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REVIEW ARTICLE

MJM BIOLABS

Medicinal Plants Used in East Africa with Potential Against COVID-19 Infection; A Mechanistic Approach

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ABSTRACT

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was first reported in Wuhan, China in December 2019 and was quickly escalated into a global pandemic by the World Health Organisation (WHO) in 2020. Subsequently, concerted efforts were directed towards designing therapies and development of vaccines. To date safety and efficacy concerns still linger. Evidence suggests that in Traditional African Medicine there have been encounters with patients treated for COVID-19-like symptoms, and there are substantial claims of clinical efficacy. Such claims, coupled with the immense global disease burden attributed to the disease, has increased the prominence of plant-derived biomolecules in the search for potential therapeutic agents against SARS-CoV-2. Medicinal plants used in East Africa for COVID-like ailments have primarily been subjected to in-vitro and in-silico studies. Such studies tend to reveal the mechanistic pathways upon which activity is achieved and is the fundamental basis of this review. We therefore uncover potentially useful plants and their active phytoconstituents, as well as identify their proposed therapeutic targets both on susceptible host cells and on the virus. Despite the downgrading of COVID-19 to an endemic disease, the virus continues to mutate and long-term adverse effects like Long-COVID continue to impact public health. Therefore, the findings from this review can form the basis for further clinical investigation on the identified medicinal plants used in East Africa. As such, a number may find application in preventive medicine or as safe and efficacious standalone or adjuvant treatments for coronaviruses in future.

Keywords: COVID-19, SARS-CoV-2, East Africa, Traditional African Medicine

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INTRODUCTION

The novel coronavirus that causes the COVID-19, SARS-CoV-2 was first reported in Wuhan, China in December 2019. This novel disease quickly cascaded into a global pandemic as declared by the World Health organisation on 11th March 2020 (WHO, 2020). The rapid spread was in part due to its mode of human-to-human transmission. This is mainly via droplets or direct contact exacerbated by high social mobility of modern times as well as the innate virulent characteristics of the virus (Hu et al., 2020).

As of 30th September 2023, Kenya confirmed 343,995 cases and 5,689 deaths, the vast majority occurring before June 2022 (WHO, 2023b). Kenya followed the global trend where its fatalities and hospital admissions declined in 2022. Eventually the WHO downgraded it from a global health emergency in March 2023, but provided guidelines for long term disease management (Wise, 2023). This action suggests that although we are in the post-pandemic phase, the virus and its long-term effects such as long COVID may continue to linger.

It is noteworthy that SARS-CoV-2 constantly keeps mutating. Prominent variants include alpha, beta, delta and omicron, each eliciting unique properties with regard to transmissibility, severity of disease, and susceptibility to natural or vaccine-induced immune responses as well as monoclonal antibodies. For instance, Omicron, identified in November 2021, exhibits remarkable mutations on the spike that are associated with increased infectivity and also aid in immune evasion (Jacobs et al., 2023). Global epidemiological suggests that EG. 5 a subvariant of Omicron is mostly responsible for a surge in infections leading to September 2023. Fortunately, these spike mutations did not result in changes in disease severity (Dyer, 2023; Zappa et al., 2023)

Globally, the conventional healthcare system is fashioned around allopathic interventions as recommended by international and country specific guidelines (MOH-Kenya, 2021; WHO, 2022). Current therapy is characterised by antiviral agents, mono and polyclonal antibodies, janus kinase inhibitors, steroids and convalescent plasma therapy as well as vaccination as a preventive strategy (Yuan et al., 2023)(WHO, 2023a). The therapeutic landscape is fraught with many challenges that have been extensively reviewed by others (Robinson et al., 2022)(M. Singh & De Wit, 2022). Similarly, vaccines do provide hope but also present with limitations. For example, frequent mutations reported in Kenyan epidemiological data is associated with limited effectiveness. The long-term effects of vaccination are yet to be established too, a factor that could partly be driving the high levels of vaccine hesitancy (Mohamed et al., 2022)(Lazarus et al., 2023). The unmet needs highlighted led us to focus our current research the on safety and efficacy evaluation of local medicinal plants for which there are claims of effectiveness in management of COVID-19 like symptoms.

China, where the pandemic was first reported, has illustrated the benefits of alternative therapeutic models in COVID-19, some of which have been successfully integrated with modern medical practice (X. V. Wu et al., 2021). East Africa, like China, is rich indigenous knowledge and the practice of robust age-long traditional forms of medicine continue to linger on. Despite this rich heritage coupled with a vast biodiversity of flora, there has been paucity of data with respect to current, reliable and robust scientific knowledge on the potential of phytomedicines in mitigating COVID-19 in our settings (Gwenzi & Rzymski, 2021).

Our group is in advanced stages of investigating safety and efficacy of traditionally used medicinal plants with the view of validating their anti-COVID 19 claims. Several African groups have reviewed the topic (Adeleye et al., 2021; Attah et al., 2021; Binyane et al., 2022) Ours is unique in that we focus on unravelling the definite cellular and molecular basis of therapeutic activity for plants used in East African traditional medicine.

It is proposed that SARS-CoV-2 pathogenesis follows three sequential steps namely viral replication, host immune hyperactivity and pulmonary destruction (C. Li et al., 2021). From the clinical perspective, the phases are viremia phase, the acute phase characterised by dysregulated immune response and multiple organ damage and finally the recovery phase (Lin et al., 2020). As such therapeutic interventions against COVID-19 can be fashioned around either virus or host factors.

METHODOLOGY

We conducted a literature search for scientific and peer reviewed articles published in English after Jan 1, 2000 focussing on ‘African medicinal plants with COVID-19 potential’ in the following electronic databases: PubMed, PubChem, Google Scholar, HINARI, African Journals OnLine (AJOL) and Web of Science. Our MeSH words included: East Africa, COVID-19, SARS-COV-2 and Traditional African Medicine.

All included information were restricted to research articles published in the English language. Anecdotal evidence based on widely utilised plant-based therapies against COVID-19 were also included.

We excluded studies carried out on plants that were not endemic to East Africa or were not widely used in traditional/complementary medicine or nutrition in the region. We also excluded studies that were limited to previous outbreaks of coronaviruses such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) because their occurrence had little impact on the disease burden in East Africa.

Plant-based Diet

The East African staple diet is rich in plant-based foods; such as whole grains, legumes, vegetables, potato, sweet potato, yams, pumpkin, banana, and lower consumption of meat. Losso and colleagues hypothesised that this diet was in part responsible for lower COVID-19 reported cases compared to non-African countries with comparable populations (Losso et al., 2021). The stated diet is an excellent source of protease inhibitors including the trypsin and trypsin-chymotrypsin inhibitors that are readily bioavailable and can inhibit SARS-CoV-2 attachment to host cells. They can also help prevent blood clotting, a factor associated with severity, including fatalities associated with COVID-19 (Srikanth & Chen, 2016)(Otlewski & Polonica, 1996).

In countries like Uganda, Rwanda and Burundi coloured beans, *Phaseolus spp*, which are particularly rich in the proteases, constitute up to three meals of the average household's diet. These countries recorded disproportionately low morbidity and mortality rates, particularly at the peak of the pandemic. Comparable results were reported in tofu (a soy-based staple) consuming countries of the Far East. China and Japan, for instance, recorded fewer cases and deaths per capita compared to predominantly Caucasian countries. The isoflavone genistein is considerably present in soy products and has been shown to suppress TMPRSS2 gene expression (Akiyama et al., 1987). TMPRSS2 plays a supportive role to ACE-2 in viral attachment and entry into host cells and has been proposed as a therapeutic target in COVID-19. A meta-analysis assessing racial differences reported that Caucasian men showed higher TMPRSS2 gene expression than their African and Asian counterparts (C. Zhou et al., 2017). These differences may be attributed to dietary differences with regard to dry beans-based diet.

The proposition that plant-based diets could be beneficial seems to have been validated by recent epidemiological studies evaluating COVID-19 disease severity in diverse populations (Soltanieh et al., 2023)(H. Kim et al., 2021)

Therapeutic targets

There are numerous potential targets for therapeutic interventions that have been reviewed elsewhere (Y. W. Zhou et al., 2021) and have been summarised in the table below and illustrated in Figure 2.

Table 1:

Therapeutic Targets in COVID 19

VIRUS		HOST	
Target	**Examples**	**Target**	**Examples**
Structural proteins	Spike glycoprotein, M, E, N proteins	Host genes	ACE2, TMPRSS2, Cathepsin L, ADAM-17, CD147, HMGB1, SWI/MNF chromatin remodelling complex, Neuropilin1, RAB 7A, Specific host RNAs
Non-structural proteins	RdRp, M^{pro}, PL^{pro},Nsp	Epigenetic mechanisms	ACE2, Envelope protein, M^{pro}, PL^{pro}, IFN, IL-6, NF- κB
Accessory proteins	ORF3a, ORF7a, ORF8, ORF9a	Important pathways	Endocytic pathways, Autophagic pathways, Metabolism related signalling pathways, Exosomal pathways, Immune system related pathways, Others

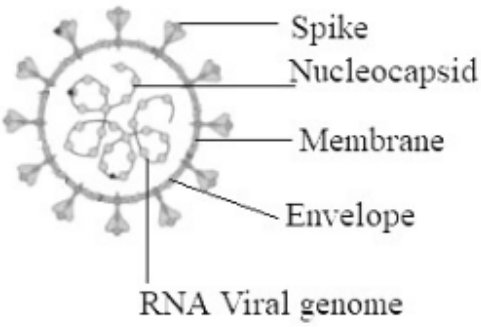

Figure 1: *Structure of SARS-CoV-2 illustrating the structural proteins*

Viral entry is one of the most promising therapeutic targets against SARS-COV-2 for several reasons; entry is the initial step in COVID-19 infection, since the virus relies on the host cell for replication and propagation. Secondly, major mediators of infection (both viral and host cell) can easily be accessed as extracellular targets. Focus on viral entry has taken a two-pronged approach. Individual compounds (both synthetic and natural) have been shown to inhibit SARS-COV-2 entry in vitro by targeting either the virus or the host via various mechanisms. Nevertheless, clinical uptake has been limited to a few, majorly due to safety and efficacy concerns in humans. Antibody and antibody-like products have also been extensively studied and tested as promising targets viral entry (Sabbah et al., 2021; Xiu et al., 2020).

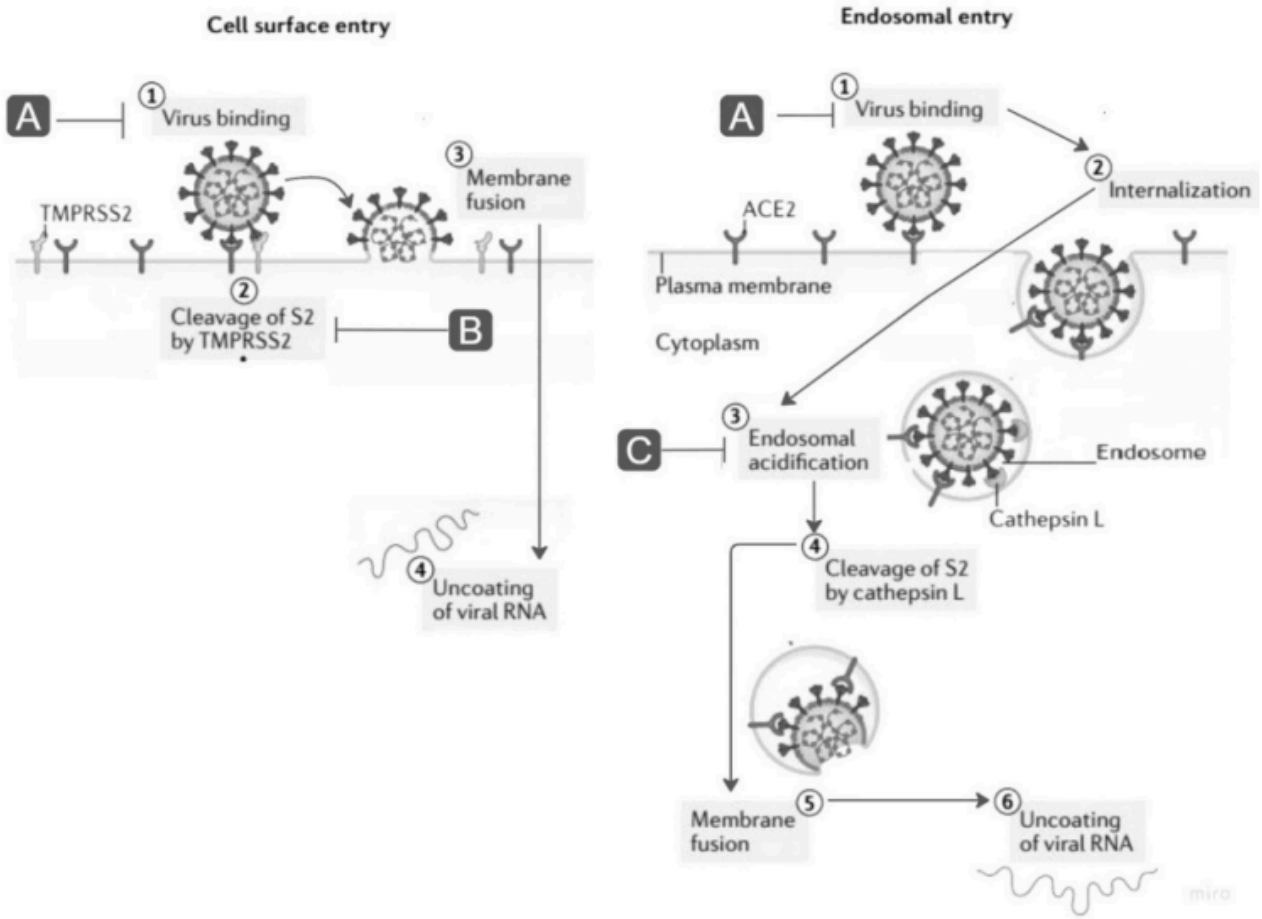

Figure 2: *SARS-CoV-2 entry pathways: Left; Cell surface pathway and Right; Endosomal Entry pathway. A, B and C represent potential phytotherapeutic targets*

Therapeutic targets: Computer Aided Drug Design

Emerging technologies in Computer Aided Drug Design (CADD) such as molecular docking and molecular dynamics simulation are increasingly being utilised to identify potential lead biomolecules. Such techniques can significantly expedite the process of screening and drug development particularly in emergency situations such as pandemics. In silico analysis of African plants has remarkably reduced investigational time required to identify 'hits and further evaluations of their suitability as safe and effective potential treatments in SARS-COV-2 infections (Ubani et al., 2020). It is noteworthy that in silico analyses are valuable in providing preliminary understanding of ligand–protein interactions but cannot be solely relied upon in drug development. Findings require experimental validations using in vitro, in vivo and ultimately clinical studies. Documented hit compounds are discussed in the later sections of this review.

SARS-CoV-2

Recent in silico studies involving phytocompounds isolated from Sub-Saharan plants have yielded numerous hits, on the basis of binding affinity to targeted COVID-19 proteins. Nevertheless, physicochemical and pharmacokinetics properties of molecular inhibitors of SARS-COV-2 are fundamental considerations with respect to the eventual safety and effectiveness. In silico absorption, distribution, metabolism, excretion and toxicology (ADMET) can help better understand the potential therapeutic properties of the candidate. They are used as an effective approach to screen of potential small drug-leads for a specific target receptor.

Many investigators apply the Lipinski rule of five (drug likeness) to assess for the physicochemical properties. The parameters evaluated define the physiochemical ranges required for a drug to be suitable for oral drug use, also called their drug-likeness (Lipinski, 2004) in addition to various methods for evaluation of ADMET. From the resource's standpoint, such an investigation can mitigate the risk of late-stage disapproval of lead compounds. Actually, some cited studies reported remarkable reduction in the number of potential compounds consequent to ADMET screening.

SARS-CoV-2 Enzymes

Targeting enzymes that play critical roles in the life cycle of these SAR-CoV-2 has also been explored. Hypothetically, inhibiting any of these could reduce the virulence and transmissibility of the virus. Notably, SARS-CoV-2 main protease (M^{pro}) also called SARS-CoV-2 3C-like main protease ($3CL_{pro}$) (Huff et al., 2022) (Mamidala et al., 2020), SARS-CoV-2 RNA-dependent RNA polymerase (SARS-CoV-2 RdRp) (C. Wu et al., 2020)(Kirchdoerfer & Ward, 2019), and the SAR-CoV-2 receptor binding domain (RBD) (Rodriguez-Morales & …, 2020)(P. Zhou et al., 2020) have been comprehensively investigated as potential therapeutic targets. Of these M^{pro} has attracted the most interest because its importance in viral replication.

Molecular docking and molecular dynamics simulation studies have shown that phytocompounds isolated from plants used in East African traditional medicine do exhibit favourable binding modes in the active site of target enzymes with corresponding strong interactions.

Table 2:

Potential Lead Phytocomponds Against SARS-COV-2 Identified by Target Binding Strength on Major Enzyme Viral Targets

Phytocompound	Plant source	Target	Binding strength (kcal/mol)	Reference
arabic acid	*Acacia senegal*	$3CL^{pro}$	-5.2	(Dwarka et al., 2020)
L-canavanine	*Sutherlandia frutescens*	$3CL^{pro}$	-5.2	(Dwarka et al., 2020)
uzarin	*Xysmalobium undulatum*	RdRp	-3.5	(Dwarka et al., 2020)
Curcumin,	*Curcuma longa*	RdRp	-6.7	(J. Singh et al., 2020)
Demethoxycurcumin	*Curcuma longa*	RdRp	-6.5	(J. Singh et al., 2020)
Piperine	*Piper nigrum*	RdRp	-6.0	(J. Singh et al., 2020)
Nimbolide	*Azardirachta indica*	RdRp	-7.8	(Sharma et al., 2020)
Hesperidine	Not Specified	RdRp	-8.8	(Tomic et al., 2020)

	Ancistrocladus robertsoniorum	M^{pro}	-12.26	(Kuhana A et al., 2021)
	Ancistrocladus tanzaniensis	M^{pro}	-11.28	(Kuhana A et al., 2021)
Chrysoeriol-7-O-b-D-glucuronopyranoside	*Conyza sumatrensis*	M^{pro}	-6.7	(Fouedjou et al., 2021)
Crocin	*Crocus Sativus*	M^{pro}	-8.2	(Aanouz et al., 2021)
Digitoxigenin	*Nerium Oleander*	M^{pro}	-7.2	(Aanouz et al., 2021)
β-Eudesmol	*Lauris Nobilis*	M^{pro}	-7.1	(Aanouz et al., 2021)
margonolone	*Azadirachta indica*	M^{pro}	-7.9	(Abdalla et al., 2021)
Nimbolide	*Azadirachta indica*	M^{pro}	-12.3	(Srivastav et al., 2020)
Luteolin-7-O-glucoronide	*Ocimum sanctum*	M^{pro}	-6.8	(Abdalla et al., 2021)
Sesamin	*Sesamum indicum*	M^{pro}	-8.2	(Natesh et al., 2021)
Hisperidine	Not Specified	M^{pro}	-5.8	(Tomic et al., 2020)

These studies compare the affinity and binding strengths of the phytocompounds with drugs that were originally indicated for other diseases but were candidates for repurposing during the pandemic. The binding energies of interaction with M^{pro} reference drugs such as chloroquine (-6 kcal/mol), nelfinavir (-7.8 kcal/mol) (Aanouz et al., 2021)(Fouedjou et al., 2021). Cited findings in Table 1 show comparable to superior energy values of interaction attributable to the tested compounds.

Notably, Nimbolide obtained from the leaves *Azadirachta indica* reported a remarkably high binding strength for the viral enzyme M^{pro}. The Neem tree is fondly referred to as Mwarubaini in Swahili, loosely translated as 'The cure for forty diseases. Traditionally, it has a well-established reputation as an antiviral, acting via multiple direct and indirect mechanisms. It is also among the more promising anti-COVID-19 plants based on our yet to be published work. Similarly, the ubiquitous flavonoid hesperidine when obtained from the native medicinal plants *Ancistrocladus robertsoniorum* and *Ancistrocladus tanzaniensis* reported comparable binding strength for M^{pro}.

Spike glycoprotein

This is the most studied therapeutic intervention point with regard to SARS-CoV-2 structural proteins. It is domiciled on the virion envelope and plays a key role in virus entry specifically by mediating receptor recognition and fusion between the virus and host cell membranes. Structurally, it contains membrane-distal S1 and membrane-proximal S2 subunits. A component of the S1 subunit is the Receptor-Binding Domain responsible for binding to ACE2. This triggers a cascade of events that characterise fusion and entry (Y. W. Zhou et al., 2021). In the initial stages of the pandemic, a myriad of drugs approved for RNA-viruses were tested as direct inhibitors to S-glycoprotein and several were shown to strongly bind to it (Toor et al., 2021). It is against this backdrop that various plant-derived compounds were mechanistically evaluated as presented in the table below.

Table 3:

Binding Strength of Phytocompounds Against S-glycoprotein

Phytocompound	Plant source	Binding strength (kcal/mol)	ADMET studies	Reference
β-tocopherol	*Moringa oleifera*	-7.7	Yes	(Siddiqui et al., 2010)
Chrysoeriol-7-O-b-D-glucuronopyranoside	*Conyza sumatrensis*	-8	No	(Fouedjou et al., 2021)
Margonolone	*Azadirachta indica*	-7.2	Yes	(Abdalla et al., 2021)
Luteolin-7-O-glucoronide	*Ocimum sanctum*	-7.6	Yes	(Abdalla et al., 2021)
Sesamin	*Sesamum indicum*	-7.0	Yes	(Natesh et al., 2021)
Hesperidin	*Citrus limon* peel	−8.1	No	(Tomic et al., 2020)
cannabigerolic acid CBGA	*Cannabis sativa*	-6.6	No	(Van Breemen et al., 2022)
tetrahydrocannabinolic acid THCA-A	*Cannabis sativa*	-6.5	No	(Van Breemen et al., 2022)
Withanolide A	*Withania somnifera*	-7.0	No	(Mondal et al., 2022)

It is generally accepted that docking scores exceeding -7 kcal/mol are considered as high scores and therefore points to strong ligand-receptor interactions (Hall & Ji, 2020). From the findings presented in Table 3 we can deduce that six of the eight reviewed phytocompounds show strong interactions with the spike glycoprotein. Notably, Hesperidin scored highly against both the M^{pro} enzyme and S-glycoprotein. Ability of a therapeutic agent to simultaneously inhibit multiple viral targets can yield better treatment outcomes when compared to single target alternatives. This approach is gaining popularity when screening both natural and synthetic anti-COVID-19 candidates (Velagacherla et al., 2023).

ACE2

Sufficient ACE2 expression is a prerequisite to SARS-COV-2 infection in humans. ACE 2 is highly expressed in the epithelium of the upper airway, the usual first site of infection (Nawijn et al., 2020). Plausibly, ACE2 can be a valuable molecular target in the fight against the disease. Nevertheless, the receptor is ubiquitous in distribution and has been reported to have a dual role, one protective and the other destructive. The challenge that naturally presents is to find out the dominant role and develop appropriate therapies.

For instance, the downregulation of ACE2 can lead to exacerbation of inflammatory events attributed to over-expression of angiotensin 2 in the RAAS system. Similarly, inducers of ACE2 can exert anti-inflammatory and anti-fibrotic effects that are beneficial in COVID-19 infections. Also, ACE2 in systemic circulation, can bind SARS-COV-2 depleting available virions for interaction with membrane bound receptors. It is also known that virulence and infectivity of COVID 19 among children is much lower in comparison to older demographics. This phenomenon appears ironic considering that ACE2 expression is much higher in children compared to geriatrics (Banu et al., 2020)(Y. Li et al., 2020).

In light of the stated contradictions, the paradigm in the development of treatment from the perspective of the molecular target should be the disruption of protein-receptor interaction as opposed to manipulation of cell surface receptor expression.

Table 4:

Binding Strength of Phytocompounds Against ACE-2

Phytocompound	Plant source	Binding strength (kcal/mol)	ADMET	Reference
Vinecin 2	*Piper longum*	-11.755	Yes	(Jindal & Rani, 2022)
Margonolone	*Azadirachta indica*	-8.5	Yes	(Abdalla et al., 2021)
Nimbolide	*Azadirachta indica*	-16.7	Yes	(Srivastav et al., 2020)
Luteolin-7-O-glucoronide	*Ocimum sanctum*	-8.2	Yes	(Abdalla et al., 2021)
Withanolide A	*Withania somnifera*	-7.0	No	(Mondal et al., 2022)

From Table 4 above we notice that the highest binding strength scores are reported for phytoconstituents obtained from *Piper longum* and *Azadirachta indica*. Both of these plants have widespread use in traditional medicine against respiratory ailments. Such phytoconstituents appear promising as eventual therapeutic agents especially due to the causal role ACE2 plays in COVID-19 infection. Actually, several phytochemical groups such as flavonoids, alkaloids, terpenoids and phenols have been associated with ACE2 inhibition (Adil et al., 2023).

TMPRSS2

The host cell membrane serine protease TMPRSS2 plays a secondary but critical role to ACE-2 in viral fusion and entry. After fusion takes place, TMPRSS2 mediates a series of events characterised by the activation and internalisation of the virus into the host cell. As a therapeutic alternative, we can target TMPRSS2-dependent entry into target cells. Phytocompounds that strongly bind to this protease are summarised in the table below.

Table 5:

Binding Strength of Phytocompounds Against TMPRSS2

Phytocompound	Plant source	Binding strength (kcal/mol)	ADMET	Reference
β-tocopherol	*Moringa oleifera*	-7.7	Yes	(Siddiqui et al., 2010)
Vinecin 2	*Piper longum*	-7.913	Yes	(Jindal & Rani, 2022)

Although TMPRSS2 plays an adjunct role to ACE2 in viral entry, phytotherapeutic agents like Vinecin 2 that have dual blocking action can, in theory provide more efficacious therapeutic options against COVID-19 compared to those that inhibit ACE2 only.

ACE2-RBD complex

The rationale of disrupting binding between SARS-CoV-2 spike protein and ACE2 in COVID-19 is now well understood. Some in silico studies have attempted to not just target the S-glycoprotein and ACE2 distinctly, but to evaluate the effect of candidate therapeutic agents on the actual interaction between the two. The spike protein comprises two functional regions: The S1 and S2. The S1 region contains the ACE2 receptor binding motif (RBM) domiciled in the Receptor binding domain (RBD) while the S2 region is responsible for membrane fusion. In summary, phytocompounds can bind to the S protein RBD and ACE2 complex (RBD-ACE2) negating the ability to form a stable bond and ultimately disrupting entry into the host cell (Hanson et al., 2020)(Ma et al., 2021).

Table 6:

Binding Strength of Phytocompounds Against RBD-ACE2 Complex

Phytocompound	Plant source	Binding strength (kcal/mol)	ADMET	Reference
withanone	*Withania somnifera* leaf	-9.4		(Balkrishna et al., 2021)
β-sitosterol	*Moringa oleifera*	-8.66	Yes	(Siddiqui et al., 2010)

One molecular dynamic simulation study reported that withanone, obtained from the leaves of renowned Indian medicinal plant *Withania somnifera* (Ashwagandha) was actively involved at the binding interface. First it formed H-bonds with both the protein and its receptor. Further, presence of withanone had a profound destabilizing effect on ionic interactions at the protein-receptor complex. The binding interface is generally more hydrophilic than the protein interiors and generates electrostatic interactions that play a central role in binding, in addition to directing of the cascade of events that follow. The electrostatic component of binding free energy reduction recorded with the introduction of withanone was a substantial 4.3 kcal/mol from an initial 11.55 kcal/mol without the ligand (Balkrishna et al., 2020). In vitro, commercial withanone efficiently inhibited ACE2-RBD interaction in a dose dependent fashion in the concentration range of 0.1–1 ng/mL. Next, withanone was administered to humanized zebrafish model induced SARS-CoV-2 recombinant S-protein. It was efficacious in controlling immunological responses and also helped to limit pathological responses in secondary organs (Balkrishna et al., 2021).

In Kenya, a herbal tea called 'Dawa' that is taken as a warm drink was popularised during the peak of the COVID-19 pandemic. Anecdotal evidence suggests that the drink can help alleviate symptoms in mild to moderate disease. Its major constituents include ginger, lemon, turmeric and Garlic in varied ratios. A study by Sankar and group reported that each of the plant ingredients possesses at least three phytocompounds that significantly destabilise the ACE2-RBD complex (Sankar et al., 2021).

Cytokine storm

Cytokines are critical for the effective functioning of the immune system. A wide range of pathophysiological processes essential for survival, such as, inflammation, tissue repair, fibrosis, and coagulation are mediated by cytokines. Nevertheless, a dysfunctional immune system can result in excess production of cytokines, referred to as a cytokine storm. It is characterised by systemic hyper inflammation that can be harmful to multiple organs and may even result in death (De Jesus et al., 2015). Of note, this phenomenon is associated with pulmonary oedema, acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). Therefore, Cytokine storm is a fundamental pathogenic factor for SARS-CoV-2 infections, as well as other coronaviruses. COVID-19 patients have elevated levels pro-inflammatory cytokines, including IL-1, IL-2, IL-6, IL-10, IFN-ɣ, TNF-α, IFN- ɣ-inducible protein 10 (IP-10), granulocyte macrophage-colony stimulating factor (GM-CSF), and monocyte chemoattractant protein-1 (MCP-1), and their titres do correlate with the disease severity (Del Valle et al., 2020)(Huang et al., 2020). The cytokine storm can also trigger another cascade of immunological events characterised by upregulation inflammatory activity of resident macrophages. They further secrete IL-1β and IL-6 that mediate the recruitment of neutrophils and CD8+ T cells to the site of infection. These cells further release compounds such as reactive oxygen species (ROS), matrix-metalloproteinase (MMPs), leukotriene that exacerbate injury to lung parenchyma (H. Li et al., 2020).

Wan and group recently observed that COVID-19 patients admitted to intensive care unit (ICU) had remarkably higher titres of pro-inflammatory cytokines such as IL-2, IL-7, IL-10, IP-10, TNF-α, GM-CSF), macrophage inhibitory protein 1-alpha (MIP1-α), macrophage chemoattractant protein1(MCP-1) as compared to patients not admitted to ICU (Wan et al., 2020). Phytocompounds that suppress the titres of pro-inflammmatory cytokines can produce a marked clinical improvement among COVID-19 patients majorly by ameliorating inflammation and lung damage.

Table 7:

Phytocompounds that Regulate Cytokine Production

Plant source	Phytocompound	Cytokine regulation	Reference
Withania somnifera leaf	*Withaferin A*	↓IL-2, IL-6, TNF-α, IFN-γ, IFN-γ protein 10 (IP-10)	(Mandlik & Namdeo, 2021)
Methanolic extract of root		↓IL-1β, TNF-α, ⊥ nitric oxide synthase (iNOS) and cyclooxygenase-II (COX-II)	(Devkar et al., 2016)
Aqueous extract of root		↓Nuclear factor kappa B (NF-κB), P38 and mitogen activated protein kinase (MAPKs) signalling pathway	(Gupta & Kaur, 2018)
Glycyrrhiza glabra (liquorice) rhizome	*Glycyrrhizin*	↓IL-1β, IL-6 and TNF-α, CXCR4/CXCR1 on neutrophils	(S. A. Lee et al., 2019)
		↓TLR2 signalling pathway	(Kong et al., 2019)
	Glycyrrhizic acid	↓NF-κB, JNK and MAPK	(Zhao et al., 2016)
Allium sativum aqueous extract	Not Specified	↑IL-12 and IFNγ in Th1, IL-1β, ↓IL-6 and TNF-α	(Hsieh et al., 2019)
Zingiber officinale	Not Specified	↓IL-1β, IL-6 and TNF-α	(Çifci et al., 2018)
Moringa oleifera root	Not Specified	↓NO and TNF-α	(Cui et al., 2019)
Cinnamomum verum	Not Specified	↓IL-1β, IL-6, TNF-α and NO	(Ho et al., 2013)
Cinnamomum verum ethanolic extract	Not Specified	↑IL-8	(Schink et al., 2018)
Azadirachta indica leaf	Not Specified	↓IL-6, MCP-1 and TNF-α	(J. W. Lee et al., 2017)
Ocimum tenuiflorum	*Eugenol*	↓IL-6, MIP-1α, MCP-1 and TNF-α	(Choudhury & Bashyam, 2014)
Camellia sinensis	*Theanine*	↓IL-1β, IL-6, and TNF-α, ↑IL-10/IFN-γ	(Wang et al., 2018)
Piper longum	*Piperlongumine*	↓IL-6, TNF-α, iNOS	(N. Kim et al., 2018)

Based on the referenced studies we can infer that select plants and their bio-active phytoconstituents do possess the ability to suppress inflammation generally and COVID-19 associated cytokine storm in particular by inhibiting the releases of specific pro-inflammatory cytokines. In addition, compounds like Withaferin inhibit the NF-κB mediated transcription and translation of nitric oxide synthase (iNOS) and cyclooxygenase-II (COX-II). These two compounds contribute to nitrosative stress and further exacerbate hyper-inflammatory responses associated with SARS-COV-2 infection (Devkar et al., 2016).

Inflammasome silencers

Inflammasomes are receptors or sensors that form part of the innate immune system that detect Pathogen-associated molecular patterns (PAMP) and damage-associated molecular patterns (DAMP). In response to these molecules (exogenous or endogenous) that can elicit immune responses, inflammasomes participate in the activation of immune responses. A cascade of events follow that culminate in the stimulation of the maturation and secretion of the proinflammatory cytokines. In summary, SARS-CoV-2 N protein promotes assembly and activation of NOD-like receptor pyrin domain-containing 3 (NLRP3) inflammasomes. In turn NLRP3 activates caspase-1. Next caspase-1

catalyzes proteolytic processing of pro-interleukin (IL)-1β into mature IL-1β. Excess IL-1β then induces systemic inflammation via NF-κB pathways resulting in secretion of large amounts of pro-inflammatory cytokines such as IL-6, TNF- α, IFN-α, IFN-β, and TGF-β (Pan et al., 2021).

In Kenya, a herbal tea called 'Dawa' that is taken as a warm drink was popularised during the peak of the COVID-19 pandemic. Anecdotal evidence suggests that the drink can help alleviate symptoms in mild to moderate disease. Its major constituents include ginger, lemon, turmeric and Garlic in varied ratios. A study by Sankar and group reported that each of the plant ingredients possesses at least three phytocompounds that significantly destabilise the ACE2-RBD complex (Sankar et al., 2021).

The outstanding anti-inflammatory properties of curcumin, obtained from *Curcuma longa* are well known. Curcumin exerts its potent anti-inflammatory property primarily through the direct down-regulation of NLRP3 inflammasomes (Hasanzadeh et al., 2020).

In vitro, using paraquat induced Acute Lung Injury in human lung fibroblasts, curcumin treatment reduced the expression levels of Thioredoxin interacting protein (TXNIP), NLRP3, IL-1β, IL-18 and caspase-1. The effect was reported to be mediated by the effective inhibition of NLRP3-dependent caspase-1 activation and IL-1β secretion pathway (Ren et al., 2019).
Several studies have proposed alternative mechanisms by which curcumin may portend its beneficial properties in COVID-19 as well as other diseases whose pathogenesis is related to inflammation and hyperoxidation and have been reviewed elsewhere (Saeedi-Boroujeni et al., 2020).

Viral entry (in-vitro studies)

Breemen and group recently demonstrated cannabidiolic acid (CBDA) or cannabigerolic acid (CBGA) obtained from *Cannabis sativum* could prevent infection of Vero-E6 cells by blocking SARSCoV-2 cell entry. These compounds are known to have an affinity for S-glycoprotein, the investigators did not conclusively determine the exact mechanism of activity. It is noteworthy that the discussed mechanisms are not mutually exclusive and some may take place concurrently.

Interestingly, using microscopic and fluorescence techniques, the investigators reported a marked reduction in viral RNA in cells treated with the two phytocompounds at safe doses (Van Breemen et al., 2022). This is one of the pioneer studies that have quantified actual reduction of infection of in phytocompound-treated susceptible cells exposed to SARS-CoV-2.
Several groups have investigated the protection of susceptible cells in-vitro when treated with medicinal plant extracts and have reported positive results (Y. Zhou et al., 2021). Although many do not elucidate the actual mechanism of activity, our group is in the process of investigating the actual mechanism of action for some of the cited medicinal plants such as *Artemisia affra*, *Azadirachta indica*, *Moringa oleifera* and *Ocimum spp*.

Conclusion

Shortly after the emergence of the pandemic, numerous traditional claims of efficacy of herbal medicines followed. These claims had varying degrees of veracity with some reporting various levels of scientific validation. China was the pioneer in approving the utilisation of renowned TCM formulas (Liahuaqingwen, Jinhuaqinggan and Xuebijing) for the management of mild and severe cases of COVID-19. At the time, the approvals were based on in-vitro investigations and anecdotal clinical data which may not have conclusively addressed issues of safety. Then, experts advised the use of herbal medicines with caution (Yang, 2020).

Today, the questions of safety and efficacy of both natural and synthetic potential treatments against COVID-19 have not been conclusively addressed. With regard to natural remedies, major strides have been made in identifying candidate plants and their phytoconstituents through in-vitro, in-vivo and in-silico studies. Our reliance on pre-clinical findings is because there is paucity of regional data with respect to high-quality, rigorously peer-reviewed clinical trials of herbal drugs in high impact publications. Therefore, more detailed pharmacokinetic, pharmacodynamic and clinical data should be obtained through well designed clinical studies.

In this review, we comprehensively summarise current knowledge on the subject and report that medicinal plants used to manage COVID-19 and COVID-like ailments in East Africa have undergone scientific evaluation and some of the results are promising. Our focus on the mechanistic pathways highlights potential compounds that can be further studied in pre-clinical and clinical settings. Such herbal formulations can be useful as potential adjuvants, prophylactics, and treatment options for COVID-19 and other coronaviruses that may emerge in future.

Aggressive containment and mitigation efforts globally seem to have significantly suppressed COVID-19 prevalence. Nevertheless, it is widely acknowledged that emergence of novel severe respiratory viral diseases tends to follow a cyclic pattern (Baker et al., 2022). This justifies the development of a repository of knowledge and possibly potent plant-derived anti-viral formulations as a precaution.

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Ethical consideration

This is a systematic review and thus was not subjected to evaluation by our institutional Review and Ethics Committee

Conflicts of Interest

All authors declare no conflict of interest.

REFERENCES

Aanouz, I., Belhassan, A., & El-Khatabi, K. (2021). Moroccan Medicinal plants as inhibitors against SARS-CoV-2 main protease: Computational investigations. Journal of Biomolecular Structure and Dynamics, 39(8), 2971–2979. https://doi.org/10.1080/07391102.2020.1758790

Abdalla, M., Mohapatra, R. K., Sarangi, A. K., Mohapatra, P. K., Eltayb, W. A., Alam, M., El-Arabey, A. A., Azam, M., Al-Resayes, S. I., Seidel, V., & Dhama, K. (2021). In silico studies on phytochemicals to combat the emerging COVID-19 infection. Journal of Saudi Chemical Society, 25(12). https://doi.org/10.1016/J.JSCS.2021.101367

Adeleye, O. A., Femi-Oyewo, M. N., Bamiro, O. A., Bakre, L. G., Alabi, A., Ashidi, J. S., Balogun-Agbaje, O. A., Hassan, O. M., & Fakoya, G. (2021). Ethnomedicinal herbs in African traditional medicine with potential activity for the prevention, treatment, and management of coronavirus disease 2019. Future Journal of Pharmaceutical Sciences, 7(1). https://doi.org/10.1186/S43094-021-00223-5

Adil, M., Tiwari, P., Chen, J.-T., & Kanwal, S. (2023). Plant-Derived Bioactive Compounds as Potential ACE-2 Inhibitors Against SARS-CoV-2 Infection. In Ethnopharmacology and Drug Discovery for COVID-19: Anti-SARS-CoV-2 Agents from Herbal Medicines and Natural Products (pp. 225–242). Springer, Singapore. https://doi.org/10.1007/978-981-99-3664-9_8

Akiyama, T., Ishida, J., Nakagawa, S., Ogawara, H., Watanabe, S., Itoh, N., Shibuya, M., & Fukami, Y. (1987). Genistein, a specific inhibitor of tyrosine-specific protein kinases. Journal of Biological Chemistry, 262(12), 5592–5595. https://doi.org/10.1016/S0021-9258(18)45614-1

Attah, A., Fagbemi, A., … O. O.-F. in, & 2021, U. (2021). Therapeutic Potentials of Antiviral Plants Used in Traditional African Medicine With COVID-19 in Focus: A Nigerian Perspective. Frontiers in Microbiology, 12, 596855.

Baker, R. E., Mahmud, A. S., Miller, I. F., Rajeev, M., Rasambainarivo, F., Rice, B. L., Takahashi, S., Tatem, A. J., Wagner, C. E., Wang, L.-F., Wesolowski, A., Jessica, C., & Metcalf, E. (2022). Infectious disease in an era of global change. Nature Reviews Microbiology, 20(4), 193–205. https://doi.org/10.1038/s41579-021-00639-z

Balkrishna, A., Pokhrel, S., Singh, H., Joshi, M., Prakash Mulay, V., Haldar, S., & Varshney, A. (2021). Withanone from *Withania somnifera* Attenuates SARS-CoV-2 RBD and Host ACE2 Interactions to Rescue Spike Protein Induced Pathologies in Humanized Zebrafish Model. Drug Design, Development and Therapy, 15–1111. https://doi.org/10.2147/DDDT.S292805

Balkrishna, A., Pokhrel, S., Singh, J., & Varshney, A. (2020). *Withania somnifera* may inhibit novel coronavirus (COVID-19) entry by disrupting interactions between viral S-protein receptor binding domain and host ACE2 …. https://doi.org/10.21203/rs.3.rs-17806/v1

Banu, N., Panikar, S. S., Leal, L. R., & Leal, A. R. (2020). Protective role of ACE2 and its downregulation in SARS-CoV-2 infection leading to Macrophage Activation Syndrome: Therapeutic implications. Life Sciences, 256, 117905. https://doi.org/10.1016/J.LFS.2020.117905

Binyane, M. E., & Mfengwana, P.-M.-A. H. (2022). Traditional Medicinal Plants as the Potential Adjuvant, Prophylactic and Treatment Therapy for COVID-19 Disease: A Review. Medicinal Plants. https://doi.org/10.5772/INTECHOPEN.104491

Choudhury, S., & Bashyam, L. (2014). Ocimum sanctum leaf extracts attenuate human monocytic (THP-1) cell activation. Journal of Ethnopharmacology, 154(1), 148–155.

Çifci, A., Tayman, C., Yakut, H. İ., Halil, H., Çakir, E., Çakir, U., & Aydemir, S. (2018). Ginger (*Zingiber officinale*) prevents severe damage to the lungs due to hyperoxia and inflammation. Turkish Journal of Medical Sciences, 48(4), 892–900. https://doi.org/10.3906/SAG-1803-223

Cui, C., Chen, S., Wang, X., Yuan, G., Jiang, F., Chen, X., & Wang, L. (2019). Characterization of *Moringa oleifera* roots polysaccharide MRP-1 with anti-inflammatory effect. International Journal of Biological Macromolecules, 132, 844–851. https://doi.org/10.1016/J.IJBIOMAC.2019.03.210

De Jesus, A. A., Canna, S. W., Liu, Y., & Goldbach-Mansky, R. (2015). Molecular mechanisms in genetically defined autoinflammatory diseases: Disorders of amplified danger signaling ⋆. Annual Review of Immunology, 33, 823–874. https://doi.org/10.1146/ANNUREV-IMMUNOL-032414-112227

Del Valle, D. M., Kim-Schulze, S., Huang, H. H., Beckmann, N. D., Nirenberg, S., Wang, B., Lavin, Y., Swartz, T. H., Madduri, D., Stock, A., Marron, T. U., Xie, H., Patel, M., Tuballes, K., Van Oekelen, O., Rahman, A., Kovatch, P., Aberg, J. A., Schadt, E., … Gnjatic, S. (2020). An inflammatory cytokine signature predicts COVID-19 severity and survival. Nature Medicine, 26(10), 1636–1643. https://doi.org/10.1038/S41591-020-1051-9

Devkar, S. T., Kandhare, A. D., Zanwar, A. A., Jagtap, S. D., Katyare, S. S., Bodhankar, S. L., & Hegde, M. V. (2016). Hepatoprotective effect of withanolide-rich fraction in acetaminophen-intoxicated rat: decisive role of TNF-α, IL-1β, COX-II and iNOS. Http://Dx.Doi.Org/10.3109/13880209.2016.1157193, 54(11), 2394–2403. https://doi.org/10.3109/13880209.2016.1157193

Dwarka, D., Agoni, C., Mellem, J., … M. S.-S. A. J. of, & 2020, U. (2020). Identification of potential SARS-CoV-2 inhibitors from South African medicinal plant extracts using molecular modelling approaches. South African Journal of Botany, 1(133), 273–284.

Dyer, O. (2023). Covid-19: Infections climb globally as EG.5 variant gains ground. BMJ, 382, p1900. https://doi.org/10.1136/BMJ.P1900

Fouedjou, R. T., Chtita, S., Bakhouch, M., Belaidi, S., Ouassaf, M., Djoumbissie, L. A., Azefack, L., Faizan, T. &, Qais, A., Tapondjou, A., & Qais, F. A. (2021). Cameroonian medicinal plants as potential candidates of SARS-CoV-2 inhibitors. Taylor & Francis. https://doi.org/10.1080/07391102.2021.1914170

Gupta, M., & Kaur, G. (2018). Withania somnifera as a Potential Anxiolytic and Anti-inflammatory Candidate Against Systemic Lipopolysaccharide-Induced Neuroinflammation. Neuromolecular Medicine, 20(3), 343–362. https://doi.org/10.1007/S12017-018-8497-7

Gwenzi, W., & Rzymski, P. (2021). When silence goes viral, Africa sneezes! A perspective on Africa's subdued research response to COVID-19 and a call for local scientific evidence. Environmental Research, 194, 110637. https://doi.org/10.1016/J.ENVRES.2020.110637

Hall, D. C., & Ji, H. F. (2020). A search for medications to treat COVID-19 via in silico molecular docking models of the SARS-CoV-2 spike glycoprotein and 3CL protease. Travel Medicine and Infectious Disease, 35, 101646. https://doi.org/10.1016/J.TMAID.2020.101646

Hanson, Q. M., Wilson, K. M., Shen, M., Itkin, Z., Eastman, R. T., Shinn, P., & Hall, M. D. (2020). Targeting ACE2-RBD Interaction as a Platform for COVID-19 Therapeutics: Development and Drug-Repurposing Screen of an AlphaLISA Proximity Assay. ACS Pharmacology and Translational Science, 3(6), 1352–1360. https://doi.org/10.1021/ACSPTSCI.0C00161/ASSET/IMAGES/LARGE/PT0C00161_0005.JPEG

Hasanzadeh, S., Read, M., Bland, A., … M. M.-P., & 2020, U. (2020). Curcumin: an inflammasome silencer. Elsevier, 159, 104921.

Ho, S., Chang, K., Chemistry, P. C.-F., & 2013, U. (2013). Inhibition of neuroinflammation by cinnamon and its main components. Elsevier, 138(4), 2275–2282.

Hsieh, C. C., Liu, K. F., Liu, P. C., Ho, Y. T., Li, W. S., Peng, W. H., & Tsai, J. C. (2019). Comparing the Protection Imparted by Different Fraction Extracts of Garlic (*Allium sativum* L.) against Der p-Induced Allergic Airway Inflammation in Mice. International Journal of Molecular Sciences, 20(19). https://doi.org/10.3390/IJMS20194879

Hu, B., Guo, H., Zhou, P., & Shi, Z.-L. (2020). Characteristics of SARS-CoV-2 and COVID-19. Nature Reviews Microbiology 2020 19:3, 19(3), 141–154. https://doi.org/10.1038/s41579-020-00459-7

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., Cheng, Z., Yu, T., Xia, J., Wei, Y., Wu, W., Xie, X., Yin, W., Li, H., Liu, M., … Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet (London, England), 395(10223), 497. https://doi.org/10.1016/S0140-6736(20)30183-5

Huff, S., Kummetha, I. R., Tiwari, S. K., Huante, M. B., Clark, A. E., Wang, S., Bray, W., Smith, D., Carlin, A. F., Endsley, M., & Rana, T. M. (2022). Discovery and Mechanism of SARS-CoV-2 Main Protease Inhibitors. Journal of Medicinal Chemistry, 65(4), 2866–2879. https://doi.org/10.1021/ACS.JMEDCHEM.1C00566

Jacobs, J. L., Haidar, G., & Mellors, J. W. (2023). COVID-19: Challenges of Viral Variants. Annual Review of Medicine, 74, 31–53. https://doi.org/10.1146/ANNUREV-MED-042921-020956

Jindal, D., & Rani, V. (2022). In Silico Studies of Phytoconstituents from *Piper longum* and Ocimum sanctum as ACE2 and TMRSS2 Inhibitors: Strategies to Combat COVID-19. Applied Biochemistry and Biotechnology, 1–18. https://doi.org/10.1007/S12010-022-03827-6/FIGURES/6

Kim, H., Rebholz, C. M., Hegde, S., Lafiura, C., Raghavan, M., Lloyd, J. F., Cheng, S., & Seidelmann, S. B. (2021). Plant-based diets, pescatarian diets and COVID-19 severity: a population-based case–control study in six countries. BMJ Nutrition, Prevention & Health, 4(1), 257. https://doi.org/10.1136/BMJNPH-2021-000272

Kim, N., Do, J., Bae, J., Jin, H., Kim, J., … K. I.-J. of, & 2018, U. (2018). Piperlongumine inhibits neuroinflammation via regulating NF-κB signaling pathways in lipopolysaccharide-stimulated BV2 microglia cells. Journal of Pharmacological Sciences. 2018 Jun 1;137(2):195-201, 137(2), 195–201.

Kirchdoerfer, R., & Ward, A. (2019). Structure of the SARS-CoV nsp12 polymerase bound to nsp7 and nsp8 co-factors. Nature Communications, 10(1), 2342.

Kong, D., Wang, Z., Tian, J., Liu, T., & Zhou, H. (2019). Glycyrrhizin inactivates toll-like receptor (TLR) signaling pathway to reduce lipopolysaccharide-induced acute lung injury by inhibiting TLR2. Journal of Cellular Physiology, 234(4), 4597–4607. https://doi.org/10.1002/JCP.27242

Kuhana A, T., Kilembe, J. T., Matondo, A., Yussuf, K. M., Nininahazwe, L., Nkatu, F. K., Tshingamb, M. N., Vangu, E. K., Kindala, J. T., Mihigo, S. O., Kayembe, S. J., Kafuti, Y. S., Clement, A., & Taba, K. M. (2021). Computational analysis by molecular docking of thirty alkaloid compounds from medicinal plants as potent inhibitors of SARS-CoV-2 main protease. SDRP Journal of Computational Chemistry & Molecular Modeling, 4(4), 487–503. https://doi.org/10.25177/JCCMM.4.4.RA.10699

Lazarus, J. V., Wyka, K., White, T. M., Picchio, C. A., Gostin, L. O., Larson, H. J., Rabin, K., Ratzan, S. C., Kamarulzaman, A., & El-Mohandes, A. (2023). A survey of COVID-19 vaccine acceptance across 23 countries in 2022. Nature Medicine, 29(2), 366–375. https://doi.org/10.1038/s41591-022-02185-4

Lee, J. W., Ryu, H. W., Park, S. Y., Park, H. A., Kwon, O. K., Yuk, H. J., Shrestha, K. K., Park, M., Kim, J. H., Lee, S., Oh, S. R., & Ahn, K. S. (2017). Protective effects of neem (*Azadirachta indica* A. Juss.) leaf extract against cigarette smoke- and lipopolysaccharide-induced pulmonary inflammation. International Journal of Molecular Medicine, 40(6), 1932–1940. https://doi.org/10.3892/IJMM.2017.3178

Lee, S. A., Lee, S. H., Kim, J. Y., & Lee, W. S. (2019). Effects of glycyrrhizin on lipopolysaccharide-induced acute lung injury in a mouse model. Journal of Thoracic Disease, 11(4), 1287–1302. https://doi.org/10.21037/JTD.2019.04.14

Li, C., He, Q., Qian, H., & Liu, J. (2021). Overview of the pathogenesis of COVID□19 (Review). Experimental and Therapeutic Medicine, 22(3), 1–10. https://doi.org/10.3892/ETM.2021.10444

Li, H., Liu, L., Zhang, D., Xu, J., Dai, H., Tang, N., Su, X., & Cao, B. (2020). SARS-CoV-2 and viral sepsis: observations and hypotheses. The Lancet, 395(10235), 1517–1520. https://doi.org/10.1016/S0140-6736(20)30920-X

Li, Y., Zhou, W., Yang, L., Research, R. Y.-P., & 2020, U. (2020). Physiological and pathological regulation of ACE2, the SARS-CoV-2 receptor. Pharmacological Research, 157, 104833.

Lin, L., Lu, L., Cao, W., & Li, T. (2020). Hypothesis for potential pathogenesis of SARS-CoV-2 infection–a review of immune changes in patients with viral pneumonia. Emerging Microbes & Infections, 9(1), 727. https://doi.org/10.1080/22221751.2020.1746199

Lipinski, C. A. (2004). Lead- and drug-like compounds: the rule-of-five revolution. Drug Discovery Today: Technologies, 1(4), 337–341. https://doi.org/10.1016/J.DDTEC.2004.11.007

Losso, J. N., Losso, M. J. N., Toc, M., Inungu, J. N., & Finley, J. W. (2021). The Young Age and Plant-Based Diet Hypothesis for Low SARS-CoV-2 Infection and COVID-19 Pandemic in Sub-Saharan Africa. Plant Foods for Human Nutrition, 76(3), 270–280. https://doi.org/10.1007/S11130-021-00907-6/TABLES/1

Ma, L. le, Liu, H. min, Liu, X. mei, Yuan, X. yu, Xu, C., Wang, F., Lin, J. zhi, Xu, R. chun, & Zhang, D. kun. (2021). Screening S protein – ACE2 blockers from natural products: Strategies and advances in the discovery of potential inhibitors of COVID-19. European Journal of Medicinal Chemistry, 226, 113857. https://doi.org/10.1016/J.EJMECH.2021.113857

Mamidala, E., Davella, R., & … S. G. (2020). In silico identification of clinically approved medicines against the main protease of SARS-CoV-2, causative agent of covid-19. Arxiv.Org.

Mandlik, D. S., & Namdeo, A. G. (2021). Pharmacological evaluation of Ashwagandha highlighting its healthcare claims, safety, and toxicity aspects. Journal of Dietary Supplements, 18(2), 183–226. https://doi.org/10.1080/19390211.2020.1741484

Mohamed, K., Rzymski, P., Islam, M. S., Makuku, R., Mushtaq, A., Khan, A., Ivanovska, M., Makka, S. A., Hashem, F., Marquez, L., Cseprekal, O., Filgueiras, I. S., Fonseca, D. L. M., Mickael, E., Ling, I., Arero, A. G., Cuschieri, S., Minakova, K., Rodríguez-Román, E., … Rezaei, N. (2022). COVID-19 vaccinations: The unknowns, challenges, and hopes. Journal of Medical Virology, 94(4), 1336–1349. https://doi.org/10.1002/JMV.27487

MOH-Kenya. (2021). INTERIM GUIDELINES ON MANAGEMENT OF COVID-19 IN KENYA COVID-19, Infection Prevention and Control (IPC) and Case Management. 1(1–74).

Mondal, P., Natesh, J., Ajees, A., Salam, A., Thiyagarajan, S., Syed, &, & Meeran, M. (2022). Traditional medicinal plants against replication, maturation and transmission targets of SARS-CoV-2: computational investigation. Taylor & FrancisP Mondal, J Natesh, AA Abdul Salam, S Thiyagarajan, SM MeeranJournal of Biomolecular Structure and Dynamics, 2022•Taylor & Francis, 40(6), 2715–2732. https://doi.org/10.1080/07391102.2020.1842246

Natesh, J., Mondal, P., Penta, D., … A. S.-C. in biology, & 2021, U. (2021). Culinary spice bioactives as potential therapeutics against SARS-CoV-2: Computational investigation. Computers in Biology and Medicine., 1(128), 104102.

Nawijn, M., Biology, W. T.-M. S., & 2020, undefined. (2020). Can ACE 2 expression explain SARS-CoV-2 infection of the respiratory epithelia in COVID-19? Embopress.Org, 16(7). https://doi.org/10.15252/msb.20209841

Otlewski, J., & Polonica, D. K. (1996). Squash inhibitor family of serine proteinases. Acta Biochimica.

Pan, P., Shen, M., Yu, Z., Ge, W., & Chen, K. (2021). SARS-CoV-2 N protein promotes NLRP3 inflammasome activation to induce hyperinflammation. Nature Communications, 12(1), 1–17.

Ren, Y., Yang, Z., Sun, Z., Zhang, W., Chen, X., & Nie, S. (2019). Curcumin relieves paraquat‐induced lung injury through inhibiting the thioredoxin interacting protein/NLR pyrin domain containing 3‐mediated inflammatory pathway. Molecular Medicine Reports, 20(6), 5032–5040. https://doi.org/10.3892/MMR.2019.10612

Robinson, P. C., Liew, D. F. L., Tanner, H. L., Grainger, J. R., Dwek, R. A., Reisler, R. B., Steinman, L., Feldmann, M., Ho, L. P., Hussell, T., Moss, P., Richards, D., & Zitzmann, N. (2022). COVID-19 therapeutics: Challenges and directions for the future. Proceedings of the National Academy of Sciences of the United States of America, 119(15). https://doi.org/10.1073/PNAS.2119893119

Rodriguez-Morales, A., & … J. C.-O.-. (2020). Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel Medicine and Infectious Disease., 1(34), 101623.

Sabbah, D. A., Hajjo, R., Bardaweel, S. K., & Zhong, H. A. (2021). An Updated Review on Betacoronavirus Viral Entry Inhibitors: Learning from Past Discoveries to Advance COVID-19 Drug Discovery. Current Topics in Medicinal Chemistry, 21(7), 571–596. https://doi.org/10.2174/1568026621666210119111409

Saeedi-Boroujeni, A., Mahmoudian-Sani, M. R., Bahadoram, M., & Alghasi, A. (2020). COVID-19: A Case for Inhibiting NLRP3 Inflammasome, Suppression of Inflammation with Curcumin? Wiley Online Library, 128(1), 37–45. https://doi.org/10.1111/bcpt.13503

Sankar, M., Ramachandran, B., Pandi, B., Mutharasappan, N., Ramasamy, V., Prabu, P. G., Shanmugaraj, G., Wang, Y., Muniyandai, B., Rathinasamy, S., Chandrasekaran, B., Bayan, M. F., Jeyaraman, J., Halliah, G. P., & Ebenezer, S. K. (2021). In silico Screening of Natural Phytocompounds Towards Identification of Potential Lead Compounds to Treat COVID-19. Frontiers in Molecular Biosciences, 8, 637122. https://doi.org/10.3389/FMOLB.2021.637122/BIBTEX

Schink, A., Naumoska, K., Kitanovski, Z., Kampf, C. J., Fröhlich-Nowoisky, J., Thines, E., Pöschl, U., Schuppan, D., & Lucas, K. (2018). Anti-inflammatory effects of cinnamon extract and identification of active compounds influencing the TLR2 and TLR4 signaling pathways. Food & Function, 9(11), 5950–5964. https://doi.org/10.1039/C8FO01286E

Sharma, A., Vora, J., Patel, D., Sinha, S., Jha, P. C., Shrivastava, N., & Patel, B. V. (2020). Identification of natural inhibitors against prime targets of SARS-CoV-2 using molecular docking, molecular dynamics simulation and MM-PBSA approaches. Taylor & Francis, 40(7), 3296–3311. https://doi.org/10.1080/07391102.2020.1846624

Siddiqui, S., Upadhyay, S., Ahmad, R., Abul Barkat, M., Jamal, A., Alothaim, A. S., Zaheen Hassan, M., Akhlaquer Rahman, M., Arshad, M., Ahamad, T., Faheem Khan, M., Shankar, H., Ali, M., Kaleem, S., & Ahmad, J. (2010). Interaction of Bioactive Compounds of *Moringa oleifera* Leaves with SARS-CoV-2 Proteins to Combat COVID-19 Pathogenesis: a Phytochemical and In Silico Analysis. https://doi.org/10.1007/s12010-022-04040-1

Singh, J., Malik, D., and, A. R.-J. of B. S., & 2022, undefined. (2020). Computational investigation for identification of potential phytochemicals and antiviral drugs as potential inhibitors for RNA-dependent RNA polymerase of COVID-19. Taylor & Francis, 40(8), 3492–3507. https://doi.org/10.1080/07391102.2020.1847688

Singh, M., & De Wit, E. (2022). Antiviral agents for the treatment of COVID-19: Progress and challenges. https://doi.org/10.1016/j.xcrm.2022.100549

Soltanieh, S., Salavatizadeh, M., Ghazanfari, T., Jahromi, S. R., Yari, Z., Mansournia, M. A., Nazemipour, M., Kheradmand, J. A., Ardestani, S. K., Karimi, S., & Hekmatdoost, A. (2023). Plant-based diet and COVID-19 severity: results from a cross-sectional study. BMJ Nutrition, Prevention & Health, 0, e000688. https://doi.org/10.1136/BMJNPH-2023-000688

Srikanth, S., & Chen, Z. (2016). Plant protease inhibitors in therapeutics-focus on cancer therapy. Frontiers in Pharmacology, 7(DEC). https://doi.org/10.3389/FPHAR.2016.00470/FULL

Srivastav, A. K., Gupta, S. K., & Kumar, U. (2020). Computational Studies Towards Identification of Lead Herbal Compounds of Medicinal Importance for Development of Nutraceutical Against COVID-19 - Google Search. Theoretical and Computational Chemistry, 1(1).

Tomic, N., Pojskic, L., Kalajdzic, A., Ramic, J., & Kadric, N. L. (2020). Screening of Preferential Binding Affinity of Selected Natural Compounds to SARS-CoV-2 Proteins Using in Silico Methods. Eurasian Journal of Medicine and Oncology, 4(4), 319–323. https://doi.org/10.14744/ejmo.2020.72548

Toor, H. G., Banerjee, D. I., Lipsa Rath, S., & Darji, S. A. (2021). Computational drug re-purposing targeting the spike glycoprotein of SARS-CoV-2 as an effective strategy to neutralize COVID-19. European Journal of Pharmacology, 890. https://doi.org/10.1016/j.ejphar.2020.173720

Ubani, A., Agwom, F., Morenikeji, O. R., Shehu, N. Y., Umera, E. A., Umar, U., Omale, S., Aguiyi, J. C., Nnadi, N. E., & Luka, P. D. (2020). Molecular docking analysis of selected phytochemicals on two SARS-CoV-2 targets. F1000Research, 9, 1157. https://doi.org/10.12688/F1000RESEARCH.25076.1

Van Breemen, R. B., Muchiri, R. N., Bates, T. A., Weinstein, J. B., Leier, H. C., Farley, S., & Tafesse, F. G. (2022). Cannabinoids Block Cellular Entry of SARS-CoV-2 and the Emerging Variants. Cite This: J. Nat. Prod, 2022, 176–184. https://doi.org/10.1021/acs.jnatprod.1c00946

Velagacherla, V., Suresh, A., Mehta, C. H., Nayak, U. Y., & Nayak, Y. (2023). Multi-Targeting Approach in Selection of Potential Molecule for COVID-19 Treatment. Viruses, 15(1). https://doi.org/10.3390/V15010213

Wan, S., Yi, Q., Fan, S., Lv, J., Zhang, X., Guo, L., Lang, C., Xiao, Q., Xiao, K., Yi, Z., Qiang, M., Xiang, J., Zhang, B., & Chen, Y. (2020). Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized patients with 2019 novel coronavirus pneumonia (NCP). MedRxiv, 2020.02.10.20021832. https://doi.org/10.1101/2020.02.10.20021832

Wang, D., Gao, Q., Zhao, G., Kan, Z., … X. W.-J. of agricultural, & 2018, undefined. (2018). Protective effect and mechanism of theanine on lipopolysaccharide-induced inflammation and acute liver injury in mice. ACS Publications, 66(29), 7674–7683. https://doi.org/10.1021/acs.jafc.8b02293

WHO. (2020). Timeline of WHO's response to COVID-19. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/interactive-timeline?gclid=Cj0KCQjw5oiMBhDtARIsAJi0qk2r-V_1V0gSHZ6qqzjyW5vDmgTH_GECaAYux2jKozc927Eie6XRTzsaApx4EALw_wcB#event-115

WHO. (2022). Guideline Therapeutics and COVID-19: living guideline. 142.

WHO. (2023a). COVID-19 Vaccines Advice.

WHO. (2023b). Kenya: WHO Coronavirus Disease (COVID-19) Dashboard With Vaccination Data | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data.

Wise, J. (2023). Covid-19: WHO declares end of global health emergency. BMJ, 381, p1041. https://doi.org/10.1136/BMJ.P1041

Wu, C., Liu, Y., Yang, Y., Zhang, P., B, W. Z.-… P. S., & 2020, U. (2020). Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. Acta Pharmaceutica Sinica B, 10(5), 766–788.

Wu, X. V., Dong, Y., Chi, Y., Yu, M., & Wang, W. (2021). Traditional Chinese Medicine as a complementary therapy in combat with COVID-19—A review of evidence-based research and clinical practice. Journal of Advanced Nursing, 77(4), 1635–1644. https://doi.org/10.1111/JAN.14673

Xiu, S., Dick, A., Ju, H., Mirzaie, S., Abdi, F., Cocklin, S., Zhan, P., & Liu, X. (2020). Inhibitors of SARS-CoV-2 Entry: Current and Future Opportunities. Journal of Medicinal Chemistry, 63(21), 12256–12274. https://doi.org/10.1021/ACS.JMEDCHEM.0C00502

Yang, Y. (2020). Use of herbal drugs to treat COVID-19 should be with caution. The Lancet, 395(10238), 1689–1690. https://doi.org/10.1016/S0140-6736(20)31143-0

Yuan, Y., Jiao, B., & Qu, L. (2023). The development of COVID-19 treatment. Front. Immunol., 14.

Zappa, M., Verdecchia, P., Andolina, A., & Angeli, F. (2023). The old and the new: The EG.5 ('Eris') sub-variant of Coronavirus. European Journal of Internal Medicine, 0(0). https://doi.org/10.1016/j.ejim.2023.09.003

Zhao, H., Zhao, M., Wang, Y., Li, F., & Zhang, Z. (2016). Glycyrrhizic Acid Prevents Sepsis-Induced Acute Lung Injury and Mortality in Rats. Journal of Histochemistry and Cytochemistry, 64(2), 125. https://doi.org/10.1369/0022155415610168

Zhou, C., Young, D., … E. Y.-A. journal of, & 2017, U. (2017). TMPRSS2:ERG Gene Fusions in Prostate Cancer of West African Men and a Meta-Analysis of Racial Differences. American Journal of Epidemiology, 182(12), 1352–1361.

Zhou, P., Yang, X.-L., Wang, X.-G., Hu, B., Zhang, L., Zhang, W., Si, H.-R., Zhu, Y., Li, B., Huang, C.-L., Chen, H.-D., Chen, J., Luo, Y., Guo, H., Jiang, R.-D., Liu, M.-Q., Chen, Y., Shen, X.-R., Wang, X., … Shi, Z.-L. (2020). A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020 579:7798, 579(7798), 270–273. https://doi.org/10.1038/s41586-020-2012-7

Zhou, Y., Gilmore, K., Ramirez, S., Settels, E., Gammeltoft, K. A., Pham, L. V., Fahnøe, U., Feng, S., Offersgaard, A., Trimpert, J., Bukh, J., Osterrieder, K., Gottwein, J. M., & Seeberger, P. H. (2021). In vitro efficacy of artemisinin-based treatments against SARS-CoV-2. Scientific Reports, 11(1). https://doi.org/10.1038/S41598-021-93361-Y

Zhou, Y. W., Xie, Y., Tang, L. S., Pu, D., Zhu, Y. J., Liu, J. Y., & Ma, X. L. (2021). Therapeutic targets and interventional strategies in COVID-19: mechanisms and clinical studies. Signal Transduction and Targeted Therapy 2021 6:1, 6(1), 1–25. https://doi.org/10.1038/s41392-021-00733-x