non-pharmaceutical interventions (NPIs) have demonstrated their significance in effectively reducing the transmission of the virus and subsequent mortality rates over various periods and waves of infection (Hale et al., 2020). However, specific policies have had detrimental impacts on the economics of several nations, resulting in prolonged recovery periods for some of these economies (Gozzi et al., 2021; Hsiang et al., 2020; Jena et al., 2021). One of the initiatives to receive significant advocacy was the implementation of face coverings, with a particular emphasis on nose masks, the most cost-effective NPI currently available (Agyapon-Ntra and Mcsharry, 2023). A study conducted by Mitze et al. (2020) found that the use of face masks in Germany resulted in a significant reduction in the number of COVID-19 cases. Over 20 days, face masks contributed to a 45 % decrease in infection rates. Furthermore, the economic impact of implementing face masks was shown to be minimal in comparison to alternative public health measures such as closures and contact restrictions/bans (Mitze et al., 2020; Vardavas et al., 2021).

Nevertheless, as COVID-19 spread within the surrounding communities, attributed to the delayed implementation of restrictions, non-compliance with regulations, and poor contact tracing, there was an observed prioritization of diagnostic testing, particularly for individuals exhibiting respiratory symptoms (Schuchat, 2020). The implementation of the "limiting contact" effectively decreased the frequency and length of interactions, thus resulting in a decrease in the number of opportunities for viral replication through contact, ultimately leading to a reduction in the basic viral reproduction number (R_0) (Oraby et al., 2021).

The variability in the occurrence, length, and scheduling of lockdown measures worldwide presented a challenge in accurately measuring the impact of restrictions on the management of COVID-19 transmission. The implementation of lockdown measures led to significant economic consequences, with many individuals experiencing job losses and financial instability. Furthermore, these restrictions have had a profound impact on individuals' mental health, thus complicating the evaluation of the cost-benefit analysis associated with the approach of limiting social interaction (Oraby et al., 2021).

2. Medicinal plants used in the treatment of COVID-19

Traditional medicine plays an important role in therapeutic treatment in the modern age. It has been shown to be an effective tool in allowing researchers to search for potential drugs or leads for further development (Choudhury et al., 2020). Medicinal plants are currently being studied in large quantities and evaluated for their bio-efficacy and safety with the WHO being actively involved, this has led to the worldwide trade of traditional medicines increasing by an annual rate of 10–15 % per annum (Joshi et al., 2015). Many modern synthetic drugs are derived from traditionally used medicinal plants, via the synthesis and development of drugs or desired compounds through their plant-based origins. More modern drug development processes are targeted towards the identification and synthesis of the bioactive compounds from natural products (Choudhury et al., 2020). Newman and Cragg (2020), have shown that approximately 41.1 % of all the drugs developed since 1981 have been derived from natural products (Fig. 3). It is notable that of the 1881 newly developed drugs in the past 30 years only 14 are from unaltered natural 22 products, with the majority being compounds derived from natural products (Newman and Cragg, 2020).

Many medicinal plants have also been investigated for their potential to treat COVID-19 infection. Medicinal plants exhibit a diverse range of antiviral effects with many interacting with viral haemagglutinin, a glycoprotein that plays a major role in the early stages of infection (Adkihari et al., 2020). In their study, Jalali et al. (2021) noted that some herbal medicines such as members from the *Citrus* spp, *Andrographis paniculata* (Green Chiretta) and *Cuminum cyminum* (Cumin) have been shown to be effective as anti-inflammatory agents against symptoms associated with COVID-19 infection including coughs and fever (Jalali et al., 2021). In another web-based survey performed by Khadka et al. (2021), 63 medicinal plants used around the world in households as a treatment for COVID-19 were determined to have been used in larger frequencies. They, however, noted that further research would need to be undertaken to determine the efficacy of these plant-based treatments (Khadka et al., 2021). These studies and the available evidence highlight the potential of medicinal plants to be used in conjunction with conventional COVID-19 treatment strategies and suggest further study and clinical development. A term clustering map shows the strong relationship in occurrences between COVID-19 and traditional medicine (Fig. 4).

Traditional medicinal treatments were implemented in nations with a strong herbal medicine background. The term clustering map shows the strong relationship in occurrences between COVID-19 and traditional medicine (Fig. 4). Ten clusters were observed between the terms with various forms of traditional medicine such as Ayuverda and Traditional Chinese Medicine (TCM) being shown to strongly link to COVID-19. This link highlights the ongoing research of medicinal plants used in TCM as a viable method to treat COVID-19 infection.

Chinese medicinal plants have already been evaluated for the treatment of COVID-19 patients and have shown varying levels of efficacy (Luo et al., 2020a). Multiple studies have highlighted the efficacy of various traditional Chinese medicines such as San Wu Huangqin Decoction (SWHD), Lianhua Qingwen Capsule (LQC), and Yinhuapinggan granule (YG) in antiviral therapy (Li et al., 2020). San Wu Huangqin Decocotion was found to inhibit the PR8 (mouse adapted H1N1 influenza virus) viral replication at various stages, this was corroborated by measuring the inhibition of the viral induced cytopathic effect on cells via crystal violet staining (Ma et al., 2018). Lianhua Qingwen capsules were shown to accelerate the improvement of acute exacerbation of COPD (chronic obstructive pulmonary disease) via a decrease in the pro-inflammatory cytokines (IL-8, TNF-

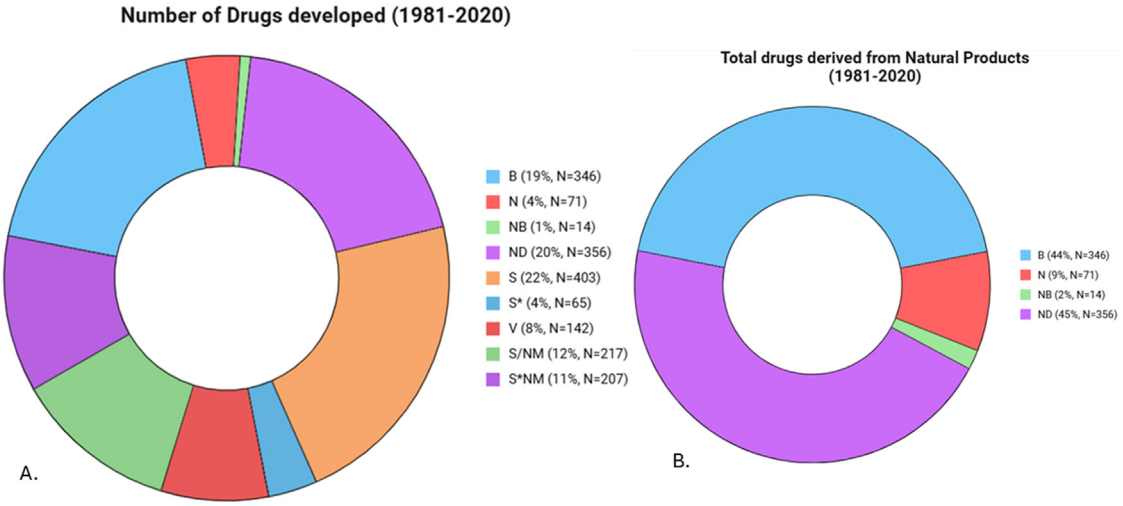

Fig. 3. A. The distribution of newly developed drugs since 1981 (adapted from Newman and Cragg, 2020). B- biological macromolecules, N- unaltered natural products, NB- botanical, ND- natural product derivatives, S- synthetic drug, S*- synthetic drug (formerly natural based. Fig. 3.B. The total number of drugs derived from natural products.

α, IL-17, and IL- 23) (Xia et al., 2020). Yinhuapinggan granules were observed to have significant effects on ameliorating influenza virus-induced inflammation (Du et al., 2009). The mechanism of anti-inflammatory action was determined to be the inhibition of the TLRs/MyD88 mediated NF-kB signaling pathway, inhibiting the influenza virus replication (Peng et al., 2016).

The Indian traditional system of medicine known as Ayurveda, Yoga, Unani, Siddha and Homeopathy (AYUSH) is one of the oldest in the world (Adhikari et al., 2021). The Indian ministry of AYUSH provided the population with a list of traditional formulations to be used as a prophylactic measure during the COVID-19 pandemic (Ahmad et al., 2020). An interdisciplinary AYUSH research and development taskforce was formed to further conduct systematic clinical trials on the selected formulations suggesting a shift towards evidence-based use of medicines and traditional medicine to combat COVID-19 (Bharskar, 2022).

There are numerous traditional South African plants used to treat viral infections. In a study performed by Dwarka et al. (2020) various South African medicinal plants were highlighted for their potential against COVID-19. The plants were selected for the study based on their traditional usage for flu, respiratory ailments and colds as well as their antioxidant and antiviral activity (Dwarka et al., 2020). The study noted that four bioactive compounds, arabic acid from *Acacia senegal*, L, canavanine found in *Sutherlandia frutescens*, hypoxoside isolated from *Hypoxis hemerocallidea* and uzarin from *Xysmalobium undulatum* exhibited potential for further investigation.

Artemisia annua, a close relative of the African species *Artemisia afra,* has been shown to inhibit the viral replication of SARS-CoV (Verma et al., 2020). Although they are different species it has been reported that many compounds within the Artemisia species are conserved, suggesting *A. afra's* candidacy in anti-COVID-19 and potential antiviral testing (Abad et al., 2012). Helichrysetin a compound found in various *Helichrysum* species was observed to inhibit MERS- CoV (Jo et al., 2019). A formulation derived from *Pelargonium sidoides,* EPs® 7630, exhibited a low selectivity index of 2.3 when tested against the human coronavirus strain 229E in Caco-2 cells while β-sitosterol, present in *Dodonaea viscosa* and *Prunus africana*, showed antiviral activity against the human coronavirus (HCOV- NL63) (Verma et al., 2020). These results highlight the potential of traditional medicinal plants to be used in conjunction with conventional treatments against COVID-19.

As mentioned previously, medicinal plants have been used throughout history for various medicinal benefits and have served as a reservoir of new compounds that are yet to be identified. In previous coronavirus pandemics such as severe acute respiratory syndrome coronavirus (SARS-CoV, 2002/2003) and Middle East respiratory syndrome coronavirus (MERS-CoV, 2012), medicinal plants aided in combating these viruses. Lin et al. (2017) displayed the inhibition of MERS-CoV by resveratrol through decreased expression of nucleocapsid (N) protein which is required for MERS-CoV replication (Lin et al., 2017). Khan et al. (2023), also alludes to the inhibition of SARS-CoV by *Glycyrrhiza glabra* and Cinatl et al. (2003), confirm (in a Vero E6 cell line infected with SARS-CoV) the inhibition of SARS-CoV by a bioactive compound present in *Glycyrrhiza glabra* (Glycyrrhizin) (Cinatl et al., 2003; Khan et al., 2021). Glycyrrhizin displayed a half-maximal effective concentration (EC_{50}) of 300 mg/L when administered during and after virus adsorption and a half maximal cytotoxic concentration (CC_{50}) of greater than 20 000 mg/L resulting in a selectivity index of 67 (Cinatl et al., 2003). Thus, Glycyrrhizin selectively targets SARS-CoV. From these studies, the effect of medicinal plants was further investigated on SARS-CoV-2: Table 1 and Figs. 5 & 6A, 6B, 6C:

3. Discussion

Coronavirus disease 19 (COVID-19) is an infectious disease arising from SARS-CoV-2 (Morens et al., 2020). Previous coronavirus outbreaks such as SARS-CoV and MERS-CoV were incomparable to the incidence and mortality rates of COVID-19 (Pormohammad et al., 2020). Due to the high incidence rates of COVID-19, repurposing of existing therapeutics such as antimalarials (chloroquine and hydroxychloroquine), remdesivir and vaccine development were prioritized (Ho et al., 2021; Saha et al., 2020; Venkatesan, 2021). The repurposed therapeutics (chloroquine and hydroxychloroquine) presented several challenges such as adverse effects and papers citing the efficacy of chloroquine and hydroxychloroquine have also been retracted (Ho et al., 2021; Lee et al., 2021). Medicinal plants have been considered as a reservoir for compounds arising from secondary metabolism in these plants (Roy et al., 2022). Various medicinal plants and compounds derived thereof have been used for previous coronavirus pandemics (SARS-CoV and MERS-CoV) with favourable results (Khalifa et al., 2021). Thus, these medicinal plants and compounds derived thereof were considered for combating COVID-19. Although, *in-silico* and in vitro studies (Table 1) display favourable results, various factors need to be considered when utilizing medicinal plants as the main therapeutic and not as adjunctive therapy. Firstly, thorough clinical trials need to be conducted to elucidate the efficacy, dosage and adverse effects of the medicinal plants or compounds derived

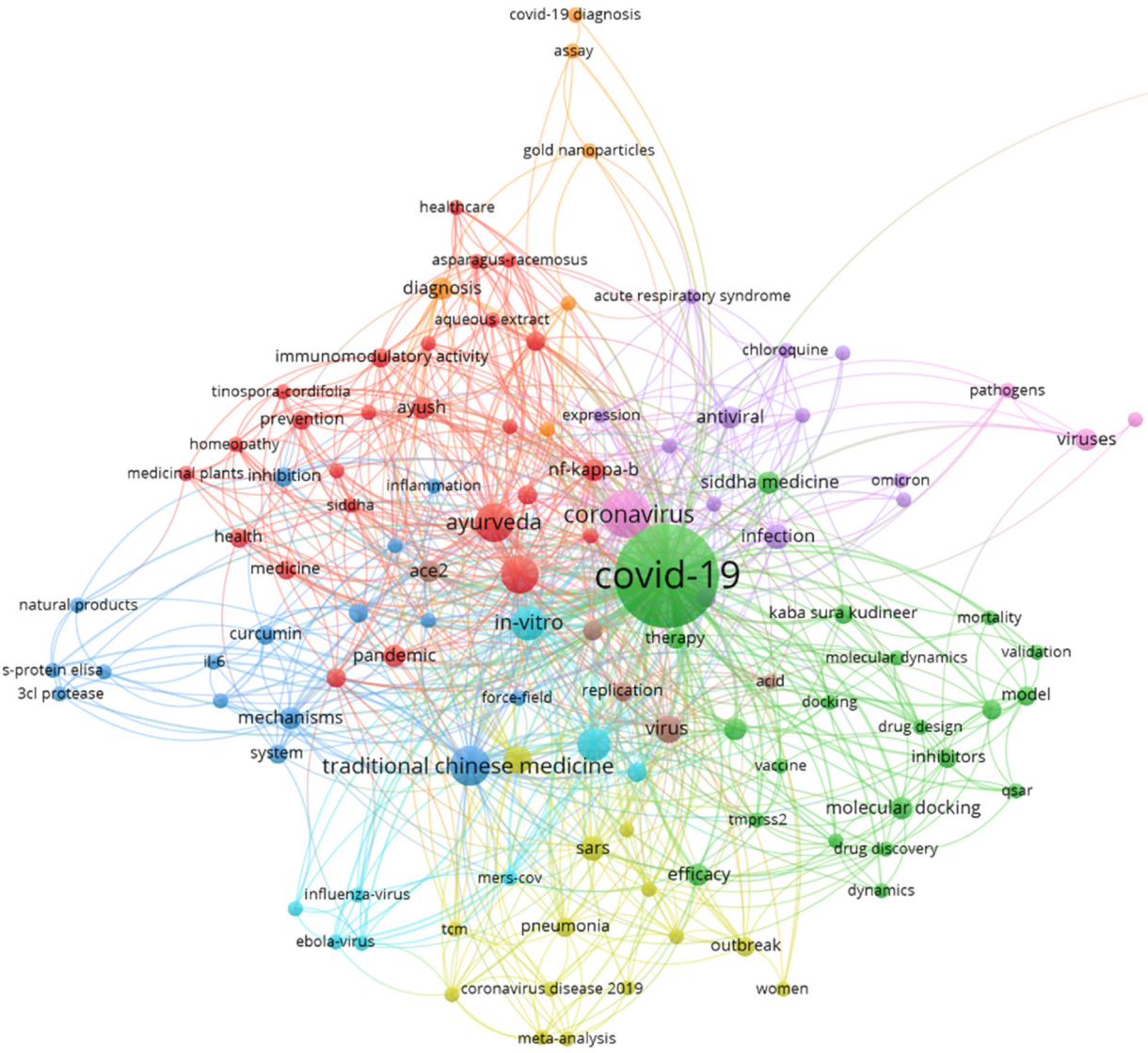

Fig. 4. Term clustering map based on the co-occurrences between COVID-19, Government and traditional medicines. The different colors are the different clusters of closely related terms.

thereof (Al-Jamal et al., 2024). Secondly, the medicinal plant or compounds derived thereof may be altered by the gut microbiome such that the arising metabolite displays enhanced anti-COVID-19 activity or decreased anti-COVID-19 activity (Wang et al., 2023; Zhou et al., 2023). The dysbiosis of the gut microbiome in COVID-19 may prevent the generation of metabolites with enhanced anti-COVID-19 activity thus, equilibration of the gut microbiome through strategies such as fecal microbiota transplantation may be required (Wang et al., 2023; Zhou et al., 2023). Thirdly, certain medicinal plants and compounds derived thereof display poor bioavailability thus, the chemical structure needs to be altered or a nanocarrier needs to be used to enhance the delivery of the medicinal plant or active compound to the target site (Dubey et al., 2022; Hoever et al., 2005). Dubey et al., displayed that nanoparticles encapsulated with glycyrrhizic acid specifically target regions with significant inflammation such as the lungs where there was a notable increase in the amount of glycyrrhizic acid nanoparticles in a coronavirus mouse hepatitis virus (MHV-A59) induced mouse model of COVID-19 (Dubey et al., 2022). Hoever et al., displayed modification of the chemical structure of glycyrrhizin through the addition of 2-acetamido-β-D-glucopyranosylamine into the glycoside chain of glycyrrhizin substantially enhanced anti-SARS-CoV activity (Hoever et al., 2005; Khan et al., 2021). Lastly, medicinal plants and compounds derived thereof from different regions display differing activity thus standardized extraction methods and collection from one site (where activity was elucidated) needs to be considered (Lim et al., 2021). Thus, thorough chemotaxonomic analysis needs to be conducted.

As mentioned previously, various countries such as India and China used medicinal plants as part of their response to COVID-19 (Ahmad et al., 2020; Al-Kuraishy et al., 2022; Luo et al., 2020b). The WHO mandated the use of medicinal plants and compounds derived thereof with safety, efficacy and quality records as suitable for complementary therapy for COVID-19 (WHO, 2020). Various clinical studies highlight the use of medicinal plants and compounds derived thereof for symptom management (Khalil et al., 2024). In an open-label clinical trial, patients in the intervention group were administered remdesivir or favipiravir together with 1000 mg of quercetin for seven days (Shohan et al., 2022). Quercetin together with either remdesivir or favipiravir resulted in lower serum levels of alkaline phosphatase (ALP), q-C-reactive protein (q-CRP) and lactate dehydrogenase (LDH) (key markers in COVID-19) as well as increased hemoglobin levels and respiratory rates in patients (Shohan et al., 2022). More clinical trials are required to fill the gap in cases where a medicinal plant or compound derived thereof is used in conjunction with a

Table 1
Therapeutic potential of medicinal plants in combating COVID-19.

Plant	Common name	Family name	Mechanism of action	Clinical studies	Refs.
Andrographis paniculata (Burm.f.) Nees	Kalmegh	Acanthaceae	*Andrographis paniculata* and the major component, andrographolide, inhibited key proteins of SARS-COV-2 (spike glycoprotein, human angiotensin converting enzyme 2 (hACE2) and 3-chymotrypsin-like protease (3CLpro) determined using *in-silico* approaches (molecular docking and molecular simulations). Furthermore, in a study where human lung epithelial cells (Calu-3) were infected with SARS-COV-2 as a model, *Andrographis paniculata* and andrographolide inhibited virion production with 50 % minimum inhibitory concentration (IC_{50}) values of 0.04 μg/mL and 0.03 μM, respectively, determined using the plaque assay.	The safety and efficacy of a herbal combination (comprising of *Phyllanthus niuri, Andrographis paniculata, Glycyrrhiza glabra, Anacardium occidentale* leaf and *Zingiber officinale* rhizome) was evaluated on COVID-19 patients. The trial was completed but no results have been posted	(Clinical Trials.Gov, 2025b; Intharuksa et al., 2022; Sa-Ngiamsuntorn et al., 2021)
Glycyrrhiza glabra L.	Licorice	Fabaceae	Rizvi et al. (2022), evaluated the effect of *Glycyrrhiza glabra* extract (GG) on COVID-19 using a hamster model. The *Glycyrrhiza glabra* extract prevented loss in body weight and substantially decreased viral lung load by 40 %. *Glycyrrhiza glabra* extract also displayed immunomodulatory activity through reduced $Th2^1$ and $Th17^2$ differentiation and decreased cytokine production (IL-4^3 and IL-$17A^4$). Through *in-silico* studies (molecular docking and molecular simulations), Glyasperin A inhibited non-structural protein-15 (nsp-15) and Glycyrrhizic acid inhibited the spike protein.	The safety and efficacy of a herbal combination (comprising of *Phyllanthus niuri, Andrographis paniculata, Glycyrrhiza glabra, Anacardium occidentale* leaf and *Zingiber officinale* rhizome) was evaluated on COVID-19 patients. The trial was completed but no results have been posted	(Clinical Trials.Gov, 2025b; Rizvi et al., 2022; Sinha et al., 2021)
Nigella sativa L.	Black cumin	Ranunculaceae	*Nigella sativa* displays potential against COVID-19 as the bioactive constituent (Nigellidene) through *in-silico* approaches (molecular docking) inhibited $nsp2^5$ and $IL1R^6$. In a rat model, *Nigella sativa* displayed antioxidant, hepatoprotective and anti-inflammatory effects.	An open label randomized controlled clinical trial was conducted using *Nigella sativa* oil (NSO). The objective of the study was symptom management and reduced recovery time. 62 % of patients taking *Nigella sativa* oil recovered within 14 days whereas only 36 % of patients taking NSO recovered in 14 days.	(Clinical Trials.Gov, 2025a; Imran et al., 2022; Koshak et al., 2021)
Curcuma longa L.	Turmeric	Zingiberaceae	In human neuroblastoma cells (SH-SY5Y), curcumin and curcuminoids (Me08 and Me23) decreased the expression of proinflammatory cytokines (IL-6^7, TNF-α^8 and IL-17^9). Curcuminoid (Me23) downregulated plasma membrane associated transmembrane protease serine 2 (TMPRSS2) thereby lowering the increased ROS^{10} level induced by SARS-COV-2. Lastly, curcuminoids also reduced viral replication in SH-SY5Y^{11} cells overexpressing ACE-2	Fessler et al., investigated the effect of curcumin on dysregulated proinflammatory cytokines after COVID-19 recovery and vaccination. The trial found that four weeks of two daily doses of modified curcumin with enhanced bioavailability (HydroCurc) resulted in decreased concentrations of pro-inflammatory cytokines and chemokines: Nuclear factor-kappa β (NFK-β), IL-6, IFN-γ^{12}, monocyte chemoattractant protein (MCP-1), tumor necrosis factor alpha (TNF-α) and IL-$1\beta^{13}$	(Fessler et al., 2023; Nicoliche et al., 2024)
Camellia sinensis (L.) Kuntze	Tea plant	Theaceae	Catechins isolated from *Camellia sinensis* (, epicatechin gallate and gallocatechin gallate displayed intracellular inhibition of 3CLpro in HEK293T/17^{14} cells transfected with the 3CLpro activity detection system. The ratios of inhibition were 93.55 ± 0.06, 93.66 ± 0.14, 79.69 ± 1.70 and 93.56 ± 0.04, respectively.	No clinical study	(Liu et al., 2022)
Azadirachta indica A.Juss	Neem	Meliaceae	Severe COVID-19 leads to central nervous system (CNS) disorders (meningitis, encephalopathy, venous sinus thrombosis and Guilliain Barre syndrome). Thus, to evaluate the effect of *Azadirachta indica* bark extract (Neem bark extract, NBE) on severe COVID-19, an in vivo system (m-CoV-RSA$59)^{15}$ was used. Neem bark extract taken orally and intranasally displayed significant efficacy in preventing CNS and liver injury. In the DCM fraction of NBE, Nimbin/4-epinimbin compounds were identified as the active compounds targeting murine-β coronaviruses (m-CoV). *In silico* studies (Molecular modeling) confirmed the binding of Nimbin/4 epinimbin to the SARS-CoV-2 spike protein with high affinity	Neem extract has displayed promising anti-SARS-CoV-2 effects in vitro. Thus, in a double blind randomized controlled trial, the prophylactic effect of Neem was evaluated for individuals who encountered COVID-19 positive individuals. Participants received 50 mg of Neem extract twice daily for 28 days. Neem extract was 55 % effective in preventing COVID-19 infection upon exposure to individuals with COVID-19	(Nesari et al., 2021; Sarkar et al., 2022)
Echinacea purpurea (L.) Moench	Purple coneflower	Asteraceae	The hydroethanolic extract of *Echinacea purpurea* (Echinaforce) completely inactivated SARS-CoV-2 in Vero $E6^{16}$ cells infected with SARS-CoV-2 at 50 μg/mL, determined through the limiting dilution assay	In a randomized, open, controlled, exploratory clinical study, *Echinacea purpurea* was administered at 4000 mg to participants with acute respiratory symptoms for 10 days. In acute respiratory symptom episodes, it reduced the viral load by approximately 99 %. The time for viral clearance was also reduced to 4.8 days in comparison to the control	(Kolev et al., 2022; Signer et al., 2020)

(*continued*)

Table 1 (*Continued*)

Plant	Common name	Family name	Mechanism of action	Clinical studies	Refs.
Artemisia annua L.	Sweet wormwood	Asteraceae	Gendrot et al. (2020) hypothesized that antimalarial drugs may be the reason for a minimal pandemic in Africa in comparison to Europe and USA. Thus, the combination of Mefloquine and Artesunate (semi-synthetic derivative of artemisinin) inhibited viral activity by 72.1 ± 18.3 % in Vero E6 cells infected with the SARS-CoV-2 IHUMI-3 strain. Furthermore, the cytokine storm which typically occurs in SARS-CoV-2 leads to the dysregulation of pro-inflammatory cytokines such as IL-1β, IL-6 and Interferon gamma (IFN-γ). Artesunate displays anti-inflammatory effects through the inhibition of IL-1β, IL-6 by inhibiting nuclear factor kappa beta (NFKβ)	In an open-label, non-randomized and controlled trial, artemisinin in combination with piperaquine reduced the number of days of undetectable SARS-CoV-2 RNA from 19.3 days (control) to 10.6 days (artemisinin + piperaquine). Furthermore, the percentage of patients with undetectable viral RNA after 28 days was 100 % (artemisinin + piperaquine) and 72.2 % for the control group. This highlights how artemisinin in combination with piperaquine may be used as adjunctive therapy for COVID-19	(Gendrot et al., 2020; Li et al., 2021)
Zingiber officinale Roscoe	Ginger	Zingiberaceae	Through computational analysis, a compound isolated from *Zingiber officinale* (4-gingerol) had the lowest binding energy against SARS-CoV-2 Mpro[17] thus, 4-gingerol could be an inhibitor of SARS-CoV-2. Another compound, Sesquiphellandrene, binds the spike protein thereby preventing the interaction between the spike protein and ACE-2. This disruption in the interaction may result in the prevention of viral entry. Bioactive compounds (10-Shogaol and Zingiberene) downregulated TNF-α, IL1-β and IL-6. Lastly, 6-gingerol downregulated IL-6, IL-8[18], PGE2[19] and iNOS[20]	In an open label, randomized clinical trial, Ashwagandha (*Withania somnifera*) in combination with Shunti (*Zingiber officinale*) were taken twice daily for 15 days orally. The number of days for COVID-19 recovery was 6.9 days for the group taking the combination and 13 days for the control group. The proportion of participants that displayed viral clearance was 76 % for the participants taking the combination and 60.8 % for the control group. Thus, the combination of *Withania somnifera* and *Zingiber officinale* may be used as adjunctive therapy to reduce clinical recovery time and clearance of COVID-19	(Sheikh et al., 2023; Singh et al., 2023)
Allium sativum L.	Garlic	Amaryllidaceae	The active compound from *Allium sativum*, Allicin, can inhibit key pro-inflammatory cytokines involved in COVID-19 (IL-1β, IL-6 and TNF-α). In a previous study, Allicin and S-allylcystein isolated from *Allium sativum* stimulate nitric oxide and produce hydrogen sulfide which in turn inhibits the ACE receptor. The angiotensin converting enzyme (ACE) receptor is imperative in COVID-19 as it enables the entry of SARS-CoV-2 into cells thus inhibition of ACE also limits the entry of SARS-CoV-2.	In a phase III randomized clinical trial, a polyherbal formulation comprising of Ashwagandha, Boswellia, Ginger and Turmeric (BV-4051) was administered to patients for 14 days. In the group taking BV-4051, the duration of illness was reduced, symptoms such as cough, smell, fever and taste disorders were statistically less severe. The levels of IL-6 were decreased with BV-4051	(Chitre et al., 2023; Ni et al., 2020; Pandey et al., 2021)
Phyllanthus emblica L.	Amla	Phyllanthaceae	Through molecular docking and network pharmacology, compounds present in *Phyllanthus emblica* (Chlorogenic acid, Quercetin and Myricetin) inhibited vital SARS-CoV-2 proteins. Furthermore, network pharmacology elucidated immune modulation.	In a randomized double-blind controlled trial, *Phyllanthus emblica* shortened the length of stay to 4 days in comparison to the control which was 7 days. *Phyllanthus emblica* also decreased the severity of symptoms associated with COVID-19 (fever, cough, shortness of breath and myalgia). Lastly, *Phyllanthus emblica* also significantly improved the oxygen saturation level, percentage of lung involvement on CT[21] and improved C-reactive protein test results	(Chikhale et al., 2021; Varnasseri et al., 2022)
Tinospora cordifolia (Thunb.) Miers	Guduci	Menispermaceae	Through an *in-silico* approach (molecular docking and molecular simulations), compound present in *Tinospora cordifolia* (Tinocordiside) was identified as an inhibitor of the main protease of SARS-CoV-2 (SARS-CoV-2^{Mpro}). The evaluation of the ADMET[22] profile displayed that Tinocordiside has drug-like properties and is safe.	*Tinospora cordifolia* at 500 mg was administered to 43 patients for 14 days and an immunomodulatory effect was displayed as the levels of highly sensitive C-reactive protein (biomarker for inflammation in the body) were reduced. In another clinical study, two 500 mg tablets of *Tinospora cordifolia* were administered daily for 28 days. The viral clearance for patients taking *Tinospora cordifolia* at day 7 and 14 were 97.5 % and 100 % whereas the viral clearance in the control group (conventional treatment) was 15.6 % and 82.3 %	(Alam et al., 2021; Shree et al., 2022; Verma et al., 2023)
Pelargonium sidoides DC.	South African Geranium	Geraniaceae	*Pelargonium sidoides* DC. root extract EPS 7630 displays antiviral and immunomodulatory effects which decreases the length of disease and the severity of symptoms. In a human lung cell line (Calu-3) infected with SARS-CoV-2, EPS 7630 inhibited SARS-CoV-2 growth with an IC_{50} of 1.61 μg/mL. Prodelphinidins present in EPS 7630 inhibit SARS-CoV-2 entry at 10 μg/mL. EPS 7630 inhibited key pro-inflammatory cytokines (IL-8, IL-13[23], TNF-α), growth factors (CD40L[24], PDGF[25], VEGF-A[26]) and chemokines (CXCL9[27], CXCL10[28])	No clinical trial has specifically been performed to evaluate the effect of *Pelargonium sidoides* DC. root extract EPS 7630 on SARS-CoV-2. In an open-label, uncontrolled clinical trial for human coronavirus, patients received a 20 mg tablet of EPS 7630 three times a day. The patients with human coronavirus (common cold) had a pronounced improvement in common cold symptoms after 5 days.	(Keck et al., 2021; Papies et al., 2021)

(*continued*)

Table 1 (*Continued*)

Plant	Common name	Family name	Mechanism of action	Clinical studies	Refs.
Ocimum sanctum L.	Holy basil	Lamiaceae	Through molecular docking and molecular simulations, three compounds from *Ocimum sanctum* (Vicenin, isorientin 4′-O glucoside 2′′–0-p-hydroxybenzoagte and ursolic acid) inhibited the main protease (M^{pro}) of SARS-CoV-2. Furthermore, ADMET profile prediction displayed that the three compounds were safe and possessed drug-like properties.	In a randomized placebo-controlled pilot clinical trial, a herbal combination of *Tinospora cordifolia*, Swasari Ras, *Withania somnifera* and *Ocimum sanctum* was administered to patients twice daily. On day 3, 71,1 % of patients taking the herbal combination recovered whereas only 50 % of patients had recovered in the placebo group. On day 7, 100 % of patients (herbal combination) fully recovered whereas only 60 % of patients (placebo) fully recovered by day 7. The fold change of pro-inflammatory cytokines (IL-6 and TNF-α) and inflammation marker (hs-CRP) decreased by 2.5, 20 and 12.4, respectively.	(Devpura et al., 2021; Shree et al., 2022)
Withania somnifera (L.) Dunal	Ashwagandha	Solanaceae	Through molecular docking and molecular simulations, a compound from *Withania somnifera*, Withanone, displayed strong binding affinity to the spike protein and main protease of SARS-CoV-2. Withanone specifically interacts with asparagine at position 343 (Asn343) thereby inhibiting viral replication as Asn343 is part of a glycosylation site which aids in proper stability and function of the spike protein.	In a randomized placebo-controlled pilot clinical trial, a herbal combination of *Tinospora cordifolia*, Swasari Ras, *Withania somnifera* and *Ocimum sanctum* was administered to patients twice daily. On day 3, 71,1 % of patients taking the herbal combination recovered whereas only 50 % of patients had recovered in the placebo group. On day 7, 100 % of patients (herbal combination) fully recovered whereas only 60 % of patients (placebo) fully recovered by day 7. The fold change of pro-inflammatory cytokines (IL-6 and TNF-α) and inflammation marker (hs-CRP) decreased by 2.5, 20 and 12.4, respectively.	(Devpura et al., 2021; Patil et al., 2021)

T helper 2 cells, [2]T helper 17 cells, [3]Interleukin 4, [4]Interleukin 17A, [5]Non-structural protein 2, [6]Interleukin 1 receptor, [7]Interleukin 6, [8]Tumor necrosis factor alpha, [9]Interleukin 17, [10]Reactive oxygen species, [11]Human neuroblastoma cells, [12]Interferon gamma, [13]Interleukin 1 beta, [14]Human embryonic kidney 293T/17 cells, [15]Mouse coronavirus RSA59, [16]African green monkey kidney epithelial cells, [17]Severe acute respiratory syndrome-2 main protease, [18]Interleukin 8, [19]Prostaglandin E2, [20]Inducible nitric oxide, [21]Computed tomography, [22]Absorption, distribution, metabolism, excretion and toxicity, [23]Interleukin 13, [24]Cluster of differentiation 40 ligand, [25]Platelet derived growth factor, [26]Vascular endothelial growth factor A, [27]C-X-C motif chemokine ligand 9, [28]C-X-C motif ligand 10.

repurposed therapeutic (e.g. remdesivir) or a vaccine (Shohan et al., 2022). Medicinal plants are linked to indigenous knowledge holders thus, benefit-sharing agreements may be required which may be viewed as a hindrance in the drug discovery pipeline (Sanghera et al., 2015). Evaluation of all the factors relating to the utilization of medicinal plants for combating COVID-19 should be critically conducted to aid with future coronavirus pandemics as previous investigations for Spanish influenza (1918), SARS-CoV (2003) and MERS-CoV (2012) formed the backbone for COVID-19 research particularly medicinal plant research (Buchy et al., 2021).

In addition to the response to COVID-19 using medicinal plants, there were various non-pharmaceutical interventions that could be considered and refined for future coronavirus pandemics. Various countries enforced lockdowns, mandated the wearing of masks in public as well as social distancing which also aided in slowing down the transmission rate (Bo et al., 2021; Imai et al., 2020). Non-

Fig. 5. Medicinal plants with therapeutic potential against COVID-19. A. *Andrographis paniculata* (Burm.f.) Nees, B. *Glycyrrhiza glabra* L., C. *Nigella sativa* L., D. *Curcuma longa* L., E. *Camellia sinensis* (L.)Kuntze, F. Azadirachta indica A.Juss, G. *Echinacea purpurea* (L.)Moench, H. *Artemisia annua* L., I. *Zingiber officinale* Roscoe, J. *Allium sativum* L., K. *Phyllanthus emblica* L., L. *Tinospora cordifolia* (Thunb.)Miers, M. *Pelargonium sidoides* DC., N. *Ocimum sanctum* L., O. *Withania somnifera* (L.) Dunal (Agnieszka Kwiecień Nova, 2021; Berger, 2020; Bright Kwame Ayisi, 2023; Johansson, 2011; Gilles Ayotte, 1948; Zell, 2009a, 2009b; Hernandez, 2021; Karim, 2007; Konsek, 2016; Lalithamba, 2010, Monfils, 2008; NS, 2020; Yuriy Danilevsky, 2018).

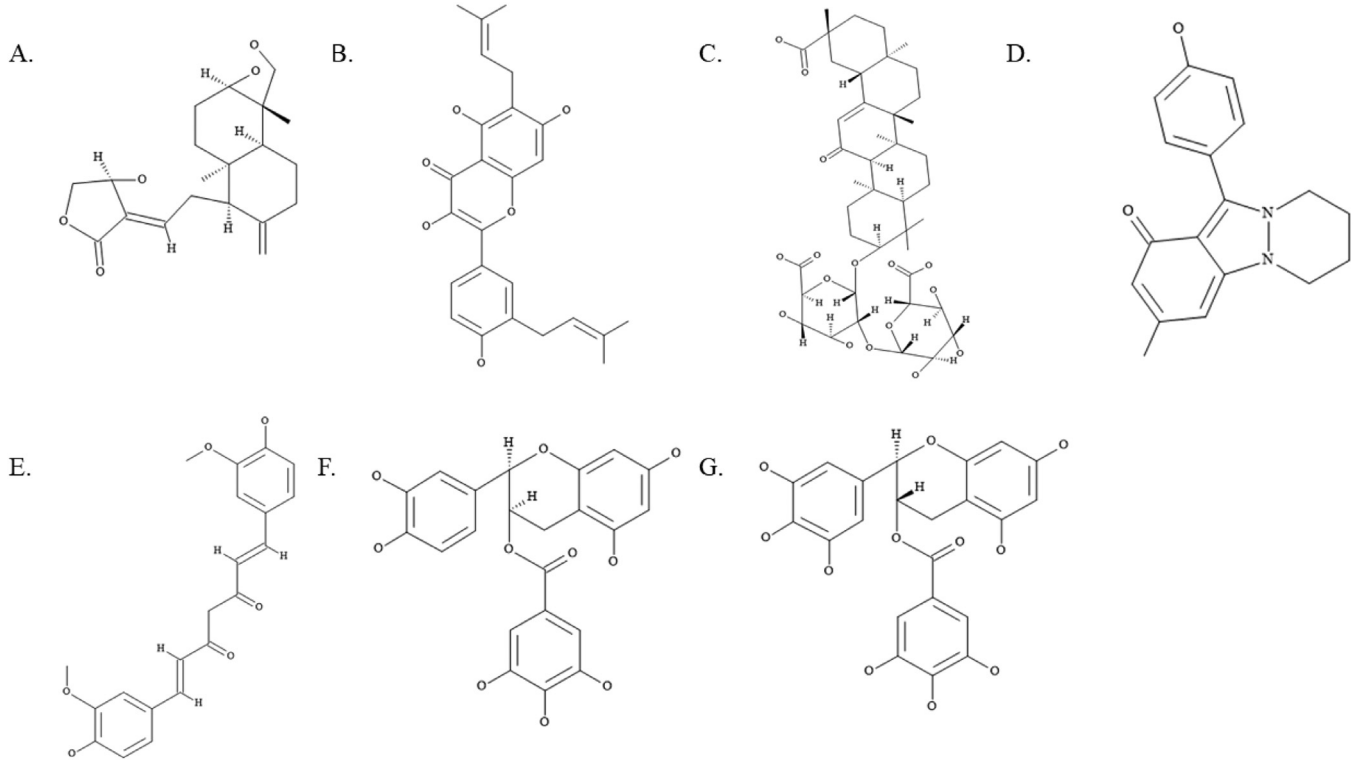

Fig. 6A. Bioactive compounds isolated from medicinal plants with therapeutic potential against COVID-19: A. Andrographolide, B. Glyasperin A, C. Glycyrrhizic acid, D.Nigellidene, E. Curcumin, F. Epicatechin gallate, G. Gallocatechin gallate.

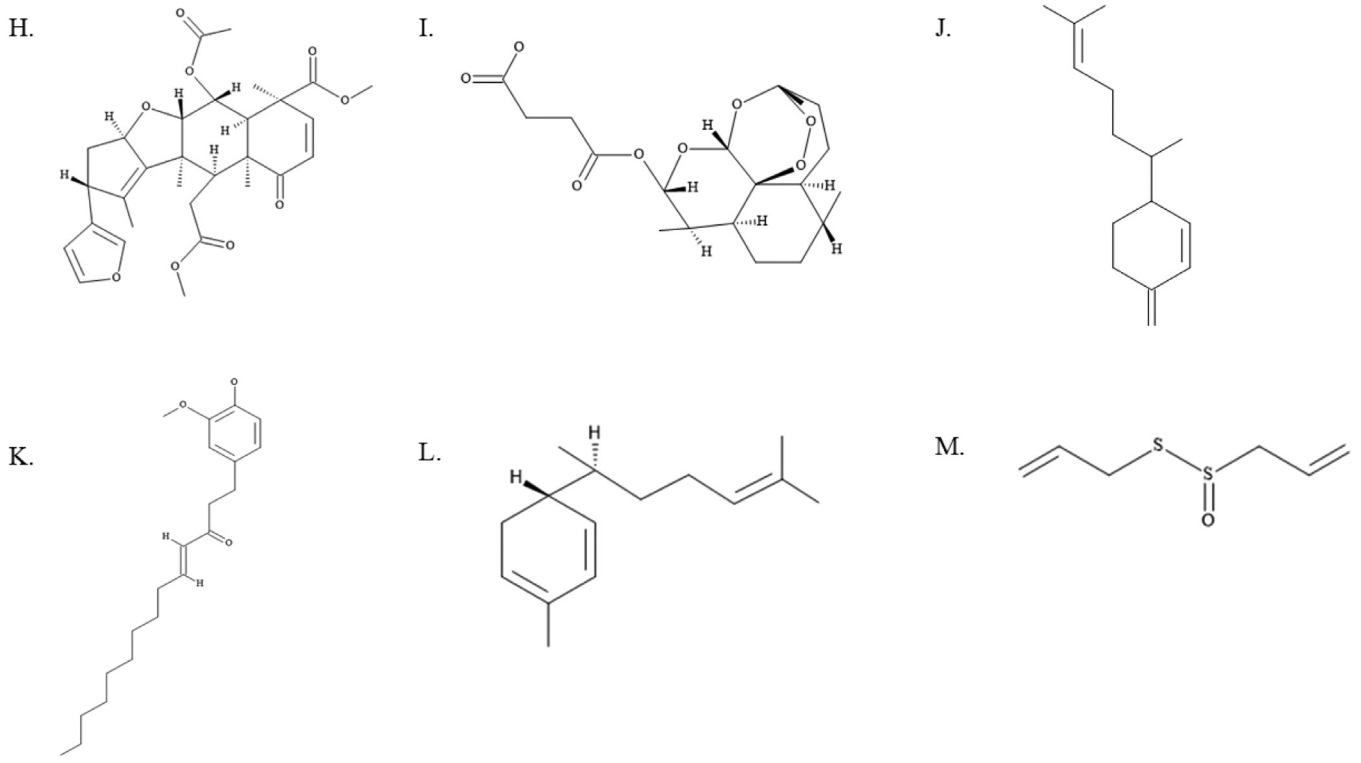

Fig. 6B. H. 4-epinimbin, I. Artesunate, J. Sesquiphellandrene, K. 10-Shogaol, L. Zingiberene, M. Allicin, N. Tinocordiside.

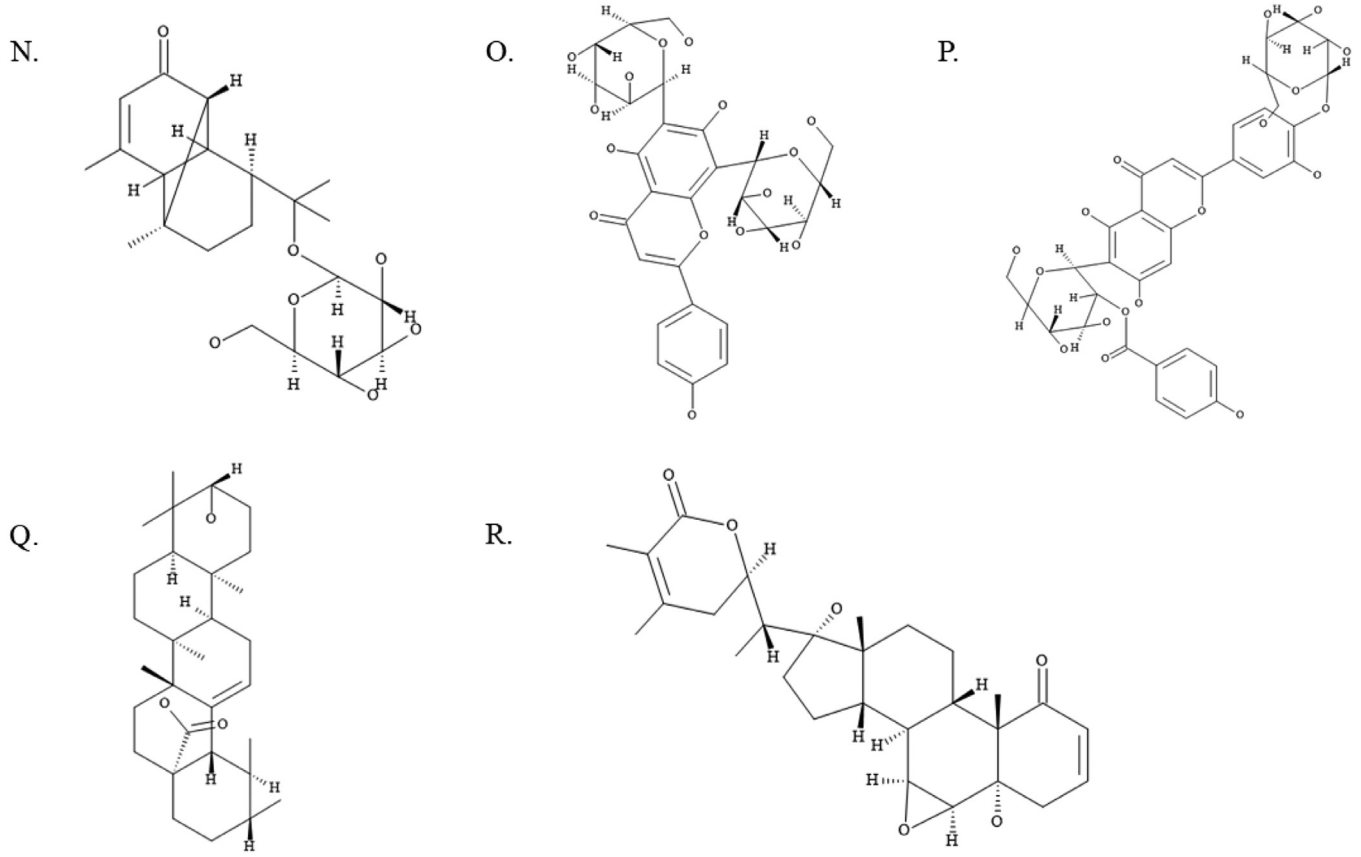

Fig. 6C. N. Tinocordiside, O. Vicenin, P. Isorientin 4′-O-glucoside 2′′-O-p-hydroxybenzoagte, Q. Ursolic acid, R. Withanone.

pharmaceutical interventions were challenging in low-middle income countries (LMIC) due to the social inequities thus, the non-pharmaceutical interventions could not be adhered to completely and the hospitals in these regions were not effective for a pandemic such as COVID-19 (Boro and Stoll, 2022). Thus, the resolution of social inequities in LMIC may enhance the effectiveness of non-pharmaceutical interventions for future coronavirus pandemic. Various governments prioritized vaccine development with the hopes of attaining global herd immunity against COVID-19 (Kashte et al., 2021). Thus, the WHO together with Coalition for epidemic preparedness innovations (CEPI) and other health organizations developed the COVID-19 vaccine global access (COVAX) facility to ensure fair distribution of vaccines globally, especially in LMIC (Xie et al., 2024). However, delays in manufacturing, vaccine hoarding by first world countries and vaccine hesitancy slowed immunization efforts in various countries (Ferranna, 2024). Thus, stronger global cooperation is required for future pandemics.

Funding

Funding from the National Research Foundation (Grant number: 98,334), the South African Medical Research Council Self-Initiated Research Grant [SAMRC SIR] and the University of Pretoria supported the publication of this work.

Declaration of competing interest

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as any potential conflict of interest.

CRediT authorship contribution statement

Brandon Alston: Conceptualization, Data curation, Investigation, Methodology, Validation, Writing – original draft, Investigation. **Jacqueline Maphutha:** Data curation, Investigation, Validation. **Jessica Ackron:** Data curation, Investigation, Validation. **Anna-Mari Kok:** Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing. **Namrita Lall:** Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Validation, Writing – review & editing.

Acknowledgments

The authors would like to acknowledge the University of Pretoria, the National Research Foundation and the South African Medical Research Council [SAMRC] for their support. Images and graphs were made using Biorender.com.

References

Abad, M.J., Bedoya, L.M., Apaza, L., Bermejo, P., 2012. The artemisia L. Genus: a review of bioactive essential oils. Molecules 17, 2542–2566. https://doi.org/10.3390/molecules17032542.

Achaiah, N.C., Subbarajasetty, S.B., Shetty, R.M., 2020. R(0) and R(e) of COVID-19: can we predict when the pandemic outbreak will be contained? Indian J. Crit. Care Med. 24, 1125–1127. https://doi.org/10.5005/jp-journals-10071-23649.

Adhikari, B., Marasini, B.P., Rayamajhee, B., Bhattarai, B.R., Lamichhane, G., Khadayat, K., Adhikari, A., Khanal, S., Parajuli, N., 2021. Potential roles of medicinal plants for the treatment of viral diseases focusing on COVID-19: a review. Phytotherapy Res. 35, 1298–1312. https://doi.org/10.1002/ptr.6893.

Agnieszka Kwiecień Nova 2021. Withania somnifera. *Wikimedia commons.*

Agyapon-Ntra, K., Mcsharry, P.E., 2023. A global analysis of the effectiveness of policy responses to COVID-19. Sci. Rep. 13, 5629. https://doi.org/10.1038/s41598-023-31709-2.
Ahmad, S., Zahiruddin, S., Parveen, B., Basist, P., Parveen, A., Gaurav, Parveen, R., Ahmad, M., 2020. Indian medicinal plants and formulations and their potential against COVID-19-preclinical and clinical research. Front. Pharmacol. 11, 578970. https://doi.org/10.3389/fphar.2020.578970.
Al-Jamal, H., Idriss, S., Roufayel, R., Abi Khattar, Z., Fajloun, Z., Sabatier, J.M., 2024. Treating COVID-19 with medicinal plants: is it even conceivable? A comprehensive review. Viruses 16. https://doi.org/10.3390/v16030320.
Al-Kuraishy, H.M., Al-Fakhrany, O.M., Elekhnawy, E., Al-Gareeb, A.I., Alorabi, M., De Waard, M., Albogami, S.M., Batiha, G.E., 2022. Traditional herbs against COVID-19: back to old weapons to combat the new pandemic. Eur. J. Med. Res. 27, 186. https://doi.org/10.1186/s40001-022-00818-5.
Alam, S., Sarker, M.M.R., Afrin, S., Richi, F.T., Zhao, C., Zhou, J.-R., Mohamed, I.N., 2021. Traditional herbal medicines, bioactive metabolites, and plant products against COVID-19: update on clinical trials and mechanism of actions. Front. Pharmacol. 12. https://doi.org/10.3389/fphar.2021.671498.
Balkhair, A.A., 2020. COVID-19 pandemic: a new chapter in the history of infectious diseases. Oman. Med. J. 35, e123. https://doi.org/10.5001/omj.2020.41.
Berger, M. 2020. Artemisia annua. *Wikimedia commons.*
Bharskar, G.R., 2022. A review on Adansonia digitata: an African tree. Res. J. Sci. Technol. 14, 127–132. https://doi.org/10.52711/2349-2988.2022.00021.
Birra, D., Benucci, M., Landolfi, L., Merchionda, A., Loi, G., Amato, P., Licata, G., Quartuccio, L., Triggiani, M., Moscato, P., 2020. COVID 19: a clue from innate immunity. Immunol. Res. 68, 161–168. https://doi.org/10.1007/s12026-020-09137-5.
Bo, Y., Guo, C., Lin, C., Zeng, Y., Li, H.B., Zhang, Y., Hossain, M.S., Chan, J.W.M., Yeung, D.W., Kwok, K.O., Wong, S.Y.S., Lau, A.K.H., Lao, X.Q., 2021. Effectiveness of non-pharmaceutical interventions on COVID-19 transmission in 190 countries from 23 January to 13 April 2020. Int. J. Infect. Dis. 102, 247–253. https://doi.org/10.1016/j.ijid.2020.10.066.
Boro, E., Stoll, B., 2022. Barriers to COVID-19 health products in low-and middle-income countries during the COVID-19 pandemic: a rapid systematic review and evidence synthesis. Front. Public Health 10, 928065. https://doi.org/10.3389/fpubh.2022.928065.
Brian, D.A., Baric, R.S., 2005. Coronavirus genome structure and replication. Curr. Top. Microbiol. Immunol. 287, 1–30. https://doi.org/10.1007/3-540-26765-4_1.
Bright Kwame A. 2023. Azadirachta indica. *Wikimedia commons.*
Buchy, P., Buisson, Y., Cintra, O., Dwyer, D.E., Nissen, M., Ortiz De Lejarazu, R., Petersen, E., 2021. COVID-19 pandemic: lessons learned from more than a century of pandemics and current vaccine development for pandemic control. Int. J. Infect. Dis. 112, 300–317. https://doi.org/10.1016/j.ijid.2021.09.045.
C. T. Johansson 2011. Camellia sinensis *Wikimedia commons.*
Cantuti-Castelvetri, L., Ojha, R., Pedro, L.D., Djannatian, M., Franz, J., Kuivanen, S., Van Der Meer, F., Kallio, K., Kaya, T., Anastasina, M., Smura, T., Levanov, L., Szirovicza, L., Tobi, A., Kallio-Kokko, H., Österlund, P., Joensuu, M., Meunier, F.A., Butcher, S.J., Winkler, M.S., Mollenhauer, B., Helenius, A., Gokce, O., Teesalu, T., Hepojoki, J., Vapalahti, O., Stadelmann, C., Balistreri, G., Simons, M., 2020. Neuropilin-1 facilitates SARS-CoV-2 cell entry and infectivity. Science (1979) 370, 856–860 . https://doi.org/10.1126/science.abd2985.
Cao, X., 2020. COVID-19: immunopathology and its implications for therapy. Nat. Rev. Immunol. 20, 269–270. https://doi.org/10.1038/s41577-020-0308-3.
Chen, J., Zhang, Z.Z., Chen, Y.K., Long, Q.X., Tian, W.G., Deng, H.J., Hu, J.L., Zhang, X.X., Pu, L., Xiang, J.L., Wang, D.X., Hu, P., Zhou, F.C., Li, Z.J., Xu, H.M., Cai, X.F., Wang, D.Q., Hu, Y., Tang, N., Liu, B.Z., Wu, G.C., Huang, A.L., 2020. The clinical and immunological features of pediatric COVID-19 patients in China. Genes. Dis. 7, 535–541. https://doi.org/10.1016/j.gendis.2020.03.008.
Chikhale, R.V., Sinha, S.K., Khanal, P., Gurav, N.S., Ayyanar, M., Prasad, S.K., Wanjari, M.M., Patil, R.B., Gurav, S.S., 2021. Computational and network pharmacology studies of phyllanthus emblica to tackle SARS-CoV-2. Phytomed. Plus 1, 100095. https://doi.org/10.1016/j.phyplu.2021.100095.
Chitre, D., Nadkarni, S., Jagtap, N., Tulle, R., Gitte, A., Rahate, P., Chaskar, S., Dey, D., 2023. Phase III randomized clinical trial of BV-4051, an Ayurvedic polyherbal formulation in moderate SARS-CoV-2 infections and its impact on inflammatory biomarkers. Phytotherapy Res. 37, 1232–1241. https://doi.org/10.1002/ptr.7683.
Choudhury, P.R., Talukdar, A.D., Nath, D., Saha, P., Nath, R., 2020. Traditional folk medicine and drug discovery: prospects and outcome. In: Patra, J.K., Shukla, A.C., Das, G. (Eds.), Advances in Pharmaceutical Biotechnology: Recent Progress and Future Applications. Springer Singapore, Singapore.
Cinatl, J., Morgenstern, B., Bauer, G., Chandra, P., Rabenau, H., Doerr, H.W., 2003. Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated coronavirus. Lancet 361, 2045–2046. https://doi.org/10.1016/s0140-6736(03)13615-x.
Clinical Trials.Gov. 2025a. *Effects of Nigella sativa as a treatment of patients with upper respiratory tract infection caused by SARS-coronavirus-2: a prospective, randomized, open-label controlled clinical study* [Online]. Available: https://clinicaltrials.gov/study/NCT04401202?cond=COVID-19&term=SARS-CoV2&intr=Nigella%20sativa&rank=3 [Accessed 20/01/2025 2025].
Clinical Trials.Gov. 2025b *Efficacy and immunomodulator impact of herbal combination on COVID-19 patients recovery* [Online]. Available: https://clinicaltrials.gov/study/NCT06636760?cond=Covid19&term=SARS-CoV2&intr=Andrographis%20Paniculata&rank=2&tab=table [Accessed 20/01/2025 2025].
D'arienzo, M., Coniglio, A., 2020. Assessment of the SARS-CoV-2 basic reproduction number, R (0), based on the early phase of COVID-19 outbreak in Italy. Biosaf. Health 2, 57–59. https://doi.org/10.1016/j.bsheal.2020.03.004.
Daly, J.L., Simonetti, B., Klein, K., Chen, K.E., Williamson, M.K., Antón-Plágaro, C., Shoemark, D.K., Simón-Gracia, L., Bauer, M., Hollandi, R., Greber, U.F., Horvath, P., Sessions, R.B., Helenius, A., Hiscox, J.A., Teesalu, T., Matthews, D.A., Davidson, A.D., Collins, B.M., Cullen, P.J., Yamauchi, Y., 2020. Neuropilin-1 is a host factor for SARS-CoV-2 infection. Science (1979) 370, 861–865. https://doi.org/10.1126/science.abd3072.
Devpura, G., Tomar, B.S., Nathiya, D., Sharma, A., Bhandari, D., Haldar, S., Balkrishna, A., Varshney, A., 2021. Randomized placebo-controlled pilot clinical trial on the efficacy of ayurvedic treatment regime on COVID-19 positive patients. Phytomedicine 84, 153494. https://doi.org/10.1016/j.phymed.2021.153494.
Donnat, C., Holmes, S., 2023. Modeling the heterogeneity in COVID-19′s reproductive number and its impact on predictive scenarios. J. Appl. Stat. 50, 2518–2546. https://doi.org/10.1080/02664763.2021.1941806.
Du, L., He, Y., Zhou, Y., Liu, S., Zheng, B.J., Jiang, S., 2009. The spike protein of SARS-CoV—a target for vaccine and therapeutic development. Nat. Rev. Microbiol. 7, 226–236. https://doi.org/10.1038/nrmicro2090.
Dubey, A.K., Chaudhry, S.K., Singh, H.B., Gupta, V.K., Kaushik, A., 2022. Perspectives on nano-nutraceuticals to manage pre and post COVID-19 infections. Biotechnol. Rep. 33, e00712. https://doi.org/10.1016/j.btre.2022.e00712.
Dwarka, D., Agoni, C., Mellem, J.J., Soliman, M.E., Baijnath, H., 2020. Identification of potential SARS-CoV-2 inhibitors from South African medicinal plant extracts using molecular modelling approaches. South Afr. J. Bot. 133, 273–284. https://doi.org/10.1016/j.sajb.2020.07.035.
Ejaz, H., Alsrhani, A., Zafar, A., Javed, H., Junaid, K., Abdalla, A.E., Abosalif, K.O.A., Ahmed, Z., Younas, S., 2020. COVID-19 and comorbidities: deleterious impact on infected patients. J. Infect. Public Health 13, 1833–1839. https://doi.org/10.1016/j.jiph.2020.07.014.
Fehr, A.R., Perlman, S., 2015. Coronaviruses: an overview of their replication and pathogenesis. Methods Mol. Biol. 1282, 1–23. https://doi.org/10.1007/978-1-4939-2438-7_1.
Ferranna, M., 2024. Causes and costs of global COVID-19 vaccine inequity. Semin. Immunopathol. 45, 469–480. https://doi.org/10.1007/s00281-023-00998-0.
Fessler, S.N., Chang, Y., Liu, L., Johnston, C.S., 2023. Curcumin confers anti-inflammatory effects in adults who recovered from COVID-19 and were subsequently vaccinated: a randomized controlled trial. Nutrients 15. https://doi.org/10.3390/nu15071548.
Gallo, G., Calvez, V., Savoia, C., 2022. Hypertension and COVID-19: current evidence and perspectives. High Blood Press. Cardiovasc. Prevent. 29, 115–123. https://doi.org/10.1007/s40292-022-00506-9.
Gallo Marin, B., Aghagoli, G., Lavine, K., Yang, L., Siff, E.J., Chiang, S.S., Salazar-Mather, T.P., Dumenco, L., Savaria, M.C., Aung, S.N., Flanigan, T., Michelow, I.C., 2021. Predictors of COVID-19 severity: a literature review. Rev. Med. Virol. 31, 1–10. https://doi.org/10.1002/rmv.2146.
García, L.F., 2020. Immune response, inflammation, and the clinical spectrum of COVID-19. Front. Immunol. 11, 1441. https://doi.org/10.3389/fimmu.2020.01441.
Gendrot, M., Duflot, I., Boxberger, M., Delandre, O., Jardot, P., Le Bideau, M., Andreani, J., Fonta, I., Mosnier, J., Rolland, C., Hutter, S., La Scola, B., Pradines, B., 2020. Antimalarial artemisinin-based combination therapies (ACT) and COVID-19 in Africa: in vitro inhibition of SARS-CoV-2 replication by mefloquine-artesunate. Int. J. Infect. Dis. 99, 437–440. https://doi.org/10.1016/j.ijid.2020.08.032.
G. Ayotte 1948. Allium Sativum. Wikimedia commons.
Gozzi, N., Bajardi, P., Perra, N., 2021. The importance of non-pharmaceutical interventions during the COVID-19 vaccine rollout. PLoS Comput. Biol. 17, e1009346. https://doi.org/10.1371/journal.pcbi.1009346.
Guan, W.J., Ni, Z.Y., Hu, Y., Liang, W.H., Ou, C.Q., He, J.X., Liu, L., Shan, H., Lei, C.L., Hui, D.S.C., Du, B., Li, L.J., Zeng, G., Yuen, K.Y., Chen, R.C., Tang, C.L., Wang, T., Chen, P.Y., Xiang, J., Li, S.Y., Wang, J.L., Liang, Z.J., Peng, Y.X., Wei, L., Liu, Y., Hu, Y.H., Peng, P., Wang, J.M., Liu, J.Y., Chen, Z., Li, G., Zheng, Z.J., Qiu, S.Q., Luo, J., Ye, C.J., Zhu, S.Y., Zhong, N.S., 2020. Clinical characteristics of coronavirus disease 2019 in China. New Engl. J. Med. 382, 1708–1720. https://doi.org/10.1056/NEJMoa2002032.
Guo, T., Fan, Y., Chen, M., Wu, X., Zhang, L., He, T., Wang, H., Wan, J., Wang, X., Lu, Z., 2020. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMa Cardiol. 5, 811–818. https://doi.org/10.1001/jamacardio.2020.1017.
H. Zell 2009a. Andrographis paniculata. *Wikimedia commons.*
H. Zell 2009b Nigella Sativa. Wikimedia commons.
Hale, T., Hale, A.J., Kira, B., Petherick, A., Phillips, T., Sridhar, D., Thompson, R.N., Webster, S. & Angrist, N. 2020. Global assessment of the relationship between government response measures and COVID-19 deaths. *medRxiv*., 2020.07.04.20145334. 10.1101/2020.07.04.20145334
Hatmal, M.M., Alshaer, W., Al-Hatamleh, M.a.I., Hatmal, M., Smadi, O., Taha, M.O., Oweida, A.J., Boer, J.C., Mohamud, R., Plebanski, M., 2020. Comprehensive structural and molecular comparison of spike proteins of SARS-CoV-2, SARS-CoV and MERS-CoV, and their interactions with ACE2. Cells 9. https://doi.org/10.3390/cells9122638.
Hernandez, W.R.R. 2021. Echinacea purpurea. Wikimedia commons.
Ho, T.C., Wang, Y.H., Chen, Y.L., Tsai, W.C., Lee, C.H., Chuang, K.P., Chen, Y.A., Yuan, C.H., Ho, S.Y., Yang, M.H., Tyan, Y.C., 2021. Chloroquine and hydroxychloroquine: efficacy in the treatment of the COVID-19. Pathogens 10. https://doi.org/10.3390/pathogens10020217.
Hoever, G., Baltina, L., Michaelis, M., Kondratenko, R., Baltina, L., Tolstikov, G.A., Doerr, H.W., Cinatl, J., 2005. Antiviral activity of glycyrrhizic acid derivatives against SARS— coronavirus. J. Med. Chem. 48, 1256–1259. https://doi.org/10.1021/jm0493008.

Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., Schiergens, T.S., Herrler, G., Wu, N.H., Nitsche, A., Müller, M.A., Drosten, C., Pöhlmann, S., 2020. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 181,. https://doi.org/10.1016/j.cell.2020.02.052 271-280.e8.

Hsiang, S., Allen, D., Annan-Phan, S., Bell, K., Bolliger, I., Chong, T., Druckenmiller, H., Huang, L.Y., Hultgren, A., Krasovich, E., Lau, P., Lee, J., Rolf, E., Tseng, J., Wu, T., 2020. The effect of large-scale anti-contagion policies on the COVID-19 pandemic. Nature 584, 262–267. https://doi.org/10.1038/s41586-020-2404-8.

Hu, B., Guo, H., Zhou, P., Shi, Z.L., 2021. Characteristics of SARS-CoV-2 and COVID-19. Nat. Rev. Microbiol. 19, 141–154. https://doi.org/10.1038/s41579-020-00459-7.

Huang, Z., Huang, J., Gu, Q., Du, P., Liang, H., Dong, Q., 2020. Optimal temperature zone for the dispersal of COVID-19. Sci. Total Environ. 736, 139487. https://doi.org/10.1016/j.scitotenv.2020.139487.

Imai, N., Gaythorpe, K.A.M., Abbott, S., Bhatia, S., Van Elsland, S., Prem, K., Liu, Y., Ferguson, N.M., 2020. Adoption and impact of non-pharmaceutical interventions for COVID-19. Wellcome Open. Res. 5, 59. https://doi.org/10.12688/wellcomeopenres.15808.1.

Imran, M., Khan, S.A., Abida, Alshammari, M.K., Alkhaldi, S.M., Alshammari, F.N., Kamal, M., Alam, O., Asdaq, S.M.B., Alzahrani, A.K., Jomah, S., 2022. Nigella sativa L. and COVID-19: a glance at the Anti-COVID-19 chemical constituents, clinical trials, inventions, and patent literature. Molecules 27. https://doi.org/10.3390/molecules27092750.

Intharuksa, A., Arunotayanun, W., Yooin, W., Sirisa-Ard, P., 2022. A comprehensive review of Andrographis paniculata (Burm. f.) Nees and its constituents as potential lead compounds for COVID-19 drug discovery. Molecules 27, 4479. https://doi.org/10.3390/molecules27144479.

Jackson, C.B., Farzan, M., Chen, B., Choe, H., 2022. Mechanisms of SARS-CoV-2 entry into cells. Nat. Rev. Mol. Cell Biol. 23, 3–20. https://doi.org/10.1038/s41580-021-00418-x.

Jalali, A., Dabaghian, F., Akbrialiabad, H., Foroughinia, F., Zarshenas, M.M., 2021. A pharmacology-based comprehensive review on medicinal plants and phytoactive constituents possibly effective in the management of COVID-19. Phytotherapy Res. 35, 1925–1938. https://doi.org/10.1002/ptr.6936.

Jena, P.R., Majhi, R., Kalli, R., Managi, S., Majhi, B., 2021. Impact of COVID-19 on GDP of major economies: application of the artificial neural network forecaster. Econ. Anal. Policy 69, 324–339. https://doi.org/10.1016/j.eap.2020.12.013.

Jiang, S., Hillyer, C., Du, L., 2020. Neutralizing antibodies against SARS-CoV-2 and other human coronaviruses. Trends Immunol. 41, 355–359. https://doi.org/10.1016/j.it.2020.03.007.

Jo, S., Kim, H., Kim, S., Shin, D.H., Kim, M.S., 2019. Characteristics of flavonoids as potent MERS-CoV 3C-like protease inhibitors. Chem. Biol. Drug Des. 94, 2023–2030. https://doi.org/10.1111/cbdd.13604.

Joshi, T., Kumar, N., Kothiyal, P., 2015. A review on cleome viscosa: an endogenous herb of Uttarakhand. Int. J. Pharma Res. Rev. 4, 25–31.

Karim, M.M. 2007. Ocimum Sanctum. Wikimedia commons.

Kashte, S., Gulbake, A., El-Amin Iii, S.F., Gupta, A., 2021. COVID-19 vaccines: rapid development, implications, challenges and future prospects. Hum. Cell 34, 711–733. https://doi.org/10.1007/s13577-021-00512-4.

Keck, T., Strobl, A., Weinhaeusel, A., Funk, P., Michaelis, M., 2021. Pelargonium extract EPs 7630 in the treatment of human corona virus-associated acute respiratory tract infections - a secondary subgroup-analysis of an open-label, uncontrolled clinical trial. Front. Pharmacol. 12, 666546. https://doi.org/10.3389/fphar.2021.666546.

Khadka, D., Dhamala, M.K., Li, F., Aryal, P.C., Magar, P.R., Bhatta, S., Thakur, M.S., Basnet, A., Cui, D., Shi, S., 2021. The use of medicinal plants to prevent COVID-19 in Nepal. J. Ethnobiol. Ethnomed. 17, 26. https://doi.org/10.1186/s13002-021-00449-w.

Khalifa, S.a.M., Yosri, N., El-Mallah, M.F., Ghonaim, R., Guo, Z., Musharraf, S.G., Du, M., Khatib, A., Xiao, J., Saeed, A., El-Seedi, H.H.R., Zhao, C., Efferth, T., El-Seedi, H.R., 2021. Screening for natural and derived bio-active compounds in preclinical and clinical studies: one of the frontlines of fighting the coronaviruses pandemic. Phytomedicine 85, 153311. https://doi.org/10.1016/j.phymed.2020.153311.

Khalil, M., Abdallah, H., Calasso, M., Khalil, N., Daher, A., Missaoui, J., Diab, F., Zeaiter, L., Vergani, L., Di Ciaula, A., Portincasa, P., 2024. Herbal medicine in three different Mediterranean living areas during the COVID-19 pandemic: the role of polyphenolic-rich thyme-like plants. Plants 13, 3340. https://doi.org/10.3390/plants13233340.

Khan, T., Khan, M.A., Mashwani, Z.U., Ullah, N., Nadhman, A., 2021. Therapeutic potential of medicinal plants against COVID-19: the role of antiviral medicinal metabolites. Biocatal. Agric. Biotechnol. 31, 101890. https://doi.org/10.1016/j.bcab.2020.101890.

Kolev, E., Mircheva, L., Edwards, M.R., Johnston, S.L., Kalinov, K., Stange, R., Gancitano, G., Berghe, W.V., Kreft, S., 2022. Echinacea Purpurea for the long-term prevention of viral respiratory tract infections during COVID-19 pandemic: a randomized, open, controlled, exploratory clinical study. Front. Pharmacol. 13, 856410. https://doi.org/10.3389/fphar.2022.856410.

Konsek, M. 2016. Zingiber Officinale. Wikimedia commons.

Koshak, A.E., Koshak, E.A., Mobeireek, A.F., Badawi, M.A., Wali, S.O., Malibary, H.M., Atwah, A.F., Alhamdan, M.M., Almalki, R.A., Madani, T.A., 2021. Nigella sativa for the treatment of COVID-19: an open-label randomized controlled clinical trial. Complement. Ther. Med. 61, 102769. https://doi.org/10.1016/j.ctim.2021.102769.

Kunutsor, S.K., Laukkanen, J.A., 2020. Renal complications in COVID-19: a systematic review and meta-analysis. Ann. Med. 52, 345–353. https://doi.org/10.1080/07853890.2020.1790643.

Lalithamba 2010. Phyllanthus emblica. *Wikimedia commons.*

Lee, T.C., Senecal, J., Hsu, J.M., Mcdonald, E.G., 2021. Ongoing citations of a retracted study involving cardiovascular disease, drug therapy, and mortality in COVID-19. JAMa Intern. Med. 181, 1535–1537. https://doi.org/10.1001/jamainternmed.2021.4112.

Lee, Y., Jehangir, Q., Li, P., Gudimella, D., Mahale, P., Lin, C.H., Apala, D.R., Krishnamoorthy, G., Halabi, A.R., Patel, K., Poisson, L., Balijepally, V., Sule, A.A., Nair, G.B., 2022. Venous thromboembolism in COVID-19 patients and prediction model: a multicenter cohort study. BMC Infect. Dis. 22, 462. https://doi.org/10.1186/s12879-022-07421-3.

Li, G., Yuan, M., Li, H., Deng, C., Wang, Q., Tang, Y., Zhang, H., Yu, W., Xu, Q., Zou, Y., Yuan, Y., Guo, J., Jin, C., Guan, X., Xie, F., Song, J., 2021. Safety and efficacy of artemisinin-piperaquine for treatment of COVID-19: an open-label, non-randomised and controlled trial. Int. J. Antimicrob. Agents 57, 106216. https://doi.org/10.1016/j.ijantimicag.2020.106216.

Li, Q., Guan, X., Wu, P., Wang, X., Zhou, L., Tong, Y., Ren, R., Leung, K.S., Lau, E.H., Wong, J.Y., 2020. Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia. New Engl. J. Med. 382, 1199–1207. https://doi.org/10.1056/NEJMoa2001316.

Lim, X.Y., Teh, B.P., Tan, T.Y.C., 2021. Medicinal plants in COVID-19: potential and limitations. Front. Pharmacol. 12, 611408. https://doi.org/10.3389/fphar.2021.611408.

Lin, M., Wynne, J.F., Zhou, B., Wang, T., Lei, Y., Curran, W.J., Liu, T., Yang, X., 2021. Artificial intelligence in tumor subregion analysis based on medical imaging: a review. J. Appl. Clin. Med. Phys. 22, 10–26. https://doi.org/10.1002/acm2.13321.

Lin, S.C., Ho, C.T., Chuo, W.H., Li, S., Wang, T.T., Lin, C.C., 2017. Effective inhibition of MERS-CoV infection by resveratrol. BMC Infect. Dis. 17, 144. https://doi.org/10.1186/s12879-017-2253-8.

Liu, S.Y., Wang, W., Ke, J.P., Zhang, P., Chu, G.X., Bao, G.H., 2022. Discovery of Camellia sinensis catechins as SARS-CoV-2 3CL protease inhibitors through molecular docking, intra and extra cellular assays. Phytomedicine 96, 153853. https://doi.org/10.1016/j.phymed.2021.153853.

Liu, Y., Gayle, A.A., Wilder-Smith, A., Rocklöv, J., 2020. The reproductive number of COVID-19 is higher compared to SARS coronavirus. J. Travel. Med. 27. https://doi.org/10.1093/jtm/taaa021.

Luan, J., Lu, Y., Jin, X., Zhang, L., 2020. Spike protein recognition of mammalian ACE2 predicts the host range and an optimized ACE2 for SARS-CoV-2 infection. Biochem. Biophys. Res. Commun. 526, 165–169. https://doi.org/10.1016/j.bbrc.2020.03.047.

Luo, L., Jiang, J., Wang, C., Fitzgerald, M., Hu, W., Zhou, Y., Zhang, H., Chen, S., 2020. Analysis on herbal medicines utilized for treatment of COVID-19. Acta Pharm. Sin. B 10, 1192–1204.

Ma, Q., Yu, Q., Xing, X., Liu, S., Shi, C., Luo, J., 2018. San Wu Huangqin decoction, a Chinese herbal formula, inhibits influenza a/PR/8/34 (H1N1) virus infection In vitro and In vivo. Viruses 10. https://doi.org/10.3390/v10030117.

Mayi, B.S., Leibowitz, J.A., Woods, A.T., Ammon, K.A., Liu, A.E., Raja, A., 2021. The role of Neuropilin-1 in COVID-19. PLoS Pathog. 17, e1009153. https://doi.org/10.1371/journal.ppat.1009153.

Mishra, J., Mishra, P., Arora, N.K., 2021. Linkages between environmental issues and zoonotic diseases: with reference to COVID-19 pandemic. Environ. Sustain. (Singap) 4, 455–467. https://doi.org/10.1007/s42398-021-00165-x.

Mitze, T., Kosfeld, R., Rode, J., Wälde, K., 2020. Face masks considerably reduce COVID-19 cases in Germany. Proc. Natl. Acad. Sci. U.S.A. 117, 32293–32301. https://doi.org/10.1073/pnas.2015954117.

Monfils, L. 2008. Curcuma longa. *Wikimedia commons.*

Montani, D., Savale, L., Noel, N., Meyrignac, O., Colle, R., Gasnier, M., Corruble, E., Beurnier, A., Jutant, E.M., Pham, T., Lecoq, A.L., Papon, J.F., Figueiredo, S., Harrois, A., Humbert, M., Monnet, X., 2022. Post-acute COVID-19 syndrome. Eur. Respir. Rev. 31. https://doi.org/10.1038/s41591-021-01283-z.

Morens, D.M., Breman, J.G., Calisher, C.H., Doherty, P.C., Hahn, B.H., Keusch, G.T., Kramer, L.D., Leduc, J.W., Monath, T.P., Taubenberger, J.K., 2020. The origin of COVID-19 and why it matters. Am. J. Trop. Med. Hyg. 103, 955–959. https://doi.org/10.4269/ajtmh.20-0849.

NS. 2020. Tinospora Cordifolia. Wikimedia commons.

Nalbandian, A., Sehgal, K., Gupta, A., Madhavan, M.V., Mcgroder, C., Stevens, J.S., Cook, J.R., Nordvig, A.S., Shalev, D., Sehrawat, T.S., Ahluwalia, N., Bikdeli, B., Dietz, D., Der-Nigoghossian, C., Liyanage-Don, N., Rosner, G.F., Bernstein, E.J., Mohan, S., Beckley, A.A., Seres, D.S., Choueiri, T.K., Uriel, N., Ausiello, J.C., Accili, D., Freedberg, D.E., Baldwin, M., Schwartz, A., Brodie, D., Garcia, C.K., Elkind, M.S.V., Connors, J.M., Bilezikian, J.P., Landry, D.W., Wan, E.Y., 2021. Post-acute COVID-19 syndrome. Nat. Med. 27, 601–615. https://doi.org/10.1038/s41591-021-01283-z.

Nesari, T.M., Bhardwaj, A., Shrikrishna, R., Ruknuddin, G., Ghildiyal, S., Das, A., Pandey, A.K., Chaudhary, N., Soman, G., Barde, M., 2021. Neem (Azadirachta Indica A. Juss) capsules for prophylaxis of COVID-19 infection: a pilot, double-blind, randomized controlled trial. Altern. Therap. Health Med. 27, 196–203 PMID: 33891569.

Newman, D.J., Cragg, G.M., 2020. Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019. J. Nat. Prod. 83, 770–803. https://doi.org/10.1021/acs.jnatprod.9b01285.

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. Crit. Care (Fullerton) 24, 422. https://doi.org/10.1186/s13054-020-03120-0.

Nicoliche, T., Bartolomeo, C.S., Lemes, R.M.R., Pereira, G.C., Nunes, T.A., Oliveira, R.B., Nicastro, A.L.M., Soares, É., .N.., Da Cunha Lima, B.F., Rodrigues, B.M., Maricato, J.T., Okuda, L.H., De Sairre, M.I., Prado, C.M., Ureshino, R.P., Stilhano, R.S., 2024. Antiviral, anti-inflammatory and antioxidant effects of curcumin and curcuminoids in SH-SY5Y cells infected by SARS-CoV-2. Sci. Rep. 14, 10696. https://doi.org/10.1038/s41598-024-61662-7.

Oraby, T., Tyshenko, M.G., Maldonado, J.C., Vatcheva, K., Elsaadany, S., Alali, W.Q., Longenecker, J.C., Al-Zoughool, M., 2021. Modeling the effect of lockdown timing as a COVID-19 control measure in countries with differing social contacts. Sci. Rep. 11, 3354. https://doi.org/10.1038/s41598-021-82873-2.

Pandey, R.K., Pandey, R.K., Shukla, S.S., Pandey, P., 2021. A review on corona virus and treatment approaches with Allium sativam. Futur. J. Pharm. Sci. 7, 159. https://doi.org/10.1186/s43094-021-00310-7.

Papies, J., Emanuel, J., Heinemann, N., Kulić, Ž., Schroeder, S., Tenner, B., Lehner, M.D., Seifert, G., Müller, M.A., 2021. Antiviral and immunomodulatory effects of pelargonium sidoides DC. Root extract EPs® 7630 in SARS-CoV-2-infected human lung cells. Front. Pharmacol. 12, 757666. https://doi.org/10.3389/fphar.2021.757666.

Patil, V.S., Hupparage, V.B., Malgi, A.P., Deshpande, S.H., Patil, S.A., Mallapur, S.P., 2021. Dual inhibition of COVID-19 spike glycoprotein and main protease 3CLpro by Withanone from Withania somnifera. Chin. Herb. Med. 13, 359–369. https://doi.org/10.1016/j.chmed.2021.06.002.

Patra, R., Chandra Das, N., Mukherjee, S., 2021. Targeting human TLRs to combat COVID-19: a solution? J. Med. Virol. 93, 615–617. https://doi.org/10.1002/jmv.26387.

Peng, H., He, Y., Zheng, G., Zhang, W., Yao, Z., Xie, W., 2016. Meta-analysis of traditional herbal medicine in the treatment of nonalcoholic fatty liver disease. Cell. Mol. Biol. 62, 88–95 *(Noisy-le-grand)*PMID: 27188741.

Pormohammad, A., Ghorbani, S., Khatami, A., Farzi, R., Baradaran, B., Turner, D.L., Turner, R.J., Bahr, N.C., Idrovo, J.P., 2020. Comparison of confirmed COVID-19 with SARS and MERS cases - clinical characteristics, laboratory findings, radiographic signs and outcomes: a systematic review and meta-analysis. Rev. Med. Virol. 30, e2112. https://doi.org/10.1002/rmv.2112.

Rao, S., Lau, A., So, H.C., 2020. Exploring diseases/traits and blood proteins causally related to expression of ACE2, the putative receptor of SARS-CoV-2: a mendelian randomization analysis highlights tentative relevance of diabetes-related traits. Diabetes Care 43, 1416–1426. https://doi.org/10.2337/dc20-0643.

Redlin, M., 2022. Differences in NPI strategies against COVID-19. J. Regul. Econ. 62, 1–23. https://doi.org/10.1007/s11149-022-09452-9.

Rizvi, Z.A., Babele, P., Sadhu, S., Madan, U., Tripathy, M.R., Goswami, S., Mani, S., Kumar, S., Awasthi, A., Dikshit, M., 2022. Prophylactic treatment of Glycyrrhiza glabra mitigates COVID-19 pathology through inhibition of pro-inflammatory cytokines in the hamster model and NETosis. Front. Immunol. 13, 945583. https://doi.org/10.3389/fimmu.2022.945583.

Roy, A., Khan, A., Ahmad, I., Alghamdi, S., Rajab, B.S., Babalghith, A.O., Alshahrani, M.Y., Islam, S., Islam, M.R., 2022. Flavonoids a bioactive compound from medicinal plants and its therapeutic applications. Biomed. Res. Int., 5445291. https://doi.org/10.1155/2022/5445291 2022.

Sa-Ngiamsuntorn, K., Suksatu, A., Pewkliang, Y., Thongsri, P., Kanjanasirirat, P., Manopwisedjaroen, S., Charoensutthivarakul, S., Wongtrakoongate, P., Pitiporn, S., Chaopreecha, J., Kongsomros, S., Jearawuttanakul, K., Wannalo, W., Khemawoot, P., Chutipongtanate, S., Borwornpinyo, S., Thitithanyanont, A., Hongeng, S., 2021. Anti-SARS-CoV-2 activity of andrographis paniculata extract and its major component andrographolide in human lung epithelial cells and cytotoxicity evaluation in major organ cell representatives. J. Nat. Prod. 84, 1261–1270. https://doi.org/10.1021/acs.jnatprod.0c01324.

Saha, R.P., Sharma, A.R., Singh, M.K., Samanta, S., Bhakta, S., Mandal, S., Bhattacharya, M., Lee, S.S., Chakraborty, C., 2020. Repurposing drugs, ongoing vaccine, and new therapeutic development initiatives against COVID-19. Front. Pharmacol. 11, 1258. https://doi.org/10.3389/fphar.2020.01258.

Sanghera, G.S., Bhatia, D., Thind, K.S., 2015. Access and benefit sharing on the use of indigenous traditional knowledge. In: Salgotra, R.K., Gupta, B.B. (Eds.), Plant Genetic Resources and Traditional Knowledge For Food Security. Springer Singapore, Singapore.

Sarkar, L., Oko, L., Gupta, S., Bubak, A.N., Das, B., Gupta, P., Safiriyu, A.A., Singhal, C., Neogi, U., Bloom, D., Banerjee, A., Mahalingam, R., Cohrs, R.J., Koval, M., Shindler, K.S., Pal, D., Nagel, M., Sarma, J.D., 2022. Azadirachta indica A. Juss bark extract and its Nimbin isomers restrict β-coronaviral infection and replication. Virology 569, 13–28. https://doi.org/10.1016/j.virol.2022.01.002.

Schuchat, A., 2020. Public health response to the initiation and spread of pandemic COVID-19 in the United States, February 24-April 21, 2020. Morb. Mortal. Wkly. Rep. 69, 551–556. https://doi.org/10.15585/mmwr.mm6918e2.

Seyed Hosseini, E., Riahi Kashani, N., Nikzad, H., Azadbakht, J., Hassani Bafrani, H., Haddad Kashani, H., 2020. The novel coronavirus Disease-2019 (COVID-19): mechanism of action, detection and recent therapeutic strategies. Virology 551, 1–9. https://doi.org/10.1016/j.virol.2020.08.011.

Sheikh, H.I., Zakaria, N.H., Abdul Majid, F.A., Zamzuri, F., Fadhlina, A., Hairani, M.a.S., 2023. Promising roles of Zingiber officinale roscoe, Curcuma longa L., and Momordica charantia L. as immunity modulators against COVID-19: a bibliometric analysis. J. Agric. Food Res. 14, 100680. https://doi.org/10.1016/j.jafr.2023.100680.

Shohan, M., Nashibi, R., Mahmoudian-Sani, M.R., Abolnezhadian, F., Ghafourian, M., Alavi, S.M., Sharhani, A., Khodadadi, A., 2022. The therapeutic efficacy of quercetin in combination with antiviral drugs in hospitalized COVID-19 patients: a randomized controlled trial. Eur. J. Pharmacol. 914, 174615. https://doi.org/10.1016/j.ejphar.2021.174615.

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. J. Biomol. Struct. Dyn. 40, 190–203. https://doi.org/10.1080/07391102.2020.1810778.

Signer, J., Jonsdottir, H.R., Albrich, W.C., Strasser, M., Züst, R., Ryter, S., Ackermann-Gäumann, R., Lenz, N., Siegrist, D., Suter, A., Schoop, R., Engler, O.B., 2020. In vitro virucidal activity of Echinaforce®, an Echinacea purpurea preparation, against coronaviruses, including common cold coronavirus 229E and SARS-CoV-2. Virol. J. 17, 136. https://doi.org/10.1186/s12985-020-01401-2.

Singh, A.K., Gupta, R., Ghosh, A., Misra, A., 2020. Diabetes in COVID-19: prevalence, pathophysiology, prognosis and practical considerations. Diabetes Metab. Syndr. 14, 303–310. https://doi.org/10.1016/j.dsx.2020.04.004.

Singh, H., Yadav, B., Rai, A.K., Srivastava, S., Saiprasad, A., Jameela, S., Singhal, R., Muralidharan, S., Mohan, R., Chaudhary, S., Rana, R., Khanduri, S., Sharma, B.S., Chandrasekhararao, B., Srikanth, N., Dhiman, K.S., 2023. Ashwagandha (Withania somnifera) and Shunthi (Zingiber officinale) in mild and moderate COVID-19: an open-label randomized controlled exploratory trial. Complement. Ther. Med. 76, 102966. https://doi.org/10.1016/j.ctim.2023.102966.

Sinha, S.K., Prasad, S.K., Islam, M.A., Gurav, S.S., Patil, R.B., Alfaris, N.A., Aldayel, T.S., Alkehayez, N.M., Wabaidur, S.M., Shakya, A., 2021. Identification of bioactive compounds from Glycyrrhiza glabra as possible inhibitor of SARS-CoV-2 spike glycoprotein and non-structural protein-15: a pharmacoinformatics study. J. Biomol. Struct. Dyn. 39, 4686–4700. https://doi.org/10.1080/07391102.2020.1779132.

Song, W., Gui, M., Wang, X., Xiang, Y., 2018. Cryo-EM structure of the SARS coronavirus spike glycoprotein in complex with its host cell receptor ACE2. PLoS Pathog. 14, e1007236. https://doi.org/10.1371/journal.ppat.1007236.

Sun, J., He, W.T., Wang, L., Lai, A., Ji, X., Zhai, X., Li, G., Suchard, M.A., Tian, J., Zhou, J., Veit, M., Su, S., 2020. COVID-19: epidemiology, evolution, and cross-disciplinary perspectives. Trends Mol. Med. 26, 483–495. https://doi.org/10.1016/j.molmed.2020.02.008.

Van Boheemen, S., De Graaf, M., Lauber, C., Bestebroer, T.M., Raj, V.S., Zaki, A.M., Osterhaus, A.D., Haagmans, B.L., Gorbalenya, A.E., Snijder, E.J., Fouchier, R.A., 2012. Genomic characterization of a newly discovered coronavirus associated with acute respiratory distress syndrome in humans. mBio 3. https://doi.org/10.1128/mBio.00473-12.

Vardavas, C.I., Nikitara, K., Aslanoglou, K., Hilton-Boon, M., Phalkey, R., Leonardi-Bee, J., Magiorkinis, G., Katsaounou, P., Pharris, A., Severi, E. & Suk, J.E. 2021. Effectiveness of non-pharmaceutical measures (NPIs) on COVID-19 in Europe: a systematic literature review. *medRxiv*., 2021.11.11.21266216. 10.1101/2021.11.11.21266216

Varnasseri, M., Siahpoosh, A., Hoseinynejad, K., Amini, F., Karamian, M., Yad, M.J.Y., Cheraghian, B., Khosravi, A.D., 2022. The effects of add-on therapy of Phyllanthus Emblica (Amla) on laboratory confirmed COVID-19 cases: a randomized, double-blind, controlled trial. Complement. Ther. Med. 65, 102808. https://doi.org/10.1016/j.ctim.2022.102808.

Venkatesan, P., 2021. Repurposing drugs for treatment of COVID-19. Lancet Respir. Med. 9, e63. https://doi.org/10.1016/S2213-2600(21)00270-8.

Verma, M., Rawat, N., Rani, R., Singh, M., Choudhary, A., Abbasi, S., Kumar, M., Kumar, S., Tanwar, A., Misir, B.R., Khanna, S., Agrawal, A., Faruq, M., Rai, S., Tripathi, R., Kumar, A., Pujani, M., Bhojani, M., Pandey, A.K., Nesari, T., Prasher, B., 2023. Adhatoda vasica and tinospora cordifolia extracts ameliorate clinical and molecular markers in mild COVID-19 patients: a randomized open-label three-armed study. Eur. J. Med. Res. 28, 556. https://doi.org/10.1186/s40001-023-01507-7.

Verma, S., Twilley, D., Esmear, T., Oosthuizen, C.B., Reid, A.M., Nel, M., Lall, N., 2020. Anti-SARS-CoV natural products with the potential to inhibit SARS-CoV-2 (COVID-19). Front. Pharmacol. 11, 561334. https://doi.org/10.3389/fphar.2020.561334.

Wang, K., Chen, W., Zhang, Z., Deng, Y., Lian, J.Q., Du, P., Wei, D., Zhang, Y., Sun, X.X., Gong, L., Yang, X., He, L., Zhang, L., Yang, Z., Geng, J.J., Chen, R., Zhang, H., Wang, B., Zhu, Y.M., Nan, G., Jiang, J.L., Li, L., Wu, J., Lin, P., Huang, W., Xie, L., Zheng, Z.H., Zhang, K., Miao, J.L., Cui, H.Y., Huang, M., Zhang, J., Fu, L., Yang, X.M., Zhao, Z., Sun, S., Gu, H., Wang, Z., Wang, C.F., Lu, Y., Liu, Y.Y., Wang, Q.Y., Bian, H., Zhu, P., Chen, Z.N., 2020a. CD147-spike protein is a novel route for SARS-CoV-2 infection to host cells. Signal. Transduct. Target. Ther. 5, 283. https://doi.org/10.1038/s41392-020-00426-x.

Wang, M., Zhang, Y., Li, C., Chang, W., Zhang, L., 2023. The relationship between gut microbiota and COVID-19 progression: new insights into immunopathogenesis and treatment. Front. Immunol. 14, 1180336. https://doi.org/10.3389/fimmu.2023.1180336.

Wang, M.Y., Zhao, R., Gao, L.J., Gao, X.F., Wang, D.P., Cao, J.M., 2020b. SARS-CoV-2: structure, biology, and structure-based therapeutics development. Front. Cell. Infect. Microbiol. 10, 587269. https://doi.org/10.3389/fcimb.2020.587269.

Wielgat, P., Rogowski, K., Godlewska, K., Car, H., 2020. Coronaviruses: is Sialic acid a gate to the eye of cytokine storm? From the entry to the effects. Cells 9. https://doi.org/10.3390/cells9091963.

World Health Organization. 2020. *WHO supports scientifically-proven traditional medicine* [Online]. Available: https://www.afro.who.int/news/who-supports-scientifically-proven-traditional-medicine [Accessed 27/01/2025 2025].

Xia, Q.D., Xun, Y., Lu, J.L., Lu, Y.C., Yang, Y.Y., Zhou, P., Hu, J., Li, C., Wang, S.G., 2020. Network pharmacology and molecular docking analyses on Lianhua Qingwen capsule indicate Akt1 is a potential target to treat and prevent COVID-19. Cell Prolif. 53, e12949. https://doi.org/10.1111/cpr.12949.

Xie, H., Guo, M., Yang, Y., 2024. Exploring the processes and mechanisms by which nonprofit organizations orchestrate global innovation networks: a case study of the COVAX program. Heliyon 10, e27098. https://doi.org/10.1016/j.heliyon.2024.e27098.

Yang, Y., Yang, M., Peng, Y., Liang, Y., Wei, J., Xing, L., Guo, L., Li, X., Li, J., Wang, J., Li, M., Xu, Z., Zhang, M., Wang, F., Shi, Y., Yuan, J., Liu, Y., 2022. Longitudinal analysis of antibody dynamics in COVID-19 convalescents reveals neutralizing responses up to 16 months after infection. Nat. Microbiol. 7, 423–433. https://doi.org/10.1038/s41564-021-01051-2.

Yesudhas, D., Srivastava, A., Gromiha, M.M., 2021. COVID-19 outbreak: history, mechanism, transmission, structural studies and therapeutics. Infection 49, 199–213. https://doi.org/10.1007/s15010-020-01516-2.

Yuki, K., Fujiogi, M., Koutsogiannaki, S., 2020. COVID-19 pathophysiology: a review. Clin. Immunol. 215, 108427. https://doi.org/10.1016/j.clim.2020.108427.

Yuriy Danilevsky 2018. Glycyrrhiza glabra *Wikimedia commons.*

Zhang, J., Lu, H., Zeng, H., Zhang, S., Du, Q., Jiang, T., Du, B., 2020. The differential psychological distress of populations affected by the COVID-19 pandemic. Brain Behav. Immun. 87, 49–50. https://doi.org/10.1016/j.bbi.2020.04.031.

Zheng, Y.Y., Ma, Y.T., Zhang, J.Y., Xie, X., 2020. COVID-19 and the cardiovascular system. Nat. Rev. Cardiol. 17, 259–260. https://doi.org/10.1038/s41569-020-0360-5.

Zhou, B., Pang, X., Wu, J., Liu, T., Wang, B., Cao, H., 2023. Gut microbiota in COVID-19: new insights from inside. Gut Microbes 15, 2201157. https://doi.org/10.1080/19490976.2023.2201157.

Zhou, M.Y., Xie, X.L., Peng, Y.G., Wu, M.J., Deng, X.Z., Wu, Y., Xiong, L.J., Shang, L.H., 2020. From SARS to COVID-19: what we have learned about children infected with COVID-19. Int. J. Infect. Dis. 96, 710–714. https://doi.org/10.1016/j.ijid.2020.04.090.