Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Herbal supplements as treatment options for COVID-19: A call for clinical development of herbal supplements for emerging and re-emerging viral threats in Sub-Saharan Africa

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ABSTRACT

The advent of Corona virus Disease 2019 (COVID-19) distorted health systems of many countries. Efforts have been made to either develop new treatment solutions such as vaccines or repurpose previously adopted drugs. Challenges in accessing available treatment, inadequate, non-existent, or overstretched healthcare facilities, long COVID disease, cultural practices and beliefs about vaccination, vaccine hesitancy, availability, accessibility and perceived safety of herbal supplements seem to be major factors propelling individuals to use herbal supplements. Published reports advocating for clinical development of herbal supplements for COVID-19 and other emerging and re-emerging viral diseases are sparse. This paper aims to review the pathogenesis of COVID-19, use of herbal products during the pandemic and make case for clinical development of herbal supplements through the adoption of modern and acceptable technologies and research processes.

This was a scoping review. Database searches of Google Scholar, PubMed and ResearchGate among others were performed using related keywords to identify relevant journals and lists of primary articles. Clinical trial databases:-Clinicaltrial.gov, Pan African Clinical Trial Registry (PACTR) and WHO international clinical trial registry (ICTRP) were reviewed to extract data.

The use of herbal supplements during COVID-19 was not only peculiar to individuals living in Sub-Saharan Africa, but a global practice. Herbal supplements recommended to manage COVID-19 have not been validated using clinical trials. Available data showed that the number of herbal supplements undergoing clinical trial for COVID-19 indication in Africa was low.

The availability of medicinal plants in Sub-Saharan Africa if well explored has great potentials to address various emerging and re-emerging viral diseases confronting the region.

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The economic potential of clinically validated herbal supplements are huge, and tapping into this opportunity created by preference of population to herbal supplement could increase export of herbal supplement and gross domestic product (GDP) of respective countries in Africa.

Introduction

The Corona virus Disease 2019 (COVID-19) since reported in late 2019 has placed a significant health burden across countries. The disease which the World Health Organization (WHO) declared a pandemic has resulted in several mortalities across countries; and has had significant social, medical and economic impacts globally [1]. In an effort to control the spread of the disease caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS CoV-2), various measures including non-pharmacological approaches have been adopted with a view to curtailing its spread, reduce person to person transmission, mortality and morbidity associated with the disease. Since the pandemic began, Health systems across the world have been stretched; and in poorer nations, the gaps have been widened [1–3].

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) which is a novel beta coronavirus can cause symptoms ranging from mild to severe. However, a good number of infected individuals may be asymptomatic, but can also transmit the infection to other individuals [1]. As at the time of documenting this report, the collective number of confirmed cases globally was 594,367,247, while the number of COVID-19 related deaths was 6,451,016 [4]. Nonetheless, due to limited resources available to most countries in Africa, there were limitations assessing available and approved testing diagnostics for massive diagnosis and identification of populations at risk. This precipitated the underdiagnosis reported within the continent especially among individuals who are asymptomatic Fig. 1 [2,3].

COVID-19 transmission has been found to be mainly enabled through proximal contact with air droplets and physical contact from infected persons, in addition to the exposure to aerosol in enclosed spaces [5]. Since the first incident of the disease was reported from Wuhan city in China, several other cases have been reported from all parts of the world and caused millions of deaths [6]. SARS-CoV-2 causes a wide variety of respiratory symptoms which range from those similar to that of the common cold to more severe illness like pneumonia, and its major route of transmission is through droplet

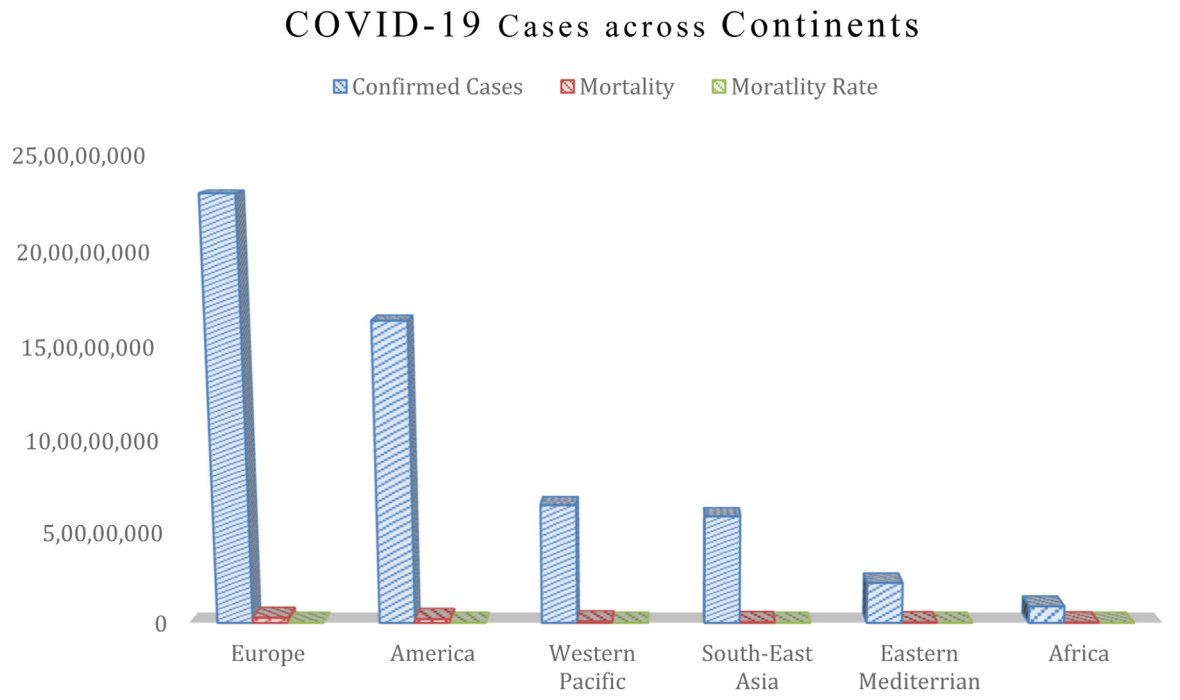

Fig. 1. COVID-19 confirmed cases, mortality and mortality ratio across various continents. Source of Data: WHO COVID 19 Dashboard. Available https://covid19.who.int/table. Accessed 7 July 2022

Table 1
Previous and currently circulating COVID-19 variants. Source of Data: World Health Organization. (2022). Historical working definitions and primary actions for SARS-CoV-2 variants. https://www.who.int/docs/default-source/coronaviruse/annex2_previous_vocs_and_definitions.pdf.

WHO label	Pango lineage*	GISAID clade	Nextstrain clade	Earliest documented samples	Date of designation
Alpha	B.1.1.7	GRY	20I (V1)	United Kingdom, Sep-2020	VOC: 18-Dec-2020 Previous VOC: 09-Mar-2022
Beta	B.1.351	GH/501Y.V2	20H (V2)	South Africa, May-2020	VOC: 18-Dec-2020 Previous VOC: 09-Mar-2022
Gamma	P.1	GR/501Y.V3	20J (V3)	Brazil, Nov-2020	VOC: 11-Jan-2021 Previous VOC: 09-Mar-2022
Delta	B.1.617.2	G/478K.V1	21A, 21I, 21J	India, Oct-2020	VOI: 4-Apr-2021 VOC: 11-May-2021 Previous VOC: 7-Jun-2022
Omicron**	B.1.1.529	GR/484A	21K, 21L, 21M, 22A, 22B, 22C, 22D	+S:R346K +S:L452X +S:F486V	Multiple countries, Nov-2021

* Includes all descendent lineages.
** Includes BA.1, BA.2, BA.3, BA.4, BA.5 and descendent lineages. It also includes BA.1/BA.2 circulating recombinant forms such as XE. WHO emphasizes that these descendant lineages should be monitored as distinct lineages by public health authorities and comparative assessments of their virus characteristics should be undertaken.

spread [7–9]. Patients who are infected with SARS-CoV-2 usually have a lengthy course of infections and are at increased risk of death [10].

Five different types of SARS-COV-2 with their composite molecular genetics have been identified (Table 1). They comprised of the alpha variant [B.1.1.7] (first documented in the UK in September 2020 and designated a variant of concern on 18 December 2020); the beta variant [B.1.351] (first documented in South Africa in May 2020, and designated a variant of concern on 18 December 2020); the Gamma variant [P.1] (first documented in Brazil in November 2020, and designated a variant of concern in 11 January 2021). Other identified variants were, the delta variant [B.1.617.2] (first documented in India in October 2020 and designated a variant of concern 11 May 2021), and the omicron variant (first documented in multiple countries in November 2021 and designated a variant of concern on November 26 2021). [11,12].

Pathogenesis of COVID-19

The SARS-CoV-2 expresses a precise spike glycoprotein (Fig. 2) which has a strong binding affinity for angiotensin converting enzyme 2 (ACE2) receptors. Studies have shown that pathogenesis of SARS-CoV-2 and that of SARS-CoV-1 might look similar; but that the affinity which SARS-CoV- 2 has for S-Protein is higher than that for SARS-CoV-1. This property confers more pathogenicity to the virus [8,13]. This also implies that human organs which express higher concentrations of ACE2 are more prone to destructive tendencies of the SARS-CoV-2. Priming of the viral spike protein is accomplished by transmembrane protease serine 2 (TMPSS2) [6]. The fusion of the virus to the host cell takes place through various cleavage steps and finally cell entry (Fig. 3) [14]. The coronavirus then expresses and replicates their genomic RNA which is then incorporated into new viral particles [14]. After unrestrained replications of the virus, which multiplies the number of infected epithelial cells and cellular debris, large quantities of cytokines are released, followed by serious inflammation, which reduce the number of CD4+ memory T helper cells and amplifies the cytotoxic activity of CD8 [15,16]. Infection with this virus stimulates a pro-thrombotic and pro-inflammatory reaction which may enhance the risk of severe thrombotic disor-

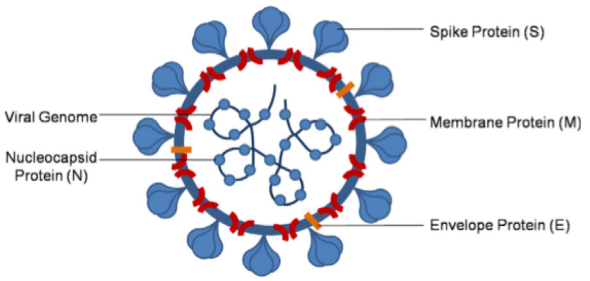

Fig. 2. Structure of SAR-CoV-2. Adopted from Yashika et al., [13].

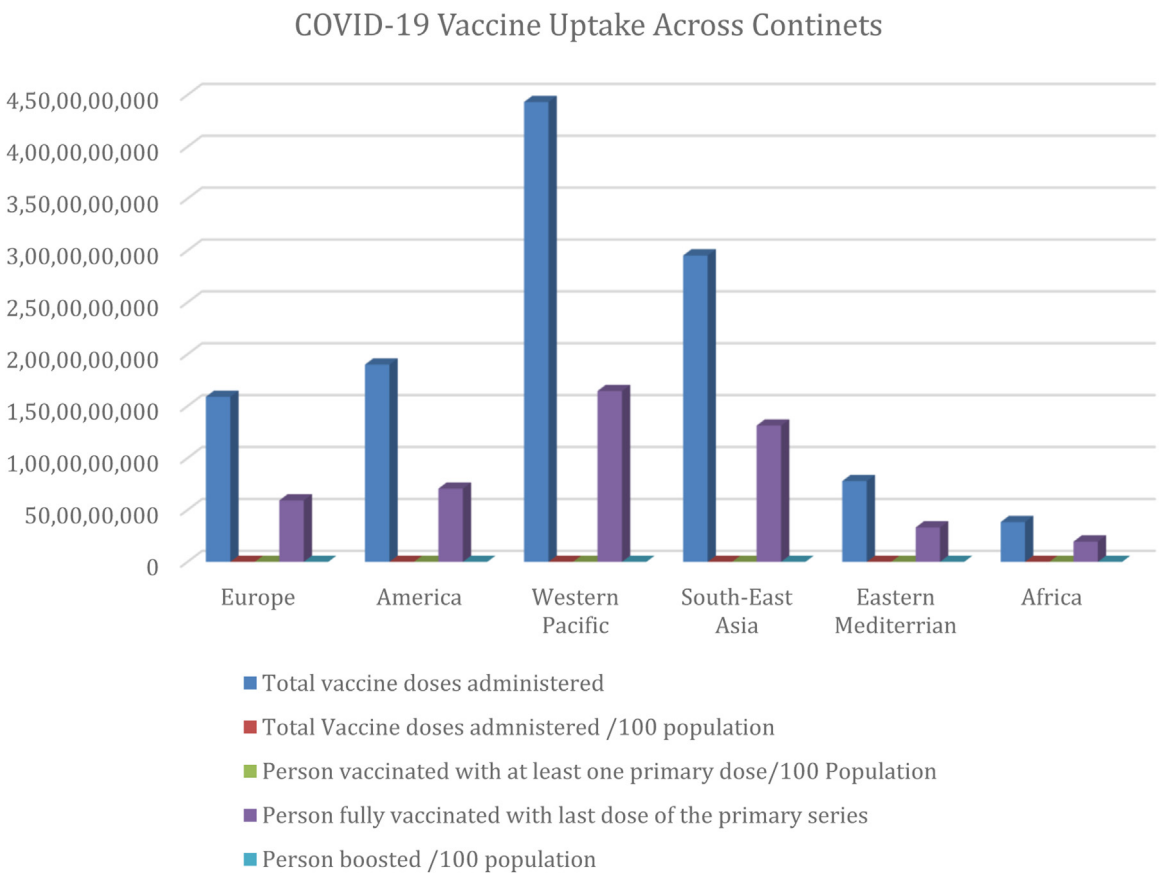

Fig. 3. COVID-19 Vaccination Analysis across continents. Source of Data: WHO COVID 19 Dashboard. Available https://covid19.who.int/table. Accessed 7 July 2022.
Graph shows that uptake of COVID-19 Vaccines is lowest among populations in Africa.

ders [17]. Many studies propose instant apparent increases in both arterial (largely Myocardial Infarction and stroke), and venous thromboembolic events (VTEs) [18–22].

Available COVID-19 Treatment Options and Challenges to using available treatment

Various treatment options for COVID-19 have been developed and various approaches adopted for treating and reducing mortalities associated with the disease. Among such treatment options are vaccines (Table 2) and other repurposed drugs (Table 3). In spite of availability of vaccines for managing COVID-19, uptake of such vaccines remains low in Africa (Fig. 4) [23]. Another challenge to deploying vaccines for managing COVID-19 are reported cases of viral escape and long COVID-19 among individuals who have been vaccinated [24–26]. Low uptake of available COVID-19 vaccines has been attributed to vaccine hesitancy, cultural and religious beliefs and fear of health complications and possible death following vaccination [27]. It has been reported that about 10-20% of individuals who previously suffered from COVID-19 were estimated to suffer long COVID. Such individuals exhibit over 200 symptoms some of which are fatigue, breathlessness and mental health issues which persisted months after they had recovered from the disease. Researchers are yet to unravel the mechanisms behind this disorder and possible solution to limiting a worldwide estimate of over 145 million of individuals who are prone to this disorder [28,25].

In vitro studies have revealed that the omicron variant evades antibody neutralization in persons who were previously infected with or who were vaccinated against SARS-CoV-2 [24,26]. Data from epidemiological studies proposed that vaccine effectiveness was decreased [31] and the rates of reinfection were much higher for the omicron variant than for the beta (B.1.351) and delta variants [32]. Pre-delta variant studies showed that vaccines had high effectiveness [33,34,35] which remained largely intact for up to 6 months [36]. Early research on the delta variant suggested only a modest difference in vaccine effectiveness [7] but subsequent reports suggested protection against delta infection might be somewhat lower than previous variants [18,19,17,37,21]. A US study found vaccine effectiveness fell from 92% to 80% as delta cases rose, although vaccine effectiveness against hospitalization remained at 90% [22].

Table 2
Vaccines approved in the high-income countries and selected vaccines of global relevance [29].

	Manufacturer	Vaccine type	Dosage Overall	Dosage Overall	efficacy Current approvals*
mRNA-1273	Moderna (USA)	mRNA	Two doses 28 days apart	94·1% 14 days after second dose	The USA, Europe, and the UK
BNT162b2	Pfizer–BioNTech (USA)	mRNA	Two doses 21 days apart	52% after one dose; 94·6% 7 days after the second dose	The USA, Europe, and the UK
Ad26.COV2.S	Johnson & Johnson (USA)	Viral vector	One dose	Vaccine efficacy against COVID-19 is 66·1%; vaccine efficacy against severe COVID-19 is 85·4% (at 28 days)	The USA and Europe
ChAdOx1 nCoV-19 (AZD1222)	Oxford–AstraZeneca (UK)	Viral vector	Two doses 28 days apart (intervals of >12 weeks studied)	Overall vaccine efficacy is 70·4% at 14 days or more after second dose	WHO and COVAX, the UK, Europe, the USA, India, and Mexico
NVX-CoV2373	Novavax (USA)	Protein subunit	Two doses	89·7% in the UK after two doses	Emergency use authorisation* application planned
Gam-COVID-Vac (Sputnik V)	Gamaleya National Research Center for Epidemiology and Microbiology (Russia)	Viral vector	Two doses (first, rAd26; second, rAd5) 21 days apart	91·6% at 21 days after first dose (day of dose two)	Russia, Belarus, Argentina, Serbia, UAE, Algeria, Palestine, and Egypt
CoronaVac	Sinovac Biontech (China)	Inactivated virus	Two doses 14 days apart	83·5% at 14 days or more after dose two	China, Brazil, Columbia, Bolivia, Chile, Uruguay, Turkey, Indonesia, and Azerbaijan
BBIBP-CorV	Sinopharm ½ (China)	Inactivated virus	Two doses 21 days apart	78·1% or more after dose two	China, UAE, Bahrain, Serbia, Peru, and Zimbabwe

Table 3
Immunomodulatory therapies recommended by the Infectious Diseases Society of America (IDSA) and/or FDA for COVID-19 treatment [30].

Therapeutic	Adult patient population	Dosing	Potential adverse reactions	Certainty of recommendation
Glucocorticoids (Dexamethasone preferred)	Hospitalized and/or severe COVID-19 disease.	Dexamethasone 6 mg IV or PO × 10 days or until discharge	Hyperglycemia, neurological side effects (agitation/confusion), adrenal suppression, risk of bacterial or fungal infection	Moderate
Tocilizumab	Hospitalized with severe COVID-19 disease, elevated inflammatory markers, requiring supplemental oxygen, NIMV, IMV, or ECMO.	Weight < 30 kg: 12 mg/kg IV over 60 min. Weight > 30 kg: 8 mg/kg IV over 60 min. (Maximum dose 800 mg)	Increased risk of infection, gastrointestinal perforation (seen in non-COVID settings)	Low
Sarilumab	Hospitalized who meet criteria for tocilizumab, but it is not available.	400 mg IV over 60 min.	Increased risk of infection	Very low
Baricitinib	Hospitalized with severe COVID-19 disease and elevated inflammatory markers, requiring supplemental oxygen, NIMV, IMV, or ECMO. Also indicated for use with remdesivir when corticosteroid contraindicated.	Baricitinib 4 mg PO daily × 14 days or until discharge.	Increased risk of infection, bowel perforation, thromboembolism, ischemic colitis, elevated transaminases, seizure	Moderate
Convalescent plasma (high-titer antibody)	Outpatient or hospitalized, with immunosuppressive disease or receiving immunosuppressive treatment, early in disease course	NA	Circulatory overload, transfusion-associated lung injury, allergic transfusion reaction, thromboembolism	Low

Certainty of Recommendation Grades (based on data from clinical trials, and the risk of bias, inconsistency, indirectness, imprecision, and publication bias noted in the studies):
High: Based on data from clinical trials, the true effect lies close to that of the estimate of the effect.
Moderate: Based on data from clinical trials, the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low Certainty: Based on data from clinical trials, the true effect may be substantially different from the estimate of the effect.
Very Low Certainty: Based on data from clinical trials, the true effect is likely to be substantially different from the estimate of the effect.
IV, intravenous; PO, oral; NIMV, non-invasive mechanical ventilation; IMV, invasive mechanical ventilation; ECMO, extracorporeal membrane oxygenation; NA, not applicable.

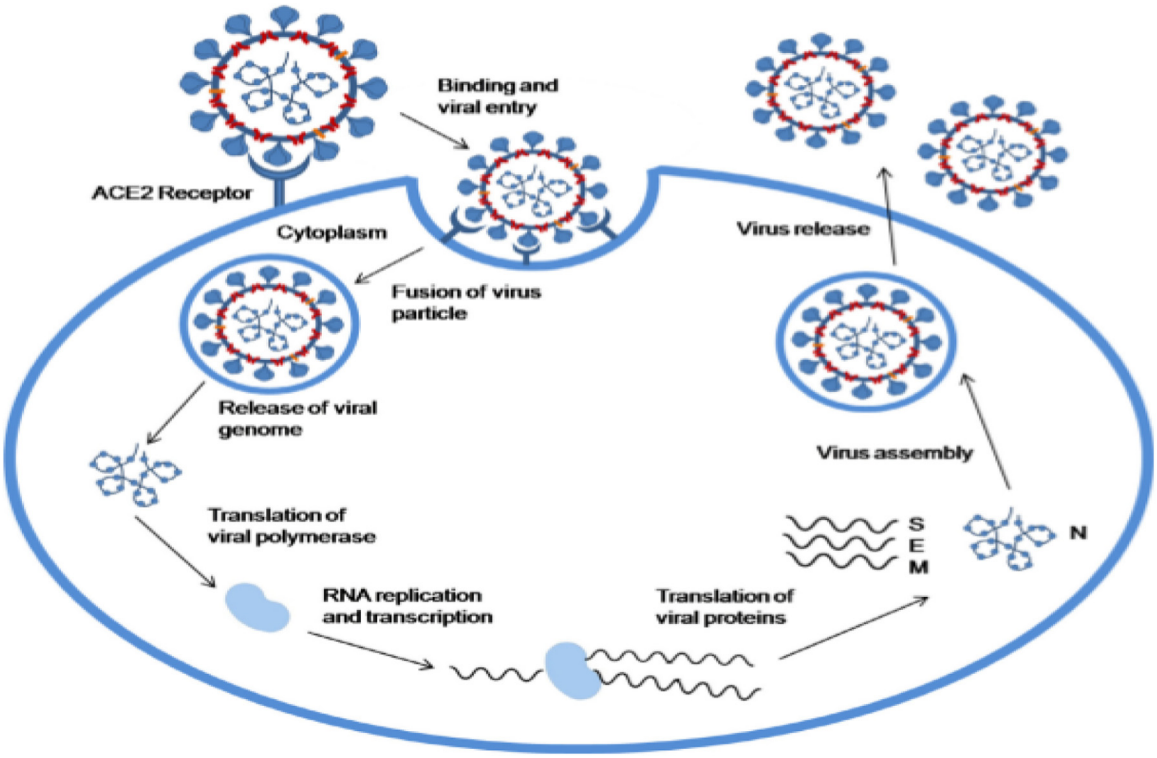

Fig. 4. Pathogenesis of SAR-COV-2. Adopted from Yashika et al., [13].

Concern about waning COVID-19 vaccine effectiveness has prompted intense public discussion about the need for booster vaccinations and the introduction of herbal remedies. Furthermore, in spite of the availability of vaccines, several countries are still reporting COVID-19-related deaths because of lack of immunization following vaccination and occurrence of different variants which might precipitate viral vaccine escape [38,39]. Also, the persistence of long COVID (for which no new treatment options seem hypothesized and investigated to manage the symptoms) among individuals who recovered from COVID following either vaccination or deployment of other available treatment remains a global concern [25]. Since perceived gaps still exist regarding unmet demands for improving care for serious and critically ill COVID-19 patients, and other observed challenges to accessing validated treatment options such as: cost, distribution challenges, low vaccine uptake and vaccine hesitancy across Africa, the need to explore the use of herbal remedies as treatment options for COVID-19 are being proposed not just for COVID-19, but for other emerging viruses of global health significance.

Use of herbal supplements for COVID-19

As COVID-19 ravaged the world, Epidemiologists have projected that based on poor health system in Africa, mortality from the disease within the region might likely be on the increase. In fact, some opinion from the West has projected that human bodies would be found across major streets in Africa if the continent did not put in place urgent measures to curtail the spread of the disease through community infection [40]. Unfortunately, Africa recorded the least mortalities from COVID-19 (Fig. 1). Till date, the world has been hypothesizing the reasons responsible for the low mortalities recorded in Africa. While several reasons have been hypothesized, strong evidences suggest that Africans practically survived COVID-19 based on the use of herbal supplements which are available within the region. Investigations into mostly used herbal supplements during COVID-19 showed that garlic, ginger, lemon, turmeric, onions, Negro pepper, and black pepper among other items were widely consumed primarily as immune boosters to limit the infection [40].

For centuries, herbal supplements have been used to manage different medical conditions including viral infection. The advent of COVID-19 distorted the health systems of many countries and there was urgency to research and develop quick treatment solutions which would help reduce mortalities associated with the disease. Challenges in accessing available treatment options made countries seek for alternative treatment options including the use of herbal medicine. Inadequate, non-existent, or overstretched healthcare facilities, cultural practices and beliefs in Africa were reported as possible reasons for resorting to using herbal remedies as alternatives to prevent or alleviate the symptoms of COVID-19 [27]. Due to their availability, accessibility, affordability, and the belief that they are effective and safe, herbal preparations and alternative curative and preventive approaches have been explored in managing various diseases in Africa [41]. Antwi-Baffour et al., [42] re-

Table 4
Summary of some herbal remedies used for COVID-19 from different continents.

Continent	Medicinal plants for COVID-19	Conditions managed in COVID-19	Bioactive compounds	Proposed action	References
Africa	Sclerocarya birrea, Pyrenacantha kaurabassana, Moringa oleifera, Azadirachta indica, Curcuma longa, Piper guineense, Eucalyptus globulus, Thymus maroccanus, Zingiber officinale, Allium cepa, Olea europaea, Allium sativum	Pneumonia, fever, cough, asthma, or breathing problems	Phenolic moieties, Enzymes,	Antioxidant, anti-inflammatory	[49,51,27];
Americas and the Caribbean	Spondias mombin, Plectranthus amboinicus, Ocimum gratissimum, Libidibia ferrea, Dysphania ambrosioides, Citrus limon, Bixa orellana, Alpinia zerumbet, Erythroxylum coca, Matricaria recutita, Piper aduncum, Allium sativum, Zingiber officinale, Eucalyptus globulus, Salvia rosmarinus, Morus alba, Eucalyptus spp, Cúrcuma longa, Coriandrum sativum, Cinchona pubescens, Azadirachta indica	Fever, breathing, immune boosters, cough	Flavonoids, phenols, polyphenols, carotenoids,	Antiviral, anti-inflammatory, anti-immunomodulatory, antioxidant	[52,53,54,55,56]
Asia and the Middle East	Lianhua qingwen, Jinhua qinggan, Xuebijing liquoric, Scutellaria baicalensis, Pinellia rhizome, Forsythia suspensa, Prunus armeniaca, Peganum harmala, Camellia sinensis, Nigella sativa, Pimpinella anisum, Trigonella foenum-graecum Ocimum sanctum, Curcuma longa, Zingiber officinale, Tinospora cordifolia	fever, cough, fatigue, acute upper respiratory, tract infection, febrile diseases, Forsythaside, amygdalin	Glycyrrhetinic acid, glycyrrhizin, baicalin, baicalein, Forsythaside, amygdalin,	Anti-inflammation, antitussive, expectant effects, scavenging free radicals	[57,58,59,60,61]
Australia	Eucalyptus globulus	Improves breathing, nasal congestion, asthma	Eucalyptol and Jensenone	Anti-inflammatory, immunomodulatory	[55,70]
Europe	Echinacea purpurea, Andrographis paniculate	Cough, fever, flu, pharyngitis	Alkylamides, caffeic acids, polysaccharides, and chicoric acids	Antiviral, immunomodulatory, and anti-inflammatory	[62,63]

ported that approximately 80% of the African population used herbs to manage various diseases. Since use of herbs is a documented practice among Africans, the advent of the pandemic and the exploration of herbs to manage diseases was not a new phenomenon since medicinal plants are usually the primary source of healthcare in many communities in Africa.

In an effort to introduce herbal product to manage COVID-19, Madagascar came up with herbal tonic code named COVID-Organics. The product was reported to contain Artemisia annua, Cinnamomum camphora and other phytochemicals such as essential oils, flavonoids, coumarins, polysaccharides, saponins, tannins, and pentacyclic triterpenes [43,44]. However, its acceptance by population within the Africa region was with mixed feelings since the herbal product was not validated using clinical trials. Furthermore, in the same effort to provide herbal solution for COVID-19, the National Institute for Pharmaceutical Research and Development Nigeria (NIPRD), repurposed NIPRIMUNE as an adjunct therapy for COVID-19. It is worthy of note that the repurposed herbal product for treating COVID-19 has not been validated using clinical trials. The herbal-based supplement was first developed in 2018 for managing patients with HIV/AIDS [45]. In another development, the Ghana Center for Awareness repurposed a herbal mixture for COVID-19 . This was code named CoA mixture. This herbal supplement was reported to contain about 160 phytochemicals with immune supporting properties [46].

Exploring the use of herbal supplement to manage COVID-19 among infected individuals in Nigeria, a group of researchers formulated a herbal supplement code named Combi-5. This supplement comprised of Zingiber officinale (Ginger), Curcuma longa (Tumeric), Piper guineense (black pepper), Allium sativum (Garlic) and Xylopia aethiopica (Negro pepper). The researchers have published a case report and case series showing how successful the herbal supplement was used to manage COVID-19 infected subjects with mild to moderate symptoms [47,48].

A recent review by Chikowe et al. [49] identified 30 Malawian plants with various activities against COVID-19 (Table 4). The plants were repurposed to manage pneumonia, fever, cough, asthma, or breathing problems which are typical symptoms of COVID-19. The fear of COVID-19 was reported to cause many Ugandans to resort to herbal remedies such as ginger and lemon as preventive measures and immune boosting benefits against COVID-19 [50].

In Morocco, El Alami et al., [51] reported that Eucalyptus globulus, Thymus maroccanus, Zingiber officinale, Allium cepa, Olea europaea, and Allium sativum were commonly used herbal remedies among Moroccans against COVID-19.

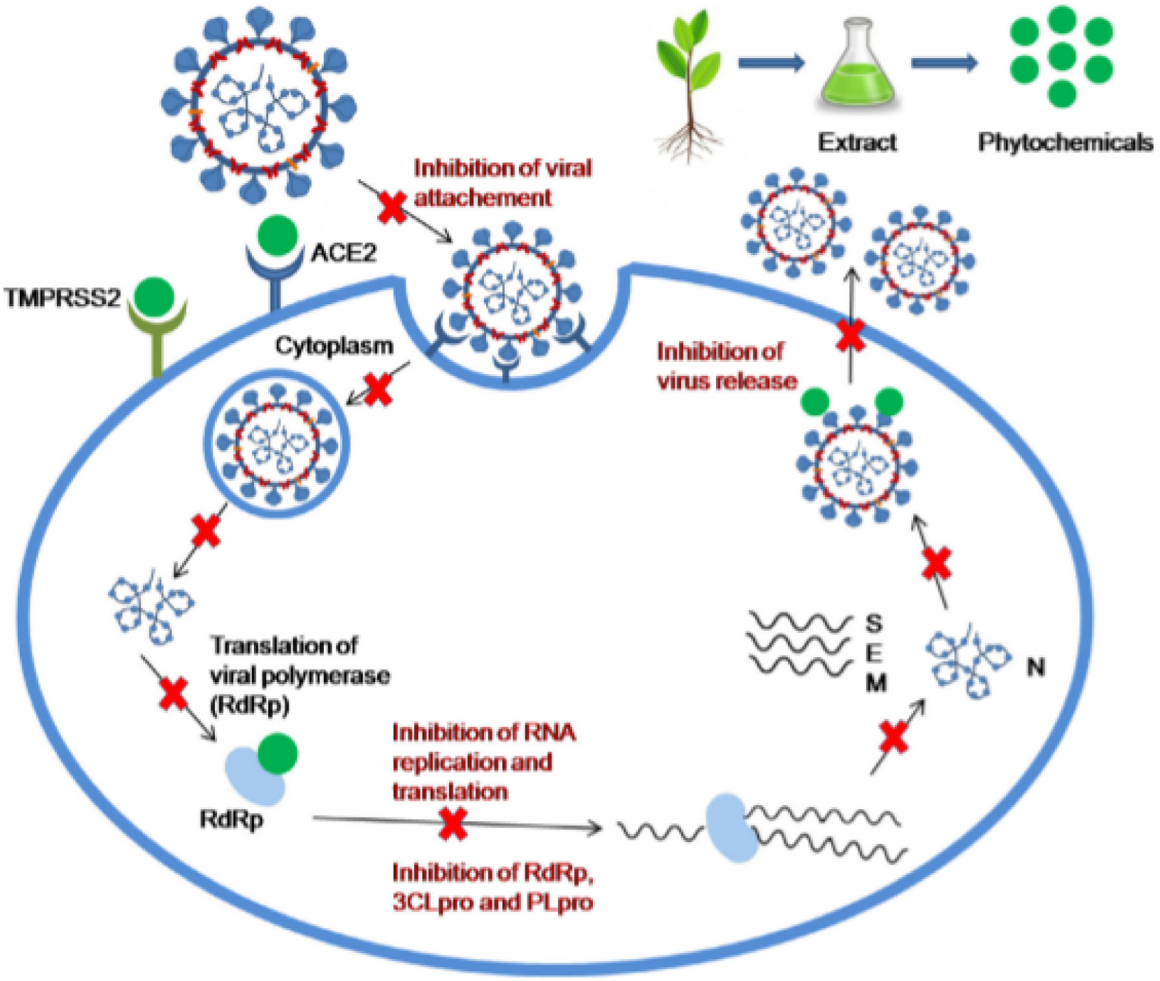

Fig. 5. Schematic representation of key areas herbal supplements play inhibitory roles in the COVID-19 pathogenesis. Adopted from [13]. Angiotensin converting enzyme2 (ACE2); 3-chymotrypsin-like protease (3CLpro); Transmembrane protease serine 2 (TMPRSS2); papain-like protease (PLpro); RNA-dependent RNA polymerase (RdRp).

Similarly, In Nigeria, Orisakwe et al., [27] reported plants with anti-inflammatory and antioxidant properties, such as garlic, guava, ginger, neem, and papaya, as commonly acclaimed herbal remedies for COVID-19. A few research institutes in Africa have sought approval for herbal remedies to treat COVID-19. The low death rates recorded in Africa due to COVID-19 have been attributed partly to the use of herbal remedies which are available within the continent. Many of these herbal remedies have been reported to possess immunoprotective, free radical scavenging and antioxidant properties [40]. The use of herbal supplement to manage COVID-19 was not only peculiar to Africans, but also was a common practice among individuals in various continents (Table 4).

Mechanism of action of herbal-based products on SARS-CoV-2

The pathogenesis of COVID-19 infection is multifaceted. In severe infection, there is accelerated release of inflammatory cytokines resulting in cytokine storm and dysregulation of individual's immune system [64]. Release of cytokine storm precipitates respiratory distress, multiple organ failure, disseminated intravascular coagulation (DIC) and possibly death [64].

There are basically two key crucial pathways required for COVID-19 pathogenesis. The first is inhibition of the virus from attaching to host cell and the second is limiting the virus from replicating within the host cell [13]. The likely effects of herbal products to exert their effect have been premised on ability to limit either or all of these essential processes.

Many herbal supplements have been identified to achieve their benefits by preventing the fusion of SARS-COV-2 to host cells, inhibition of entry into human cells, inhibition of viral RNA transcription and translation, decrease intracellular acidity thereby limiting viral replication, viral transport within the host cell and inhibit the release of proinflammatory cytokines thus preventing cytokine storm and death (Fig. 5) [64,13]. The ability of herbal-based products to suppress the progression of COVID-19 is attributed to multiple array of phytochemicals:–Tannins, Flavonoids, Terpenes, Glycosides, Carbohydrates and

Saponins among others. All of these chemicals have been reported to limit oxidative stress, improve immunity, possess antiviral, anti-inflammatory and antibacterial properties [47].

Discussion

The use of herbal supplements has persisted for years. Populations across the globe have relied on herbal remedies to meet basic health needs. Increased use of herbal products is precipitated by high cost of conventional drugs worsened by out-of-pocket spending for healthcare which is very common in many countries in Africa. As demand for herbal-based products increase, there is an urgent need to upscale the clinical development of such products with a view to ascertaining their clinical usefulness in managing various diseases including COVID-19 and other emerging and re-emerging viral threats. As new viral diseases and microorganisms which are highly resistant to validated and available treatment solutions emerge, there is need for Scientists in Africa to accelerate the search, identification, isolation and clinical development of new treatment options sourced from herbal-based products. The efforts of World Health Organization (WHO), African Center for Disease Control (ACDC) and other respective agencies in Africa towards accelerating the clinical development of novel treatment options using resources which are indigenous to the people cannot be overemphasized. Inability of African countries to manufacture the drugs her citizens consume has been a big challenge. Currently, Africa contributes only about 3% of total drugs produced globally, but about 95% of medicine consumed in the continent are imported [65]. Accelerating the local production of clinically validated herbal-based products could help in changing the paradigm.

The WHO has recognized the critical role of herbal medicine in meeting global health needs especially among individuals living in Africa [23]. This is premised on the long history of use of herbal medicine as means of providing care for individuals seeking healthcare [64]. The organization however recommended that applicable evidence based approach should be adopted for validating the safety and efficacy of herbal products targeted for population use through the application of rigorous clinical trial process [23]. The WHO in advocating for accelerated clinical development of herbal-based solutions came up with various suggestions which if implemented would help to achieve the desired goal. Some of these recommendations include: encouraging countries to upscale the implementation of policies centered on the use of herbal medicine, integration of herbal medicine into the training curriculum of healthcare professionals and advocating for more clinical development of herbal-based products using evidence based approach [66]. While some of these efforts have been implemented in part by some countries in Africa, more efforts are still required across countries within the continent [66] with a view to achieving deliverables for universal health coverage.

An effective universal health coverage supports accessing health care services which are economical, effective, accessible and preventive. While out of pocket expenditure for healthcare is common in Africa, the need to develop herbal based products which are safe, accessible cost effective with scientifically proven efficacy seem to be the most likely alternative for achieving sustainable healthcare especially among individuals living in resource limited economies .

Clinical trial investigates the safety and efficacy of an investigational new drug (IND) on human subjects. Is often designed to generate new evidences using validated scientific approach which will help improve health outcomes. While it is the gold standard for assessing the efficacy and safety of herbal medicine, evidence has shown that few of such trials for COVID-19 and other related emerging viral infections are conducted in sub-Saharan Africa. Available data from clinicaltrial.gov showed that the number of herbal supplements undergoing clinical trial in Africa for either curative or supportive care among COVID-19 infected subjects was scanty when compared with that conducted in Asia. As of the time of documenting this manuscript, a search on clinical trial.gov showed that a total of 20 herbal supplement clinical trial was on going for COVID-19 indication in Asia and Africa. Of this number, only one (1) is ongoing in Africa as against 19 in Asia. Search on other databases such as Pan African Clinical Trial Registry (PACTR) and WHO international clinical trial registry (ICTRP) showed no result. This data show there still exists wide gap in conducting COVID-19 related clinical trial using herbal supplements within the region. That more clinical trial on herbal supplements for COVID-19 was on going in Asia cannot be over emphasized. Many Countries in Asia including China have adopted the use of clinically validated herbal medicine as one of the main streams for achieving quality healthcare; and have integrated complimentary and integrative medicine into its national policy for health. Considering the various health challenges confronting Africa compounded by emerging of deadly viral threats such as Ebola, Monkey pox, Lassa virus among others, high cost of available treatment for diseases caused by these viral threats, a responsibility is placed on African leaders, and health agencies to advocate for massive clinical development of herbal-based supplement.

The economic potentials inherent in clinical development of herbal-based products are enormous; and different countries in Africa should be able to harvest from it through making polices and providing conducive research and regulatory environments to ‘cut from the cake’.

According to report from Procedure Research, the global market size of clinical trial is estimated to worth around US$ 84.43 billion by 2030 from US$ 48.4 billion in 2020, growing at a compound average growth rate (CAGR) of 5.7% from 2021 to 2030 (Procedure Research. Available at https://www.globenewswire.com/news-release/2022/01/27/2374515/0/en/Clinical-Trials-Market-Size-Worth-Around-US-84-43-Bn-by-2030.html).

On the other hand, a report from Global plant Extract Report projected that the global market price for herbal based products would worth over US$ 47.42 Billion by 2028. (Global Plant Extracts Market Report and Market analysis. Available at https://www.globenewswire.com/en/news-release/2022/08/04/2491986/28124/en/Global-Plant-Extracts-Market-Report-to-Reach-47-42-Billion-by-2028.html).

Furthermore, Data Bridge Market Research (DBMR) analyses showed that herbal extracts market was valued at US$ 8.26 billion in 2021 and was expected to reach US$15.23 billion by 2029, at a CAGR of 7.95% within the forecast period of 2022 to 2029. (Data Bridge Market Research on Global Phytomedicines and Herbal Extracts Market-Industry Trends and Forecast. Available at https://www.databridgemarketresearch.com/reports/global-phytomedicines-and-herbal-extracts-market)

Some major factors that will be responsible for driving this increase have been identified. These are: increase in demand for clinically validated herbal products, high inclination of respective populations towards herbal-based products, application of modern and advanced technology to improve the process of plant extraction, increase regulatory requirements for approvals and use of high-tech manufacturing equipment and chemical apparatus to accelerate the clinical development process (Data Bridge Market Research on Global Phytomedicines and Herbal Extracts Market-Industry Trends and Forecast. Available at https://www.databridgemarketresearch.com/reports/global-phytomedicines-and-herbal-extracts-market)

In spite of this huge economic potentials of herbal product, available report suggests that ethical and regulatory restrictions towards approval of herbal-based protocols and products still exist in some countries within the continent; and this has been identified as a challenge (Global Plant Extracts Market Research and Market analysis. Available at https://www.globenewswire.com/en/news-release/2022/08/04/2491986/28124/en/Global-Plant-Extracts-Market-Report-to-Reach-47-42-Billion-by-2028.html.).

For effective clinical trial of herbal medicines, ethical and regulatory frameworks which will support the conduct of such trials should be provided. Previous studies have reported that ethical committee in some countries within the continent used between 8-72 weeks to review herbal medicine clinical trial protocol [67,68,69]. Other issues which have been identified were insufficient proof of efficacy and safety pre-clinical data, standardization and quality assurance [68]. Strengthening the capacities of regulatory agencies, researchers and ethical review committees through training could be helpful.

Following these reports, there are supporting evidences that preference of individuals to herbal- based products is on the increase. Based on this, Research Scientists should invest more efforts towards taking herbal-based products to clinical trial. This is with a view to bringing to the market products which are validated using evidence base approach. The Alma declaration of 1978 strongly supported the development of treatment solutions which are indigenous to the people using resources available and accessible within communities [4].

For effective and accelerated clinical development of herbal-based supplements, the need to address infrastructural challenges for herbal clinical trial becomes critical. Prior to subjecting herbal supplements to clinical trial, extensive pre-clinical studies are required. These studies include toxicity and safety evaluation of herbal supplements which should be performed using modern technologies. Premised on the Organization and Economic Cooperation Development (OECD) recommendations, safety evaluation studies should be performed in a good laboratory practice (GLP) approved facility. In many research institutions within the sub-Saharan Africa, facilities needed for carrying out robust pre-clinical studies may not be available; and where they are available may not be sufficiently equipped to handle robust testing. Furthermore, accepting data emanating from such laboratories might have questionable quality issues since the laboratory generating the data may lack GLP approval. Some testing facilities may lack storage capacities for preserving under approved temperature and environmental conditions human cell lines which might be used for pre-clinical studies. Modern equipment for performing toxicogenomic evaluation (Micro array), product characterization (Liquid Chromatography Mass Spectrometry (LCMS) and identification (Nuclear Magnetic Resonance (NMR) and Fourier Transform Infrared Spectroscopy (FTIRS)) prior to taking identified, potential and effective molecules to clinical trials remain another huge gaps. There is need for respective countries in Africa to provide pre-clinical research laboratories under one room which shall be equipped to handle all types of pre-clinical evaluations of herbal remedies. Africa is blessed with lots of medicinal plants with potentials to address various diseases confronting the region. Developing these into acceptable treatment options using clinical trials will not just help the region meet her ever increasing health needs, but also result in massive export of such products thus adding to the continent's gross domestic product (GDP). Health systems across countries within the continent should be strengthened to enable the region attract a higher percentage of clinical trials.

Conclusion

The use of herbal supplements in Africa has been a long practice. Emerging and re-emerging viral threats if not curtailed using validated and multiple approach treatment solutions could put more pressure on health systems within the region. As new viruses emerge with their constantly changing genomic compositions, it becomes increasingly difficult to use a single treatment option to manage the associated crisis. The need to deploy clinically validated herbal supplements which are known to be holistic, complimentary and integrative should strongly be considered. Providing solution to numerous infectious diseases confronting Africans lies within the continent. While research is business and funders always fund studies in the area of their interest, organizations, institutions and health agencies within the continent should accelerate funding of herbal medicine clinical trial with a view to developing treatment solutions which are cheaper, indigenous and acceptable to the people. The economic potentials of herbal-based products are huge; and tapping into this opportunity created by preference of populations to herbal-based products could increase drug export and the GDP of respective countries in Africa.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

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