*ejpmr, 2020,7(8), 72-101*

**SJIF Impact Factor 6.222**

**EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH**

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

# AN INSIGHT INTO THE PREVENTION AND MANAGEMENT OF SEVERE ADVERSE RESPIRATORY SYNDROME SARS COV- 2 (COVID 19) FROM MODERN MEDICINES AND ANTIVIRALS ALTERNATIVES FROM NATURAL PRODUCTS IN LOW MIDDLE INCOME COUNTRIES

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**Article Received on 04/06/2020** **Article Revised on 24/06/2020** **Article Accepted on 14/07/2020**

**ABSTRACT**

Viral infections play a significant role in the evolution of human diseases, and the recent outbreaks of Severe acute respiratory syndrome (SARS-Cov-2), the causal agent of Coronavirus disease (COVID-19), in the advent of globalization have underscored their prevention as a critical issue in safeguarding public health. The World Health Organization (WHO) declared the Coronavirus Disease (COVID-19) as a Public Health Emergency of international concern on the 30th January 2020. There are currently reported cases worldwide, with early cases from China and countries in Europe like Italy, Spain,and the USA. COVID 19 is a serious threat to low middleincome countries (LMIC), most especially the migratory or displaced population due to wars and other natural disasters. The resource-limited countries are particularly vulnerable to the spread of COVID-19 with an anticipated knock-on effect in primary health services. Herbal products have formed the basis for the treatment of diseases in traditional medicine systems for thousands of years,and continue to play a major role in the primary health care for over 80 % of the world's population. Natural medicines also have a role in the prevention and management of viruses, like influenza and respiratory illnesses, and can support the general public health preventive measures. This writeup was motivated by the search for a collective approach in resource-poor countries the approach in prevention and management of COVID 19 using modern classical therapy and natural herbal. The challenges of ethical and regulatory issues in the use of treatment protocols not yet approved for COVID 19 and the use of alternative natural products has been discussed in this paper.A data mining approach was used to source out potential published works in this domain since the outbreak of SARS 2002, by the experts in natural product and herbal medicine research. This data mining helped us to relate some of these findings with herbal products reported in Cameroon pharmacopeia. From our review, it was evident that Traditional Chinese Medicine (TCM) has developed alternative and complementary therapy for the Corona virus since the early 2000s that are effectively in use. In Cameroon also, some studies on related plants have been pooled together that could stimulate future studies on antivirals from the Cameroonian traditional pharmacopeia.

**KEYWORDS:** Antiviral, Herbal medicines, COVID-19, SARS-CoV-2, Natural products, respiratory virus, low medium income countries.

## 1. INTRODUCTION

### 1.1. Severe acute respiratory syndrome coronavirus (SARS-COV 2)

Viral infections play an important role in human diseases, and recent outbreaks in the advent of globalization have underscored their prevention as a critical issue in safeguarding public health.[1,2] Despite the progress made in immunization and drug development, many viruses lack preventive vaccines and efficient antiviral therapeutic control strategies, which are often challenged by the generation of viral escape mutants. It is, therefore, of great interest to identify novel antiviral drugs of pharmaceutical importance from natural products that are an excellent source for such discoveries.[2]

Coronavirus (CoV) is an enveloped, positive-sense single-stranded RNA (ssRNA) virus belonging to the Coronaviridae family.[1,2] The CoV family consists of several species and causes upper respiratory tract and gastrointestinal infections in some mammals and birds. In humans, it is the main cause of common cold. However, complications, including pneumonia and severe acute respiratory syndrome (SARS) can occur in some cases.[3,4] The known human CoV (HCoV), includes the HCoV-229E, -OC43, -NL63, -HKU1, and the more widely known strain is the severe acute respiratory syndrome coronavirus (SARS-CoV), which was a global threat with high mortality in 2003.[5] The coronavirus encodes more than a dozen proteins, some of which are vital for viral entry and replication. Among these proteins, the most widely studied are the papain-like protease (PLpro), 3C-like protease (3CLpro), and spike protein. All of these three proteins are potentially attractive targets for drug development.[5,6,7]

In 2012, the WHO designated a sixth type of HCoV infection identified as the Middle East respiratory syndrome coronavirus (MERS-CoV), which is associated with high fatality[8], and declared it coronavirus disease (COVID-19). COVID-19 was considered and declared as a Public Health Emergency of international concern on 30 January 2020, and there are now reported cases in most countries with China and other countries in Europe like Italy, Spain, and the USA. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1,2] is the virus strain that is the causal agent of coronavirus disease (COVID-19), considered as a respiratory illness. It is generally referred to as corona virus based on the provisional nomenclature 2019 novel coronavirus (2019-nCOV).[3,4,5] By molecular positioning, SARS-CoV-2 is a positive-sense single-stranded RNA Virus,[6,7] known to be contagious to humans by the World Health Organization's (WHO) report.[8] The WHO had designated SARS-CoV-2 a fast-spreading pandemic and a public health emergency of global concern.[9, 10, 11] COVID-19 was first discovered in Wuhan,and was first referred to as Wuhan virus before the WHO designation of Wuhan coronavirus.[12,13]

In terms of systematics, SARS-CoV-2 is a strain of severe acute respiratory syndrome-related coronavirus (SARSr-Cov-2).[5, 14] It is considered to be zoonotic and has genetic similarities with bat coronaviruses, which is an indication of its possible origin from a bat-borne virus.[15,16] Other animal reservoirs indicators like the pangolin have been reported as a source of transmission to humans.[7,15,16] Since the virus shows little genetic variability, there is an indication that the spillover event that introduced SARS-COV-2 to humans has possibly happened in 2019, as has been observed.

### 1.2. The structure of SARS-CoV-2 virion

As the structure of SARS.CoV-2 indicates in figure 1, each SARS-CoV-2 virion is estimated at 50–200 nm in diameter. [11] Just like other coronaviruses, SARS-CoV-2 has four structural proteins, known as the S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins. The N protein contains the RNA genome, while the S, E, and M proteins together create the assemblage of the viral envelope.[15,12] The spike protein most recently has been elucidated and imaged at the atomic level using cryogenic electron microscopy[5,16] and reported to be the protein responsible for assisting the virus to attach and fuse with the membrane of any potential host cell.[4,20]

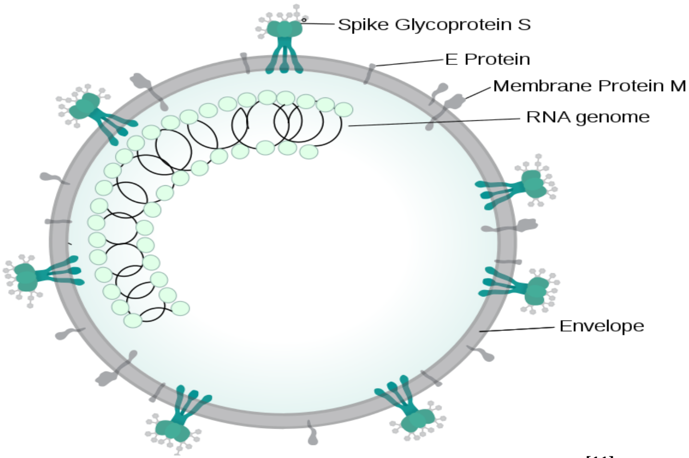


**Figure 1: The structure of SARS-CoV-2 virion.[11]**

**2.0. Method and approach of review**

The National Library of Medicine (PubMed) database, Google Scholar and other search engines were used for searches from their earliest records till May 2020, using the keywords coronavirus, influenza, colds, influenza herbal therapy, SARs-COV-2, common mutant cold, herbal therapy, influenza-like illnesses, complementary treatment for influenza, dietary supplements for upper respiratory tract infection (URTI). More relevant and related information were obtained by web search engines. Trials Register (CENTRAL), MedLine, and EMBASE. To identify unpublished research, we searched *Clinical trials.gov*, National Research Register (UK), and the Meta-Register. Searches were not limited by language. We additionally searched bibliographies of identified reviews and contacted expert tradi-practitioners inclusive in the field. The data was obtained from epidemiological, human experimental, animal experimental, *in vitro* studies, to build a structured, systematic review. The data mining approach was used to source out potential published work in this domain since 2002 by the experts in natural research. This data mining helped us to create an information base of herbal product studies in low middle income countries and the Cameroonian pharmacopeia.

**2.1. Overview of Epidemiological Studies on Coronavirus.**

Field studies have shown that COVID 19 as a fast-spreading pandemic can result in 1.4-3.9 new cases when no members of the community are immune, and there are no preventive measures put in place.[9,20] Human-to-human potential transmission of SARS-CoV-2 was confirmed on 20 January 2020, during the 2019-2020 coronavirus pandemic.[8,17] The virus can spread rapidly between people through close contact and respiratory droplets produced from coughs or during sneezing of an infected unprotected person within a range of about 1.8 meters.[17,18] Indirect contact through contaminated surfaces is another possible cause of infection.[9,17] Preliminary research has shown that the virus may remain viable on plastic and steel for up to three days but does not survive on cardboard for more than one day or on copper for more than four hours.[19,21] The virus is deactivated by soap and detergents, which can destabilize its lipid bilayer.[19,20] The Viral RNA has also been reported in stool samples from infected individuals and confirmed to be airborne to disprove earlier reports.[20,21] The virus can penetrate the human cells by binding to the receptor angiotensin converting enzyme 2 (ACE2).[4,19]

The degree to which the virus is infectious during the incubation or latent period is not clear. However, reports indicate the pharynx reaches peak viral load (PVL) at about 4 days after a healthy person is infected,[22,23,24] or during the first week of symptoms, and then subsequently declines. On 1 February 2020, WHO reported that the transmission of COVID 19 from latent asymptomatic cases was likely not the main source of transmission.[25] It is important to note that an epidemiological model of the beginning of the pandemic in China suggested that "pre-symptomatic shedding may be typical among documented infections" and that subclinical infections may have been the source of the majority of infections.[7,26]

**2.2. COVID-19 diagnostics/ testing**

COVID-19 affects different people in different ways. Most infected people are known to develop mild to moderate symptoms such as; cold symptoms, fever, tiredness, dry cough.[3,9] Other people may experience aches and pains, nasal congestion, runny nose, sore throats, and diarrhea. On average, it takes about 5–6 days from when someone is infected with the virus for symptoms to show. However, in some cases, it can take up to 14 days for symptoms to be expressed.[27] Subjects with mild symptoms who are asymptomatic are advised to practice self-isolation as a precautionary health measure. Medical attention is necessary for the event of a fever, a cough, and breathing difficulties. COVID-19 testing can identify the SARS-CoV-2 virus using methods that detect the presence of the virus itself (RT-PCR), isothermal nucleic acid amplification, and antigen).[23] Methods for the detection of antibodies produced in response to infection are also in use in the current pandemic testing. Detection of antibodies (serology) can be used both for diagnosis and population surveillance. Antibody tests show how many people have had the disease, including those whose symptoms were minor or who were asymptomatic.[17]

An accurate mortality rate of the disease and the level of herd immunity in the population can be determined from the results of this test. However, the duration and effectiveness of this immune response are still unclear,[1,28] and the rates of false positives and false negatives have to be considered during the interpretation.

Due to limited testing as of March 2020, no countries had reliable data on the prevalence of the virus in their population.[2,29] From the 29th April 2020, the countries that published their testing data have, on average, conducted several tests linked to only 1.4 % of their population, and no country has tested samples equal to more than 14 % of its population.[30] There are also variations in how much testing has been done across countries.[4] This variability is likely to affect reported case fatality rates, which have probably been overestimated in many countries, due to sampling bias.[5,6,7]

**2.2.1. Polymerase chain reaction**

Polymerase chain reaction (PCR) is a process that causes a very small, well-defined segment of DNA to be amplified or multiplied many hundreds of thousands of times, so that there is enough of it to be detected and analyzed.[26] Viruses such as SARS-CoV-2 do not contain DNA, but only RNA.[27] When a respiratory sample is collected from a subject being tested, it is treated with certain chemicals,[3,11,28] which remove extraneous substances and extract only the RNA from the sample. The reverse transcription polymerase chain reaction (RT-PCR) is a technique that first uses reverse transcription to convert the extracted RNA into DNA and then uses PCR to amplify a piece of the resulting DNA, thus creating enough to be examined to determine if it matches the genetic code of SARS-CoV-2.[29] The Real-time PCR (qPCR) provides advantages during the PCR portion of this process, including automating it and enabling high-throughput and more reliable instrumentation and has become the preferred method. The test can be done on respiratory samples obtained by various methods, including a nasopharyngeal swab or sputum sample,[29] as well as on saliva.[30] Results are generally available within a few hours to 2 days.[31] The RT-PCR test performed with throat swabs is only reliable in the first week of the disease. Later on, the virus can disappear from the throat while it continues to multiply in the lungs. For infected people tested in the second week, alternatively, sample material can then be taken from the deep airways by suction catheter, or coughed up material (sputum) can be used.[32]

Saliva is a common and transient medium for virus transmission, and results provided to the FDA indicates that testing saliva may be as effective as nasal and throat swabs.[28] The FDA has granted Emergency Use Authorization (EUA) for a test that collects saliva instead of using the traditional nasal swab.[27] It is anticipated that this will reduce the risk for health care professionals and will be much more comfortable for the patient,[28] thus enabling quarantined people to collect their samples more efficiently.[32]

**2.2.2. Isothermal amplification assays**

There are a number of isothermal nucleic acid amplification methods that, in principle, work like PCR, amplifying a piece of the virus' genome, but are faster than PCR because repeated cycles of heating and cooling of the test sample are not involved.[28,29]

**2.2.3. Antigen**

The antigen is the part of a pathogen that elicits an immune response to any pathogen invasion. While RT-PCR tests look for RNA from the virus, the antibody tests only detect human antibodies that have been generated against the virus (detectable days or weeks after the infection has set in). The antigen tests, therefore, look for protein from the surface of the virus.[28] In the case of coronavirus, these are usually proteins from the surface spikes, and a nasal swab is used to collect samples from the nasal cavity.[30] One of the difficulties of antigen tests has been in finding a protein target unique to SARS-CoV-2,[27] with the related coronaviruses that cause the common cold.[28,30]

Antigen tests are considered as the only way possible to scale up testing to the numbers that will be needed to detect acute infection on the scale required.[27] Isothermal nucleic acid amplification tests, such as the test from Abbot Labs, can only process one sample at a time per machine. The RT-PCR tests are accurate, although it takes too much time, energy, and trained personnel to run the tests.[30] An antigen test works by taking a nasal swab from a patient and exposing it to paper strips that contain artificial antibodies designed to bind to coronavirus antigens. Any antigens that are present will bind to the strips and give a visual readout. The process can take less than 30 minutes and can deliver results on the spot with less expensive equipment or extensive training.[29]

**2.2.4. Medical imaging:** Chest CT scans are not recommended for routine screening of coronaviruses. However, Radiologic findings in COVID19 are not specific.[24,29] Typical features on CT initially include bilateral multilobar ground-glass opacities with a peripheral or posterior distribution.[29] Subpleural dominance, crazy paving, and consolidating could easily develop with disease progression.[30,32]

**2.2.5. Serology tests:** This test relies on test blood samples, not a nasal or throat swab, and can identify subjects who were infected and have recovered or are in recovery from Covid-19, including asymptomatic subjects.[5,28] Most serological tests are in the process of research and development.[27] Part of the immune response to infection is the production of antibodies, including IgM and IgG. According to the FDA, IgM antibodies to SARS-CoV-2 are generally detectable in the blood several days after initial infection, although levels throughout the infection are not well characterized.[24] IgG antibodies to SARS-CoV-2 generally become detectable 10–14 days after infection, although they may be detected earlier, and normally peak around 28 days after the onset of infection.[15,29] Since antibodies are slow to present, they are not the best markers of acute infection, but as they may persist in the bloodstream for many years, they are ideal for detecting historic infections.[27]

Antibody tests can be used to determine the percentage of the population that has contracted the disease, and that is therefore presumed to be immune. However, there is no evidence on how broad, long, or how effective this immune response is [30]. As of April 2020, most countries are considering issuing the so-called immunity passports or risk-free certificates to people who have antibodies against Covid-19, thus enabling them to travel or return to work with the assumption that they are protected against reinfection.[27] However, according to the World Health Organization as of 24 April 2020, “There is currently no evidence that people who have recovered from COVID-19 and have antibodies are protected from a second infection.[27]

**2.2.6. Public health algorithm for virus prevention/treatment**.

There are no specific treatments for CoV infection, and preventive vaccines are still in the exploratory stage or in-progress.[11] It is for this reason that social engineering behavior, like washing of hands, social distancing of one meter, wearing of masks, total or partial confinement, quarantine, restriction of movement seems to be the way to control fast- spreading of the pandemics worldwide.[9] Thus, the situation reflects the need to develop effective antivirals for prophylaxis and treatment of CoV infections.[6,11]

There is an urgent need to discover novel antivirals as the viruses are responsible for a number of human pathologies, including cancer. Complex syndromes like Alzheimer's disease type 1diabetes and hepatocellular carcinoma have also been associated with viral infections.[20] Due to the increased global travel and rapid urbanization, epidemic outbreaks caused by emerging and reemerging viruses represent a critical threat to public health, particularly when preventive vaccines and antiviral therapies are unavailable. To date, many viruses remain without effective immunization, and only a few antiviral drugs are licensed for clinical practice.[2,21]

Vaccination is the main public health approach to preventing influenza-like pathogens. This vaccination aims to reduce a person's susceptibility to developing the flu by stimulating a specific immune response. Personal measures such as avoiding crowded places can reduce exposure to people with the virus in the first place, which is not easy if it is a crowded space like a school, university, or shopping center.[1,13] It is important for infected people to stay at home to rest and avoid contact with others while they are still capable of contaminating others. Measures to prevent spreading of the virus to others include using alcohol-based hand sanitizers after using a tissue and gloves etiquette, where a person is encouraged to cough or sneeze into a tissue or their elbow rather than hands or the air. These personal measures also reduce the risk of spreading other airborne viruses such as the common cold. In the past two decades, viral respiratory tract infections, especially influenza viruses, have had a major impact on communities worldwide as a result of the unavailability of effective treatment or vaccine. The frequent alterations in the antigenic structures of respiratory viruses, particularly for RNA viruses, pose difficulties in production of effective vaccines.[26]

### 2.3. Treatment options for COVID- 19 currently in use

#### 2.3.1 Therapeutic drugs combination

**Hydroxychloroquine, Azithromycin and zinc combination protocol**

The FDA issued warnings on the use of quinine since 1994 and more, recently, about its minimal effectiveness in treating leg cramps. In 2006, all sales of unapproved drugs that contained quinine except for the branded drug, *Qualaquin,* were banned due to the risk of serious side effects or death.[33] Hydroxychloroquine and a related drug, chloroquine, are currently under study as possible treatments for COVID-19.[34] These drugs have not yet been approved by the FDA for use. It is, however, advised not to use these medications to treat COVID-19 unless recommended by an authorized health officer.[35,36]

#### *2.3.2. Pharmaceutical importance of Hydroxychloroquine*

Hydroxychloroquine belongs to a class of drugs known as disease-modifying antirheumatic drugs (DMARDs). It can reduce skin problems in lupus and prevent swelling/pain in arthritis.[27,31] It is used to prevent or treat malaria caused by female anopheles mosquito bites.[37] The United States Centre for Disease Control (CDC) provides updated guidelines and travel recommendations for the prevention and treatment of malaria in different parts of the world.[38]

Hydroxychloroquine is a 4 aminoquinoline derivative with immunosuppressive, anti-autophagy, and antimalarial activities.[35] Although the precise mechanism of action is unknown, hydroxychloroquine may suppress immune function by interfering with the processing and presentation of antigens and the production of cytokines.[40,41] As a lysosomotropic agent, hydroxychloroquine raises intra-lysosomal pH, impairing autophagic protein degradation; hydroxychloroquine-mediated accumulation of ineffective autophagosomes may result in cell death and in tumor cells reliant on autophagy for survival.[42] Also, this agent is highly active against the erythrocytic forms of *Plasmodium vivax* and *P malaria* and most strains of *P. falciparum* but not the gametocytes of *P. Falciparum.*[37,42]

#### *2.3.3. Mechanisms of action of hydroxychloroquine and chloroquine as antimalarial drug*

Despite widespread clinical use of antimalarial drugs such as hydroxychloroquine and chloroquine in the treatment of rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and other inflammatory rheumatic diseases, an insight into the mechanism of action of these drugs is still in unknown.[36] Hydroxychloroquine and chloroquine are weak bases and have a characteristic large volume of distribution and a half-life of around 50 days. These drugs highly interfere with lysosomal activity and autophagy, interact with membrane stability and alter signaling pathways and transcriptional activity, which may result in inhibition of cytokine production and modulation of certain co-stimulatory molecules.[44] These modes of action, together with the drug's chemical properties, might explain the clinical efficacy and well-known adverse effects (such as retinopathy) of these drugs. The unknown dose–response relationships of these drugs and the lack of definitions of the minimum dose needed for clinical efficacy and what doses are toxic are big challenges to clinical practice.[45] Other challenges with the drug include patient non-adherence and possible concentration-dependent variations in blood drug levels. Available mechanistic data can also give an insight into the immunomodulatory potency of hydroxychloroquine, and this can provide the rationale to investigate for more potent or selective inhibitors.[46]

Hydroxychloroquine and chloroquine may inhibit certain cellular functions and molecular pathways involved in immune activation, partly by accumulating in lysosomes and autophagosomes of phagocytic cells and changing local pH concentrations.[47] The inhibition of MHC class II expression, antigen presentation, and immune activation (reducing CD154 expression by T cells).[44] Inhibition of the production of various pro-inflammatory cytokines, such as IL-1, IFNα, and TNF, which can protect against cytokine-mediated cartilage resorption.[45] Interference with Toll-like receptor 7 (TLR7) and TLR9 signaling pathways and interference with cyclic GMP-AMP (cGAMP) synthase (cGAS) activity.[48]

**2.3.4. Pharmacokinetics of hydroxychloroquine**

The most frequently used antimalarial drugs can be grouped into different classes based on their core structure. Hydroxychloroquine and chloroquine belong to a class of drugs known as 4-aminoquinolines, unlike other less frequently used antimalarial drugs that belong to other groups (such as the endoperoxidases (artemisinin) or acridines (mepacrine).[39]

In figure 2, the chemical structure of hydroxychloroquine (HCQ) and chloroquine (CQ) is shown with the basic side chain. The active metabolites hydroxychloroquine and chloroquine are also illustrated. Generally, both drugs have a flat aromatic core structure and are weak bases due to the presence of a basic side chain.[40] The basic side chain possibly contributes to the accumulation of these drugs in intracellular compartments, especially lysosomal compartments, which seem to be vital for their activity and the potential interaction of these drugs with nucleic acids.[41]

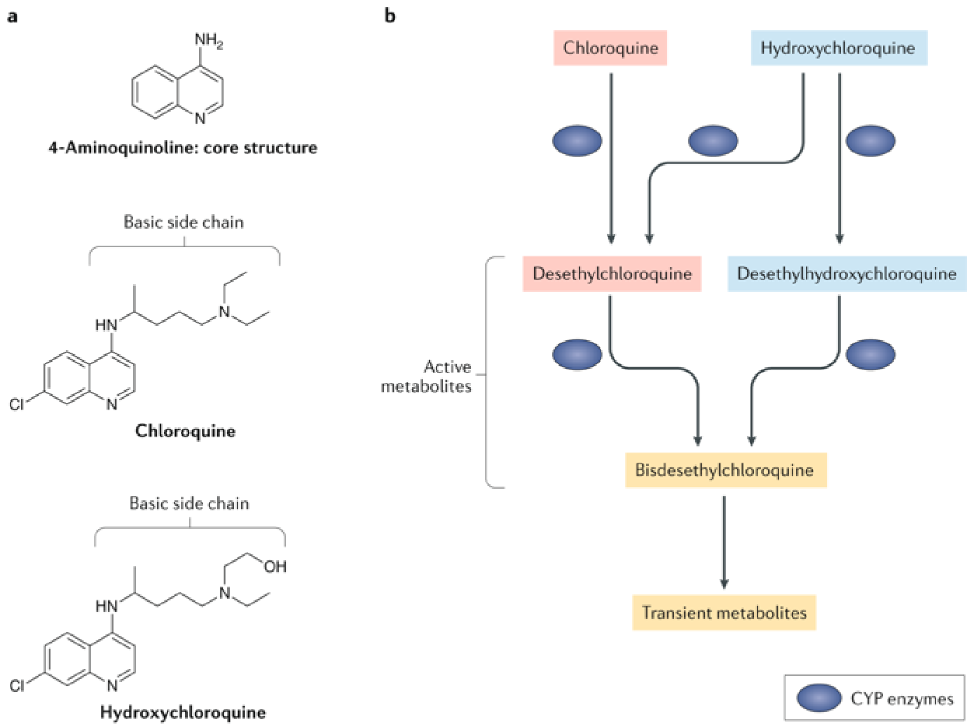


**Figure 2: Chemical structure of Hydroxychloroquine (HCQ) and chloroquine (CQ).**

**Figure 2: Pharmacokinetic properties of hydroxychloroquine and chloroquine.[41]**
**a** -Hydroxychloroquine and chloroquine belong to a class of drugs known as 4-aminoquinolines. These drugs have a 4-aminoquinoline core structure and a basic side chain. **b**-Cytochrome P450 (CYP) enzymes mediate dealkylation of chloroquine and hydroxychloroquine. Desethylchloroquine is an immediate downstream product of CYP-mediated dealkylation of both drugs, whereas desethylhydroxychloroquine is a metabolite of only hydroxychloroquine. Bisdesethylchloroquine is a downstream metabolite of both drugs.

Summary Pharmacokinetics Hydroxychloroquine (HCQ) and chloroquine (CQ) is shown in figure 3. Some of the pharmacokinetic properties of hydroxychloroquine and chloroquine show variation. The large volume of distribution and long half-life is characteristic of both drugs; however, these drugs have significant differences in renal clearance rates.

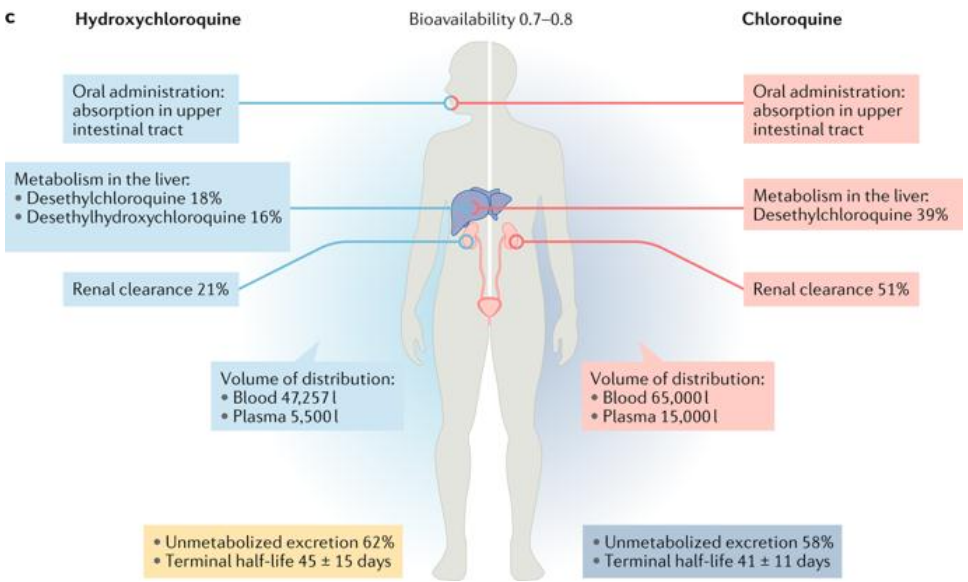


**Figure 3: Summary Pharmacokinetics Hydroxychloroquine (HCQ) and chloroquine (CQ).**

### 2.4. Azithromycin

#### 2.4.1.Azithromycin-Hydroxychloroquine Combination in Sars-CoV-2 Pneumonia.

Since the end of December 2019, a new coronavirus, close to the 2002 SARS coronavirus, caused serious pneumonia throughout the world. There is currently no strong evidence of an efficient specific treatment.[59] Azithromycin is a macrolide antibiotic with immunomodulatory properties. The addition of Azithromycin to a hydroxychloroquine-based treatment showed an apparent accelerated viral clearance in infected patients. Interventional randomized clinical trials, 405 participants started in May 2020 to end in August 2021.[60,61]

Azithromycin is a semi-synthetic macrolide antibiotic of the azalide class. It is used to treat certain bacterial infections, most often bacteria causing middle ear infections, tonsillitis, throat infections, laryngitis, bronchitis, pneumonia, and sinusitis.[59]

It is also effective against certain sexually transmitted infectious diseases, such as non-gonococcal urethritis and cervicitis. Like other macrolide antibiotics, azithromycin inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit of the bacterial 70S ribosome[60] The chemical structure is illustrated in figure 4 below.

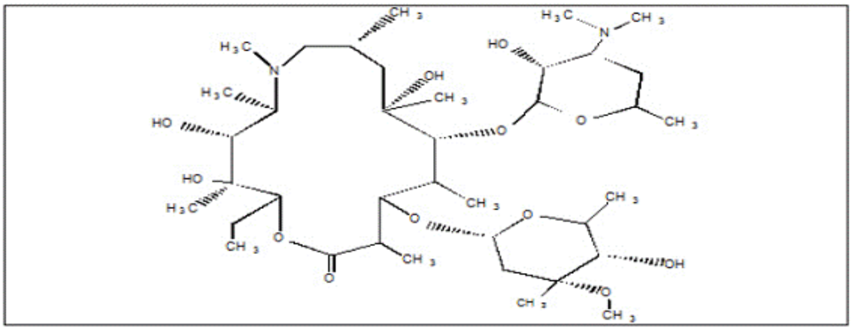

**Figure 4: Chemical Structure of Azithromycin.**

Azithromycin is an antibiotic used for the treatment of several bacterial infections.[62,63] This includes middle ear infections, strep throat, pneumonia, traveler's diarrhea, and some other intestinal infections.[64] It can also be used for several sexually transmitted infections, including chlamydia and gonorrhea infections.[65] In combination with other medications, it may be used for malaria treatment.[65] It can be taken by mouth or intravenously with doses once per day.[66]

Common side effects of azithromycin include nausea, vomiting, diarrhea, and upset stomachs.[60] Indication of allergic reactions such as anaphylaxis, QT prolongation, or a type of diarrhea caused by Clostridium difficile is possible.[66] No harm has been found with its use during pregnancy.[67] Its safety during breastfeeding is not confirmed, but it is likely to be safe.[63,68]

### 2.4.2. Mechanism of action of Azithromycin

Azithromycin prevents bacteria from growing by interfering with their protein synthesis. It binds to the 50S subunit of the bacterial ribosome, thus inhibiting translation of mRNA. Nucleic acid synthesis is not affected.[66,69]

### 2.4.3. Pharmacokinetics of Azithromycin

Azithromycin is an acid-stable antibiotic, so it can be taken orally with no need of protection from gastric acids. From food effect studies, it is readily absorbed, but absorption is greater on an empty stomach. Time to peak concentration ($T_{max}$) in adults is 2.1 to 3.2 hours for oral dosage forms.[70] Due to its high concentration in phagocytes, azithromycin is actively transported to the site of infection. During active phagocytosis, large concentrations are released, and the concentration in the tissues can be over 50 times higher than in plasma due to the effect of ion trapping and its high lipid solubility.[63-68] The half-life allows a large single dose to be administered and yet maintain bacteriostatic levels in the infected tissue for several days.[71]

Following a single dose administration of 500 mg, the apparent terminal elimination half-life of azithromycin is 68 hours.[71] Biliary excretion, predominantly unchanged, is a major route of elimination. Over the course of a week, about 6 % of the administered dose appears as unchanged drug in urine. The mechanism of action of Azithromycin macrolide, the PK profile, route of administration, disease target, and adverse effects in humans are illustrated in figure 5.[60]

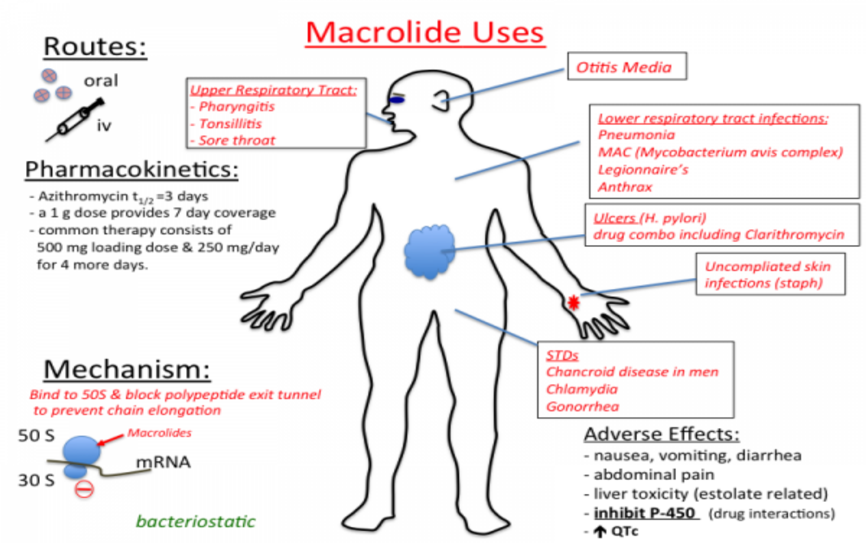


**Figure 5: Mechanism of action of Azithromycin.[60]**

### 2.5. Zinc

Zinc is a mineral also called an "essential trace element" because very small amounts are necessary for human health.[72,73] Since the human body does not store excess zinc, it must be consumed regularly as part of the diet. Common dietary sources of zinc include red meat, poultry, and fish.[84] Zinc deficiency can cause short stature, reduced ability to taste food, and the inability of testes and ovaries to function properly.[74]

Zinc is used for the treatment and prevention of zinc deficiency and its consequences, including stunted growth and acute diarrhea in children, slow wound healing, and Wilson's disease.[75] Zinc is also used for many other conditions. There is some scientific evidence to support its use for some of these conditions, but for most, there is no good scientific evidence to support its use. It is important to note that many zinc products also contain another metal called cadmium. This is because zinc and cadmium are chemically similar and often occur together in nature.[76] Exposure to high levels of cadmium over a long time can lead to kidney failure. The concentration of cadmium in zinc-containing supplements can vary as much as 37-fold. Zinc is needed for the proper growth and maintenance of the human body. It is found in several systems and biological reactions, and it is needed for immune function, wound healing, blood clotting, thyroid function, and much more.[77,78]

Zinc plays a key role in maintaining vision, and it is present in high concentrations in the eye. Zinc deficiency can alter vision, and severe deficiency can cause changes in the retina.[88] Zinc might also have effects against viruses and appears to lessen symptoms of the rhinovirus (common cold), but researchers can't yet explain exactly how this works.[79,80] Low zinc levels can be associated with male infertility, sickle cell disease, HIV, major depression, and type 2 diabetes, and can be fought by taking a zinc supplement.

*In vitro* studies in South Korea shows that Zinc can block viral replication by blocking virus formation of RNA dependent RNA polymerase complex that attaches to the human ribosome for transcription. Zinc also contains an ionophore (Pytithone) which helps to create a permeable cell wall for zinc penetration and block viral replication.[79]

**2.5.1. Zinc products commercially available include**
**Zinc gluconate**: As one of the most common over-the-counter forms of zinc, zinc gluconate is often used in cold remedies, such as lozenges and nasal sprays.[80]

**Zinc acetate**: Like zinc gluconate, zinc acetate is often added to cold lozenges to reduce symptoms and speed up the rate of recovery.[81]

**Zinc sulphate**: In addition to helping prevent zinc deficiency, zinc sulphate has been shown to reduce the severity of acne.[81,82]

**Zinc picolinate:** Some research suggests that your body may absorb this form better than other types of zinc, including zinc gluconate and zinc citrate.[79]

**Zinc orotate**: This form is bound to orotic acid and one of the most common types of zinc supplements on the market.[82]

**Zinc citrate**: One study showed that this type of zinc supplement is as well-absorbed as zinc gluconate but has a less bitter, more appealing taste.[75] Many ready-to-eat breakfast cereals are fortified with zinc. Oysters, red meat, and poultry are excellent sources of zinc. Baked beans, chickpeas, and nuts (such as cashews and almonds) also contain zinc.[82]

**2.6. Ivermectin**
Ivermectin is a widely used drug for the treatment and control of several neglected tropical diseases.[51] The drug has an excellent safety profile, with more than 2.5 billion doses distributed in the last 30 years, and its potential to reduce malaria transmission by killing mosquitoes is under clinical research in several trials around the world.[51] Ivermectin inhibits the *in vitro* replication of some positive, single-stranded RNA viruses, such as, dengue virus (DNV),[50], Zika virus[52] yellow fever virus[54] and others.[50,53] Reports have shown that ivermectin is a potent inhibitor of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication *in vitro*.[48] Given the corona virus disease (COVID-19) pandemic, this has understandably resonated widely in the global press. Figure 6 shows the molecular structure of ivermectin.

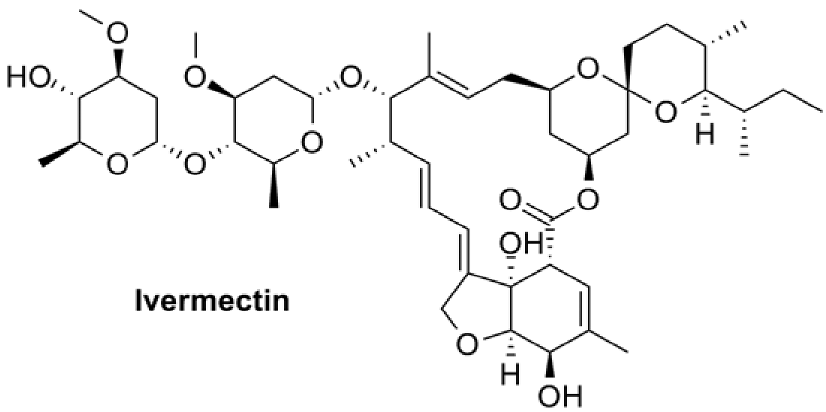


**Figure 6: Molecular structure of ivermectin.[55]**

Preliminary *in vitro* studies have reported that Ivermectin showed a 5,000-fold reduction in SARS-CoV-2 RNA levels, when compared with those in controls, after infected Vero/ hSLAM cells were incubated for 48 hours with 5 μM ivermectin.[53] The ivermectin $IC_{50}$ for the virus was calculated at approximately 2.5 μM. These concentrations are the equivalent of 4,370 and 2,190 ng/mL, respectively, especially 50- to 100-fold the peak concentration ($C_{max}$) achieved in plasma after the single dose of 200μg/kg (14mgina70-kg adult). The drug is commonly used for the control of onchocerchiasis.[54,56] Pharmacokinetic studies in healthy volunteers have suggested that single doses of up to 120 mg of ivermectin can be safe and well tolerated.[56] However, even with this dose, which is 10-fold greater than those approved by the US Food and Drug Administration (FDA), the $C_{max}$ values reported were about 250 ng/Ml,[57,58] one order of magnitude lower than effective *in vitro* concentrations against SARS-CoV-2. These findings have not been promising and may seem to discourage follow-up clinical trials with ivermectin. However, some *in vivo* effect may be possible even if efficacious *in vitro* concentrations are physiologically unattainable. Until a better understanding of ivermectin's antiviral mode of action and of appropriate *in vitro* systems for testing is defined, there is caution against using findings in Vero cells as more than a qualitative indicator of potential efficacy.[58]

**2.7. Remdesivir antiretroviral Data for Covid-19**
Preliminary findings from a major vaccine clinical trial of the antiviral drug Remdesivir indicate it speeds recovery time for some patients. But much more testing lies ahead. The antiviral Remdesivir is a molecule that impersonates the virus's genetic building blocks, disrupting its ability to replicate.[2,3,6] In late January and early February 2020, as the novel coronavirus that causes Covid-19 began to spread outside of China. Andre Kalil

and collaborators at the University of Nebraska Medical Center in Omaha with researchers at the National Institutes of Health, with no known treatments or vaccines against the deadly respiratory virus, were keen to launch a clinical trial of the most promising candidates, starting with Remdesivir, a medicine developed by US-based drug maker Gilead to treat Ebola. Kalil, with the support of NIH, led an unusual Ebola vaccine trial during the 2014-15 West African outbreak that created a new model for evaluating experimental drugs during a public health crisis.[14] NIH offered the first peek at results in which preliminary data showed that Remdesivir speeds up the recovery of some Covid-19 patients. "Specifically, the median time to recovery was 11 days for patients treated with Remdesivir compared with 15 days for those who received placebo," according to the statement. The finding, though modest, would represent the first treatment shown to improve outcomes in patients infected with the coronavirus. The chemical structure of Remdesivir is illustrated in figure 7 below.

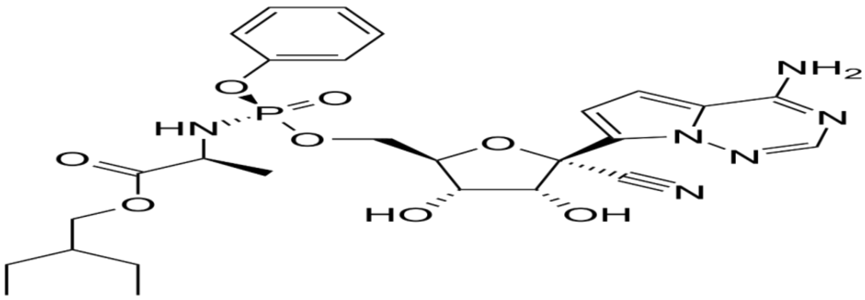


**Figure 7. Chemical structure of remdesivir.**

Preclinical studies showed that Remdesivir was not suitable for oral delivery due to almost complete first-pass clearance. Suboptimal for IM route. Studies assessing IM administration did show a slow and variable release from muscle, evidence for IM metabolism, and delayed appearance of the pharmacologically active triphosphate GS443902 in PBMCs.[6] Therefore, it was concluded that IV administration delivers GS-443902 more rapidly and consistently into target cells. The *in vivo* studies in rats and monkeys indicated that renal and biliary excretion were the major routes of elimination. In IV administration, there was absolute bioavailability, F=100 %. The Sponsor claims that Remdesivir is not suitable for oral delivery as its poor hepatic stability would likely result in almost complete first-pass clearance.[14]

## 3.0. Global traditional medicine in low medium income countries

### 3.1. The importance of natural Anti-viral bioactive products

Traditional medicine is the sum of knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures that are used to maintain health, prevent, diagnose, improve, or treat physical and mental illnesses.[83] Traditional medicine that has been adopted by other populations (outside its indigenous culture) is often termed complementary or alternative medicine (CAM).[84,86]

The World Health Organization reported that 80 % of the emerging world's population relies on traditional medicine for therapy. During the past decades, the developed world has also witnessed an ascending trend in the utilization of CAM, particularly herbal remedies.[87] Herbal medicines include herbs, herbal materials, herbal preparations, and finished herbal products that contain parts of plants or other plant materials as active ingredients. While 90 % of the population in Cameroon uses herbal remedies for their primary healthcare, surveys carried out in developed countries like the USA show a far lesser use. However, medicinal plants, unlike pharmacological drugs, commonly have several chemicals working together catalytically and synergistically to produce a combined effect that surpasses the total activity of the individual constituents.[88]

### 3.2. Herbal Medicine in China

Traditional herbal medications have been used by ancient nations for the prevention or treatment of coronavirus, colds, and flu for a very long time. A variety of herbs, as shown in table 1, have been widely used as medications for clearing viral respiratory infections.[90] The control and treatment of influenza depend mainly on chemical or biochemical agents that are isolated from plants. These agents include a variety of polyphenols, flavonoids, saponins, glucosides, and alkaloids.[91] The herbal medicine, maoto, has been traditionally prescribed to patients with influenza in Japan. Maoto is one of Kampo (traditional Japanese herbal medicines), composed of 4 medicinal herbs, Ephedrae Herba (stem of *Ephedra sinica* Staph), Cinnamomi Cortex (bark of *Cinnamomum cassia* Blume), Armeniacae Semen (kernel of *Prunus armeniaca* Linne´), and Glycyrrhizae Radix (root of *Glycyrrhiza uralensis* Fisher).[92] The administration of oral maoto granules to adults with seasonal influenza was well tolerated and associated with equivalent clinical and virological efficacy to neuraminidase inhibitors. Studies revealed that glycyrrhizin might protect mice, which were exposed to a lethal amount of influenza virus through the stimulation of interferon-gamma production by T cells.[93] Glycyrrhizin is also known to exert immunomodulatory and anti-inflammatory effects and is, therefore, a candidate drug for the control of H5N1-induced pro-inflammatory gene expression.[94,95] The investigators concluded that the antiviral activity of glycyrrhizin was mediated by an interaction with the cell membrane, which most likely resulted in reduced endocytotic activity and hence reduced virus uptake. These insights might be a potential for the invention of structurally related compounds leading to effective anti-influenza therapeutics.[96,97] There is scientific evidence about the supportive effects of several complementary medicines for corona virus and other respiratory tract infections and colds.

**3.2.1. Traditional Chinese Medicine and prevention of COVID-19**

Chinese doctors and scientists have suggested using Traditional Chinese Medicine (TCM) as a source of medicines that can be used directly against the Coronavirus. The reason for this is that TCM also proved to be effective by patients with severe acute respiratory syndrome (SARS) during the SARS epidemic.[97] The Chinese Government stimulated the use of TCM herbs. As a result, 85 percent of COVID-19 patients received combined treatment with regular medication and traditional remedies. Various TCM formulas have been used, including Yin Qiao San, Yu Ping Feng San, and Lian Hua Qing Wen capsules. The latter formula has now been taken by the Chinese doctors from Wuhan to Italy, where they are assisting the Italian doctors with their knowledge and expertise in the treatment of patients with COVID-19. Despite the need for clinical studies to investigate the exact effects, the practical results are promising.[98]

**3.2.2. Research on TCM and COVID-19**

Currently, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2, formerly known as 2019-nCoV, the causative pathogen of Coronavirus Disease 2019 (COVID-19)) has rapidly spread across China and around the world, causing an outbreak of acute infectious pneumonia. No specific anti-virus drugs or vaccines are available for the treatment of this sudden and lethal disease. The supportive care and non-specific treatment to ameliorate the symptoms of patients are the only options currently. At the top of these conventional therapies, greater than 85% of SARS-CoV-2 infected patients in China are receiving Traditional Chinese Medicine (TCM) treatment.[99]

In 2003, patients with severe acute respiratory syndrome (SARS) who were treated with TCM benefited from shorter hospitalization, decrease in steroid-related side effects, and improvement of symptoms.[101,102] Notably, genomic and *in silico* structural characterization of novel coronavirus revealed that it is closely related to the SARS coronavirus, further suggesting that TCM may have potential use in the current outbreak.[103,105] Indeed, the Chinese government is advising doctors to consider combining Western antiviral drugs with TCM remedies in combating novel coronavirus pneumonia. However, there were few studies to help select suitable herbal drugs before costly biological experiments and clinical trials.[106,108]

Classically, whether a TCM remedy can be clinically used for viral infections depends on two aspects: 1) clinical symptoms and signs of the patient, and 2) the type of TCM remedy and its traditional indications. TCM formulas have been used in China for over 2000 years. According to their effectiveness, TCM remedies are divided into various types, each corresponding to a group of diseases.[109] On the other hand, research has shown that many TCM remedies have antiviral ingredients. Selecting specific TCM formulae through integrative methods based on both disease symptom and pathogen-directed cause will greatly increase the clinical potential. However, it is still a challenge to experimentally screen many TCM remedies for the treatment of novel coronavirus pneumonia in a short time.[110, 111]

Zhang et al.[97] have provided *in silico* methods to narrow down TCM remedies that may directly inhibit the coronaviral reproduction. Two principles for selection were proposed: oral effectiveness to inhibit viral infection and compatibility of patient manifestation. The identified TCM remedies should contain anti-novel coronavirus chemicals that meet the requirement for orally administered medical drugs. Meanwhile, the identified TCM remedies should be of the types of TCM remedies that have activity against virus-caused pneumonia. To this end, the authors conducted a series of *in silico* analyses. Several natural compounds have been selected, which were experimentally validated for their potential activity against SARS or Middle East respiratory syndrome coronavirus. The molecular structures of these natural compounds have evaluated for their biological and pharmacological activities, and ability to interact, or dock, with the main proteins of the novel coronavirus. Positive docking suggests their ability to inhibit the novel coronavirus infection. First, TCM herbs that contained at least two natural compounds were selected from the Traditional Chinese Medicine Systems Pharmacology (TCMSP) database.[90] These medicinal plants were classified by the types of diseases they are used to treat. Only those belonging to the types that have been classically used to treat viral pneumonia were selected for further studies.

**Table 1. Herbal Therapies for Respiratory Viruses in China.[95,97]**

| Herb | Active Ingredients/Mechanism of Action | Responsive Virus or Illness |
|---|---|---|
| Maoto | Helps virus-bound natural antibodies | Seasonal influenza |
| Licorice roots | Glycyrrhizin stimulation of interferon-gamma production by T cells immunomodulation, reduction of virus uptake by host cells | Influenza virus A2 (H2N2), H5N1 virus, influenza A |
| ***Clinacanthus siamensis*** | Enhancement of anti-influenza virus | IgG and IgA antibodies influenza virus |
| *Punica granatum* (pomegranate | Polyphenols | Viral replication suppression, virucidal influnza A virus. |
| *Epimedium koreanum* | Reduction in viral replication, enhancement secretion | Influnza A subtypes (HINI, of type I interferon and pro- inflammatory H5N2, H7N3) cytokines immunomodulation |
| *Psidium guajava* Linn (guava tea) | Inhibition of viral haemogglutination | Influenza A (HINI) |
| *Scutellaria baicalensis* Georgi (Baicalin) | Neuraminidase inhibiton, virus budding prevention | Influenza virus, common cold |
| *Paeonia lactiflora* Pall | Inhibition of viral RNA and viral proteins synthesis | Viral influenza viruses haemagglutination, viral binding to and penetration into host cells |

### 3.3. Chinese Herbal Plants approach to COVID 19

Although the WHO declaration indicates that there is no specific medicine recommended to prevent or treat the novel coronavirus", Chinese medicine (CM) approaches including oral administration of preventive herbal formulae, have always been recommended for prevention and treatment of infectious diseases, even during the current outbreak of COVID-19.[102,103] The COVID-19 being a fast-spreading pandemic that originated from Wuhan provoked rapid research in traditional Chinese medicine to fight the pandemic. A natural Chinese remedy called bitter tea has been reported to be effective for COVID 19 prevention and management. This decoction is a combination of fresh tea made of fresh ginger, garlic, lemon, and honey with a zinc supplement. This treatment has been adapted by the national diagnostics treatment plan of China for coronavirus.[104]

Human research evidence on CM in preventing and controlling infections to provide guidance for the prevention of COVID-19, SARS and H1N1 influenza, by health authorities in China, the use of CM to prevent epidemics of infectious diseases was traced back to ancient Chinese practice cited in Huangdi's Internal Classic (an ancient Chinese medical text) where preventive effects were recorded [105]. Based on the results, 3 studies followed using CM for the prevention of SARS and 4 studies for H1N1 influenza. In these studies, none of the participants who took CM contracted SARS, while the infection rate of H1N1 influenza in the CM group was significantly lower than the non-CM group (relative risk 0.36, 95% confidence interval 0.24–0.52; n=4). Based on that information, 23 provinces in China issued CM programs for the prevention of COVID-19 using the following herbs.[106]

*Radix glycyrrhizae*(Gancao) or liquorice root, is one of the 50 fundamental herbs used in traditional Chinese medicine.[99] *Radix saposhnikoviae* (Fangfeng), *Saposhnikovia divaricate* known as *fángfēng* meaning "protect against the wind" in Chinese is the sole species in the genus *Saposhnikovia* (family Apiaceae), still frequently referenced under the obsolete genus name "Ledebouriella" in many online sources devoted to traditional Chinese medicine (TCM).[91]

*Radix astragali* (Huangqi), is a popular traditional Chinese medicine, and its active compounds may help strengthen the immune system and reduce inflammation. This compound is sometimes also given by injection route in a hospital setting.[98,102]

*Lonicerae japonicae* Flos (Jinyinhua), is one of the most commonly used traditional Chinese medicines, contains biologically active compounds such as caffeic acid derivatives, essential oil, flavonoids, iridoid glycosides and terpenoids, and has anti-inflammatory, antitumor, antioxidant, antiallergy, immunomodulating and antibacterial activity biological activities.[98,103,107]

*Fructus forsythia* also called *Lian qiao* in Mandarin for a long time is known as the panacea for people who are particularly susceptible to skin infections, and it has a broad-spectrum antimicrobial activity (Staphylococcus aureus and Shigella), and antiviral activity in certain inhibitions on influenza virus, *Leptospira*, and other pathogens. It also has anti-inflammatory and antipyretic effects.[100]

*Bupleurum spp is* known as a large genus of annual or perennial herbs or woody shrubs, with about 190 species, belonging to the family Apiaceae, with lots of promising antiviral activity.[105]

*Heteromorpha spp*. is a genus of plants within the family Apiaceae commonly known as the celery, carrot or parsley family, or simply as umbellifers. Together with *Scrophularia scorodonia* (the genus *Scrophularia* of the family Scrophulariaceae comprises about 200 species of herbaceous flowering plants commonly known as figworts, and all exert antiviral activity against HCoV-22E9, a species of CoV which infects humans and bats, and along with human coronavirus OC43 it is one of the viruses responsible for the high-risk population, but prospective and rigorous population studies are warranted to confirm the potential preventive effect of CM.[105,112]

***Lycoris radiate*** (known as the red spider lily, hell flower, red magic lily, or equinox flower, is a plant in the amaryllis family Amaryllidaceae, commonly known as the amaryllis family. This plant has been extensively used in CM for the treatment of influenza virus.[97,105]

### 3.4. Antiviral Natural products of African Pharmacopoeia

Phytomedicine has been classified into four categories by the African Organization for Intellectual properties (OAPI nations). An intergovernmental organization of 17 countries: Benin, Niger, Burkina Faso, Senegal, Cameroon, Chad, Congo, Togo, Central African Republic, Ivory Coast, Gabon, Guinea, Guinea Bissau, Equatorial Guinea, Mali, the Comoros, and Mauritania. In favour of the development of traditional medicines in all member states in accordance with the standards of the World Health Organization. These countries developed a protocol in 2004 at the Bamako meeting for the harmonization of phytomedicines from traditional pharmacopeia in all its member states.[113] Figure 8 gives a schematic illustration categorization of the classification of improved traditional medicines from the organization of intellectual property (OAPI) member states.

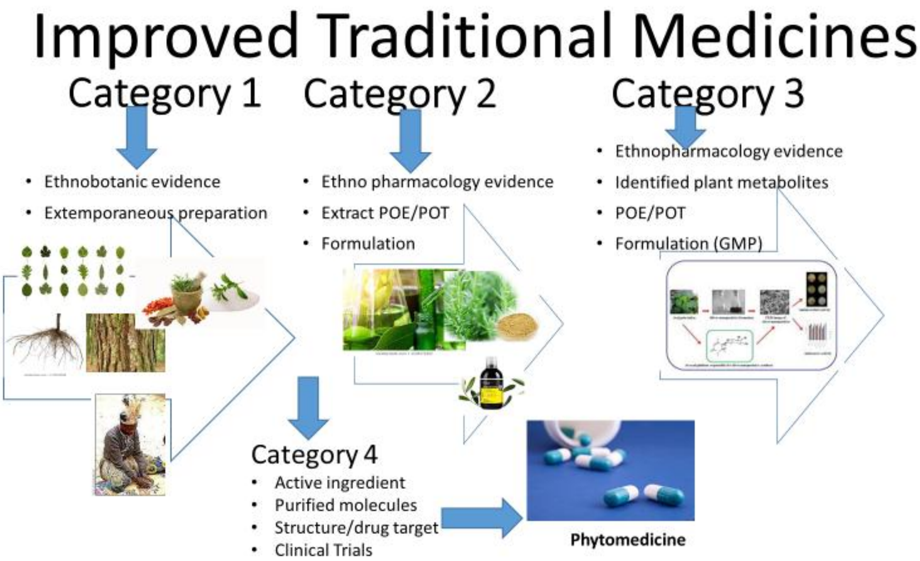


**Figure 8: Categorization of Improved traditional medicine in OAPI Countries.**

### 3.5. Neem Antiviral activity

***Azadirachta indica A. Juss***, commonly known as neem, neem tree, or Indian lilac,[114,132,144] is a tree in the mahogany family or family Meliaceae. It is one of two species in the genus *A. indica* and is native to the India subcontinent introduced to tropical and semi-tropical regions. Neem trees also grow in the Sudano Sahelian climatic region of Cameroon. Its fruits and seeds are the sources of neem oil. Many scientists are interested in conducting studies in this domain in India, and very interesting findings have been reported relating to antiviral activity. Neem efficacy, particularly against pox viruses, smallpox, chicken pox, and warts, have traditionally been tested with a paste of neem leaves – in most cases are usually rubbed directly onto the infected skin.[115,145]

Studies with smallpox, chicken pox, and fowl pox have shown promising results from the use of neem plants. Crude neem extracts absorbed the viruses, effectively preventing them from entering uninfected cells.[146] However, no antiviral effects have been shown once the infection was established within the cell.[147]

Recent preclinical preliminary studies have shown that neem leaves possess some antiviral activity.[142] Studies have shown that aqueous neem-leaf extracts have low to moderate inhibition of the viral DNA polymerase of the hepatitis B virus.[148] In Germany, studies conducted on the ethanolic neem-kernel extract were effective against herpes virus.[140] Neem has been effective in horticultural studies, as the crude extracts have been demonstrated to effectively bind some plant viruses and prevent infection.[145] This result is promising, and further testing has been done using an array of extremely virulent and difficult diseases of patient population, some wildlife, and livestock. Aqueous leaf extract shows antiviral activity against the Vaccinia virus, chikungunya, and measles virus.[148]

There are certain bioactive compounds in neem that possess an antiviral ability and prevent them from causing infection.[140] Neem also inhibits viral transmission by interacting with the surface of the cells to prevent the cell from becoming infected by the virus. Neem has shown to be effective against several viral diseases in different clinical studies that have demonstrated the antiviral potential.[19,148] Neem extracts have been established as phytoantiviral agents tested for the management of chickenpox, shingles, herpes, hepatitis in clinical research.

***Acacia senegal (L.)** Willd. (Leguminosae: Mimosoideae,* also known as gum Arabic, is a native to semidesert and drier regions of sub-Saharan Africa. It is a medicinal plant in parts of Northern Nigeria, Cameroon, West Africa, North Africa, and other parts of the world.[116,127] African herbalists use gum acacia to bind pills and to stabilize emulsions. It is also used in aromatherapy for applying essential oils.[127]

Additionally, it has been documented to be used as an antitussive and an expectorant, and against colds, coughs, diarrhea, dysentery, gonorrhea, hemorrhage, sore throat, typhoid, and for urinary tract ailments.[116,128] Recently, it has been reported that *A. senegal* bark extracts were evaluated *in vitro* for their antimicrobial potential against human pathogenic isolates (*Escherichia coli*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Shigella dysenteriae*, *Salmonella typhi*, *Streptococcus pyogenes*, *Pseudomonas aeruginosa*, and *Proteus vulgaris*). The extract was found to exhibit significant antibacterial activity which, was suggested to be due to the presence of tannins and saponins in the plant. It was also reported that the plant extract might not be toxic to humans following *in vitro* cytotoxicity evaluation.[129,132]

***Aloe ferox Mill. (Xanthorrhoeaceae)** Bitter Aloe or Cape Aloe. Aloe ferox* is native to South Africa and Lesotho and is considered to be the most common Aloe species in South Africa. The bitter latex, known as Cape Aloe, is used as laxative medicine in Africa and Europe and is considered to have bitter tonic, antiviral, antioxidant, anti-inflammatory, antimicrobial, and anticancer properties.[117,133] Studies show that *A. ferox* gel contains at least 130 medicinal agents with antiviral, anti-inflammatory, analgesic, calming, antiseptic, germicidal, antiparasitic, antitumor, and anticancer effects encompassing all of the traditional uses and scientific studies were done on *A. ferox* and its constituents.[119, 121,134]

***Artemisia herba-alba** Asso (Med)* family *Asteraceae. Artemisia herba-alba* is commonly known as wormwood or desert wormwood. It is a greyish, strongly aromatic perennial dwarf shrub native to Northern Africa, Arabian Peninsula, and Western Asia and was later introduced to West and Central Africa.[122,135] *A. herba-alba* has been used in folk medicine by many cultures since ancient times. In Cameroon folk medicine, it is used to treat common colds, diabetes, bronchitis, diarrhea, hypertension, and neuralgias.[126,137] Herbal tea from *A. herba-alba* is used as an analgesic, antibacterial, antispasmodic, and hemostatic agents in folk medicines.[138] The antifungal and antiviral activity of *Artemisia herba-alba* was found to be associated with two major volatile compounds isolated from the fresh leaves of the plant. The compound carvone and piperitone were isolated from *Artemisia herba-alba*.

***Centella asiatica (L.) Urb. (Apiaceae)***
This is a medicinal plant that has been used since prehistoric times. It has a pan-tropical distribution and is used in many healing cultures, including Ayurvedic medicine, and African traditional medicine.[130] To date, it continues to be used within the structure of folk medicine and is increasingly being located at the interface between traditional and modern scientifically oriented medicine. Traditionally, *C. asiatica* is used for wound healing; burns, ulcers, leprosy, tuberculosis, lupus, skin diseases, eye diseases, fever, inflammation, asthma, hypertension, rheumatism, syphilis, epilepsy, diarrhea, and mental illness and is also eaten as a vegetable or used as a spice.[135,139]

The active constituents are characterized by their clinical effects in the treatment of chronic venous disease, wound healing, and cognitive functions, amongst others.[140] *C. asiatica* contains a variety of pentacyclic triterpenoids that have been extensively studied. The compound Asiaticoside and madecassoside are the two important active compounds used in drug preparations.

***Catharanthus roseus (L.)** G. Don (Apocynaceae)Madagascan Periwinkle.*
*Catharanthus roseus* is a well-known medicinal plant that has its roots from the African continent. The interest in this species arises from its therapeutic role, as it is the source of the anticancer alkaloids vincristine and vinblastine, whose complexity renders them impossible to be synthesized in the laboratory; the leaves of this species are still so far the only source of the bioactive molecule.[141] *C. roseus* originates from Madagascar but now has a wide distribution throughout Africa, and the story on the traditional use of this plant can be retraced to Madagascar, where healers have been using it extensively to treat several ailments. It is commonly used in traditional medicine as a bitter tonic, galactogogue, and emetic. Application for treatment of rheumatism, skin disorders, and venereal diseases have also been reported.[142]

*C. roseus* has been found to contain many phytochemicals (as many as 130 constituents), and the principal component is vindoline of up to 0.5%. Other biologically active compounds are serpentine, catharanthine, raubasine, akuammine, lochnerine, lochnericine, and tetrahydroalstonine.[143]

***Cyclopia genistoides*** *(L.) Vent. (Fabaceae) or* Honeybush.

*Cyclopia genistoides* is an indigenous herbal tea of South Africa and later found in some parts of West and Central Africa, considered as a health food. Traditionally, the leafy shoots and flowers are fermented and dried to prepare tea. It has also been used since prehistoric times for its direct positive effects on the urinary system.[138] It is a drink that is mainly used as a tea substitute because it contains no harmful substances such as caffeine. A decoction of honeybush has been used as a restorative and as an expectorant in chronic catarrh and pulmonary tuberculosis.[144,146] Drinking an infusion of honeybush could increase the appetite, but no indication is given of the specific species.[146]

***Momordica charantia Linn. (Cucurbitaceae)*** Bitter Melon.

*Momordica charantia*, also known as bitter melon, is a tropical vegetable grown throughout Africa and commonly used in Cameroon. The leaf may be made into a tea called "cerassie," and the juice extracted from the various plant parts (fruit pulp, seeds, leaves, and whole plant), is a very common folklore remedy for diabetes.[129,131,147] *M. charantia* has a long history of use as a folklore hypoglycemic agent, where the plant extract has been referred to as vegetable insulin [148] Several active compounds have been isolated from *M. charantia*, and some mechanistic studies have been done. [151,152] Khanna et al.[128,137] have reported the isolation from fruits, seeds, and tissue culture of seedlings, of "polypeptide," a 17-amino acid, 166-residue polypeptide which did not cross-react in an immunoassay for bovine insulin. Galactose binding lectin isolated from the seeds of *M. charantia* has been evaluated for its antilipolytic and lipogenic activities in isolated rat adipocytes and found comparable to insulin.[154] Extracts of fruit pulp, seed, leaves, and whole plant of *M. charantia* have shown hypoglycemic effects in various animal models.[155]

***Pelargonium sidoides DC (Geraniaceae)***

*Pelargonium sidoides* is native to the coastal regions of South Africa, and available ethnobotanical information shows that the tuberous *P. sidoides* is an important traditional medicine with a rich ethnobotanical history in Africa.[156]

There are numerous studies about *P. sidoides* and respiratory tract infections.[157,162] These studies showed that *P. sidoides* might be effective in alleviating symptoms of acute rhinosinusitis and the common cold in adults. It may be effective in relieving symptoms of acute bronchitis in adults and children and sinusitis in adults.[158] *P. sidoides* extract modulates the production of secretory immunoglobulin A in saliva, both interleukin-15 and interleukin-6 in serum, and interleukin-15 in the nasal mucosa.[154]

***Artemisia annua***, also known as **sweet wormwood,** is a common type of wormwood native to temperate Asia but naturalized in many countries, including parts of Central Africa, Cameroon.[155,156] Artemisia *annua* belongs to the plant family of Asteraceae and is an annual short-day plant. In traditional Chinese medicine (TCM), and part of Cameroon folk medicine, *A. annua* is traditionally used to treat fevers.

The proposed mechanism of action of artemisinin involves cleavage of endoperoxide bridges by iron, producing free radicals such as hypervalent iron-oxo species, epoxides, aldehydes, and dicarbonyl compounds, which damage biological macromolecules causing oxidative stress in the cells of the parasite.[160] Malaria is caused by apicomplexans, primarily *Plasmodium falciparium*, which largely resides in red blood cells and itself contains iron-rich heme-groups (in the form of hemozoin).[161] In 2015 artemisinin was shown to bind to a large number of targets suggesting that it acts in a promiscuous manner.[162]

### 3.6. Antioxidant activity of *A annua*

Apart from the active compound artemisinin, some studies have shown that *A. annua* is one of the four medical plants with the highest oxygen radical absorbance capacity (ORAC) level.[133] *Artemisia annua* possesses the capacity to produce high phenolic compounds, which result in high antioxidant activity. Five major groups (coumarins, flavones, flavonols, phenolic acids, and miscellaneous) containing over 50 different phenolic compounds were identified, analyzing *A. Annua*.[150,163]

#### 3.6.1. Artemisinin and flavonoids

They are generally known for their redox properties involved in the delay or inhibition of the initiation or propagation in oxidizing chain reactions.[136] Even though the beneficial effect of these phenolic compounds on a great number of diseases is often discussed, different studies show beneficial effects of flavonoids bioactive compound produced by *A. annua*. It has been stated that there is a negative correlation between the presence of the mentioned components and cardiovascular diseases,[165] cancer, and parasitic disease such as malaria.[152]

In the last 20 years, researchers focused on the activity of artemisinin against malaria. Therefore, fewer studies have been done about the relationship between flavonoids and cancer. Despite that, recent studies show that the flavonoids present in the *A. annua* leaf is linked to the suppression of CYP 450 enzymes responsible for altering the absorption and metabolism of artemisinin in the body.[164] Further research in the synergistic effect of artemisinin and flavonoids and their biological interaction between malaria and cancer is needed.[165]

**3.6.2. Claimed effectiveness of *A annua* against COVID-19**

In April 2020, President Andry Rajoelina of Madagascar, speaking at the launch of a drink made from a variety of herbs though predominantly from *A. annua* and Ravensara[139] recommended the product as a treatment for COVID-19 patients and said students' return to schools (which were closed during the pandemic).[149] would be conditioned on their consumption of it. However, despite anecdotal reports of the use of *A. annua* against COVID-19 in China, there is no clear evidence of the effectiveness of the tea against the disease, and no clinical studies have been conducted.[141,142] The WHO warns that the drink's efficacy as a treatment for COVID-19 is unproven, while the African Union is seeking technical data from Madagascar and has asserted that there will be a scientific review based on "global technical and ethical norms."[167]

***Zingiber officinale* Ginger plant.** *Ginger* is a flowering plant that originated in China. It belongs to the Zingiberaceae family and is closely related to turmeric, cardamom, and galangal. The rhizome (underground part of the stem) is the part commonly used as a spice. It is often called *ginger* root, or simply *ginger*. Ginger has a long history of use in various forms of traditional/alternative medicine. It has been used to help digestion, reduce nausea, and help fight the flu and common cold, to name a few. Ginger can be used fresh, dried, powdered, or as an oil or juice, and is sometimes added to processed foods and cosmetics.[145,151]

Ginger contains approximately 50 % carbohydrate, 6 to 8 % fatty acids and triglycerides, and 9% protein, free amino acids, vitamins, and minerals.[146] The main bioactive constituents of ginger are volatile oils, soft resins insoluble in ether and oil, gum, starch, lignin, acetic acid, potassium oxalates, acetates, and some sulphur.[159] Depending on the rhizome being fresh or dried, it has varying levels of fatty oils, protein, carbohydrate, raw fiber, ash, water, and volatile oils. The volatile oils constitute sesquiterpenes, curcumene, geranyl acetate, terpineol, terpenes, geraniol, alpha pinene, limonene, linalool, zingiberene, beta-besabolene, and alpha-farnesene.[146] The pungent principles are gingerol, shogaol, zingerone, and paradol, Gingerol, and Shogaol are the major active components for ginger’s pharmacological effects and pungency, respectively.[135] The main aroma defining component in ginger is zingiberol while others such as gingediol, monoacyldigalactosyl-glycerol, diarylheptanoids, vitamins, and phytosterols have also been elucidated[148] The levels of constituents in ginger can vary considerably depending upon a number of Postharvest handling conditions, like storage and processing may also result in a loss of thermo-labile active constituents[152] Ginger samples derived from different origins showed no qualitative differences in major volatile compounds, although they did show some significant quantitative differences in non-volatile composition, particularly regarding the content of gingerols, the most active anti-inflammatory and antispasmodic components in this species.[152,157]

***3.7. Vernonia amygdalina* bitter leaf**

Vernonia amygdalina, commonly known as bitter leaf, is a perennial herb belonging to the Asteraceae family found in the African tropics and other parts of Africa, particularly Nigeria, Cameroon, and Zimbawe. Bitter leaf has numerous medicinal values and benefits to human health and lifestyle. The leaf has been proven to possess some antiviral, anti-bacterial, anti-inflammatory, and anti-fungal properties that make it a good home remedy to several health issues such as diarrhea, hypertension, fever, influenza-like symptoms and many others. Some people may not find the taste of bitter leaf enjoyable, but the health benefits are so much so that putting up with the taste seems worth it.[127,137,145]

**3.7.1. The pharmaceutical and medicinal importance of *V amygdalina* bitter leaf drink**

It helps get rid of fever as bitter leaf contains flavonoids that have powerful antioxidant effects in treating a variety of health issues such as a high fever. It works together with other elements such as andrographolide lactones, glucosides, diterpene, which work together to treat and trim down fever and its symptoms. It is said that a glass of bitter leaf juice is a strong herbal remedy which is said to treat malaria and fever[139] and also lowers blood pressure as research has shown that chewing on fresh bitter leaves or drinking juice extract will drastically reduce the amount of sugar in your blood and therefore help manage your blood pressure better as well as reducing the risk of diabetes.[125,126] Bitter leaf also contains traces of potassium, which is another good remedy for those suffering from high blood pressure.

The organic fraction extracts of V amygdalina have been shown in vitro studies to possess cytotoxic effects towards human carcinoma cells of the nasopharynx.[125] It is effective against amoebic dysentery, gastrointestinal disorders, and has antiviral, antimicrobial, and antiparasitic activities.[126] Figure 5 summarizes the various traditional uses of Vernonia amygdalina. Phytochemicals like saponins, alkaloids, terpenes, steroids, coumarins flavonoids, phenolic acids, lignans, xanthones, anthraquinones, edotides, and sesquiterpenes have been extracted and isolated from *Vernonia amygdalina*. These bioactive metabolites are responsible for various biological activities including, cancer chemoprevention. The chemopreventive properties of *V. amygdalina* have been attributed to their abilities to scavenge free radicals, induce detoxification, inhibit stress response proteins, and interfere with DNA binding activities of some transcription factors.[127] It works by flushing out the accumulation of salt, which affects one’s sodium levels and leads to high blood pressure. Vitamin C is a strong antioxidant mineral found in bitter leaf that plays a vital role in the body which is the maintenance of bones and teeth. It also contains a trace of vitamin K, which helps the body maintain healthy bones and prevents the weakening of bone tissue, also known as osteoporosis.[126,144] [128,145] A summary of the different multiple medicinal virtues of *Vernonia amygdalina* is well described in figure 9.

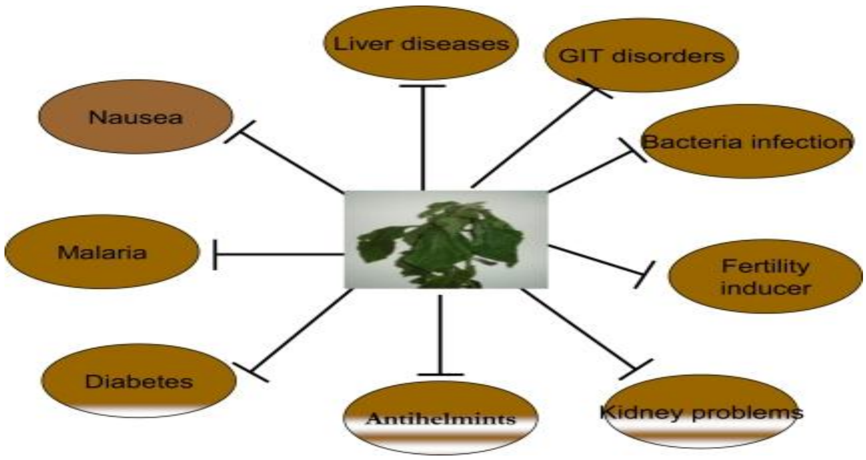


**Figure 8: Summary of the medicinal benefits of *Vernonia amygdalina* (bitterleaf).**

## 4.0. DISCUSSION

### 4.1. Challenges for traditional medicine research for lmics

With the advent of the fast-spreading pandemic COVID 19, Africa is faced with joining the race to find a treatment for the virus. Traditional medicine approach seems to be an alternative approach in low medium income countries to provide at least a short-term measure as has been the case in countries, for instance, like Madagascar and Cameroon. The LMIC are endowed with a rich biodiversity of medicinal plants, with easy access and easy to use as herbal tea under category 1 use of traditional medicine. There are already some countries that have taken the initiative of using herbal treatment for its population. Although the use of traditional herbs poses a problem of evidence base medicine to guarantee efficacy, safety, and quality (ESQ) principles with what is already in Madagascar and Cameroon, it is worth having an insight on these natural products in circulation. We have to look at WHO's position on the use of herbal medicine and our opinions as scientists.

### 4.2. Case study 1: Madagascar covid-organics "cvo" herbal drink

An "effective traditional treatment" based on the anti-malarial drug Artemisia is providing "encouraging clinical trials" against Covid-19 in the island nation of Madagascar. Called "CVO or Covid-Organics," The CVO is reported to have been developed by a team of researchers at the Malagasy Institute of Applied Research (IMRA), with the support of their peers in the United States and China. The concern now is that faced with the Covid-19 pandemic, is the CVO finally emerging from Madagascar specifically for Africans?[155]

Rajoelina believes his country has a global role to play in containing the coronavirus. After mentioning a miracle cure based on traditional plants without naming it on April 8, 2020, the Malagasy president officially launched a treatment developed by researchers at the Malagasy Institute of Applied Research (IMRA) on April 19, 2020. This announcement came at the end of a study lasting more than a month, carried out by a team of IMRA researchers, with the support of the Malagasy government and researchers in the United States and China who collaborated with the island nation in the manufacturing process of the treatment.[160] This discovery has raised a lot of ethical and regulatory concerns with the International community, especially the WHO and the Pharma companies, in a mad rush to produce a vaccine.

**Madagascar's Argument on the Preventive and curative treatment**

After encouraging initial clinical trials, April 20, 2020, marked the start of nationwide administration of Covid-Organics," an improved traditional medicine made from Artemisia and Malagasy medicinal plants. This treatment is reported to have been initially administered to students before they return to school as a preventive measure to strengthen their immune system. One month after the entry into force of the state of health emergency, within the context of easing the lockdown, the announcement of the local production of this improved traditional pharmacopeia remedy provided an opportunity to clarify its composition.

This remedy combining the medicinal plant *Artemisia annua* as the basis for preventive and curative treatment of Covid-19, with other endemic medicinal plants, has proven its efficacy on patients suffering from the virus on the island. To date, the country has 39 patients cured thanks to this remedy, and no deaths have been recorded. Artemisia, a notorious antimalarial drug. *Artemisia* *annua* is a widely used plant known for its effectiveness in the fight against malaria, which Prof. Albert Rakoto Ratsimamanga, founder of IMRA, was the first to study in Madagascar. IMRA researchers have used their years of work against malaria to develop Covid-Organics. Very on, Madagascar started a dual therapy protocol based on chloroquine and azithromycin in combination with preventive and curative treatment, including medicinal plants. The Malagasy population being adept at traditional medicine, made it possible to reveal the virtues of certain medicinal plants in the treatment of coronavirus.[157,160] After the strong declaration of the President of Madagascar to continue the supply of CVO to his population and other African countries that have expressed the need, the WHO finally decided to collaborate with Madagascar for improved research on CVO. The CVO initiative by Madagascar is subject to a lot of questions on the efficacy, safety, and quality, because the preclinical and clinical data are not scientifically available. This gap in information has obliged WHO to set in and collaborate with Madagascar to validate CVO.

### 4.3. WHO to study Madagascar's drug to treat COVID-19

Media report indicated that WHO is now in touch with Madagascar after the country's president slammed the global health body for not endorsing its drug. Matshidiso Moeti, the regional director of the WHO office in Africa, told a media briefing. "We are in touch with the government of Madagascar," over its herbal drink Covid Organics (CVO) that is believed to cure coronavirus or COVID-19 patients. The WHO's response came after Madagascar President Andry Rajoelina had slammed the global health body for not endorsing the CVO. The WHO has offered to support the design of a study to look into this product [Covid Organics] and in discussion to sort out the way forward. So far, the WHO does not have any data related to the efficiency of the CVO. "The WHO has been working in the traditional medicine sector to facilitate collaboration and to incorporate traditional medicine into national health systems.[157]

CVO reported to have been developed by the Malagasy Institute of Applied Research, has been shipped to several African countries. The COVID-19 pandemic is making the situation worse. So far, 72,336 cases of COVID-19 have been reported in Africa with 2,475 deaths. The World Health Organization notes that the use of products to treat COVID-19 which have not been robustly investigated can put people in danger. In a May 4 statement, the WHO said untested and unproven medicines give a false sense of security and distract from proven measures such as hand washing and physical distancing.

### 4.4. Case study 2: Tradipractitioners preventive approach for sars cov-2 (covid 19) in cameroon

The fast-spreading pandemic of COVID-19 has taken the world by surprise, especially in limited-resource countries. The fact that there is no known treatment or vaccine approved for COVID-19, the interest in the use of herbal product in Cameroon has become very popular. Many traditional healers and religious groups have all joined efforts in the prevention intervention process. This free-fall approach could lead to other fundamental underlying problems of efficacy and safety.

### New product from Essential oils from a combination of herbal plants

The archbishop of Douala, a metropolitan city in Cameroon Samuel Kleda on the 8th May 2020 declared at a press conference the use of a herbal product with no name for the treatment of COVID 19, and that about 500 patients who tested positive for the COVID-19 have recovered. This product so far was declared on the 18 May 2020, by Dr. Engelbert Kameni, the health officer for the Catholic health center in charge of distribution of the product to the public following fake appearances of natural products Kledavid in the market purported to be made by the arch bishop, that the product has no name, and made of a mixture of essential oils from many plants.[168,169] The concern raised by multiple charlatans cashing in on the popular declaration of the archbishop puts the population at risk of safety by consumption of these untested products. It is not yet evidenced by scientific proof of concept in the efficacy and safety of the archbishop's non-commercialized natural product. To address the problem of large-scale consumption by the population, the archbishop has approached the government to work in synergy to fight the common enemy COVID 19. However, with the rich biodiversity of herbal plants, backed up with long usage in the Cameroonian community. This product is under controversy in Cameroon, because there is no scientific evidence on the efficacy and safety of the product.. There is the need for the team to open up for collaboration with expert scientists in Cameroon to accompany them in the research towards ensuring the scientific validity of the product.[170,171]

### *4.5. The potential use of a Cameroonian functional food (Star Yellow) to curb the spread of the COVID-19 via faeces.*

A group of Cameroonian scientists has reported the occurrence and shedding of active COVID-19 virus in stools of infected persons. With that line of inference, they saw the need for the control of the possible spread of COVID 19 through feces, especially in areas with poor hygienic conditions.[124] Their argument is derived from the fact that SARS-CoV-2 being an RNA virus, its efficient control or eradication can only be totally achieved by blocking the RNA replication. One way, according to these researchers, could be by the use of a functional food with antiviral /anti RNA replicating activity to specifically target those in the digestive tract.[125] Therefore, using the main ingredients of a locally known yellow soup, with added spices of known antiviral and antioxidant activity they came up with "STAR YELLOW". The star yellow was intended to develop a zinc-rich Functional Food, that could be effective against RNA replication of the COVID-19 virus present in the gastrointestinal tract of infected persons, thereby preventing transmission of the active virus through feces.[124,125] There is also emerging evidence of patients (20 to 50 years old) testing positive for SARS-CoV-2 shortly after undergoing treatment and recovery. This could be due to reinfection from the GI tract reservoir of the virus, raising the need for treatment protocols to include action against this reservoir as could be provided by 'Star Yellow', effectively controlling the spread of SARS-COV-2 via feces until such a time that a vaccine is available.[124]

**4.6. Multippa-CIG collaborative approach for a preventive antiviral natural product for COVID 19 in Cameroon**

Tradi-practioners in collaboration with biomedical and medical scientists in Cameroon in partnership with a common initiative group (Nongovernmental organization-NGO) called Multipurpose Poverty Alleviation Common Initiative Group (MULTIPPA-CIG) Cameroon has put together a category 1 herbal extemporaneous bitter tea for local consumption, given that the road to developing a treatment for COVID 19 is still very long. MULTIPPA is a common initiative group with a registration certificate under the Ministry of Agriculture No SW/GP/02/05/4406 of 13 May 2005 in compliance with Law N° 92/006 of August 1992 relating to cooperative societies and common initiative groups and its Decree of application N° 92/455/PM of 23rd November 1992. Its objectives are to improve the socio-economic life of every member of the group and the community as a whole. To improve on the marketing of farm products, and protect the environment. To raise awareness and sensitize the local communities on the need for improved healthcare, sensitization, and crusade initiative on the negative effects of sexually transmitted diseases (HIV/AIDS), on the welfare of the community. This NGO has developed a good paradigm on health watch through the campaign of de-stigmatization of members of the local communities affected by various infectious disease that is considered as a taboo, such as Aids/HIV, leprosy, obesity, etc. Such patients are assisted to cope within their communities through support programme towards self-sufficiency.

Due to the lack of testing kits in enclaved areas in Cameroon, community dwellers with symptoms of COVID 19 have been put on the herbal mixture developed from locally available, environmentally friendly natural products. A simple decoction bitter drink has been put together as illustrated in the schematics in figure 10. The team herbalist has administered the mixture preparation locally to subjects presenting the classic symptoms of COVID 19. The product at this early stage is noncommercial and non-labelled. From promising indications, over 37 subjects who were administered this bitter tea have regained their normal daily activities from usage. This feedback is motivating enough for consideration to seek funding for future ethnobotanic, phytochemical characterization, anticovid activity screening, and safety of the bitter tea.

The challenge of proof of concept of the bitter tea after consumption by the subject participants range from difficulties getting access to testing centers. Also, there is no funding yet for phytochemical screening of the bitter tea, and preclinical testing and toxicity testing yet. The use is basically of category 1 administration. We hope that, in the near future, the bitter tea shall be tested for safety and evidence of antiviral activity. Our intention was to perform the decoction tested at preclinical levels using cell lines for proof of efficacy and do acute toxicity studies for safety. This work is just a preliminary investigation of a category 1 use of our product. Furthermore, additional studies should also examine the possibility of combination therapies with other natural agents or with standard therapeutics, as a multi-target therapy may help reduce the risk of generating drug-resistant viruses.

The process for the preparation and administration of the bitter tea is described in figure 10. Table 2 also gives the possible locally available herbal species and plant for use in the preparation of the bitter tea drink.

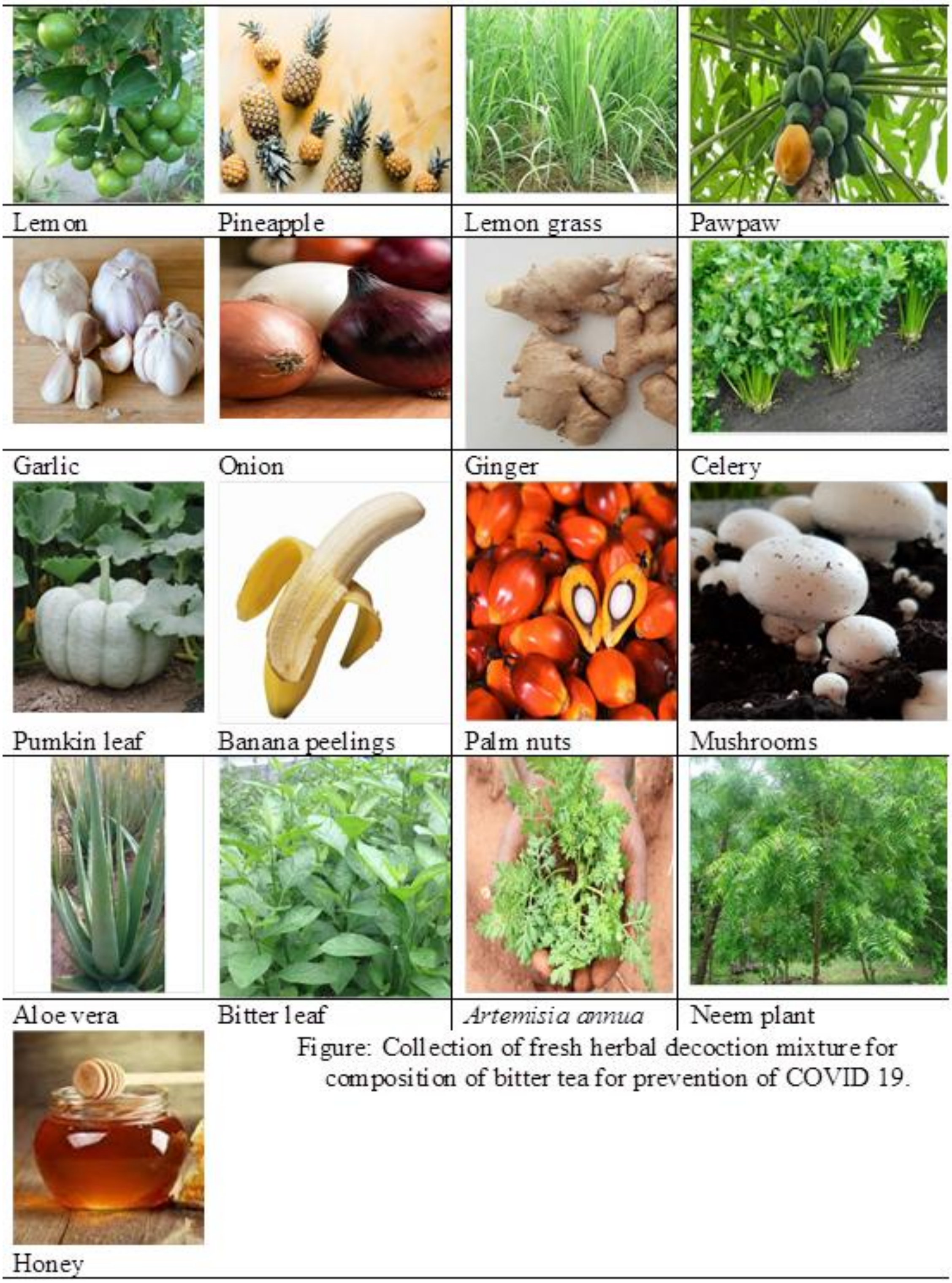


**Figure 10: Collection of the fresh herbal decoction mixture ingredients for composition of bitter tea to ensure prevention of COVID 19.**

**Table 2: MULTIPPA-CIG Bitter tea Preparation and administration process.**

***The preventive collaborative Approach processes.***

This preventive protocol was developed for use for all interested subjects showing classic symptoms of COVID 19, visiting our collaborator tradi-practitioner for treatment, which in all the cases were free and voluntary consultations.

- ✓ **BEFORE TREATMENT**
- ✓ Patient must gargle with a glass of hot salt water in the morning, afternoon, and evening to address any sore throat symptoms.

**PREPARATION OF THE DECOCTION *BITTER HOT TEA DRINK***
**HERBAL RAW MATERIALS**

1)The use of fruits sliced in lamellae for source of **antioxidants/vitamin C and Vit B-6**: fresh lemon, pawpaw leaf, ripe pineapple peelings, and lemon grass (500g). The fresh materials must be disease-free, to avoid rotten products and prevent any microbial contaminations.
3)The use of vegetables and leaves for **Zn source**: pumpkin leaves, crushed palm nuts, mushrooms, ripebanana peelings.
4)- Use **antifever bitter herbs** from either **one of the following** *Aloe vera*, bitter leaves (*Vernonia amygdalina*), Neem leaf (*Azadirachta indica* A.Juss (500g).
5- Apply honey to be added last before drinking to reduce bitter taste and enforce antibacterial effect.

- ✓ **DECOCTION PREPARATION**:
- ✓ A cooking pot was used, and 2L of clean potable water was added, and the plant materials washed and placed in the pot. This was boiled for about 30 minutes. Decoction allowed to cool down to a lukewarm temperature and then solution drained or decanted solution into a clean container. 100 ml was taken in a glass or tea-cup with honey added.
- ✓ Each subject drank three times a day for one week.

**NOTE:** Each time before drinking, the bitter tea must be heated, then honey added.
The concoction is potent and therefore eating before drinking is highly recommended. Take treatment for a week and then go for the COVID-19 test since treatment initially is based on symptoms.
The bitter tea consumption for safety, must not exceed one week. Once tested to be negative for COVID-19 subjects are advised to take a hot honey-lemon drink every morning before the start of the day for one month. This is to build the immune system and prevent reinfection by COVID 19 from the community

### 4.7. The challenges in fighting covid-19 based on the who's -ethical and regulatory position

#### *4.7.1 Vaccine development*

The most effective way forward with the COVID-19 crisis is to develop a safe, effective vaccine that is already in progress by the multiple works of scientists. Already at least 102 vaccine candidates in the research and development process worldwide, eight of them have already entered early clinical trials, and at least two have protected a small number of monkeys from infection with the novel coronavirus, SARS-CoV-2, that causes COVID-19.[3,14]

Some optimistic vaccine developers say that, if all goes perfectly, we could see large-scale production and limited deployment of vaccines as early as the end of 2020. If true, it would be an extraordinary achievement. Less than four months ago, SARS-CoV-2 was an unnamed, never-before-seen virus that abruptly emerged in the central Chinese city of Wuhan. Researchers there quickly identified it and, by late January 2020, had elucidated the genetic code that gave an opportunity for researchers around the world to get to work on defeating it. By late February 2020, researchers in multiple continents put into action clinical trials for vaccine candidates. By mid-March 2020, two of the vaccines began, and volunteers began receiving the first doses of candidate vaccines against COVID-19. However, despite this tremendous speed in vaccine research, it's unclear if researchers will be able to maintain this pace of meeting deadlines in research.

Generally, vaccines must go through three progressively more stringent human trial phases before they are considered safe and effective. The phases assess the candidates' safety profile, the strength of the immune responses they trigger, and how good they are at actually protecting people from infection and disease. Most vaccine candidates don't make it through the approval process. By some estimates, more than 90 % fail. And, though a pandemic-driven timeline could conceivably deliver a vaccine in as little as 18 months, most vaccines take years and often more than 10 years from preclinical testing to new drug application (NDA) stage.[16,24] Failure to meet timelines can cause the risk of failure. For instance, vaccine candidates usually enter the three phases of clinical trials only after being well tested in lab animals that can model human disease. But, with such a new virus, there is no established animal model for COVID-19. And amid a devastating pandemic, there's not enough time to thoroughly develop one. Some researchers are now doing that ground-level animal work in parallel with human trials.

Researchers already have reason to be a little anxious about the safety of any COVID-19 vaccine. When they tried in the past to make vaccines against some of SARS-CoV-2's coronavirus relatives, they found a small number of instances when candidate vaccines seemed to make infections worse. That is, these candidate vaccines seemed to prompt berserk immune responses that caused lung damage in monkeys and liver damage in ferrets. Researchers still don't fully understand the problem and don't know if it could happen in humans, let alone if it will show up with the new candidate vaccines against SARS-CoV-2.

**4.7.2. Improvement of TCM research**

TCM remedies should be evaluated in carefully designed clinical trials, either used alone or integrated with Western medicine, to cover the prevention, treatment and recovery of patients suffering from the novel coronavirus pneumonia. TCM practitioners around the world may speed up the experimental research and clinical use of these remedies, especially in those countries, territories or areas with reported and confirmed cases of COVID-19. Although the difficulties and challenges are fully recognized, there is the need to increase the contribution and benefits from TCM professionals that will provide treatment to many patients with pneumonia caused by 2019 novel coronavirus (2019-nCoV).

**4.7.3. COVID-Organics Towards international validation?**

To establish the credibility of this remedy internationally, Andry Rajoelina has announced the upcoming start of therapeutic trials in foreign laboratories, and negotiations are currently underway in this regard. Pending further details, this treatment is undoubtedly an interesting avenue for both preventive and curative treatment. Introduced in Madagascar in the 1960s, Artemisia has already proven its worth in China and Africa against malaria. If the results of the Malagasy study are endorsed internationally, the CVO would have the dual advantage of not requiring a heavy production line and being able to be produced on a large scale, as the country has the largest stock of Artemisia in the world.

***4.7.5. The Big picture of COVID 19 in Cameroon***

In Yaoundé, Cameroon's traditional healers are overwhelmed by the number of people seeking herbal medicine for the prevention or treatment of the coronavirus. The rush for traditional healing comes as the central African nation confirms more than 2,500 cases of COVID-19 and 121 deaths. But medical doctors caution the use of herbal medicine for the coronavirus. The demand for herbal medicine is so high that traditional healers cannot treat some patients because they have run short of the potions made from plants they harvest from the forest.

Despite a lack of scientific evidence, traditional healers claim the potions can treat all the symptoms of COVID-19 and even save the infected from death. Medical researchers, doctors, and the Cameroon government have urged patients not to rely on traditional medicine for COVID-19 and to instead seek treatment at hospitals.[170] Douala city pharmacist Merilyne Peyou notes that many Cameroonians do not live near hospitals but have easy access to traditional medicine. Many drugs herbs, and tree leaves that were effectively used to treat Africans before the arrival of modern medicine. The only challenges of African herbal medicine, are that it is difficult to preserve, may become toxic, and healers don't always know what dosage to prescribe. Cameroon's Ministry of Public Health has also released a statement warning of quacks claiming they can treat COVID-19 to financially exploit people suffering from or worried about the virus. Many Cameroonian researchers and stakeholders on African traditional medicine research have appealed to the state authorities to work in synergy to identify which herbs can treat COVID-19 and help to develop a cure.[171] They insisted on the need for both financial and moral assistance. The university researchers have indicated now is not the time for them to keep on doubting what African traditional medicine can do, but the interests and priority now is getting to rescue the world population that is suffering.

**4.7.6. Ethical issues on natural products**

From the ethical point of view, there is a complete absence of the code of conduct in the practice of TM. This has led to abuse of significant magnitude uses and sale of products without any instruction or inset and poor labeling. Sales of products without any scientific studies on the active principles and safety.[143] Lack of any norms to control what is out in the market for consumption. No formal structure or organization to train tradi-prationers on basic therapeutic techniques and handling of medicinal plant products. Lack of any documentation system, data base for information on medicinal plants, conventions, treaties and decree on medicinal plants.[146]

**4.7.7. Safety Issues of Herbal Medicine**

Along with the significant increase in worldwide consumption, the safety of herbal medicine has been highlighted. At present, there are misunderstanding and prejudice toward the safety of herbal medicine.[98] So, objective understanding, neutral and fair interpretation, and publicity are warranted. Herbal Medicine is considered by tradi-practitioners as drugs, not Food.

Advocates will advertise that herbal medicine originated from nature and belongs to green therapy and has no toxin or adverse effect, and people can take it in the long term and so forth. These sayings are slogans of the advocates who have misled people with less medical knowledge. On one hand, it will lead to many severe adverse events by misusing herbal medicine; on the other hand, it will cause people's panic and anxiety due to some adverse events reports.[123] We should recognize that herbal medicinal products are widely considered to be of lower risk compared with synthetic drugs; they are not completely free from the possibility of toxicity or adverse effects. Exaggerated propaganda and giving up the use because of adverse events are prejudice against herbal medicine. Therefore, to ensure the safe use of herbal medicinal products, herbal medicine should be managed as a drug.[146]

**4.7.8 Proof of Efficacy/ Safety and toxicity issues**

There is a lot of products with high-level media profiling by tradi-practitioners for the prevention and cure of COVID 19. To give some scientific validity for proof of efficacy and safety of natural product use in Cameroon, many Cameroonian researchers and stakeholders on African traditional medicine research have appealed to the state authorities to work in synergy in order to identify which herbs can treat COVID-19 and help to develop a cure. There is a need for Preclinical and clinical studies for proof of efficacy and safety and to determine the category of the natural product for sale and distribution. Some regulatory approval by the Ministry of health needs to sanction authorization for the production and sale of medicinal products.

## 5. CONCLUSION

The world is faced with a rapid pandemic that needs global effort to control it. It is evident that with no approved treatment for COVID 19, there is global mobilization in research for a globally accepted solution, either through vaccine development or a magic drug. On the other hand, the conception of these herbal remedies has been inspired by the Chinese experience of COVID -19 herbal approach and other works from existing data mining on antivirals from natural products done so far in Cameroon. It is evident from the literature that there is currently a renewed interest in African-plant-based medicines in the prevention and cure of various pathologies. Medicinal plants still play an important rolein the healthcare system in African countries. Nonetheless, there are still major challenges that need to be overcome and addressed for African herbal products mentioned to attain their full potential to be realized as the effective treatment of the COVID 19. This has not been validated thoroughly with robust scientific criteria to compete with existing conventional therapies. Additionally, other issues that need to be addressed are that of access and benefit sharing following the Nagoya agreement. Local laws need to be TRIPS compliant if the trade of African herbal products is to increase, and at the same time, issues of sustainable use and development of plant products need to be addressedNatural products serve as an excellent source of biodiversity for discovering novel antivirals, revealing new structure–activity relationships, and developing effective protective/therapeutic strategies against viral infections. Many natural products and herbal ingredients are observed to possess robust antiviral activity and their discoveries can further help develop derivatives and therapeutic leads. As many studies in this domain are only preliminary, further exploration in characterizing the bioactive ingredients, defining the underlying mechanisms, as well as assessing the efficacy and potential application *in vivo* is encouraged in order to help develop effective antiviral treatments. We believe that natural products will continue to play an important role and contribute to antiviral drug development. While the natural product isolated as the active compound might not be suitable for development as an effective drug, it can provide a suitable lead for conversion into a clinically useful agent.

**Authors contribution**

This work was carried out in collaboration among all authors. Authors CF, ETF, EBF, MDN, LFF, BNN, JBF, designed the study. Authors AMA, RNA, NT, JDF, CE, CW, did data mining/case studies. Authors GNT, ABN, JF, BN, JN, DMT, NK, RD, AN, MAO, PZO and BTN contributed to writing of first draft. All authors read and approved final draft.

**Consent**

It is not applicable.

**Ethical approval**

It is not applicable.

**Competing interests**

Authors have declared that no competing interest exist.

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