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Curative Potential of Nigerian Medicinal Plants in COVID-19 Treatment: A Mechanistic Approach

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Abstract

COVID-19 is a highly infectious and severe acute respiratory disorder caused by a pathogenic virus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Its clinical manifestations include fever, fatigue, cough, shortness of breath, and other complications. Mode of actions of SARS-CoV-2 includes hyper-inflammation characterized by a severe and fatal hyper-cytokinaemia with multi-organ failure; immunosuppression; reduction of angiotensin-converting enzyme 2 (ACE2) to enhance pulmonary vascular permeability and damage the alveoli and activated by open reading frame (ORF)3a, ORF3b, and ORF7a via c-Jun N- terminal kinase (JNK) pathway which induces lung damage. These mechanisms of action of the virus can be mitigated by combine therapy of the medicinal herbs based on their pharmacological activities. At present, there is no effective treatment or vaccine that can mitigate/inhibit coronavirus. Available clinical intervention for COVID-19 is only palliative and limited to support. Thus, there is an exigent need for effective and non-invasive treatment. The article critically assesses the proposed mechanism of actions of SARS-CoV-2 and presents Nigeria based medicinal plants which have pharmacological and biological activities that can mitigate the hallmarks of the pathogenesis of COVID-19. Since the clinical manifestations of COVID-19 are multifactorial and co-morbidities, we strongly recommend the use of combined therapy with two or more herbs with specific therapeutic actions being administered to combat the mediators of the disease.

Keywords: COVID-19; SARS-CoV-2; Phytochemicals; mechanistic approach; medicinal plants

1. Introduction

Novel Coronavirus disease 2019 (COVID-19) is a highly infectious and severe acute respiratory disorder caused by an infectious virus called SARS-CoV-2 which is transmitted to humans via contact and/or feeding on infected animals. The COVID-19 clinical manifestations are very similar to viral pneumonia such as fever, fatigue, cough, shortness of breath, and other complications. According to reports obtained on WHO and NCDC websites as of 16th May 2020, the Coronavirus breakout in Wuhan, a city in Hubei Province of China in November 2019 has spread to many countries in the world. This global pandemic has forced many nations to lock down their social activities, which in turn has adverse effects on the economy. Globally, more than 3,500,000 people have been confirmed infected with over 250,000 deaths. Nigeria is one of the countries seriously affected by the virus having over 6000 cases and more than 190 mortalities (WHO, 2020; NCDC, 2020). Thus, there is an exigent need for effective and non-invasive treatment.

Coronaviruses (SARS-CoV) are non-segmented positive-sense single-stranded RNA viruses with a large viral RNA genome of diameter 80–120 nm (figure1). They belong to the family of Coronaviridae, in the subfamily Orthocoronaviridae which consists of four genera namely: Alpha, Beta, Gamma, and Delta coronavirus (Chan *et al.*, 2013). Some of the proposed modes of actions of SARS-CoV-2 include hyper-inflammation characterized by a sudden and fatal hyper-cytokinaemia with multi-organ failure (Huang *et al.*, 2020); immunosuppression; reduction of Angiotensin-Converting Enzyme 2 (ACE2) to enhance pulmonary vascular permeability and damage the alveoli (Li and Clercq, 2020) and activated by ORF3a, ORF3b, and ORF7a via JNK pathway which induces lung damage (Liu *et al.*, 2014).

At present, there is no effective treatment or vaccine that can mitigate/inhibit coronavirus. Available clinical interventions for COVID-19 are only palliative and limited to support. Many research groups around the world are currently focusing on developing novel treatments such as vaccines and antivirals. This article critically assesses the proposed mechanism of actions of SARS-CoV-2 and presents Nigeria based medicinal plants which have

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pharmacological and biological activities that can mitigate the hallmarks of the pathogenesis of COVID-19. Since the clinical manifestations of COVID-19 are multifactorial and co-morbidity, we strongly recommend the use of combined therapy such that two or more herbs with specific therapeutic actions are administered. This could provide a desired medical intervention against the mediators of the disease.

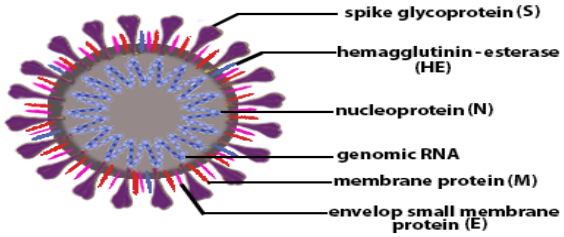


Figure 1. Structure of SARS-CoV-2

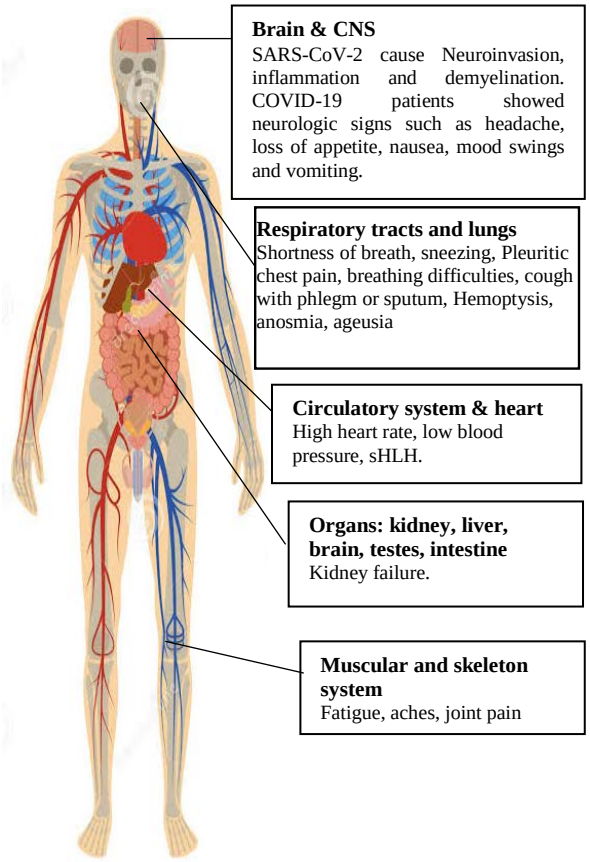
2. History and Prevalence

COVID-19, novel coronavirus pneumonia is ranked at the ninth deadliest world pandemic ever experienced in the world was first recorded in late 2019 at a Chinese city called Wuhan. Since its first outbreak, the disease has spread to every continent of the world affecting many nations. This highly infectious and severe acute respiratory disease is transmitted to humans and animals by a pathogenic virus called SARS-CoV-2. Reports from epidemiological findings documented that the disease is comparatively less life-threatening and not common in children (Lu *et al.*, 2020; Wu and McGoogan 2020). Updates by WHO on 16th May 2020 showed that COVID-19 poses a major threat to global public health. The data revealed that more than 3,500,000 confirmed cases of SARS-CoV-2 infection and over 250,000 deaths globally since the first case were reported in late 2019. In Nigeria, a country located in the western region of Africa, over 6000 cases had been confirmed with 190 mortalities (WHO, 2020; NCDC, 2020).

COVID-19 has spread rapidly from Wuhan in China to all the continents of the world within four weeks. This confirms that COVID-19 has a very high prevalence, and the global population is generally susceptible to SARS-CoV-2. Using the IDEAL model, Majumder et al. documented that the basic reproduction number (R0) of SARS-CoV-2 is 2.0–3.3 (Majumder and Kenneth, 2020), while Wu *et al.* (2020) reported that the R0 is between 2.47 and 2.86 using the SEIR model (Majumder and Kenneth, 2020). R0 is a parameter for measuring the transmission potential of contagious diseases. It indicates the average number of secondary infections that may occur in an entirely susceptible population (Remais, 2010). The values of R0 may vary between research groups due to many factors such as duration of infectiousness, probability of infection being transmitted during contact, and rate of contacts in the host population. The calculated R0 values of other beta coronaviruses are 2.2–3.6 (Lipsitch *et al.*, 2003). This revealed that SARS-CoV-2 has relatively high communicability. The median age of cases reported in China was 47 years, 3% of the cases were aged people (≥80 years), 87% of the cases were people between the age of 30 and 79 years. Forty-two percent of the cases were female, suggesting that males may be more susceptible to SARS-CoV-2 (Guan *et al.*, 2020; Wu and McGoogan 2020).

3. Pathogenesis of Coronavirus disease 2019 (COVID-19)

COVID-19, a severe acute respiratory viral infection in humans caused by SARS-CoV-2 has an average incubation period of 3 days (Guan *et al.*, 2020). The most common clinical features of COVID-19 are very similar to other viral pneumonia which include fever, fatigue, cough, shortness of breath, and other complications; organ failure and death were recorded in severe and critical cases (Figure 2) (WHO, 2020). These symptoms are markedly expressed in adults probably due to chronic underlying diseases such as heart diseases, neurodegenerative disorders, diabetes, or hypertension (Chen *et al.*, 2020). Transmission of the virus among humans occurs when there is a penetration of infected aerosols from respiratory droplets, cough, or sneeze into the lungs via inhalation through the nose or mouth.



COVID-19 has been reported to have a higher mortality rate of about 3.7% when compared with influenza with >1% mortality rate (WHO, 2020). Some scientific evidence showed that some sets of severe COVID-19 cases might have a cytokine storm syndrome and respiratory failure due to acute respiratory distress syndrome (ARDS) which is the major cause of death (Ruan *et al.*, 2020). Viral infections are the major factor that initiates secondary haemophagocytic lymphohistiocytosis (sHLH) (Ramos-casals *et al.*, 2014). sHLH also known as Macrophage Activation Syndrome (MAS) is a life-threatening medical condition which comprises a heterogeneous group of

hyper-inflammatory syndrome occurring when there is an infraction in the interplay of genetic predisposition and activators such as infections. It is characterized by a sudden and severe hyper-cytokinaemia due to inappropriate survival of histiocytes and cytotoxic T-lymphocytes and ultimately leads to haemophagocytosis, multi-organ failure, and high mortality (Henter *et al.*, 2002). Fundamental characteristics of sHLH are cytopenias, persistent fever, and hyper-ferritinaemia; pulmonary involvement occurs in approximately 50% of patients (Seguin *et al.*, 2016).

However, the immunosuppression pathway depicting how SARS-CoV-2 affects the immune system has not been fully elucidated. Nevertheless, MERS and SARS have been reported to evade immune detection and weaken immune responses. During viral infection, host factors produce an immune response against viruses. CD4+ and CD8+ are important T cells which perform a pivotal role in mitigating the virus and decreasing the chance of acquiring autoimmunity/inflammation (Cecere *et al.*, 2012). The CD4 + T cells enhance the synthesis of viral-specific antibodies by activating T cell-dependent B cells, while CD8+T cells are cytotoxic and wipe out virus-infected cells. Approximately, 80% of total inflammatory cells in the pulmonary interstitial in SARS-CoV infected patients are CD8+T cells. They perform important functions in scavenging and coronaviruses in infected cells (Maloir *et al.*, 2018). Furthermore, T helper cells produce proinflammatory cytokines through the NF-kB signaling pathway (Manni *et al.*, 2014).

4. Modes of action of SARS-CoV-2

Using sequencing technology, the analysis of SARS-CoV-2 genetic sequences showed that the complete genome sequence recognition rates of SARS-CoV and bat SARS coronavirus (SARSr-CoV-RaTG13) were 79.5% and 96.2%, respectively (Chen *et al.*, 2020). Like other coronaviruses, SARS-CoV-2 has specific genes in ORF1 regions that stimulate proteins for viral replication, spikes formation, and nucleocapsid (van Boheemen *et al.*, 2012). The SARS-CoV-2 enter into and affect the host cell by undergoing a few steps of modifications similar to other kinds of beta-coronaviruses. Thereafter, it binds to the ACE2 receptor in the alveoli of the lungs and respiratory epithelium (Liu *et al.*, 2020a, b). Binding of SARS-CoV to the receptor results in the mobilization of cellular proteases to cleave the S protein into S1 and S2 domains. These cellular proteases include cathepsins, human airway trypsin-like protease (HAT), and transmembrane protease serine 2(TMPRSS2) that split the spike protein and establish further penetration changes (Glowacka *et al.*, 2011; Bertram *et al.*, 2020). This cleavage enhances the activation of S2 via a conformational change thus allows the interpolation of the internal fusion protein (FP) into the membrane mediating the entrance of the virus into the cell.

There is a probability that SARS-CoV-2 employed a similar mechanism as SARS-CoV because its receptor-binding domain (RBD) binding motif consists of the nucleotides associated with ACE2. After SARS-CoV-2 gained entrance in its host cell, ACE2 is cleaved and ADAM metallopeptidase domain 17 (ADAM17) shed by it into the extra membrane space. This may lead to the conversion of angiotensin I to angiotensin II by ACE2, a negative regulator of the renin-angiotensin pathway, thus increasing pulmonary vascular permeability and damaging the alveoli (Chan *et al.*, 2020). After SARS-CoV-2 proteins are translated in the host cell, ORF3a protein which codes for a Ca^{2+} ion channel that is related to SARS-CoV-2 is synthesized. It interacts with TRAF3 and activates the transcription of Nuclear Factor kappa-light-chain-enhancer of activated B-cells (NF-kB) pathway, leading to the transcription of the pro-IL-1B gene (Siu *et al.*, 2019), ORF3a along with TNF receptor-associated factor 3 (TRAF3) and ORF3a mediates the inflammasome complex which contains caspase 1, Apoptosis-associated speck-like protein containing a CARD (ASC), and Nod-like receptor protein 3 (NLRP3). Second signal like the ROS production, Ca^{2+} influx, mitochondrial damage, and caspases activation converts pro-IL-1B to IL-B and results in cytokine production. Another ORF8b protein also activates the inflammasome pathway through NLRP3. This protein is longer in SARS-CoV-2 (Siu *et al.*, 2019). The E protein forming an ion channel is also involved in the overproduction of cytokines (a phenomenon known as cytokine storm syndromes which cause respiratory distress) through the NLRP3 inflammasome pathway (Nieto-Torres *et al.*, 2015).

JNK is another important pathogenic pathway of SARS-CoV. In this pathway, there is an overproduction of pro-inflammatory factors via activation of ORF3a, ORF3b, and ORF7a which may lead to increased production of proinflammatory factors, critical damage of the lung (Huang *et al.*, 2020). A cytokine profile resembling secondary haemophagocytic lymphohistiocytosis (sHLH) with a hyperinflammatory syndrome characterized by a fulminant and severe hypercytokinaemia with multiorgan failure is associated with COVID-19 disease severity. This is characterized by increased tumor necrosis factor-α, interleukin (IL)-2, IL-7, interferon-γ inducible protein 10, granulocyte-colony stimulating factor, macrophage inflammatory protein 1-α, and monocyte chemoattractant protein 1 (Huang *et al.*, 2020).

Furthermore, when compared with other kinds of respiratory syndrome coronaviruses like the Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV), SARS-CoV-2 showed higher infectivity and transmissibility but a low mortality rate. The observed increase in virulence of SARS-CoV-2 may be due to much higher strength at which SARS-CoV-2 binds to ACE2 and mutation noted in its genome sequence. The detected changes on the SARS-CoV-2 gene include differences in orf8 and orf10 proteins, alteration on Nsp 2 and 3 proteins, shorter 3b segments, absent 8a, and longer 8b (Wu *et al.*, 2020a,b; Xu *et al.*, 2020a,b).

5. Nigerian medicinal plants with pharmacological and biological action capable of mitigating SARS-CoV-2

Various therapeutic approaches have been used since time immemorial for many health ailments, apart from the pharmacological treatment. Approximately, eighty percent of the world population still depends upon the use of herbal remedies for their health care. Nigeria and many other countries in West Africa are blessed with several varieties of medicinal plants which are of use for various purposes. This traditional method of treating ailment is

transferred from one generation to the other all over the world. Dependence on plants usage has been attributed to their affordability, effectiveness, safety, cultural preferences, and ample accessibility at all times and need. Globally, traditional healers are using various medicinal plants for the treatment of COVID-19. We, therefore, present some of the Nigeria indigenous medicinal plants with therapeutic abilities which may serve as effective treatment for COVID-19 due to their antiviral, anti-inflammatory, antioxidant, antipyretic, immunomodulatory and cytoprotective properties (figure 3).

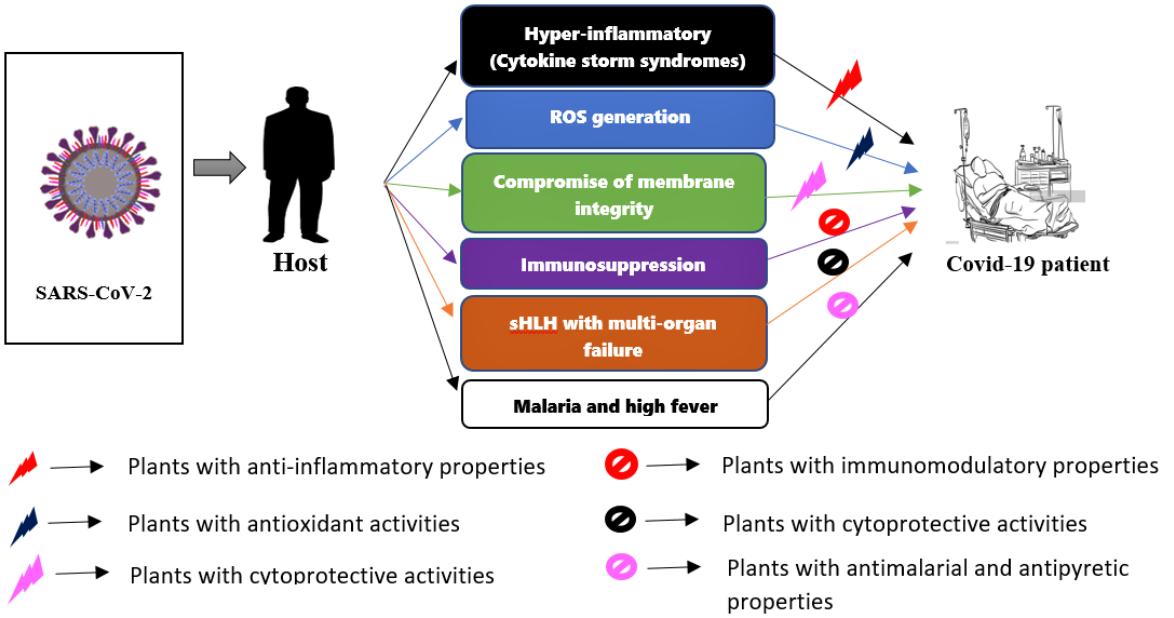


Figure 3. Pathological features of Covid-19 and possible clinical interventions by medicinal plants.

5.1. Nigerian medicinal plants with antimalarial and antipyretic properties

High fever and malaria have been reported as clinical manifestations or symptoms of COVID-19. Malaria is a global health burden caused by infection with a parasite of genus plasmodium. Scientific studies have tried to investigate the link between malaria and other diseases such as cancers, especially lymphoma, Burkitt lymphoma (caused by gamma herpes Viruses, Epstein-Barr virus), Kaposi sarcoma (caused by Kaposi sarcoma-associated herpesvirus), nasopharyngeal carcinoma and liver cancer. Nigerian indigenous medicinal plants such as *Enantiachlorantha, Khaya grandifoliola, Alstoniaboonei, Morinda lucida,* and *Azadirachta indica* are being used extensively in traditional medicine as malaria therapy. Table 1 below shows the comprehensive list of indigenous medicinal plants used for malaria therapy. The leaves, barks, roots, or whole plants are used for the treatment. Different species of the plants or parts have also been combined to formulate antimalarial herbal mixtures (Table 2). We suggest that any of these plants administered alone or in combinations may offer beneficial effects in alleviating malaria in COVID-19 patients.

Table 1. List of Nigerian medicinal plants with antimalarial properties

S/N	Botanical nomenclature	Family Names	Local Names	Common Names	Parts Used
1	*Acanthospermum hispidum*	*Compositae*	Egungun arugbo	Starrburr	Leaves, whole plant.
2	*Allium sativum*	*Liliaceae*	Ayuu	Garlic	Bulb
3	*Alstoniaboonei*	*Apocynaceae*	Ahun	Stool wood	Root, bark, leaves.
4	*Anacardium occidentale*	*Anacardaceae*	Kasu	Cashew nut tree	Bark, leaves
5	*Ananascomosus*	*Bromeliaceae*	Ope-Oyinbo Ehin-ahun Ekunkun	Pineapple	Unripe Fruit
6	*Azadirachtaindica*	*Meliaceae*	Dogonyaro	Neem	Bark, leaves
7	*Brideliaferruginea*	*Euphorbiaceae*	Ira odan		Bark, leaves
8	*Canna indica*	*Cannaceae*	Ido	Indian shot	Leaves
9	*Capsicum frutescens*	*Solanaceae*	Ata-Ijosi	Cayenne	Fruits
10	*Carica papaya*	*Caricaceae*	Ibepe	Pawpaw	Leaves, fruit
11	*Ceiba pentandra*	*Bombacaceae*	Araba	Kapok tree	Leaves

12	*Chromolaenaodorata*	*Compositae*	Ewe Akintola Ewe Awolowo	Siam weed	Root, leaves
13	*Chrysophyllumalbidum*	*Sapotaceae*	Agbalumo	African star apple	Bark, leaves
14	*Citrus aurantifolia*	*Rutaceae*	Osanwewe	Lime	Root, bark, stem-twigs, leaves, fruit
15	*Citrus aurantium*	*Rutaceae*	Osan ganinganin	Sour lime	Root, bark, stem-twigs, leaves, fruit.
16	*Citrus paradisi*	*Rutaceae*	Osan gerepu	Grape	Fruit, stem-twigs, leaves, root
17	*Curcuma longa*	*Zingiberaceae*	Laali-pupa	Turmeric	Rhizome
18	*Cymbopogon citratus*	*Poaceae*	Kooko-Oba	Lemon grass	Leaves
19	*Diospyros mespiliformis*	*Ebeneceae*	Igidudu	Ebony tree	Bark, leaves
20	*Enantiachlorantia*	*Annonaceae*	Osopa Awopa Dokitaigbo	African yellow wood	Bark
21	*Funtumiaafricana*	*Apocynaceae*	Ako-ire	Funtumia	Root
22	*Gossypium barbadense*	*Malvaceae*	Owu	Cotton	Leaves
23	*Gossypium hirsutum*	*Malvaceae*	Ela owu	Cotton	Leaves
24	*Harungana madagascariensis*	*Hypericaceae*	Asunje	Dragons blood tree	Bark, leaves
25	*Heliotropiumindicum*	*Boraginaceae*	Ogberi-akuko	Heliotrope	Whole plant.
26	*Hyptissuaveolens*	*Labiatae*	Jogbo		Leaves
27	*Khaya grandifoliola*	*Meliaceae*	Oganwo	Mahogany	Bark
28	*Lecaniodiscus cupanioides*	*Sapindaceae*	Akika		Roots
29	*Mangiferaindica*	*Anacardiaceae*	Mangoro	Mango	Bark, leaves
30	*Meliciaexcelsa*	*Moraceae*	Iroko	Iroko	Root, Bark
31	*Mondiawhitei*	*Periplocaceae*	Isirigun		Root, whole plant
32	*Morinda lucida*	*Rubiaceae*	Oruwo	Brimstone tree	Bark, leaves
33	*Musa sapientum*	*Musaceae*	Ogede were ibile	Banana	Fruits
34	*Nauclealatifolia*	*Rubiaceae*	Egberesi Gberesi	African peach	Root, bark, leaves
35	*Ocimumgratissimum*	*Labiatae*	Efirin-nla	Tea bush	Leaves
36	*Parquetinanigrescens*	*Periplocaceae*	Ogbo		Whole plant, leaves
37	*Pergulariadaemia*	*Asclepiadaceae*	Atufa, isirigun		Root, leaves
38	*Physalis angulata*	*Solanaceae*	Koropo		Leaves, whole plant
39	*Psidium guajava*	*Myrtaceae*	Gilofa	Guava	Bark, leave
40	*Pycnanthusangolensis*	*Myristicaceae*	Akomu		Bark
41	*Rauvolfia vomitoria*	*Apocynaceae*	Asofeyeje		Roots, barks, leaves
42	*Senna podocarpa*	*Caesalpiniaceae*	Asunwonibile		Bark, leaves
43	*Senna siamea*	*Caesalpiniaceae*	Kasia	Senna	Bark
44	*Solanum nigrum*	*Solanaceae*	Odu		Leaves
45	*Sphenocentrum jollyanum*	*Menispermaceae*	Akerejupon		Roots
46	*Tithoniadiversifolia*	*Compositae*	Jogbo Agbale	Tree marigold	Leaves, stem twings
47	*Tremaorientalis*	*Ulmaceae*	Afefe		Leaves, bark
48	*Vernonia amygdalina*	*Compositae*	Ewuro	Bitter leaf	Leaves
49	*Xylopia aethiopica*	*Annonaceae*	Erinje Eeru		Fruits, bark, leaves.
50	*Zingiber officinale*	*Zingiberaceae*	Ajo, Ata-ile	Ginger	Rhizome

Table 2. List of the formulation of some herbal mixture

Recipes containing two plants	Recipes containing three plants	Recipes containing four plants	Recipes containing five or more plants
Recipe 1 *Alstoniaboonei* (bark) *EnantiaChlorantha* (bark) Recipe 2 *Enantiachlorantha* (bark) *Curcuma longa* (rhizome) Recipe 3 *Citrus aurantifolia* (leaves, fruit) *Chrysophyllumalbidum* (leaves, bark) Recipe 4 *Capsicum fructescens* (fruit) *Alstoniaboonei* (bark) Recipe 5 *Citrus aurantium* (fruit) *Vernonia amygdalina* (leaves) Recipe 6 *Lecaniosdiscuscupanoides* (root) *Citrus aurantium* (fruit) Recipe 7 *Psidium guajava* (leaves) *Carica papaya* (leaves) Recipe 8 Gossypium barbadense *(leaves)* *Citrus aurantium* (fruit)	Recipe 1 *Diospyros mespiliformis* (bark) *EnantiaChlorantha* (bark) *Alstoniaboonei* (bark) Recipe 2 *Carica papaya* (fruit), *Citrus paradisi* (fruit) *Ananascomosus* (fruit) Recipe 3 *Physallisangulata* (leaves) *Tithoniadiversifolia* (leaves), *ChromolaenaOdorata* (leaves) Recipe 4 *Ocimumgratissimum* (Leaves), *Gossypium barbadense* (leaves) *Citrus aurantium* (fruit) Recipe 5 *Citrus aurantifolia* (leaves) *Curcuma longa* (rhizome) *Cymbopogon citratus* (leaves) Recipe 6 *Enantiachlorantha* (bark), *Funtumiaafricana* (root) *Zanthoxylumzanthoxyloides* (root)	Recipe 1 *Mangiferaindica* (bark, leaves), *Carica papaya* (leaves) *Alstoniaboonei* (bark) *Psidium guajava* (leaves) Recipe 2 *Ocimumgratissimum* (Leaves), *Vernonia amygdalina* (leaves), *Cymbopogon citratus* (leaves) *Azadirachtaindica* (bark, leaves) Recipe 3 Ananascomosus*(fruit)*, *Canna indica* (leaves) *Citrus aurantifolia* (fruit), *Citrus paradisi* (fruit)	Recipe 1 *Chrysophyllumalbidum* (leaves) *Citrus aurantifolia* (leaves) *Mangiferaindica* (bark, foliage leaves), *Sorghum bicolor* (leaves, stem) Anarcadiumoccidentale (bark) Recipe 2 *Psidium guajava* (bark, leaves) *Mangiferaindica* (bark, leaves), *Rauvolfia vomitoria* (bark, leaves) *Enanthiachlorantha* (bark), *Harunganamadagascariensis* (bark, leaves) *Curcuma longa* (rhizome) Recipe 3 *Curcuma longa* (foliage leaves), *Ocimumgratissimum* (Leaves) *Lecaniodiscuscupanioides* (foliage leaves) *Citrus aurantifolia* (foliage leaves), *Anarcadiumoccidentale* (foliage leaves) Recipe 4 *Lawsoniaguineensis* (leaves), *Citrus aurantifolia* (twigs, leaves, fruit) *Cymbopogon citratus* (leaves) *Carica papaya* (root) *Citrus aurantium* (fruit), Sphenocentrumjollyanum*(root)*

Table 2. List of Nigerian medicinal plants with antiviral properties

S/N	Botanical Name	Commonname	Family	Parts used
1	*Sida cordifolia*	Isankotu in Yoruba	Malvaceae	Whole plants
2	*EchinaceaPurpurea*	Dagumo/asofeyeje in Yoruba, Kashinyaro in Hausa, Yawo in Fulani	Asteraceae	Leaves
3	*Boerhaviadiffusa*	Etiponla, olowojeja in Yoruba	Nyctaginaceae	Roots
4	*Phyllanthus amarus*	Oyomokeisoamankedem" in Efik, "IyinOlobe" in Yoruba and "Ebebenizo" in Bini	Euphorbiaceae	leaves
5	*Andrographis paniculata*	Ewe-epa in yoruba	Acanthaceae	leaves
6	*Astragalus membranaceus*	Shekanbera" in Hausa and "aluki	Fabaceae	roots
7	*Borreriaverticillata*	Hausa: damfark'ami, Yoruba: irawo-ile	Rubiaceae	Whole plants
8.	Licorice (*Glycyrrhiza glabra*)	Ewe omisinmisin in Yoruba ,asukimaizaki in Hausa and Telugu in Igbo	Leguminosae	roots
9	Sage plants (*Salvia officinalis* L.)	Egbogi in Yoruba	Lamiaceae	leaves

5.2. Nigerian medicinal plants with antiviral properties

Nigerian plants have been shown to house a number of novel compounds with antiviral activities (figure 3). A number of scientific researches have elucidated the curative mechanisms by which these plants provide their therapeutic actions, while clinical research has presented the ability of some medicinal plants in treating many viral infections and diseases. For instance, *Sida cordifolia* has been reported to be a natural anti-human immunodeficiency virus (HIV) agent (Tamura *et al.,* 2010). One of the active compound isolated from the plant is (10E, 12Z)-9-hydroxyoctadeca-10,12-dienoic acid, a hydroxyl unsaturated fatty acid was found to be an exceptional NES (nuclear export signal) non-antagonistic inhibitor for nuclear export of Rev. Replication of HIV-1 is essentially dependent on the regulatory protein Rev or the Rev protein. Rev protein is involved in the nucleus-cytoplasm export of mRNA, which is very essential for the synthesis of the viral proteins necessary for viral replication. *Sida cordifolia* has also been proven to act as an immune booster serving as immune stimulants to strengthen and harmonize degenerative body systems and assist the immune system in its fight against invading antigens (bacteria and viruses) (Odukoya *et al.,* 2007).

Another plant with potent antiviral activities is *Boerhavia diffusa*. Active compound isolated from *Boerhaavia diffusa* extract is a glycoprotein with a molecular weight between 16,000 and 20,000. The protein and carbohydrates component of the glycoprotein is about 8 to 13 % and 70 to 80% is its composition respectively (Verma and Awatshi, 1979; Awasthi and Menzel, 1986). Other compounds whose biological activity with antiviral properties have been discovered from the plant include: boeravinone, Punarnavine, punarnavoside, hypoxanthine 9-L-arabinofuranoside, liirodendrin and ursolic acid (Lami *et al.,* 1992). Recipes from this plant alone or in combination with other medicinal plants show appreciable antiviral effects against many viruses which cause infections of the respiratory tract, liver and heart diseases. Obviously, there is no uniform principle of action against RNA viruses. Experimental findings on inhibition showed intense and broad antiphytoviral activity which suggested the mode of action of the glycoprotein inhibitor in medicinal plants. This causes a significantly effective antiviral drug candidtate to be synthesized in the plant cells, which then offers protection against viral infections (Verma and Awatshi, 1979).

Scientific literatures on *Echinacea* species have shown its health benefits with special focus often on immunological effects based on in vitro and in vivo studies. *Echinacea* and its preparations exert immune stimulant activity through three mechanisms: activation of phagocytosis, stimulation of fibroblasts, and the enhancement of respiratory activity that results in augmentation of leukocyte mobility. The production of cytokines (interleukin-1 (IL-1), IL-10) and tumour necrosis factor-α (TNF-α) is stimulated by *Echinacea purpurea* (Burger *et al.,* 1997). Some in vitro studies have proved the antiviral activity of various different preparations of Echinacea. Direct antiviral activity of *Echinacea purpurea* radix was analysed by means of a plaque-reduction- assay. The assay showed that the extract caused a 100% plaque-reduction down to concentrations of 200 ug/ml. The glycoprotein-containing fractions exhibited antiviral activity and decreased plaques numbers by up to 80%. It was concluded that the glycoprotein-containing fractions of *Echinacea purpurea* root extracts are able to induce the secretion of Il-1, TNF a, and IFN a, j3. Futhermore, they are at least partially responsible for the antiviral activity of Fchinacea purpurea radix (Bodinet and Beusher, 1991).

Assessment of antiviral activities of *Phyllanthus* species have shown its extract were most effective when administered either simultaneously with the initiation of virus infection or post infection but not when given pre-infection, and this suggested that the extract may act at the early stage of infection such as during viral attachment and entry as well as viral replication. The evidence from aqueous extract showed strong activity against viruses like HSV1 and HSV2 in vero cells by a process called quantitative polymerase chain reaction (Tan *et al.,* 2013). Western blot and 2D-gel electrophoresis were used to examined protein expressions of treated and untreated infected vero cells. *Phyllanthus amarus* and *Phyllanthus urinaria* showed the strongest antiviral activity against both HSV1 and HSV2 viruses. Their therapeutic actions were proposed to be at the early stage of replication and infection (Tan *et al.,* 2013). The phytochemicals contributed to the antiviral activities of the plant include rutin, gallic acid, caffeolquinic acid, geraniin, corilagen, galloylglucopyranose, digalloylglucopyranoside, trigalloyglucopyranoside, quercetin glucoside and quercetin rhamnoside (Tang *et al.,* 2010; Lee *et al.,* 2011).

The antiviral activity of *Andrographis paniculata* (Burm. f.) extract was determined using Real Time – Polymerase Chain Reaction (RT-PCR) analysis to examine its ability to inhibit virus load in A549 cells transfected with Simian Retro Virus (SRV). The immune-stimulant activity of extract was determined by its ability to enhance lymphocytes cell proliferation using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. The result of this study revealed that ethanol extract of *A. paniculata* inhibited the SRV virus titer and it was not toxic to the cell line. Also, *A. paniculata* extract at low concentration enhanced lymphocyte cell proliferation (Churiyah *et al.,* 2015). These results were also similar to that of Wiart *et al.* (2005) which demonstrated andrographolide viricidal activity against herpes simplex virus 1 (HSV-1) without significant cytotoxicity. Lin *et al.* (2008) also established that ethanol extract *A. paniculata* and andrographolide inhibited Epstein-Barr virus (EBV) lytic proteins during the viral lytic cycle in P3HR1 cells.

Astragalus membranaceus is the dry root of *Astragalus mongolicus* or *Membranous astragalus*. The active compounds isolated from *Astragalus membranaceus* are flavonoids, saponins, and polysaccharides (Kojo *et al.,* 2013). Previous studies showed that the *Astragalus membranaceus* injection showed obvious anti-influenza virus activity. It improved the survival rate of Raw264.7 cells which were infected with influenza virus, enhanced the blocking effect of influenza virus on cell cycle after infection, reduced the MDA content and increased the SOD activity. At the same time, the innate immunity was affected by regulating the expression of TLR3, TAK1, TBK1, IRF3, and IFN-β in the TLR3-mediated signalling pathway, thus exerting its antiviral effect in vitro (Yuxi *et al.,* 2019).

Borreira are genera of *Rubiaceae* widespread in tropical and subtropical Africa. Some species of these genera perform crucial functions in herbal and traditional medicine in Europe, Africa South America, Asia. They are used in the treatment and management of diseases such as respiratory infections, inflammation of eye, malaria, skin diseases, fever, hemorrhage, urinary infections, diarrheal and other digestive problems, headache, and gums. Different biological activities such as antioxidant, antimicrobial, anti-inflammatory, antitumor, anti-ulcer, larvicidal, gastrointestinal, and hepatoprotective have been reported from various extracts *Borreira*. These biological activities have been attributed bioactive compounds from the plant such as terpenoids, flavonoids, with alkaloids and iridoids as the major active principles (Lucia and Jesu, 2012). Phytochemical screening has shown the presence of alkaloid called emetine in *B. verticillata* (Moreira, 1964). And this emetine has been reported to have antiviral effect against SARS-CoV-2 virus in Vero E6 cells with the estimated 50% effective concentration at 0.46 μM when tested alongside with Remdesivir, lopinavir and homoharringtonine in their capacity to inhibit SARS-CoV-2 replication in vitro. Results have also shown that emetine, an anti-protozoal agent, potently inhibits ZIKV and EBOV infection with a low nanomolar half maximal inhibitory concentration (IC50) *in vitro* and potent activity in vivo. Two mechanisms of action for emetine were also identified which are inhibition of ZIKV NS5 polymerase activity and disruption of lysosomal function. Emetine also inhibits EBOV entry (Yang *et al.,* 2018).

It was reported that the Licorice root has been used for ages in ancient Egyptian medicine and also in Indian Ayurvedic medicine and also in traditional Chinese medicine. Licorice root had already been known for its antiviral properties, but researchers noticed that during the SARS outbreak certain groups of people drinking concoctions of traditional Chinese medicine that contained it during the SARS outbreak did not get infected with the virus despite having been exposed to it by having relatives in the same household who were infected. It was this that triggered the initial research (Jakkapong, 2020). The licorice root contains a variety of phytochemicals such as flavonoids like Glycyrrhizin, Liquiritigenin, and Glabridin that also had antiviral activity against the SARS coronavirus. But it is the the class of phytochemicals called triterpenoids also found in licorice root especially glycyrrhizic acid and glycyrrhetinic acid that was found to be extremely potent against the SARS coronavirus (Gerold *et al.,* 2005).

Glycyrrhizin affects cellular signaling pathways such as protein kinase C; casein kinase II; and transcription factors such as activator protein 1 and nuclear factor κB. Furthermore, glycyrrhizin and its aglycone metabolite 18β glycyrrhetinic acid upregulate expression of inducible nitrous oxide synthase and production of nitrous oxide in macrophages (Jeong and Kim, 2002). Preliminary results showed that glycyrrhizin induces nitrous oxide synthase in Vero cells to suppress virus replication (Cinat *et al.,* 2003).

Glycyrrhizin reduced concentrations of P24 antigen and upregulation of chemokines in patients with HIV-1 and chronic hepatitis C virus. However, infrequent side-effects such as increase in blood pressure and hypokalaemia were documented in some patients after many months of glycyrrhizin treatment (Booth *et al.,* 2003).

5.3. Nigerian medicinal plants with anti-inflammatory properties

Inflammation has been implicated in the pathogenesis of COVID-19. It is a physiological/defense response of the host to harmful stimuli such as pathogenic infections, allergens, chemical toxicity or injury to the tissues. If left uncontrolled, inflammatory response can result into deleterious effects such as cancer, cardiovascular dysfunctions, autoimmune diseases and metabolic syndrome (Bagad *et al.,* 2013). Modern medicines like non-steroid anti-inflammatory drugs, steroids, and immunosuppressant have been used to control and suppress inflammatory diseases but with associated unwanted side effects. Thus, the need for natural anti-inflammatory agents with increased pharmacological response and no or lowest degree of adverse effects (Bagad *et al.,* 2013; Oladele *et al.,* 2017) which is obtainable in medicinal plants. *Curcuma longa* (Turmeric) is one of such medicinal plants, the most essential metabolite of turmeric is curcumin and its responsible for its anti-inflammatory properties (Jurenka, 2009; Oladele *et al.,* 2020a). Many clinical studies have been carried out to prove the anti-inflammatory effect of curcumin in diseases such as rheumatoid arthritis and reduced its clinical manifestation such as joint swelling and morning stiffness when compared with standard drug, phenylbutazone (Deodhar *et al.,* 1980). Curcumin also offers beneficial effects in treatment of ulcerative colitis (Hanai *et al.,* 2006), irritable bowel syndrome (IBS) (Bundy *et al.,* 2004), psoriasis (by the selective prohibition of phosphorylase kinase) (Heng *et al.,* 2000) and acts as a reducing agent to delayed graft rejection (DGR) after kidney transplant surgery (Shoskes *et al.,* 2005).

Similarly, *Zingiber officinale* (ginger) has been shown to have potent anti-inflammatory effects. Ginger powder has had ameliorative effect in musculoskeletal and rheumatism patients through inhibiting cyclooxygenase and lipoxygenase pathway in synovial fluid (Srivastava and Mustafa, 1992). Shimoda *et al.* (2010) reported the anti-inflammatory potential of *Zingiber officinale* in acute and chronic inflammation models. The result showed that ginger possesses effective inhibitory effects on acute and chronic inflammation, and suppressed activation of macrophage via anti-inflammatory pathway. *Zingiber officinale* have been reported to decrease serum level of TNF-α and high-sensitivity C-reactive protein (hs-CRP) in type 2 diabetic patients (Mahluji *et al.,* 2013). Other medicinal plants with anti-inflammatory properties that could offer protection against coronavirus-induced inflammation include *Combretum mucronatum, Ficus iteophylla, Moringa oliefera (Moringaceae), Schwenkia americana, Alafia barteri, Dichrostachys cinerea, Capparis thoningii Schum, Cassia occidentalis (Caesalpiniaceae), Asparagus africanus,* and *Indigofera pulchra.*

5.4. Nigerian medicinal plants with immune-boosting properties

Survival of homo sapiens against traumas from foreign pathogenic microorganisms depend on the status of their immune defense mechanisms. It is well established that the immune system safeguards the host against attacks from infective microorganism such as virus, allergic or toxic molecules (chaplin, 2010). Once a defect occurs within the

immune system, it results in response impairment against infectious agents. The cause of impairment (immunosuppression) can be either intrinsic (inherited) or extrinsic and referred to as primary or secondary immunodeficiency, respectively (Abbas *et al.,* 2016; Chinen and Shearer, 2010).

Immunomodulatory agents are non-specific compounds that work without antigenic specificity similar to the adjuvants that are associated with some vaccines (Gupta *et al.,* 2010; Liu *et al.,* 2016). Medicinal plants and natural products with immunomodulatory activities have been employed in traditional medicine and phytomedicine. They improve the humoral and cell-mediated immunity and mediate the initiation of "non-specific" immune responses which include the induction of macrophages, natural killer cells, granulocytes, and the complement system. These processes trigger the synthesis and release of diverse molecules such as cytokines which participate in the improvement and modulation of the immune responses (Gummet *et al.,* 1999; Vigila and Baskaran, 2008). Put together, the entire series of reactions serves as a substitute for the present chemotherapy for immunodeficiency offering protection against infections caused by various pathogenic agents (Sultana *et al.,* 2011).

Plants that are copious carotenoids, vitamin C or flavonoids can act as an immune-stimulant. Medicinal plants that are rich in flavonoids may also possess anti-inflammatory action. They induce interferon production, enhance the activity of lymphocytes and increase phagocytosis. Examples of these immunomodulatory plants include garlic which remarkably enhance immune system activities. Garlic as an immune system booster has been found to exert an immune-potentiating effect by stimulating natural killer cell activity. Some studies strongly present garlic as a promising candidate as an immune modifier, which preserves the homeostasis of immune functions (Kyo *et al.,* 2001) because it has a higher concentration of sulfur combinations which are responsible for its therapeutic effects.

Other medicinal plants used by traditional healers as immune-boosters are garlic (*Allium sativum*), guava leave (*Psidium guajava*), lemongrass (*Cymbopogon citratus*), cinnamon (*Cinnamomum zeylanicum*).

5.5. Nigerian medicinal plants with antioxidant properties

Numerous plants that grow in Nigeria are well-known to have countless therapeutic potentials that could be due to their antioxidant properties (Oladele *et al.,* 2020b,c). Plants are known to be the main source of natural antioxidants in the form of phenolic compounds (phenolic acids, flavonoids and polyphenols). Most of the anti-inflammatory, digestive, neuroprotective, hepatoprotective and nephroprotective drugs derived from natural origin have been reported to have antioxidant/radical scavenging mechanism as part of their activity (Oladele *et al.,* 2020b,c; Oyewole *et al.,* 2017). The ingestion of natural antioxidants has been associated with the reduced risk of cancer, cardiovascular disease, diabetes and other diseases associated with ageing (Ajayi *et al.,* 2017). Hence, interest has been increased for finding antioxidants of plant source, which are safe and suitable for use in food and/or medicine. In that regard, due to the increasing numbers of diseases ravaging the continent of Africa and of course the world at large, there has been an increased interest in finding antioxidants from plant source, which are safe and suitable for use in food and/or medicine. For that reason, many indigenous plants were selected for their significant antioxidant activities.

5.5.1 Antioxidants from plants

The use of artificial and natural food antioxidants regularly in medicine and foods particularly those having fats and oils to shield the food from oxidation. Butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA) are some of those artificial natural food antioxidants which have been used expansively in food, cosmetics, and in many healing products industries. Nevertheless, due to the effect of high temperatures which bring instability in them, high volatility, synthetic antioxidant's carcinogenic behaviour, users dispositions steered to shift in respect to the producers or manufacturers from man-made to natural antioxidants (Papas, 1999).

Considering the increasing numbers of risk issues of humans to various harmful diseases, this brought about the need for the use of natural constituents present in dietary and medicinal plants as curative and helpful antioxidants. A vast number of indigenous plants in Nigeria has been reported to reveal antioxidant activity, including *Allium sativum, Zingiber officinale, Crocus sativus, Dodonaea viscose, Barlerianoctiflora, Anacardium occidentale, Datura fastuosa, Caesalpiniabonducella* and many more as in table 3. Several of these antioxidants from plants has been shown to be an active oxygen scavengers or free radical, with has no harmful effects on human body (El makawy *et al.,* 2020). For detrimental effects of reactive oxygen species to be stopped, plants have shown a powerfully in-built enzymatic and non-enzymatic scavenging capacity. These Enzymes included dehydroascorbate reductase (DHAR), catalase (CAT), glutathione S-transferase (GST), superoxide dismutase (SOD), glutathione peroxidase (GPX), ascorbate peroxidase (APX), glutathione reductase (GR), monodehydroascorbate reductase (MDHAR) and peroxidases (POX), while non-enzymatic compounds include tocopherols, ascorbate (AsA), glutathione (GSH), and carotenoids.. In plants, any form of rise in the levels of antioxidants has been established to exhibit a better resistance to different types of environmental stresses (Hasanuzzaman *et al.,* 2011).

Table 3. List of medicinal plants with antioxidant properties

S/N	Name of plants	Common English Name	Nigerian names	Family	Plant part used
1	*Zingiber officinale*, Ginger Zingiberaceae Rhiz□me Tohma *et al.*, 2017	Ginger	Atale in yoruba	Zingiberaceae	Rhizome
2	Cucurma longa	Turmeric	Gangamau (Hausa) or Atale pupa (Yoruba) or Boboch (Igbo)	Zingiberaceae	Rhizome
3	*Allium sativum* Garlic Alliaceae Bulb Elost	Garlic	Aayu in Yoruba Ayo-ishi in Igbo and Tafarunua in Hausa	Alliaceae	Bulb
4	*Cannabis sativa L*	Hemp/marijuana	Igbo in Yoruba	cannabaceae	seed
5	Ageratum conyzoides	Goat weed	Imi esu in Yoruba	asteraceae	leaves
6	Ficus exasperata	Ficus plants	Epin in Yoruba	Moraceae	leaves
7	Telifarria occidentalis	Fluted plumkin	Ugwu in Igbo	Curcurbitaceae	leaves
8	Vernonia amygdalina	Bitter leaves	Ewuro in Yoruba ,		Leaves
9	*Garcinia kola*	Bitter kola	Orogbo in Yoruba, Adu/aku-inu and Namiji goro in Hausa	Clusiaceae	*seeds*
10	Ocimum basillicum	Basil/ scent leaf	Efirin in Yoruba Nchanwu in Igbo and Dadoya in Hausa	Lamiaceae	leaves
11	Psidium guajava	guava	Psidium	Myrtaceae	*leaves*
12	xylopia aethiopica	Ethiopian pepper	Eeru/ Erunje in Yoruba, Uda in Igbo and Kimba in Hausa	Annonaceae	seeds
13	Parkia bigglobossa	Locust bean	Iru in Yoruba, ogiri in Igbo and dadawa in Hausa	Papilionacea	seeds
14	Spondia mombi	hogplum	Iyeye in Yoruba,	Anacardiaceae	leaves
15	Musa paradisiaca)	Plantain	Ogede Agbagbain Yoruba, Abrika in Igbo and ayaba in Hausa		fruits
16	Azadirachta indica	Neem tree	Dongoyaro in Yoruba, Atu yabasi / ogwu akom in Igbo and Maina in Hausa	Meliaceae	leaves

5.5.2 Antioxidants from fruits and vegetables

Consistent eating of dietary foods like fruits and vegetables is well documented to have potential in the management of various chronic ailments affecting human in Africa. These supplements of antioxidant are directly being obtained from fresh fruits and vegetables, which contain a vast quantity of alkaloids, flavonoids and antioxidant complements which can take part in the defense mechanisms against different cardiovascular ailments including different types of cancers and many health problems (Oladele *et al.,* 2020a,b; Ajayi *et al.,* 2017).

Documented reports have revealed that a diet with rich antioxidants has an great impact on health in many ways that vast variety of plants and plant parts have been established to contain a large amount of antioxidants such as strawberries, blueberries, grapes, spinach, plums, broccoli flowers, alfalfa sprouts and many more with antiviral properties. Citrus fruits like lemons, oranges etc. also contain a high quantity of natural antioxidants, most significantly vitamin C (Al-snafi, 2015; Oladele *et al.,* 2020d).

However, there are some new and unique antioxidants like derivatives of flavonoids and p-coumaric acid that have been found in spinach. NAO- a spinach-derived natural antioxidant that contains derivatives of flavonoids and p-coumaric acid playing a significant role in the prevention of prostate cancer. Recently, it has also been established that fruits like araticudomato, pindo palm and jackfruit are good sources of vitamin C, vitamin A and other phenolic compounds; analysis on these fruits is being carried out to create the genetic, chemical or biological variations so as to enhance the antioxidant potential of the same (Shebis *et al.,* 2013; Oladele *et al.,* 2020d).

5.5.3 Neem

Neem (*Azadirachta indica*) as it is fondly called is a tree inside the family of *Meliaceae*. Neem is also known as 'Dongoyaro in Yoruba, Atuyabasi /ogwuakom in Igbo and Maina in Hausa word. Seeds, oil, roots, roots, bark, leaves and seeds as parts of the tree are somehow bitter and contain compounds with a proven potential as an anti-inflammatory, anti-ulcer and antifungal, antiviral, antiplasmiodal, cytotoxic, antipyretic anti-microbial and antiseptic in nature (Emran *et al.,* 2015). The incorporated chemical constituents with many biologically energetic compounds that can be extracted from neem include flavonoids, alkaloids, carotenoids, triterpenoids, phenolic compounds, steroids and ketones. Azadirachtin is validly an incorporation of seven isomeric compounds which was labelled as azadirachtin A-G and azadirachtin E is more efficient (Verkerk and Wright, 1993).

5.5.4 Ginger

Ginger (*Zingiber officinale* Roscoe) is an important tropical valued medicinal herb that is found globally as a spice and used for healing and therapeutic proposes. Ginger belongs to the *Zingiberaceae* family which has been reported to contain over 1250 species in fifty genera, together with 4 other families which is positioned in the order Zingiberales and class Monocotyledones (Berg, 1997). It has been reported to have many vital pharmacological actions to treat various types of diseases by the actions of antiemetic, antioxidant, anti-cancer, anticoagulant property, anti-inflammatory, and soon. Clinical studies have documented its efficacy in treatment of post-operative vomiting and vomiting of pregnancy.

The pungency characteristics of ginger are said to be due to gingerols and shogaols found in them. It has been established that the main components of ginger are the aromatic essential oils, the antioxidants and the pungent oleo-resin. Pungent compound has been identified as the phenylalkylketones, known as gingerols, shogaols, and zingerone (Rajesh and Subha, 2018). All main active constituents of *Zingiber officinale* Roscoe, such as zingerone, gingerdiol, zingibrene, gingerols and shogaols, have been proven to have anti-oxidant activities (Chrubasik *et al.,* 2005), and this antioxidant activity in ginger is due to the existence of polyphenol compounds like (6-gingerol and its derivatives). The main active constituents of ginger are Volatile oil (zingiberene, curcumene, farnesene, zingiberol, D-camphor), Shogaols, Diarylheptanoids, Gingerols, Paradol, Zerumbone, 1-Dehydro-(10) gingerdione, Terpenoids and Ginger flavonoids (Baliga *et al.,* 2012); these compounds give ginger its characteristic hot sensation.

5.5.5 Ageratum conyzoides

The genus *Ageratum* is derived from the Greek words *'ageras'* meaning non-aging which refers to long life-time of plant, and the species epithet *'konyz'* is the Greek name of *Inula helenium* which resembles the plant. *Ageratum conyzoides* Linn with a Family Asteraceae is an annual herb with an extensive history of traditional medicinal use in the tropical and sub-tropical regions of the world, commonly known as Billy goat weeds. The stems and leaves of the plant are fully covered with fine white hairs (Adewole, 2002).

5.5.6 Monoterpenes and sesquiterpenes

About 51 constituents have been reported to have been obtained from the analysis of the Ageratum oil sample from Nigeria which makes it the highest to include 20 monoterpenes (6.6%) of which 1% contains sabinene, 1.6% contains β-pinene and β-phellandrene, 2.9% contains 1.8-cineole and limonene, 0.6% contains terpenen-4-ol and 0.5% contains α-terpineol and further found 20 sesquiterpenes (5.1%), and that of single substance were found to be in traces approximately 0.1%. Indian Ageratum oil from goat weed is found to contain 5.3% ocimene which was found in traces from Nigerian plant, 6.6% α-pinene, 4.4% eugenol and 1.8% methyleugenol (Rao and Nigam, 1973). The major sesquiterpenes are beta-caryophyllene, 1.9 to 10.5% from an oil sample obtained from Cameroon and 14 to 17% in a Pakistani oil sample. Another sesquiterpene, δ- cadinene occurred in approximately4.3% in the oil received from Indian plants (Rao and Nigam, 1973). Sesquiphellandrene and caryophylleneepoxide have been obtained in 1.2 and 0.5%, respectively from leaves (Ekundayo *et al.,* 1988). The plant has been examined on the basis of the scientific in vitro, in vivo or clinical evaluations to have possessed the major pharmacological activities that includes analgesic activity, antimicrobial activity, anti-inflammatory activity, spasmolytic effects, gamma radiation effects, anti-cancer and radical scavenging activity, antimalarial activity and others activities based on the listed bioactive earlier discussed (Singh *et al.,* 2013).

5.5.7 Guava

Guava has been reported to have a high number of antioxidants and anti-providing nutrients which are essential not only for proper functioning of life but also help to control the free radical activities. It also has a variety of phytochemicals which are useful for human health like diabetes, obesity and high blood pressure. There are two common methods by which antioxidants neutralize free radicals that are DPPH and FRAP assay. Extracts of guava in water and organic solvents have a large quantity of antioxidants which can stop the oxidation reaction. Pink guava also has a high antioxidant activity (Musa *et al.,* 2011). In fruits, the most abundant oxidants are polyphenols and ascorbic acid. The polyphenols are mostly flavonoids and are mainly present in glycoside and ester forms. The free elagic acid and glycosides of apigenin, myricetin, Quercetin, quercetin-3-O-glucopyranoside and morinare were found to be present in guava, and the presence of all these bioactives makes it a potent antioxidant (Nantitanon and Okonogi, 2012).

5.5.8 Allium sativum

Garlic is well accepted as a spice around the Africa continent and Nigeria, and it has been proven to act as a herbal remedy for the prevention and treatment of several diseases. It has also been reported to have an anti-bacterial, anti-viral, anti-protozoal, anti-cancer, anti-fungal, immunomodulatory, anti-inflammatory, hypoglycemic and

hypocholesterolemic potentials (Rehman and Munir, 2015), Allicin being the principal compound in aqueous garlic extract or raw garlic homogenate which is responsible for the cholesterol-lowering effect in humans and animals. When garlic bulb is crushed, the enzyme allinase activates alliin, a non-protein amino acid present in the intact garlic, to produce Allicin (Chowdhury *et al*., 2002). The phytochemical screening of garlic has also been reported to have chemical compounds such as saponin, tannin, carbohydrates, cardio glycoside, alkaloids, flavonoid, phlobatannin and glycoside (Pavni *et al*., 2011).

5.6 Nigerian medicinal plants that enhance membrane integrity

The antiviral mechanisms of different extracts preparations of many vegetal products have been through the disturbance of cell membrane integrity, thereby increasing the membrane permeability, and invariably causing the leakage of the RNA or DNA of the virus (Bouyahya *et al.,* 2019), whereas fortifying or strengthening the cell membrane with nutraceuticals that offer protection to the integrity promises to be a functional approach to preventing invasion by known viruses and by extension the novel SARS-COV-2. Among the protective vegetal natural products reported to preserve or enhance cell membrane integrity are the following, some of which also have antiviral activities against respiratory viruses causing flu (gripe), while a few others have been studied against the earlier members of the coronavirus family such as the MERS and SARS. Many bioactive compounds from the vegetal sources have been shown to interact with the surface of cell membranes to prevent viral entry, specifically binding to membrane carrier proteins, regulating ion channels, modulating enzymes, influencing the order of the membrane lipid bilateral to elicit their medicinal activities. While there exists a plethora of membrane-modulating bioactive vegetal components, nutraceuticals, and phytochemicals, a variety of peptides are also secreted by plants with lipophilic properties that enhance their ability to pass across cell membranes (Tsuchiya, 2015). Many of these structural compounds have been studied to decipher their mechanistic transportation across cellular, intracellular, and artificial membranes, as well as their effects on gene expression within the nucleus following possible participation in signalling pathways. Many of the structure-activity relationships have often been described by several authors vis-a-vis how they affect the fluidity, micro-viscosity, order, elasticity, and permeability of both biological and artificial membranes.

Among these are *Allium cepa* of the Amaryllidaceae family, rich in quercetin, which inhibits the SARS main proteases, 3CLpro and PLpro, and the Middle Eastern Respiratory Syndrome virus (MERS) 3CLpro protease, *in vitro* (Mani *et al.,* 2020). It has also been proposed that the modulation of cellular unfolded protein response (UPR) and autophagy signalling being important to coronaviruses to complete different stages of the viral life cycle during infection, if perturbed by quercetin and resveratrol through the mitochondrial permeability transition pores (MPTP) and NLRP-3 inflammasome pathways, may have anti-coronavirus effects (Nabirotchkin *et al.,* 2020). *Artemisia annua* (qinghao) is a plant of the Asteraceae family from which artemisinin is extracted. Together with its derivative, dihydroartemisinin, it has shown promise against parasites and viruses, including the human cytomegalovirus, *in vitro* (Flobinus *et al.,* 2014). The plant has also shown potent anti-HIV (Lubbe *et al.,* 2012), and anti–SARS-CoV effects (Li *et al.,* 2005). The leaf and bark of *Azadirachta indica* L belonging to the family *Meliaceae* showed antiviral activity against herpes simplex virus type-1 infection as a potent entry inhibitor (Tiwari *et al.,* 2010). Some of its bioactive compounds also boost the immune system by upregulating polymorphonuclear (PMN) leukocytes, macrophage activity, and lymphocyte proliferation response (SaiRam *et al.,* 1997). The aqueous extract of the branches was found to be effective against the Newcastle disease virus in embryonated SPF chicken eggs and SPF chickens. The plant is known to be rich in salanin, nimbin, azadirone, and azadirachtins (Ong *et al.,* 2014) and show potent antiviral activities (Sarah *et al*., 2019).

Camellia sinensis of the family Theaceae is rich in catechins and flavonoids [epigallocatechingallate] (EGCG), epicatechin (EC), epigallocatechin (EGC) and epicatechin gallate (ECG)] (Baibado *et al.,* 2011), and alkaloids (caffeine, theobromine, theophylline. They are known as anti-inflammatory and antioxidant compounds (Mahmood *et al.,* 2016) that efficiently relieve chronic obstructive lung disease (COPD), while at the same time reducing the risk of lung cancer and type 2 diabetes, which can constitute serious underlying conditions that predispose to grave clinical outcomes for the SARS-COV-2. *Chamaemelum nobile* contains apigenin, a dietary flavonoid indicated for inflammation, cold, and asthma (Kim *et al.,* 2014) based on its antioxidant, anti-inflammatory, and properties (Cardenas *et al.,* 2016). The bark of *Cinchona officinalis* (quina-quina), *Rubiaceae* is rich in quinine ((8S, 9R)-6′-methoxycinchonana-9-ol; (αR)-α-(6-methoxy-4-quinoyl)-α-[(2S, 4S, 5R)-(5-vinylquinuclidin-20yl)] methanol), which has been in use for the treatment of malaria as far back as 1632 (Baird *et al.,* 1996). It was shown to have therapeutic effects against influenza virus infections in animal studies (Seeler *et al.,* 1946). *Cinnamon verum*, of the genus Cinnamomum (Family Lauraceae), contains proanthocyanidin and (epi)catechins. It is known to have antiviral, antibacterial, antioxidant, anti-inflammatory, and immunomodulatory properties (Kumar *et al.,* 2019; Polansky and Lori, 2020). Its extract has anti-RNA viral effects and inhibited the wild type SARS infection, *in vitro* possibly blocking cell entry via endocytosis (Zhuanga *et al.,* 2009). *Citrus aurantium /Sinensis* (Rutaceae) peel, containing hesperidin and vitamin C, has antioxidant and antiviral activities (M'hiri *et al.,* 2017). The flower extract of *Citrus aurantium* protected cardiomyocyte cell membrane in Isoproterenol pre-treated male rats (Keshtkar *et al.,* 2017). *Curcuma longa* (turmeric) contains curcumin which, like pterostilbene, interacts with the C-terminal of S1 domain with significant binding energies (Jitendra *et al.,* 2020). *Cymbopogon citratus* Stapf of the Poaceae family possesses anti-allergic property indicated for the treatment of asthma by limiting the infiltration of inflammatory cells into the lungs (Santos *et al.,* 2015).

Euphorbia hirta Linn. is a common plant used to treat asthma and other respiratory diseases including chronic flu, including asthma and bronchitis due to its anti-inflammatory and antiasthmatic activities (Kumar *et al*., 2010). *Piper nigrum* is another plant whose seeds have been indicated for the treatment of pharyngitis arising from flu and viral infection (DeFilipps and Krupnick, 2018). The antiviral action has been attributed to the ability to fracture, disrupt, and completely collapses the plasma membrane of pathogens, thereby increasing cell permeabilization and disrupting membrane integrity (Zou *et al.*, 2015).

Fragaria ananassa of the rose family (Rosaceae) contains fisetin (3,3′,4′,7-tetrahydroxyflavone), a pigment flavonol is also abundant in grapes, apples, onions, and cucumbers. It is also a senolytic agent, as it selectively induces death of senescent cells to alleviate age-related diseases (Yousefzadeh *et al.,* 2018). Fisetin, quercetin, isorhamnetin, genistein, luteolin, resveratrol, and apigenin have been reported to interact with both S 1 and S2 domains of the spike protein of SARS-COV-2 with appreciable binding energies thus disrupting viral attachment and internalization into the host (Jitendra *et al.*, 2020).

Garcinia kola Heckel (Clusiaceae), known to contain the biflavonoid kolaviron, is popular for the treatment of malaria, hepatitis, neurodegenerative disease, male sexual dysfunction, and immune-destructive diseases (Farombi *et al.,* 2019; Uko *et al.,* 2001). It also protects against the oxidation of lipoprotein (Farombi *et al.,* 2008). *Garcinia kola* is also used to relieve cold and cure laryngitis (Manourova *et al.,* 2019). *Phyllanthus emblica L. (Euphorbiaceae),* contains appreciably small molecular weight tetra-O-galloyl-β-d-glucose, an anti-HBV bioactive compound (Xiang *et al.,* 2010), while *Eclipta prostrata* L. (Asteraceae) as well as peanut shells, green leafy vegetables such as spinach contain the anti-inflammatory and antioxidant luteolin (Arunachalam *et al.,* 2009). These two bioactive compounds were reported to be able to bind strongly to the S-protein of SARS-CoV. By this mechanism, they were able to delay or prevent viral entry into host cells via the membrane receptors (Yi *et al.,* 2004).

Zanthoxylum zanthoxyloides Lam. (Rutaceae), contains tortozanthoxylamide (N-(isobutyl) 3, 4-methylenedioxy cinnamoyl amide) (Dofuor *et al.,* 2019) which has anti-inflammatory, antitrypanosomal and antispasmodic properties (Guendehou *et al.,* 2018). *Zingiber officinale* Roscoe, of the Zingiberaceae family, contains gingerols which showed antiviral properties against the human respiratory syncytial virus on HEp2 and A549 cell line (Chang *et al.,* 2013). The anti-inflammatory and antioxidant properties have also been described in dopaminergic neurons in Parkinson's disease models (Park *et al.,* 2013), and other cell types. Oleoresin, gingerol, shogaol, and zingerone from ginger increased the percentage of CD3+CD4+ thus improving cellular and humoral immune response in HIV patients (Tejasari, 2007). Ginger also alleviated bronchopulmonary dysplasia and inflammation induced by hyperoxia and intrauterine LPS in a chorioamnionitis rat model (Cifci *et al.,* 2018).

Many of these vegetal products promote bronchodilation, thus relieving fluid in the lungs, preventing lung fibrosis or plague formation, naso-/trachea-pharyngeal clogging, alleviating (dry) cough, chest pain, and difficulty in breathing. Overall, these novel chemical entities can be explored as formulations or cocktail containing promising druggable agents against the novel SARS-CoV-2 for blocking receptor binding and/or viral phagocytotic internalization of the SARS-CoV-2 following the binding of the S- (spike) protein to the angiotensin-converting enzyme 2 (ACE-2) receptors, and its associated proteases such as the transmembrane protease serine 2 (TMPRSS2), Cathepsin L (CTSL) and Cathepsin B (CTSB), which are ubiquitously present in almost all of the human cells, the existence of which does not indicate that the virus can always infect the cells that express them.

5.7 Nigerian medicinal plants used in the treatment of respiratory infections, cough, and flu

Phytochemical-based treatments for respiratory infections and related syndromes have been in use in many nations in Africa for many decades (table 4). Respiratory infections particularly pneumonia, asthma, tuberculosis, sinusitis, and rhinitis represent the main factors of morbidity and mortality in both developed and developing nations of the world (Ait-Khaled *et al.,* 2007).

Table 4. Nigerian recipes for the treatment of respiratory infections, cough and flu

Recipe 1. Containing eight plants	Recipe 2. Containing sixteen plant materials
Tetrapleura tetraptera Leguminosae bark, root and leaf	Canarium scheweinfurthii called Awogba or Gbogbonise in Yoruba (part to use - Root)
Azadirachta indica A. Juss (Meliaceae) bark, root and leaf	Axonopus compessus (Poaceae) Guil & Perr. (Part to use - Stem)
Heliotropium indicum Linn. (Boraginaceae) root	Anogeissus leiocarpus, (D.C) Guil.L. & per. (Part to use -Stem).
Opuntia dillenii Haw (Cactaceae)	Capsicum annum, Linn., called Ata Ibile in yoruba (part to use -Fruit).
Khaya grandifoliola (Meliaceae)	Curculigo pilosaq, Schum.& Thonn, Engl., called Epakun in yoruba (part to use Rhyzome)
Allium sativum	Gladiolus daleni, Van. Geal called Isu Baka in Yoruba. (part to use -Rhyzome)
Capsicum frutescens	Allium ascalonicum, Linn. called Alubosa Elewe in Yoruba (part to use- Bulb)
Turmeric	Dalbergienna welwitshii, white and red species, Bal (part to use- Root)
	Solanum luberosum, L.cv called isu arinda in yoruba(part to use- tuber)
	Sphenostylis stenocarpa called Ewa sese in yoruba (beans)
	Vigna sinensi called ewa ikakure in yoruba (beans)
	Khaya grandifoliola,C.D.C (part to use - bark)
	Anhodersta djalonensis, A. Cher., called Sapo in Yoruba (part to use -bark).
	Cassia alata also called Ringwork plant is called Asunrin dudu in yoruba (root)
	Citrullus colocynthis, Linn Schard, called bara in Yoruba (fruit).
	Camphor called kafura pelebe in Yoruba Iseta (part used root).
	Local substitute salt called Obuotoyo in Yoruba,

Anogeissus leiocarpa belonging to the family of *Combretaceae* is also called "Idi Ayin" among the Yoruba people of Nigeria. It is a deciduous plant indigenous to the savannas of tropical Africa. It is also referred to as African birch. *A. leiocarpa's* root and bark are used traditionally in the treatment of cough, gonorrhea, asthma, tuberculosis.

Allium sativim belonging to the Amaryllidaceae family, known as Aayu among the Yoruba people is also popularly called garlic among the three tribes of Nigeria. It is being used as a food supplement and in folklore medicine for several centuries; it is the most researched medicinal plant (Milner, 1996). Garlic has been used useful to the treatment of a wide range of diseases such as coronary heart disease, high blood pressure, heart attack, high cholesterol, and hardening of the arteries due to its biologically active component allicin and its derivative (Mikaili *et al.,* 2013). It has also been reported that these bioactive constituents are responsible for the antiviral, antibacterial, anti-fungal, and anti-protozoa activities of *A. sativum*. According to Amagase (2006), garlic has also been used to prevent different kinds of cancer including breast cancer, bladder cancer, colon cancer, stomach cancer, prostate cancer, rectal cancer, and lung cancer, and that it could be useful in the treatment of Cardiovascular disease including Antilipemic, antihypertensive, anti-atherosclerotic, an enlarged prostate, diabetes, osteoarthritis, cold and flu, and so on. It is also effective for building the immune system, preventing tick bites, preventing and treating bacterial and fungal infections.

Azadirachta indica is a member of the Meliaceae family of mahogany usually called neem or Indian lilac (USDA, 2020). It is typically grown in tropical and semi-tropical regions. The Siddha and Ayurvedic practitioners believed that Neem plant has anthelmintic, antifungal, antidiabetic, antibacterial, contraceptive, and sedative properties (Agrawal, 2013, Ismail *et al.,* 2020). The plant is believed to be the main constituent of Unani, Ayurvedic, and Siddha medicine in the treatment of skin diseases (Tamilnadu, 2012). Short-term use of neem is safe in adults but long-term use may harm the kidneys or liver in small children. Neem oil has been documented to enhance healthy hair, detoxify the blood, ameliorate liver function, and balance blood sugar levels (Tamilnadu, 2012).

Tetrapleura tetraptera belonging to Fabaceae family is also called Aidan in Yoruba, Uhio in the Igbo language of Nigeria is a species of flowering plants in the pea family which is native to Western Africa (Margaret, 1988); it is also called Prekese or Soup Perfume in the Twi language of Ghana (Osie-Tutu *et al.,* 2010). In Tropical African traditional medicine, its fruit is frequently used for the treatment and management of some of human diseases such as hypertension, diabetes mellitus, hypertension, epilepsy, arthritis, and other inflammatory conditions, schistosomiasis, asthma, postpartum (after delivery) recovery, as immune system booster (Ojewole and Adewumi, 2004). The pod has been reported to contain polyphenol, flavonoid, tannins, and alkaloids which are antioxidants that protect the body from free radicals and oxidative damages responsible for aging.

Khaya grandifoliola belonging to the Meliaceae family is popularly called Oganwo in Yoruba native of Nigeria, and also called Benin Mahogany, African mahogany; Senegal mahogany is a tall woody tree, a medicinal plant endemic to Nigeria (Hutchinson and Dalziel, 1978). It is also found in Benin, the Democratic Republic of the Congo, Ivory Coast, Ghana, Guinea, Sudan, Togo, and Uganda. It is threatened by habitat loss. Traditionally, it has been reported to have been used in the form of concoction for the treatment of convulsion, cough, stomach ache, fever, threatened abortion, rheumatism, dermatomycosis, and malaria fever in Nigeria (Odugbemi *et al.,* 2007; Uroko *et al.,* 2020).

Heliotropium indicum known in English as Indian heliotrope is also called Agogo Igun in Yoruba native of Nigeria; it is an annual plant considered as a weed by

farmers, but as a valuable medicinal plant by traditional medicine practitioners. The plant is native to Asia. In Natore district, Bangladesh, a folk medicinal practitioner used the root for blood purification and to treat infection (Akhter *et al.*, 2016). The sap is applied to gumboil, to clean ulcers, and to cure eye infections in Nigeria and Ghana. It is also used to treat warts, inflames, and tumors. Throughout tropical Africa, it is used as an analgesic to ease rheumatic pain, as a diuretic and to treat numerous skin problems including yaws, urticaria, scabies, ulcers, eczema, impetigo. A decoction of the whole plant is used to treat thrush, diarrhea, diabetes, venereal diseases, and frequent excretion of urine (Burkill, 1935).

Opuntia dillenii belonging to the Cactaceae family of the genus Opuntia grows in dry and desert environments to a height of about 1 to 1.8 meters. It is a great medicinal herb and a shrub. The plant has suggested that the fruit may be useful as a medication for gonorrhea, whooping cough, and constipation, as well as controlling the bile secretion, spasmodic cough, and expectoration, while the leaves of the plant have been reported to have been used as a medication for wound and inflammation as well as a treatment for ophthalmic disorders (Raj, 2015; Kirtikar, 2006). Among the reported diverse pharmacological activities of this plant, anti-oxidant, anti-inflammatory, anti-tumor, neuroprotective, hepatoprotective, hypotensive, and immuno-modulation are the basis of the application of this plant in the preservation and treatment of some chronic diseases. Scientific studies on *Opuntia dillenii* can help better understand its pharmacological mechanism of action to elucidate its traditional uses and to identify its potential new therapeutic applications.

Capsicum frutescens is a member of the Solanaceae family with five domesticated species: *C. annuum, C. baccatum, C. chinense, C. frutescens*, and *C. pubescen* (Moscone *et al.*, 2007). They are normally very small and pungent. The fruit usually grows pale yellow and matures to bright red, but can also be other colors. This plant has been reported to have used in traditional medicine for the treatment of rheumatoid arthritis, osteoarthritis, digestion problems, and conditions of the heart and blood vessels. Pepper is one of the most important plants that have been used as medicine for a long time in different countries and civilizations. In old civilizations, it was used by the Mayas for treating asthma, coughs, and sore and by the Aztecs to relieve toothaches (Bosland, 1996). Dietary antioxidants have protective role against many diseases such as cancer, diabetics, cardiovascular, and anemia. Vitamins E, C, and β-carotene are important as protective antioxidants, and peppers are rich in vitamin C and E as well as carotenoids and xanthophylls (Perucka and Materska, 2007; Mateos *et al.*, 2013).

Turmeric is a medicinal plant of *Curcuma longa* which belongs to the *Zingiberaceae* family. It is popularly referred to as Atale or Ajo among the Yoruba speaking parts of Nigeria (Priyadarini, 2014; Oladele *et al.*, 2020a). Turmeric is a perennial plant. It is grouped among the rhizomatous and herbaceous plants. The rhizomes of *Curcuma longa* plants are gathered each year either for propagation in the next season or for consumption. The rhizome of *C. longa*, Linn has been reported to have many therapeutic activities such as anti-inflammatory, anti-diabetic, hepatoprotective, hypolipidemic, anti-diarrhoeal, anti-asthmatic, and anti-cancerous drug (Sastry, 2005; Sharma, 2006; Chunekar, 2010; Pandey, 2002; Oladele *et al.*, 2020a).

Honey is a sweet, viscous food substance made by honey bees and some related insects (Crane, 1990). Bees produce honey from the sugary secretions of plants (floral nectar) or secretions of other insects (such as honeydew), by regurgitation, enzymatic activity, and water evaporation. Bees store honey in wax structures called honeycombs (Crane, 1990). The variety of honey produced by honey bees (the genus Apis) is the best-known, due to its worldwide commercial production and human consumption (Al-kafaween *et al.*, 2020). Honey is collected from wild bee colonies, or hives of domesticated bees, a practice known as beekeeping or apiculture. Honey gets its sweetness from the monosaccharides: fructose and glucose, and has about the same relative sweetness as sucrose (table sugar) (NHB, 2012). The antimicrobial activity of honey against microorganisms such as bacteria, viruses, fungi, and protozoa has been reported in many scientific literatures (Carter *et al.*, 2016).

6. Conclusion

COVID-19 is a highly infectious and severe acute respiratory disorder caused by a pathogenic virus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Its clinical manifestations include fever, fatigue, cough, shortness of breath, and other complications. The mode of actions of SARS-CoV-2 includes hyper-inflammation characterized by a fulminant and fatal hyper-cytokinaemia with multi-organ failure; immunosuppression; reduction of ACE2 to enhance pulmonary vascular permeability and damage the alveoli and activated by ORF3a, ORF3b, and ORF7a via JNK pathway which induces lung damage. These mechanisms of action of the virus can be mitigated by combined therapy of the medicinal herbs based on their pharmacological activities. Furthermore, plant materials and natural products have been very effective in the treatment of symptoms related to COVID-19. Experimental research is needed to prove the efficacy of these medicinal plants and their product against COVID-19. As a recommendation, since COVID-19 is a multifactorial clinical disorder with co-morbidities, we strongly recommend the use of combined therapy with two or more herbs with specific therapeutic actions being administered to combat the key players in the pathogenesis of the disease.

Authors contribution

Conceptualization: OJO; Data curation: OJO, AEIO, OMO, OTO, OBD, ABM; Funding acquisition: OJO, AEIO, OMO; Investigation OJO, AEIO, OMO, OTO, OBD, ABM; Project administration: OJO, AEIO; Resources; OJO, AEIO, OMO, OTO, OBD, ABM; Supervision; OJO, AEIO, OMO; Roles/Writing - original draft: OJO, AEIO, OMO, OTO, OBD, ABM.

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