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Bioprospecting for Anti-COVID-19 Interventions From African Medicinal Plants: A Review

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Abstract

The emergence of the novel coronavirus (SARS-CoV-2) that emanated from Wuhan in China in 2019 has become a global concern. The current situation warrants ethnomedicinal drug discovery and development for delivery of phytomedicines with potential for the treatment of COVID-19. The aim of this review is to provide a detailed evaluation of available information on plant species used in African traditional medicines with antiviral, anti-inflammatory, immunomodulatory, and COVID-19 symptoms relieving effects. Literature from scientific databases such as Scopus, PubMed, Google scholar, African Journals OnLine (AJOL), Science Direct, and Web of Science were used for this review. A total of 35 of the 38 reviewed plants demonstrated a wide range of antiviral activities. *Bryophyllum pinnatum*, *Aframomum melegueta*, *Garcinia kola*, *Sphenocentrum jollyanum*, *Adansonia digitata*, *Sutherlandia frutescens*, *Hibiscus sabdariffa*, *Moringa oleifera*, and *Nigella sativa* possess a combination of antiviral, immunomodulatory, anti-inflammatory, and COVID-19 symptoms relieving activities. Nine, 13, and 10 of the plants representing 23.7%, 34.2%, and 26.3% of the plants studied had antiviral activity with 3 other activities, antiviral activity with 2 other activities, and antiviral with one pharmacological activity alone, respectively. The plants studied were reported to be relatively safe at the subchronic toxicity level, except for 2. The study provides baseline information on the pharmacological activities, toxicity, and chemical components of 9 African medicinal plants with antiviral, immunomodulatory, anti-inflammatory, and symptoms relieving activities, thereby making the plants candidates for further investigation for effectiveness against COVID-19.

Keywords
antiviral, immunomodulatory, anti-inflammatory, COVID-19 symptoms relieving activity, african medicinal plants

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Introduction

The end of 2019 witnessed the emergence of a novel virus called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), causing severe acute respiratory syndrome called Corona Virus Disease 2019 (COVID-19) that expanded globally from Wuhan (Hubei, China).[1,3] The SARS-CoV-2 virus was declared as a global pandemic by the World Health Organization in March 2020 and as at April 6, 2022, about 492 189 439 confirmed cases and 6 159 474 deaths were recorded globally (https://covid19.who.int/). Africa accounts for 11 787 148 confirmed cases, and 253 098 deaths with 11 016 881 recoveries, suggesting 93.47% recoveries as at April 7, 2022, a value higher than the global value of 87.02% (https://www.worldometers.info/coronavirus/).

The pathophysiology and virulence mechanism of SARS-CoV-2 has been linked to the function of non-structural and structural proteins.[4] The nonstructural proteins block the

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host innate immune response, while among the functions of the structural proteins is the promotion of viral assembly and release.[5] SARS-CoV-2 has the capacity to pass through the mucous membranes (nasal and larynx mucosa) and enter the lungs through the respiratory tract. It attacks the target organs that express angiotensin-converting enzyme 2 (ACE2), such as the lungs, heart, renal system, and gastrointestinal tract, with a full-blown wave of the attack around 7 to 14 days after onset.[6,7] Drastic reduction in B lymphocytes may occur early in the disease, which limits the production of antibodies. However, there is a significant increase in the level of IL-6, an inflammatory factor associated with and contributing to the aggravation of the disease around 2 to 10 days after onset.[4]

The clinical spectrum of COVID-19 varies from asymptomatic to symptomatic conditions characterized by severe respiratory failure that necessitates mechanical ventilation and support.[8] Pneumonia appears to be the most frequent serious manifestation of infection, characterized primarily by fever, dry cough, shortness of breath, and bilateral infiltrates on chest imaging.[9] Less common symptoms include aches and pains, headache, sore throat, red or irritated eyes, loss of taste or smell, and a rash on skin or discoloration of fingers or toes.[1,2] However, there are no specific clinical features that can yet reliably distinguish COVID-19 from other viral respiratory infections, except by specific diagnostic assays.[4] Clinical diagnosis of COVID-19 is performed by the detection of nucleic acid for SARS-CoV-2 in sputum, nasopharyngeal swabs, and secretions of the lower respiratory tract samples by real-time quantitative polymerase chain reaction (RT-qPCR) and high-throughput sequencing.[10]

As with many emerging viruses, there is no proven effective therapy for the current SARS-CoV-2 infection. Drugs repurposed to manage COVID-19 include antiviral drugs developed for other viruses (lopinavir–ritonavir, remdesivir, favipiravir, interferon-alpha [IFN-α], ribavirin, and arbidol), immunomodulators (anakinra, tocilizumab, ruxolitinib, baricitinib, and corticosteroids), antiparasitic agent (ivermectin), and antibodies from patients who have recovered from COVID-19.[11,13] Various adverse effects have been associated with these investigational interventions, including gastrointestinal events (anorexia, nausea, abdominal discomfort, acute gastritis, hemorrhage from lower digestive tract), self-limited skin eruptions (lopinavir-ritonavir), and mutagenicity with potential for teratogenicity and embryotoxicity in humans (favipiravir).[14] Vaccines, including AstraZeneca, Moderna Inc., Johnson & Johnson/Jannsen, and Pfizer-BioNTech, have been given approval for emergency use while further investigations involving entities such as CureVac, ZyCoV-D, and Novavax are still at various levels.[15] According to the WHO, a total of 11 242 252 352 vaccine doses have been administered as of April 5, 2022. As of the present time, not enough people have been vaccinated and the continuous emergence of new variants of SARS-CoV-2 has compounded the situation warranting the administration of booster vaccine doses, even with the reality of poor vaccine uptake in Africa, for example; hence the need for phytotherapy and other therapeutics options. The deleterious effects of current repurposed drugs used in the management of COVID-19 and the long process needed for vaccine development warrant ethnomedicinal drug discovery and development for the delivery of phytomedicines, with better or comparable efficacy and superior safety profile relative to current investigational drugs, for the treatment of COVID-19.

Medicinal plants have historically proven their value as source of molecules with therapeutic potentials and still represent an important tool for the identification of novel drug leads.[16] In 2002, the SARS mortality in mainland China was the lowest due to the integrative treatment approach with traditional Chinese medicine (TCM). The preventive function of TCM herbs in strengthening the immune system to reduce the number of possible onsets of infectious cases was also reported.[17] Researchers have made a case for phytomedicines in the exploration of remedies for COVID-19.[18] The authors based their argument on the fact that phytomedicines may possibly elicit one or a combination of beneficial effects against SARS-CoV-2, including preventing fusion of the virus with human cells; decreasing acidity in endosomes to hinder virus replication and blockade of the production of pro-inflammatory cytokines. Aside from this advantage of phytomedicines, orthodox (conventional) medicines (a significant number of which are synthetic in nature) may not be easily available and accessible and may be associated with relatively higher cost and side effects.

Plants and their phytoconstituents that have been reported to be active against SARS CoV *in vitro* include lycorine from *Lycoris radiata, emetin from Psychotria ipecacuanha* and cepharanthine from *Stephania cephalantha*.[19,21] Caflanone, equivir, hesperetin, myricetin, and linebacker (flavonoid phytomedicines) with potential for development into prophylactics or therapeutics against COVID-19 have been reported.[22]

Time is of the essence in the fight against this virus and due to the strong infectivity, high fatality rate, and the absence of specific medicines for SARS-CoV-2, the outbreak of the coronavirus has brought unprecedented crisis for public health and a huge economic burden to many societies in the world, including Africa.[21,23] The aim of the present review, therefore, is to provide a detailed analysis and evaluation of available information on plant species used in African traditional medicine that are known to have a range of relevant activities, including antiviral, anti-inflammatory, immunomodulatory, and symptoms relieving effects, among other actions. The review is a contribution to the resources required for bioprospecting for drugs for the management of COVID-19.

Materials and Methods

Databases and Search Terms

In this review, relevant literature was reviewed by searching through scientific databases such as Scopus, PubMed, Science Direct, Google Scholar, African Journals OnLine (AJOL), and Web of Science. The search was carried out using the

following keywords: viral infections, viral diseases, immunomodulatory, anti-inflammatory, antiviral, anticoagulant, respiratory disorder, medicinal plants, and ethnomedicinal uses.

Inclusion Criteria

All published articles of African origin covering the keywords were reviewed. All included information were restricted to research articles published in the English language and carried out in Africa from 1941 to 2020.

Exclusion Criteria

The following data types were excluded from the data used: partially accessed (abstract only) articles, publications with missing author names (anonymous publication), and articles from non-African countries, as well as articles with non-English full text.

Results

The ethnomedicinal descriptions of the 38 reviewed medicinal plants are presented in Table 1. The botanical names, plant parts, uses, and chemical constituents are highlighted. The toxicity profile of the reviewed plants and pharmacological activities ranging from antiviral, immunomodulatory, anti-inflammatory, and COVID-19 symptoms relieving activities are presented in Table 2.

Findings revealed that 92.1% (35) of the reviewed plants demonstrated a wide range of antiviral activities. Of the plants, 7.9% (3) (*Alstonia boonei*, *Hypoxis hemerocallidea*, and *Vernonia colorata*) did not possess antiviral activity; 23.7% (9) (*Bryophyllum pinnatum*, *Aframomum melegueta*, *Garcinia kola*, *Sphenocentrum jollyanum*, *Adansonia digitata*, *Sutherlandia frutescens*, *Hibiscus sabdariffa*, *Moringa oleifera,* and *Nigella sativa*) possess a combination of antiviral, immunomodulatory, anti-inflammatory, and COVID-19 symptoms relieving activities; 34.2% (13) possess antiviral and 2 other activities (antiviral, anti-inflammatory and symptoms relieving activities - *Berberis vulgaris*, *Carissa edulis*, and *Aspalathus linearis*; antiviral, immunomodulatory and anti-inflammatory activities - *Viscum album*, *Boswellia dalzieilli*, *Xylopia aethiopica*, *Lagenaria breviflora*, *Cajanus cajan*, *Persea americana*, *Centella asiatica*, *Voacanga africana* and *Euphorbia hirta*; antiviral, immunomodulatory, and symptoms relieving activities - *Pelargonium sidoides*); and 26.3% (10) possess antiviral and one other activity (antiviral and anti-inflammatory activities - *Macaranga barteri*, *Enantia chlorantha*, *Uvaria chamae*, *Spondias mombin*, *Anacardium occidentale*, *Combretum micranthum*, *Terminalia sericea*, *Toddalia asiatica*, and *Aloe ferox*; antiviral and immunomodulatory activities - *Azadiracta indica*). Furthermore, 7.9% (3) of the plants have solely antiviral activity without immunomodulatory, anti-inflammatory, and COVID-19 symptoms relieving activities (Figures 1 and 2).

All the plants with antiviral and another 3 pharmacological activities are reported to be relatively safe at the subchronic toxicity level, except *Aframomum melegueta*, with dose-dependent hepatotoxicity. Conversely, in respect to the plants devoid of antiviral activity, *Alstonia boonei* demonstrated nephrotoxicity, hematotoxicity, and immunosuppression, while *Pelargonium sidoides* was reported to be safe in mice and tolerable in adults and children.

Discussion

In terms of pathology, diffuse alveolar disease (DAD) is a common predominant pattern of lung lesions in humans with MERS-CoV, SARS-CoV, and SARS-CoV-2 infection.[442] Acute respiratory distress syndrome (ARDS), fluid accumulation, and lung damage as a result of cytokine storm, with a negative impact on the immune system, have been observed in COVID-19 patients with critical illness.[13] These observations form the basis of some of the activities of interest sought in respect of the reviewed plants, that is, antiviral, immunomodulatory, anti-inflammatory, and symptoms relieving.

The use of plants for the treatment of viral and other diseases has been reported.[443] Extracts from plants have demonstrated efficacy against coronavirus, making such plants potential sources of therapeutic agents against SARS-CoV-2.[444] The antiviral mechanisms of action of bioactive compounds of medicinal herbs may be via inhibition of viral transcription of RNA replication, inhibition of N and S protein anabolism, inhibition of 3CLpro (viral protein enzyme), and RNA polymerase activity.[445,446] In respect of the 2012 and 2013 outbreaks of MERS-CoV and SARS-CoV, herbal formulations and phytoconstituents were employed as therapeutic interventions.[447] A preponderance of medicinal plants has been scientifically verified to possess antiviral, immunomodulatory, anti-inflammatory, antipyretic, antitussive, and anticoagulant/antithrombotic properties, effects that can be considered beneficial in the treatment of COVID-19 patients.

In the course of this review, 10 plants were found that possessed a combination of antiviral, immunomodulatory, anti-inflammatory, and COVID-19 symptoms relieving activities, hence the narrative focuses on these plants.

Adansonia digitata L. (Baobab) is a succulent, deciduous tree with an enormous squat trunk, often with a very sparse crown. It is found in tropical Africa. Medicinal uses of preparations from the plant include immunostimulant, fever, cough, hemoptysis,[448] inflammation,[204] infections,[449] respiratory infections, sinusitis, asthma, and related symptoms.[197,450,451] The methanol leaf extract of *A digitata* was reported to inhibit pro-inflammatory iNOS, IκBα degradation, and NF-κB translocation from the cytosol to the nucleus when RAW264.7 cells were induced with LPS.[202] The inhibition of pro-inflammatory iNOS was reported to be possibly via the inhibition of NF-κB activation. The dichloromethane and light petroleum bark extracts of *A digitata* elicited significant anti-inflammatory effect in COX-1 and COX-2 assays.[204] The fruit pulp aqueous extract of *A digitata* also induced sustained significant anti-inflammatory effect at 400 and 800 mg/kg in respect to

Table 1. Botanical Names, Ethnomedicinal Uses, and Chemical Constituents of Identified Plants.

S/no	Botanical names (family); common/local names	Plant part/ethnomedicinal uses	Chemical constituents
1	*Macaranga barteri* Mull. Arg (Euphorbiaceae); Aarasa, Owariwa (Y), Ohaha, Ohaha eze (Ed)[24,28]	Stem bark and leaves: vermifuge, febrifuge, cough, bronchitis, diabetes, and antianaemic tonic.	Vedelianin, schweinfurthin, and mappain.
2	*Bryophyllum pinnatum* (Lam.) Oken (Crassulaceae); Air plant, cathedral bells, life plant, miracle leaf and Goethe plant, Odundun (Y), Abamoda (Y), Oda, Opue, Alupu (I)[29,34]	Root and leaves: earache, burns, abscesses, ulcer, and lithiasis. Hypertension, liver damage, infections, rheumatism and inflammation, edema, piles, cuts, eczema, epilepsy, cholera, asthma, chest colds, chicken pox and fever, antiseptic, blisters, cough suppression, and abdominal discomforts.	5 Methyl 4, 5, 7 trihydroxyl flavone 1, 4, 3, 5, 7 tetrahydroxy 5-methyl 5I-propenamine anthocyanidines 2, 24-epiclerosterol (R)-stigmasta-5, 25-dien-3β-ol], 24(R)-5α-stigmasta-7, 25-dien-3β-ol, 5α-stigmast-24-en-3β-ol and 25-methyl-5α-ergost-24 (28)en-3β-ol, 1-octane-3-*O*-α-L-arabinopyranosyl-(1-6)-glucopyranoside, isorhamnetin-3-*O*-α-L-1C4-rhamnopyranoside, 40-methoxy-myricetin-3-*O*-a-L 1C4-rhamnopyranoside and protocatechuic-40-*O*-b-D-4C1-gluco-pyranoside, bersaldegenin-1, 3, 5-orthoacetate, bufadienolide, bryophyllin B, bryophyllin C, stigmast-4, 20 (21), 23-trien-3-one, stigmata-5-en-3β-ol, α-amyrin-β-D-glucopyranoside and nundecanyl-n-octadec-9-en-1-oate and n-dodecanyl noctadec-9-en-1-oate; bersaldegenin-1-acetate, bersaldegenin-3-acetate, bersaldegenin-13,5-orthoacetate, and bufalin.
3	*Viscum album* L. (Santalaceae); European mistletoe[35,41]	Leaves: jaundice, hypertension, renal stones and diabetes, skin infections fever, gout, abscesses, otitis, and palpitations.	Mistletoe lectins I, II, and III, 5,7-dimethoxy-flavanone-4'-*O*-beta-D-glucopyranoside, 2'-hydroxy-4',6'-dimethoxy-chalcone-4-*O*-beta-D-glucopyranoside, 5,7-dimethoxy-flavanone-4'-*O*-[2"-*O*-(5"'-*O*-trans-cinnamoyl)-beta-D-apiofuranosyl]-beta-D-glucopyranoside, 2'-hydroxy-4',6'-dimethoxy-chalcone-4-*O*-[2"-*O*-(5"'-*O*-trans-cinnamoyl)-beta-D-apiofuranosyl]-beta-D-glucopyranoside, and 5,7-dimethoxy-flavanone-4'-*O*-[beta-D-apiofuranosyl-(1 --> 2)]-beta-D-glucopyranoside.
4	*Boswellia dalzielli* Hutch. (Burseraceae); Hano (H), Andakehi (F), Soma[42,46]	Gum resins: osteo and rheumatoid arthritis, abdominal pain, dysentery, asthma, bronchitis, syphilis, diuretic, fever, rheumatism, pain, leprosy, inflammation, convulsions, and mental derangement.	Incensole, gallic acid, protocatechuic acid, 4-methoxy-(E)-resveratrol-3-orutinoside, β-sitosterol, germacrene D, trans-β-caryophyllene, α-phellandrene, β-phellandrene, and ethylgallate.
5	*Enantia chlorantha* Oliver (Annonaceae); African white wood, Moambe Jaune, Uno eto, (Ib), Awopa (Y), Erumeru (I), Osumolu (Ik)[47,62]	Root, stem bark, fruit, and leaves: Malaria, fever, typhoid fever, jaundice, dysentery, high blood pressure, convulsions, diarrhea, and hepatitis.	Protoberberine (7, 8-dihydro-8-hydroxy palmatine), berberine alkaloids, palmatine, jatrorrhizine, columbamine, and pseudocolumbamine.
6	*Xylopia aethiopica* (Dunal) A. Rich (Annonaceae); Negro pepper, African pepper, Guinea pepper, West African Pepper, Ethiopian pepper, Senegal pepper[24,63,81]	Leaves, stem, and fruit: Abortifacient, ecbolics, diarrhea, dysentery, stomach disorder, bronchitis, fever, and asthma.	α-Pinene, β-pinene, 1,8-cineol, α-terpineol, terpinene-4-ol, paradol, bisabolene, α-farnesene, myrtenol, β-phellandrene, annonaceine, and 15β-acetoxy-(-)-kaur-16en-19-oic acid.
7	*Uvaria chamae* P. Beauv (Annonaceae); Cluster pear, Oko-aja (Y), Kas kaifi (H), Mmimi-ohea (I) Akotompo (Gh)[76,82,87]	Stembark and root: dysentery, diabetes, malarial, bronchitis, and yellow fever.	Uvarinol, chamanetin, uvaretin, diuvaretin, pinocembrin methyl ether derivatives of dichamanetin, chamanetin, chamuvarinin, acetogenins squamocin, desacetyluvaricin, and neoannonin.
8	*Ramalina farinacea* (L.) Ach. (Ramalinaceae)[88,94]	Lichen: mental disorders.	Usnic acid, usimines, (+)-isousnic acid and usninic acid, norstictic acid, protocetraric acid, sekikaic acid, salazinic acid, 5-hydroxysekikaic acid, 2,3-dihydroxy-4-methody-6-pentylbenzoic acid, methyl homosekikate; ramalinic acid, 3-(2-carboxy-5-methoxy-3-propylphenoxy)-2-hydroxy-4-methoxy-6-propylbenzoic acid, ramalinic acid B, 3-(2-carboxy-5-methoxy-3-propylphenoxy)-2-hydroxy-4-methoxy-6-pentylbenzoic acid, (12R)-(+)-usnic acid, methyl orsellinate, lupeol, methyl sekikate, methyl divarate, spermidine, putrescine, and 2,3-dihydroxy-4-methoxy-6-pentylphenylmethyl ester.
9	*Bambusa vulgaris* Schrad. ex J.C.Wendl (Poaceae); Bamboo, Oparun (Y), Atosi (I)[95,98]	Leaves: paralytic complaints, inflammatory disorders, and skin disorders.	Tricin (57,4′-trihydroxy-3′,5′-dimethoxyflavone), coumarins, and cyanogenic glycosides.

(Continued)

Table 1. Continued

10	*Aframomum melegueta* K Schum. (Zingiberaceae); Grains of paradise, melegueta pepper, alligator pepper, Guinea grains, or Guinea pepper. Ata-ire, Atare, Itaye (Y)[99,104]	Seed: respiratory tract infections, tuberculosis, cough, measles, sexual stimulation, inflammation, snakebites, and cancer.	3-(S)-Acetyl-1-(4′,5′-dihydroxy-3′-methoxyphenyl)-7-(3′′,4′′-dihydroxy phenyl) heptane, dihydrogingerenone A, dihydrogingerenone C, 3,5-diacetoxy-1-(3′,4′-dihydroxyl phenyl)-7-(3′′,4′′-dihydroxy-5′′-methoxyphenyl) heptane, 6-paradol, [6]-gingerol, [6]-shogaol, [8]-gingerol and dihydro [6] paradol. (S)-9-hydroxy-[6]-paradol (1) (9S)-3,9-dihydroxydihydro-[6]-paradol, [6]-gingerol, (3S,5S)-3,5-dihydroxy-1-(4-hydroxy3-methoxyphenyl)decane(4), [4]-gingerdiol(5), 1-(4-hydroxy-3-methoxyphenyl)-7-(4 hydroxy phenyl)-3-heptanone, (4E)-1-(4-hydroxy-3-methoxyphenyl)-7-(4-hydroxyphenyl)-(4E)-4-hepten-3-one, [6]-paradol, dehydro-6-gingerdione, and [6]-shogaol, 7-paradol, 1-(4´-hydroxy-3´-methoxyphenyl)-decan-3-ol, 6-gingerol, acetyl-6-gingerol, 1-(4′-hydroxy-3′-methoxyphenyl)-5-methoxy-dodecan-3-one, 6-shogaol, 1-dehydrogingerdione, 1-(4´-hydroxy-3´-methoxyphenyl)-5-methoxydecan-3-one, 1-(4´-hydroxy-3´-methoxyphenyl)-3-octen-5-one (J), gingerenone D, dihydrogingerenone A, dihydrogingerenone B, and dihydrogingerenone C, in 3,5-diacetoxy-1-(3′,4′-dihydroxyl phenyl)-7-(3′′,4′′-dihydroxy-5′′-methoxyphenyl)heptane, paradol, dehydrogingerdione, [6]-shogaol, [4]-shogaol and [6]-gingerol, 6-gingerdione, methyl-6-gingerol, rac-6-dihydroparadol, gingerdione, 5-oxo-l-(4-hydroxy-3-methoxyphenyl)decan-3-one, 1-(4-hydroxy-3-methoxyphenyl)decan-3-one, [6]-gingerol, 5-hydroxy-l-(4-hydroxy-3-methoxyphenyl)decan-3-one, [6]-shogaol and1-(4-hydroxy-3-methoxyphenyl)dec-5-en-3-one.
11	*Spondias mombin* Linn. (Anacardiaceae); Hog plum, Iyeye (Y)[105,112]	Leaves and stembark: abdominal discomfort, diabetes, wound healing, hemorrhoids, and vermifuge.	3-β-urs-12-in-3-yl (9 z) hexadec-9-enoate, betulin, campesterol, phytol, stigmasta-9-en-36,7-triol (mombintane I) and 3-hydroxy-22-epoxystigmastane (mombintane II), ellagitannins, geraniin, and galloyl geraniin, 2-*O*-caffeoyl-(+)-allohydroxycitric acid, chlorogenic acid and chlorogenic acid butyl ester.
12	*Anacardium occidentale* L. (Anacardiaceae); Cashew tree, Kaju (Y), Sashu (I), Kanju (H)[113,114]	Stembark: wounds, stomachache, cough, toothache, hypertension, diabetes, hemorrhoids, and sexual dysfunction.	Sitosteryl palmitate, oleate and linoleate, sitosterol, stigmasterol, sitosterol 3-*O*-β-D-galactopyranoside, 3-*O*-β-digalactopyranoside of stigmasterol, 3-*O*-β-D-sitosterol glycopyranoside and a mixture of anacardic acids. stigmast-4-en-3-one and stigmast-4-en-3-ol, agathisflavone.
13	*Sterculia setigera* Del. (Sterculiaceae); False plane, Kukkugi (H); bo'boli (F); Ose-awere (Y)[115,118]	Stem bark and gum: fever, malaria, jaundice, diarrhea, dysentery, sexually transmitted diseases, snakebites, leprosy, syphilis, coughs, bronchitis, rickets, and insanity.	Lupeol, catechin, 3,4-dimethoxyphenol ß-D-apiofuranosyl (1"→ 6")-β-D-glucopyranoside and procyanidin trimer, procyanidin tetramer, procyanidin dimer B.
14	*Lagenaria breviflora* Benth. Roberty (Cucurbitaceae); English wild colocynth, Tagiri (Y), Ogbenwa (I)[119,123]	Stem, leaves, and fruits: headache, vermifuge, measles, digestive disorders, and wounds.	Octadecane, hexacosane, docosane, 0, 2 methyl-E,E-3,13-octadecadieno, heptadecane, tricosane, tridecane, 1,2-benzenedicarboxylic acid, mono (2-ethylhexyl) ester, tetracontane, 3,5,24-trimethyl-and 9,12-octadecadienoic acid.
15	*Alstonia boonei* De Wild (Apocynaceae); Ahun (Y)[124,127]	Stem bark and leaves: malaria and relapsing fevers, jaundice, painful micturition, rheumatic conditions, snakebites and antidote against arrow poisoning; swellings, rheumatic and muscular pains hypertension, aphrodisiac, and diabetes.	Echitamine and echitamidine, voacangine and akuammidine, Nα-formylechitamidine, and Nα-formyl-12-methoxyechitamidine, boonein, loganin, lupeol, ursolic acid, and β-amyrin, tetrahydro-4-(7-hydroxy-10-methoxy-6, 14-dimethyl-15-m-tolylpentadec-13-enyl) pyran-2-one and isobutyryl acetate.
16	*Azadiracta indica* A. Juss (Meliaceae); Dogoyaro (Y), Atu yabasi/ Ogwu akom (I); Maina (H)[128,134]	Leaves, bark, root, and seeds: diabetes, malaria, hypertension, typhoid, diarrhea, bronchitis and cough, pains, and toothaches.	Azadirachtin A-G, azadirachtin E, salannin, meliantriol and nimbin.
17	*Cajanus cajan* L. Mill Sp (Fabaceae); Red gram, Congo pea, Gungo pea, and No-eye pea, Pigeon pea, Arhar (Hin), Tur (Ben)[135,138]	Root, stem, and leaves: diabetes, fever, malaria, dysentery, hepatitis, measles, and constipation.	Cajachalcone and 2′,6′-dihydroxy-4-methoxy chalcone.
18	*Garcinia kola* Heckel (Clusiaceae); Cida goro (Hausa), Orogbo (Yoruba), Aki-ilu (Igbo)[139,145]	Seeds and stem bark: diarrhea, laryngitis, bronchitis, gonorrhea, liver cirrhosis, and hepatitis.	Kolaviron, garcinia biflavonoid (GB)-1aglucoside, GB-1a, GB-1, GB-2, kolaflavonone, benzophenone, xanthone, coumarin, apigenin, quercetin, and garcinoic acid.
19	*Persea americana* Mill. (Lauraceae); Avocado pear, Ube-beke (I), Igba(I), Apoka (Y), Paya ahaban (Gh), Ivoka (CDR), Awuca,	Root, seed, and leaves: diabetes, malaria, hypertension, typhoid, diarrhea, bronchitis, cough, pains, and toothache.	12,4-trihydroxyheptadec-16-ene (1), 12,4-trihydroxyheptadec-16-yne (4), 12,4-trihydroxynonadecane, (2R,12Z,15Z)-2-hydroxy-4-oxoheneicosa-12,15-dienyl acetate, persenones A and B,

(Continued)

Table 1. Continued

	Pya, Afouca (IVC), Moafokhathe (SA)[146,153]		afzelin, catechin and epi-catechin. (2R,4R)-12,4-trihydroxyheptadec-16-yne(THHY), (2R,4R)-12,4-trihydroxyheptadec-16-ene (THHE), avocadenol A and C and avocadion.
20	*Sphenocentrum jollyanum* Pierre (Menispermaceae); Akerejupon (Y), Aduro koko/Okraman, Kote/Krakoo (Gh), Oban abe (RB), Ouse-abe (IVC)[154,159]	Root, stem, leaves, and fruit: wounds, fever, malaria, cough, hypertension, breast tumor, constipation, sickle cell disease, and aphrodisia.	Palmatine, jatrorrhizine, tetrahydrojatrorrhizine and columbamine, (–)-viburnitol, columbin, isocolumbin, and fibleucin.
21	*Centella asiatica* (L.) Urban (Apiaceae); Pennywort (India), Fo-titieng (China)[160,167]	Leaves and stem: leprosy, wound, burns, stress, and dermititis.	Caffeoylquinic acid, asiatic acid, madecassoside, madecassic acid, rutin, quercetin, kaempferol, centellasaponins Gand F, gallic acid, protocatechuic, gentisic, chlorogenic, caffeic, p-coumaric and ferulic acids, asiaticoside and madecassoside.
22	*Carissa edulis* (Forssk.) Vahl (Apocynaceae); Carrisse; Cìzaáki, Gizaki (H)[168,181]	Roots, leaves, root bark, stem, and aerial parts: tuberculosis, malaria, rheumatism, fever, worm infestation, pain, inflammation, chest pain and congestion, cough, helminthiasis, schistosomiasis, rabbies, and HIV/AIDS.	2-Hydroxyacetophenone; 3-*O*-acetyl chlorogenic acid, 4 flavonol glucosides: kaempferol 3-*O*-β-D glucopyranoside, quercetin-3-*O*-β-D glucopyranoside, rhamnetin-3-*O*-b-D glucopyranoside, and isorhamnetin-3-*O*-β-D-glucopyranoside, isorhamnetin-3-*O*-β-D-glucopyranoside-(200fi1000)-rhamnopyranoside, caredulis, 1-{1-[2-(2 hydroxypropoxy) propoxy] propan-2-yloxy} propan-2-ol) and (+) butyl-*O*-α-L-rhamnoside; chlorogenic acid-1-ethyl ether-1-methyl ester, caffeic acid methyl ester, kaempferol, quercetin-3-*O*-D-glucoside-7, 3,4' trimethyl ether, rutin, pinitol, β-amyrin, lupeol, stigmasterol glucoside, β-sitosterol and β-sitosterol glucoside, and nortrachelogenin.
23	*Voacanga africana* Stapf ex Scott-Elliot (Apocynaceae); Petepete (I); Ako-Dodo (Y); Kokiyar (H)[178,182,184]	Bark, leaves and stem bark: fatigue and shortness of breath, onchocerciasis and malaria.	Voacamine, voacangine and voacamine.
24	*Vernonia colorata* (Willd.) Drake (Asteraceae); Bitter leaf, Chusar doki, Fate fate (H), Olúgbù, Kírìòlògbò (I), Ewúrò oko, Ewúrò (Y)[185,195]	Leaves, root, and stem: Cough, fever, tonsillitis, inflammation, malaria, schistosomiasis, intestinal worms, bronchopulmonary diseases and pneumonia.	Vernolide, 11-β, 13-dihydrovernolide, and vernodalin.
25	*Adansonia digitata* L. (Bombaceae): Baobab, Ose (Y), Kuka (H)[196,209]	Stem bark, leaves, root-bark, fruit pulp, and seeds: fever, cough, hemoptysis, tuberculosis, malaria, inflammation, asthma, trypanosomiasis, guinea worm, (respiratory infections and sinusitis.	procyanidin B2, feruloylquinic acid; 2 flavan-3-ols, catechin, epicatechin and their oligomers procyanidin dimer I and II, procyanidin trimer I and II; quercetin 3-*O*-glucoside, kaempferol 3-*O*-galactoside, kaempferol 3-*O*-glucoside, tiliroside I and II, and kaempferol
26	*Combretum micranthum* G. Don (Combretaceae); Kinkeliba (Fr); Farar geeza (H); Ogan Ibule (Y)[210,219]	Leaves: wounds and sores, fever, cough, bronchitis, general tonic, lumbago, malaria, diabetes, liver and gall bladder ailments.	Epigallocatechin, vitexin, isovitexin, homoorientin, myricetin, 3′, 4′, 5′, 5, 7-pentahydroxyflavan, orientin, homoorientin, myricetin-3-*O*-glucoside, 2″-*O*-galloylvitexin, 2″-*O*-galloylisovitexin, 2″-*O*-galloylorientin, 2″-*O*-galloylhomoorientin, myricetin-3-o-rutinoside, stachydrine, hydroxyl-stachydrine, and choline), kinkeloids A, B, C, and D, and combretin.
27	*Terminalia sericea* Burch. ex. DC (Combretaceae); Clusterleaf, silver cluster-leaf or silver terminalia[220,226]	Root, stem bark, and leaves: venereal diseases, dysentery, colic, pneumonia, cough, skin diseases, schistosomiasis, gonorrhea, eyewash, wounds, diabetes, and stomach complaints.	Linoleic acid, lignoceric acid, arachidic acid, stearic acid, sericoside, heptadecanoic acid, palmitic acid, lauric acid, myristic acid, myristoleic acid beheric acid and palmitoleic acid, benzoic acid, hydrocinnamic acid, ferulinic acid, galacturonic acid, caffeic acid, p-coumaric acid and vanillic acid, sericic acid, resveratrol-3-rutinoside and arjunglucoside I.
28	*Euphorbia hirta* Linn. (Euphorbiaceae); Asthma herb, malnommée (Fr), nóónòn kúrcíyáá (H)[227,237]	Stem bark and leaves: asthma, cough, bronchial infections, kidney stones, bowel complaint, fever, inflammation, and pain.	Afzelin, quercitrin, myricitrin, rutin, euphorbin-A, euphorbin-B, euphorbin-C, euphorbin-D, 24,6-tri-*O*-galloyl-β-d-glucose, 1,3,4,6-tetra-*O*-galloyl-β-d-glucose, and protocatechuic acid, β-amyrin, 24-methylenecycloartenol, heptacosane, nonacosane, shikmic acid, tinyatoxin, and quercitol derivatives containing rhamnose and chtolphenolic acid.
29	*Aspalathus linearis* (Brum.f) R. Dahlgr (Fabaceae); Rooibos[238,245]	Stem bark and leaves: insomnia, allergies, inflammation, hyperlipidemia, neurological disorder, viral infections, and cancer.	(S)-and (R)-eriodictyol-6-C-beta-D-glucopyranoside, C-glucoside dihydrochalcone, aspalathin, chrysoeriol, vitexin, orientin, luteolin, uronic acid (A and B) and nothofagin.

(Continued)

Table 1. Continued

30	*Sutherlandia frutescens* R.Br (Fabaceae)[246,248]	Leaves and stem: viral infections, cancers, fever, diabetes, kidney and liver problems, rheumatism, stomach ailments; depression and stress, blood purifier, wounds, inflammation and influenza.	γ-aminobutyric acid (GABA), pinitol and L-canavanine (2-amino-4-guanidinooxybutyric acid).
31	*Pelargonium sidoides* DC. (Geraniaceae)[249,253]	Roots: diarrhoea, colic, gastritis, tuberculosis, cough, hepatic disorders, menstrual complaints, gonorrhoea, stomach ailment, tuberculosis, dysentery and respiratory-related ailments.	7-hydroxy-5,6-di-methoxycoumarin; 6,8-dihydroxy-5,7-dimethoxycoumarin; 6-methoxy-7-(sulfooxy)-2H-1-benzopyran-2-one; 6,8-Bis(sulfooxy)-7-methoxy-2H-1-benzopyran-2-one; 7-hydroxy-6-methoxy-8-(sulfooxy)-2H 1-benzopyran-2-one and 8-hydroxy-7-methoxy-6-(sulfooxy)-2H 1-benzopyran-2-one.
32	*Hypoxis hemerocallidea* Fisch.Mey. & Avé-Lall. (Hypoxidaceae); African potato[254,259]	Corm tuberculosis, cancer, prostate hypertrophy, urinary tract infections, intestinal worms, anxiety, palpitations, depression, rheumatoid arthritis, abdominal pain, fever, anorexia, vomiting; diabetes mellitus, and high blood pressure.	Sitosterol and hypoxide ((E)-1,5 bis-(4′-β D-glucopyranosyloxy-3′-hydroxyphenyl)pent-4-en-1-yne).
33	*Hibiscus sabdariffa* L. (Malvaceae) English sorrel, Florida cranberry Isapa pupa (Y), Yakuwa, Zobo (H)[260,263]	Leaves and roots: fever and hypotension, cardiac and nerve diseases; sore throats and coughs; genital problems, wounds, and abscesses.	Citric acid, hydroxycitric acid, hibiscus acid, malic acid, tartaric acid, delphinidin, hibiscin, gossypicyanin, cyanidin-3,5-diglucoside, chrysanthenin, hibiscitrin, sabdaritrin, gossypitrin, and gossytrin.
34	*Moringa oleifera* Lam. (Moringaceae) Moringa, horseradish tree, drumstick tree. Zogale (H), in Hausa, Ewe Ile/ Igbale Igi Iyanu (Y), Odudu Oyibo, Okwe Oyibo, Uhe(I)[264,268]	Leaves and root extract: cancer, diabetes, convulsion, viral infections, fever, hypertension, ulcer, and trypanosomiasis.	Myrecytin, chlorogenic acid, quercetin, kaempferol, N-α-L-rhamnopyranosyl vincosamide, phenylacetonitrile pyrrolemarumine, and 40-hydroxyphenylethanamide-α-L-rhamnopyranoside.
35	*Prunus africana* Kalkman (Rosaceae) African cherry, bitter almond and Pygeum (Cam)[269,272]	Stem bark: prostate cancer, epilepsy, diarrhea, arthritis, hemorrhage, and hypertension.	*N*-butylbenzenesulfonamide (NBBS), ursolic acid, oleanolic acid, β-amyrin, atraric acid (AA), β-sitosterol, β-sitosterol-3-*O*-glucoside, ferulic acid, and lauric acid.
36	*Toddalia asiatica* (L.) Lam. (Rutaceae) Forest pepper, Lopez root, wild orange climber tree[273,278]	Root, fruit, and leaves: malaria, fever, cough, epilepsy, neuralgia, viral diseases, and stomachache.	5, 7-dimethoxy-8(3'-hydroxy-3'-methyl-1'-butene) and benzo[c]phenanthridine-type alkaloids.
37	*Aloe ferox* Mill. (Asphodelaceae) Bitter aloe, Cape aloe, red aloe, and tap aloe[279,281]	Leaves: inflammation, cancer, and gastric disorder.	Anthrone 10-C-glucosides pyrone derivative, aloenin and glucosylated 2-acetonyl-7-hydroxy-5-methylchromones.
38	*Nigella sativa* L. (Ranunculaceae) Black cumin, nigella, kalojeera, kalonji and kalanji Asofeyeje (Y), Habatu Sauda (H)[282,284]	Seeds: astringent, diuresis, jaundice, intermittent fever, dyspepsia, paralysis, piles, and skin diseases.	The fixed oil contains unsaturated fatty acids; arachidonic, eicosadienoic, linoleic, linolenic, oleic, almitoleic, palmitic, stearic, and myristic acid as well as beta-sitosterol, cycloeucalonol, cycloartenol, sterol esters, and sterol glucosides. The volatile oil contains saturated fatty acids: nigellone which is the only component of the carbonyl fraction of the oil, thymoquinone (TQ), thymohydroquinone (THQ), dithymoquinone, thymol, carvacrol, α and β-pinene, d-limonene, d-citronellol, p-cymene. Volatile oil of the seed contains: p-cymene, carvacrol, t-anethole, 4-terpineol and longifoline. Other compounds from the seeds include: nigellidine, nigellimine, and nigellicine.

Abbreviations: Y, Yoruba; Ed, Edo; I, Igbo; H, Hausa; F, Fulfulde; Ib, Ibibios; Ik, Ikale; Hin, Hindi; Ben, Bengali; CDR, Congo DR; IVC, ivory coast; SA, South Africa; Gh, Ghana; RB, Rep. of Benin; Fr, French; Cam, Cameroon.

Table 2. Pharmacological Activities and Toxicity Profile of Identified Plants.

S/no	Botanical name	Antiviral activity		Immunomodulatory activity	Anti-inflammatory activity	Symptoms relieving activity	Toxicity profile
		Respiratory	Nonrespiratory				
1	*Macaranga barteri*[26,28,285]		Echoviruses (E7 and E19) **A:** Neutralisation assay. **B:** Inhibition of cytopathic effect in tissue culture.		**A:** Carrageenan-induced foot edema and cell-based respiratory burst assay. **B:** Inhibition of edema development and inhibition of superoxides produced in the cellular system.		Acute toxicity: LD_{50} >3000 mg/kg and 5000 mg/kg for different extracts (p.o.)
2	*Bryophyllum pinnatum*[32,34,41,286,295]	Measles virus **A:** Virucidal activity, adsorption, and post-adsorption assays using *in vitro* tissue culture on Vero cell lines.	Herpes simplex virus-1 **A:** Virucidal activity, adsorption, and post-adsorption assays using *in vitro* tissue culture on Vero cell lines.	**A:** Cell-mediated and humoral response modulation, pristane-induced lupus mice, delayed-type hypersensitivity reaction, *in vitro* and murine lymphocyte proliferation models. **B:** Reduction in % of Th1, Th2, Th17, and mature B cells and inhibition of cell-mediated and humoral immune responses, delayed-type hypersensitivity reaction, and lymphocyte proliferation.	**A:** *In vitro* protein denaturation, irritants-induced ear edema, carrageenan-induced inflammation, formaldehyde-induced paw edema, and egg albumin-induced acute inflammation models. **B:** Inhibition of protein denaturation, edema development, and arachidonic acid pathway.	**A:** Histamine-induced broncho-spasm in Guinea pig. **B:** Inhibition of bronchospasm.	Acute toxicity: LD_{50} >5000 g/kg p.o. Generally no deleterious effect upon subacute treatment.
3	*Viscum album*[39,296,301]	Human parainfluenza virus type 2 (HPIV-2) A/Gabrovo (H1N1) A/Hong Kong (H3N2) A/PR/8 (H1N1) **A:** Plaque assay. **B:** i. Direct pre-infection incubation (DPI) assay. ii. Effect on the adsorption of virus to cells. iii. Virus yield reduction assay Measles virus **A:** Virucidal activity, adsorption, and post-adsorption assays using *in vitro* tissue culture on Vero cell lines.	Herpes simplex virus-1 **A:** Virucidal activity, adsorption, and post-adsorption assays using *in vitro* tissue culture on Vero cell lines.	**A:** Investigation of lymphocyte subsets, natural killer (NK) cell activity, phagocytic and oxidative activity of polymorphonuclear leukocytes. **B:** Normalization of immune indices, increases in NK and antibody-dependent cell-mediated cytotoxicity, augmented levels of large granular lymphocytes, and increases in mitogenic responses.	**A:** Cytokine-induced PGE_2 production, LPS-induced pro-inflammatory response *in vivo, in vitro* activity in murine macrophage RAW 264.7 cells, NO release, and carrageenan-índuced edema assays. **B:** Inhibition of cytokine-induced PGE_2, LPS-induced pro-inflammatory response, activity in murine macrophage RAW 264.7 cells, and inhibition of NO release.		Signs of weakness, depression, arched back, gait, anorexia, insomnia, dizziness, and dyspnea. Coma and death in acute toxicity test.
4	*Boswellia dalzielli*[42,43,45,115,302,311]	New Castle Disease virus (NDV) Bovine parvovirus **A:** *In ovo* assay.	Astrovirus Poliovirus Herpes simplex viruses Canine parvovirus **A:** Microtitre plate inhibition tests.	**A:** Luminol chemiluminescence assay.	**A:** Carrageenan, arachidonic acid, histamine, serotonin, prostaglandin, and bradykinin models		Toxic effects in chicks and mice at 1000 and 400 mg/kg i.p., safe on acute p.o. administration at 3000 mg/kg in mice, extract of resin exudate safe on acute and 28 day

(Continued)

Table 2. Continued

S/no	Botanical name	Antiviral activity		Immunomodulatory activity	Anti-inflammatory activity	Symptoms relieving activity	Toxicity profile
		Respiratory	Nonrespiratory				
							subchronic administration.
5	*Enantia chlorantha*[48,50,52,53,55,57,59,312,316]	New Castle Disease virus (NDV) **A:** Using day-old embryonated chicken eggs.	Human immunodeficiency virus Yellow fever virus **A:** Vero cell line. **B:** Inhibition of infectivity of virus with complete absence of cytopathic effects.		**A:** Carrageenan-induced inflammation.	**A:** 2,4-Dinitrophenol (DNP)-Induced pyrexia	No toxicity with doses up to 5000 mg/kg p.o. and i.p. LD_{50} value of 324 mg/kg in an acute toxicity assay, deleterious histopathological signs noticed in the liver, lungs and kidneys following medium-to-long term use at doses greater than 500 mg/kg,
6	*Xylopia aethiopica*[72,76,80,81,115]	Measles virus **A:** Neutralization assay.		Immuno-modulatory activity **A:** Carbon clearance capability, avidity of neutrophil, inhibition of cyclophosphamide induced neutropenia, and zinc sulfate turbidity test.	**A:** i. Carrageenan-induced paw edema and turpentine oil-induced acute inflammation. ii. Hydrogen sulfide-induced inflammation.		Non-polar fraction reported to be non-toxic, methanol fraction reported to be highly toxic, and hydroalcohol extract reported to be highly toxic.
7	*Uvaria chamae* [76,85,317,320]	Measles virus **A:** Neutralization assay. **B:** Inhibition of viral-induced cytopathic effect (CPE) in tissue culture.	Herpes simplex virus-1 **A:** Virucidal activity on Vero cells.		Anti-inflammatory activity **A:** Carrageenan and formaldehyde induced paw edema tests. **B:** Inhibition of prostaglandin synthesis by inhibition of COX-1 and COX-2.		Elevation in serum AST, chloride and potassium ions, platelets; decrease in mean corpuscular hemoglobin (MCHC), deleterious histopathological manifestations in the liver and kidney, and dose-dependent cytotoxicity and genotoxicity.
8	*Ramalina farinacea*[89,92,321,323]	Respiratory syncytial virus (RSV) **A:** Modified plaque reduction assay. **B:** Inhibition of entry step of the RSV replication cycle.	Herpes simplex virus-1 Human immunodeficiency virus 1 **A:** Vector-based antiviral assay. **B:** Inhibition of entry and post-entry steps of the HIV-1 replication cycle and inhibition of HIV-1 reverse transcriptase.				Limited *in vivo* toxicity.

(Continued)

Table 2. Continued

S/no	Botanical name	Antiviral activity		Immunomodulatory activity	Anti-inflammatory activity	Symptoms relieving activity	Toxicity profile
		Respiratory	Nonrespiratory				
9	*Bambusa vulgaris*[96,324,327]	Measles virus **A:** Virucidal activity on Vero cells.			**A:** Formaldehyde-induced paw edema, acetic acid-induced vascular permeability, and subacute models. **B:** Inhibition of inflammatory parameters.	Antipyretic activity **A:** Brewer's yeast-induced pyrexia.	No mortality in acute toxicity test, animals showed no stereotypical symptoms and induction of abortion in pregnant rats.
10	*Aframomum melegueta*[96,103,328,335]	Measles virus **A:** Neutralization assay. **B:** Inhibition of viral-induced cytopathic effect (CPE) in tissue culture.	Yellow fever virus **A:** Virucidal activity on Vero cells.	**A:** Evaluation of effect on activation of RAW 264.7 macrophages. **B:** Inhibition of generation of NO and TNF-α.	**A:** Ear edema and egg albumin-induced rat paw edema models. **B:** Inhibition of acute and chronic inflammatory responses, inhibition of COX-2 enzyme activity, and expression of pro-inflammatory genes.	**A**: Anti-adhesive activity against lower respiratory tract pathogens; spasmolytic activity on isolated rat trachea.	Acute toxicity test: LD_{50} of 2154 mg/kg i.p. (methanol extract), LD_{50} of 273.9 mg/kg (seed oil); 28-day subchronic toxicity test: dose-dependent liver enlargement and elevation in ALP with no signs of steatosis or cirrhosis, and hepatotoxicity with prolonged ingestion at high dose
11	*Spondias mombin*[26,336,347]		Herpes simplex virus (HSV) type-1 Type-2 Dengue virus Echoviruses **A:** Evaluation of effect on the replication of HSV using *in vitro* and *in silico* approaches; MTT and standard cytopathic effect reduction assay in C6/36 cells in respect of Dengue virus. **B:** Demonstration of *in vitro* virucidal activity through blocking viral attachment.		**A:** Carrageenan-induced paw edema and 5-FU-induced oral mucositis models. **B:** Inhibition of LPS-induced release of TNF-α *in vivo*, iNO and TNF-α formation *in vitro*, and leukocyte migration in acute peritonitis model.		Possibility of hepatic and renal toxicity with prolonged use, and genotoxicity.
12	*Anacardium occident*[115,348,357]	Infuenza virus **A:** Inhibition of neuraminidase (NA) activity of wild-type and OST-resistant influenza virus.	Poliovirus Astrovirus Herpes simplex viruses Parvovirus **A:** Microtitre plate inhibition test.		**A:** Murine lipopolysaccharide-induced microvascular permeability and septic shock assays, carrageenan, dextran, and egg albumin-induced paw edemas, cotton pellet-granuloma and adjuvant-induced arthritis, croton oil-induced ear edema, and carrageenan-induced		Transitory hepatotoxicity —increase in ALT and AST levels; no genotoxicity at low doses, but observed at high dose; LD_{50} of 2.15 g/kg p.o. in mice; no treatment-related effects on relative

(Continued)

Table 2. Continued

S/no	Botanical name	Antiviral activity		Immunomodulatory activity	Anti-inflammatory activity	Symptoms relieving activity	Toxicity profile
		Respiratory	Nonrespiratory				
					peritonitis tests. **B:** Inhibition of PG synthesis from bovine seminal vesicles, inhibition of inflammation-associated cytokine, iNOS, and COX-2 gene expression by blocking NF-kB and MAPK pathways, inhibition of acute inflammatory responses, inhibition of mediators such as PGE and bradykinin, inhibition of cell migration to the site of inflammation and levels of TNF-α and IL-1β.		organ weights, biochemical parameters and food intake in repeated dose toxicity study.
13	*Sterculia setigera*[115,117]		Poliovirus Astrovirus Human and equine herpes simplex virus Canine and bovine parvovirus **A:** 96 well Microtitre plate inhibition test.				Slight increase in albumin and total bilirubin levels; not toxic to the liver.
14	*Lagenaria breviflora*[119,123]	Newcastle virus		Immunostimulatory activity **B:** Increase in circulating lymphocyte values thus enhanced immunological status of the body.	**A:** Inhibition of carrageenan- and histamine-induced paw edema in rats. **B:** Significant reduction in the formation of edema induced by carrageenan and histamine.		LD_{50} >5000 mg/kg but hepatotoxic at >500 mg/kg; long term administration at 500 and 1000 mg/kg may lead to cardiac and hepatic injuries.
15	*Alstonia boonei*[125,126,358,360]			**A:** Parameters assessment in phlogistic agents induced inflammation. **B**. Suppressed eosinophils, monocytes and basophils, total white blood cell, neutrophil and lymphocyte counts.	**A:** Carrageenan-induced paw edema and cotton pellet granuloma models.	Antipyretic activity **A:** Yeast-induced hyperpyrexiamodel.	Acute toxicity: LD_{50} = 4168.7 mg/kg; subchronic toxicity: toxic in high doses, nephrotoxic effect and testicular damage.
16	*Azadiracta indica*[130,131,133,134]	Coxsackie virus B-4 **A:** Plaque formation and effect of time of addition assays. **B:** Inhibition at early stage of viral genome replication.	Dengue virus type-2, Poliovirus, HIV, Antiherpetic activity **A:** Plaque reduction assay. **B:** Inhibition at early stage of viral replication and viral entry.	Immuno-stimulatory activity **A:** Macrophage phagocytic, gamma interferon and lymphocyte proliferation assays, peritoneal leukocyte count, estimation of anti-TT antibody titers, and immunohistology. **B:** Activation of cell-mediated immune mechanisms.			Acute toxicity: LD_{50} of 31.95 g/kg; subacute toxicity: deleterious histopathological observations in respect of testicle, liver and kidney at 1600 mg/kg/d.
17	*Cajanus cajan*[137,361,362]	Measles virus		**A:** Serum tumor necrosis	**A:** Carrageenan-induced rat paw		Safe on acute and

(Continued)

Table 2. Continued

S/no	Botanical name	Antiviral activity: Respiratory	Antiviral activity: Nonrespiratory	Immunomodulatory activity	Anti-inflammatory activity	Symptoms relieving activity	Toxicity profile
		A: In ovo assay and *in vivo* and *in vitro* assay techniques using embryonated chicken eggs and Hep-2 cell lines. **B:** Reduction of hemagglutination titer and inhibition of measles virus replication.		factor-α, interleukin-6, and immunoglobulin G estimation by ELISA. **B:** Increase in polymorpho-nuclear leukocytes, total leukocytes, and protein levels.	edema. **B:** Inhibition of TNF-α and IL-6 cytokines.		subchronic toxicological evaluation.
18	*Garcinia kola* Heckel[140,144,363,367]	Influenza A virus **A:** Hemagglutination assay.		Immuno-stimulatory activity **A:** *In vitro* and *in vivo* immuno-competent and immuno-compromised animal models. **B:** Modulation of the cell-mediated immune system; increase in lymphocytes count; delayed-type hypersensitivity.	**A:** Carrageenan-induced paw edema assay. **B:** Kolaviron abolished the expression of COX-2 and iNOS proteins in dimethylnitrosamine (DMN)-treated rat liver; and involvement of adrenergic and opioid systems.	Anti-asthma activity **A:** Histamine-induced bronchoconstriction assay.	Acute toxicity: LD_{50} >5000 mg/kg.
19	*Persea americana*[146,148,368]	Aujeszky's disease virus Adenovirus type 3 (AD3) **A:** *In vitro* viral replication. **B:** Agglutination of viral particles.	Dengue virus Herpes simplex virus type 1 (HSV-1) **A:** Ad3 and acyclovir-resistant HSV-1 antiviral assays in cell lines.	**A:** ELISA assay using RAW 246.7 macrophages culture. **B:** Inhibition of nitric oxide (NO) and cytokines TNF-α, IL-6, and IL-10.	**A:** Carrageenan-induced rat paw edema. **B:** Inhibition of prostaglandin synthesis in platelets.		Acute toxicity: LD_{50} <5000 mg/kg; deleterious manifestations observed in respect of histology of the liver.
20	*Sphenocentrum jollyanum*[154,155,157,159,369,370]		Poliovirus Type 2 **A:** Pre- and post-treatment assays using cell lines. **B:** Viral inhibition.	**A:** Milk-induced leukocytosis and eosinophilia in mice. **B:** Decrease in the absolute eosinophil and lymphocyte counts.	**A:** Carrageenan-induced hind paw edema.	**A:** *In vitro* antipyretic assay.	Chronic toxicity: No mortality or morbidity.
21	*Centella asiatica*[160,166,371,373]		Hepatitis B virus **A:** MTT assay.	**A:** Human lymphocyte proliferation assay. **B:** Water extract: immune stimulation via increase in proliferation and production of IL-2 and TNF-α. Ethanol extract: immuno-suppression via inhibition of mitogenesis and production of IL-2 and TNF-α.	**A:** Methyl nicotinate model of microinflamm-ation in human skin and carrageenan-induced inflammation model. **B:** Inhibition of 5-lipoxygenase, albumin denaturation, release of proinflammatory cytokines, COX-1 and COX-2, and suppression of TPA-induced production of PGE2.		Acute toxicity: LD_{50} > 4000 mg/kg; subacute and subchronic toxicity: No mortality.
22	*Carissa edulis*[170,172,174,175,177,179,374,376]	Canine distemper virus Feline herpes virus-1 **A:** Virucidal and attachment assays.	Herpes simplex virus **A:** Plaque inhibition assay and murine model using Balb/C mice.		**A:** Carrageenan-induced foot edema in chicks and rat assays.	**A:** Turpentine-induced pyrexia test.	Acute toxicity: LD_{50} >2000 mg/kg.
23	*Voacanga africana*[169,182,184,377]		HIV **A:** Voacamine—*in vitro* anti-HIV assay using 293 T and	Immuno-suppressive effect of voacamine **A:** Mitogen and LPS-induced	**A:** Carrageenan-induced paw edema, cotton-pellet granuloma,		Voacamine did not exhibit cytotoxic effect at low

(Continued)

Table 2. Continued

S/no	Botanical name	Antiviral activity: Respiratory	Antiviral activity: Nonrespiratory	Immunomodulatory activity	Anti-inflammatory activity	Symptoms relieving activity	Toxicity profile
			TZM-BL cells and binding affinity assay.	proliferation assays. **B:** Affinity for IL-2Rα, and cytotoxic effect and inhibition of lymphocyte proliferation.	acetic-acid induced vascular permeability, and formalin tests.		concentrations; subacute toxicity: reduction in pattern of weight gain.
24	*Vernonia colorata*[186,188,191,193]			**A:** CD4 count assay. **B:** Increase in production of cytokinase and enhanced maturation of leukocytes.	**A:** Carrageenan-induced rat paw edema test.		Acute toxicity: LD_{50} > 5000 mg/kg.
25	*Adansonia digitata*[196,206,209,378,380]	Newcastle disease virus Influenza virus Respiratory syncytial virus **A:** Virucidal assays.	Herpes simplex virus Sindbis virus Poliovirus HIV-1 **A:** Virus-induced cytopathic effects, HIV-1 reverse transcriptase, and HIV-protease assays. **B:** Virucidal activity, inhibition of HIV-1 reverse transcriptase (RT) and HIV-protease.	**A:** Delayed-type hypersensitivity in rat model. **B:** Increase in delayed-type hypersensitivity reaction and SRBC-induced antibody titer, phagocytic index, and cytokine modulation.	**A:** Formalin-induced rat paw edema test and cyclooxygenase inhibition assay. **B:** Inhibition of pro-inflammatory markers; COX-1 and COX-2.	Antipyretic activity **A:** BCG-induced fever model. **B:** Inhibition of release of pro-inflammatory markers.	Acute toxicity: LD_{50} ≥5000 mg/kg.
26	*Combretum micranthum*[213,214,219,381,382]		Herpes virus (1 and 2) **A:** Endpoint titration assay and plaque assay. **B:** Inhibition of in vitro replication.		**A:** Carrageenan- and formalin-induced paw edema, acetic acid-induced vascular permeability and cotton pellet granuloma tests. **B:** Inhibition of vascular permeability and leukocyte migration.		Acute toxicity: LD_{50} > 5000 mg/kg; subacute toxicity: relatively safe, induces liver damage with prolonged usage.
27	*Terminalia sericea*[226,383,387]		HIV-1 **A:** Methyl-3H thymidine triphosphate incorporation assay and reverse transcriptase and viral proteins inhibition assays. **B:** Inhibition of HIV-1 reverse transcriptase, RNA-dependent-DNA polymerase function, and ribonuclease H.		**A:** Ethanolic 24,6-trinitrobenzene sulfonic acid-induced colitis assay. **B:** Inhibition of myeloperoxidase activity and reduced neutrophil activation.		Short-term hepatotoxic, hypoglycemic, and nephrotoxic effects.
28	*Euphorbia hirta*[227,228,230,233,235,236,388,390]		Dengue virus HIV-1 HIV-2 Simian immunodeficiency virus (SIVmac251) **A:** *In vitro* assay on the MT4 human T lymphocyte cell line and direct effect on HIV-1,	**A:** Humoral antibody response, skin allograft rejection, delayed-type hyper-sensitivity reaction, lymphocyte immuno-phenotyping, intracellular cytokine estimation and	**A:** Prostaglandin E 2 inhibition assay on rabbit synovial fibroblast cells, neonatal asthmatic rat, lipopolysaccharide-induced RAW 264.7 macrophages, and adjuvant-induced arthritis assays.		Relatively safe following acute and subchronic administration.

(Continued)

Table 2. Continued

S/no	Botanical name	Antiviral activity: Respiratory	Antiviral activity: Nonrespiratory	Immunomodulatory activity	Anti-inflammatory activity	Symptoms relieving activity	Toxicity profile
			HIV-2, and SIV(mac251) reverse transcriptase (RT) activity. **B:** Inhibition of reverse transcriptase (RT) activity.	humoral immune parameters assays. **B:** Blockade of the production of the cell-mediated immune response, prolongation of graft rejection, decrease of delayed hypersensitivity response and primary antibody response; induction of changes in the expression of pro-inflammatory, antiviral, and adaptive immune cytokines.	**B:** Inhibition of PGE 2 production and reduction of nitric oxide, total leukocytes, eosinophils, and pro-inflammatory markers.		
29	*Aspalathus linearis*[237,243,391,394]	Influenza A virus, Oseltamivir-resistant influenza viruses A and B **A:** Crystal violet method using Madin-darby canine kidney (MDCK) cells and antiviral activity against influenza virus A/WSN/33. **B:** Inhibition at the late stages of the viral life cycle.	Rotavirus **A:** *In vitro* assay on MA-104 cells. HIV **A:** *In vitro* assay, HIV-induced cytopathicity using HIV (HTLV-III) infected MT-4 cells. **B**: Suppression of HIV-induced cytopathicity and inhibition of HIV-1 binding to MT-4 cells.		**A:** Lipopolysaccharide-mediated vascular inflammatory response action, UVB/HaCaT keratinocyte and rat colitis models. **B:** Inhibition of hyperpermeability, expression of cell adhesion molecules, adhesion and migration of leukocytes and pro-inflammatory cytokines; enhancement of UVB-induced inhibition of cell viability, proliferation, and induction of apoptosis, facilitating the removal of icIL-1α, prevention of DNA damage and anti-oxidative activity.	Broncho-dilatory activity **A:** *In vitro* assessment of the effect on Guinea-pig trachea. **B:** Relaxant effect mediated through dominant K^+ channel activation along with weak Ca^{++} antagonist mechanisms.	Subacute and subchronic toxicity: No mortality observed.
30	*Sutherlandia frutescens*[248,395,407]	Influenza virus (via L-canavanine) **A:** Assessment of effects on intracellular production of virus components and viral replication. **B:** Inhibition of assembly of viral ribonucleoprotein and formation of the mature envelope.	HIV Retroviruses **A:** Reverse transcriptase, protease, α- and β-glucosidase assays. **B:** Increase in CD4 counts, decrease in viral load, interaction with the permeability glycoprotein receptor and inhibition of reverse transcriptase.	**A:** *In vitro* assessment of normal human peripheral blood mononuclear cells, including levels of expression of 12 cytokines in treated cells using ELISA and assessment of cell viability in relation to cytokine secretion using adenosine triphosphate assay. **B:** Reduction in cytokine expression and secretion.	Anti-inflammatory activity **A:** Murine macrophage cell line, primary mouse macrophages, egg albumin-induced pedal edema and 12-*O*-tetradecanoyl-phorbol-13-acetate (TPA)-induced COX-2 expression assays. **B:** Reduction in macrophage production of ROS and NO, and alteration of NF-κB, ERK1/2, and JAK-STAT1 signaling pathways in macrophages; inhibitions of COX-2 expression, catalytic activity of extracellular signal-regulated protein kinase	Antithromb-otic activity **A:** Thrombin and clotting time assays.	Subchronic activity: No mortality was observed.

(Continued)

Table 2. Continued

S/no	Botanical name	Antiviral activity: Respiratory	Antiviral activity: Nonrespiratory	Immunomodulatory activity	Anti-inflammatory activity	Symptoms relieving activity	Toxicity profile
					(ERK), activation of activator protein-1 (AP-1) and attenuation of expression of its key component c-Fos.		
31	*Pelargonium sidoides*[253,408,416]	Influenza A viruses (HINI, H3N2) Coxsackie A9 virus Human coronavirus Respiratory syncytial virus Parainfluenza virus 3 **A:** Haemagglutinin and neuraminidase inhibitory and resistance assays. **B:** Inhibition of replication of viruses, haemagglutinin and neuraminidase present on the surface of the influenza virus.	HIV-1 Herpes simplex viruses (HSV-1, HSV-2). **A:** Plaque reduction assay and multiple cell culture assays. **B:** Interference with viral infectivity and blockage of the attachment of HIV-1 particles to target cells.	**A:** *In vitro* model for intracellular diseases, fibroblast-lysis and fibroblast-virus protection, biochemical and gene expression assays. **B:** Augmentation of activation of host defense mechanisms, modulation of the IFN system, and macrophage activation.		Respiratory tract diseases **A:** Ammonia- and citric acid-induced cough in mice, tracheobronchial secretion of intraperitoneally injected phenol red and acute bacterial bronchitis models. **B:** Antitussive, secretolytic and anti-inflammatory activities mediated by up-regulation of superoxide dismutase and protective effect against oxidative stress.	No toxic effects.
32	*Hypoxis hemerocallidea*[254,398,399,417,419]				**A:** Cyclooxygenase assay. **B:** Inhibition of cytokine production, COX-1 and COX-2 activity, and reduction of the activity of transcription factors.		Chronic infusion is associated with impairment of kidney function, bradycardia and transient hypotension, increase myocardial contractility and bone marrow suppression.
33	*Hibiscus sabdariffa*[263,420,426]		Measles virus **A**: Pre-and Post-inoculative treatment on Hep-2 cells.	**A:** Red blood cell-induced immunostimulation model. **B:** Increase in the production of IL-10 and decrease in the production of TNF-α.	**A:** Carrageenan-induced edema and lipopolysaccharide-induced inflammation models. **B:** Impairing cyclooxygenase-2 induction by down-regulating JNK and p38 MAPK.	Antipyretic activity **A:** Yeast-induced fever model.	Acute toxicity: LD_{50} > 5000 mg/kg; chronic toxicity: no deleterious manifestations observed.
34	*Moringa oleifera*[264,267,427]		HSV (Type 1 and 2) Hepatitis B virus (genotype C and H) **A:** Effect on virus cultured on Vero cells and transfection of selected clones (pHY-H) into Huh7 cells.	**A:** Immuno-enhancing property through the activity of sitosterol or phytosterol.	**A:** Cotton pellet-induced granuloma, carrageenan, and formaldehyde-induced paw edema tests.	Anticoagulant activity **A:** Evaluation of protease activity using human plasma clot, human fibrinogen, and casein as substrates.	Acute toxicity: $LD_{50} \leq$ 6400 mg/kg p.o.; subchronic toxicity: no deleterious manifestations observed.

(Continued)

Table 2. Continued

S/no	Botanical name	Antiviral activity: Respiratory	Antiviral activity: Nonrespiratory	Immunomodulatory activity	Anti-inflammatory activity	Symptoms relieving activity	Toxicity profile
			B: Decrease in expression of HBV surface antigen for both genotypes and reduction in replication of HBV genotype C but not genotype H.			and detection of proteolytic enzymes. **B:** Increase in caseinolytic, human plasma clot hydrolysis, fibrinogenolytic and fibrinolytic activities.	
35	*Prunus africana*[269,272]		Human cytomegalovirus (HCMV) Herpes simplex virus type 1 (HSV-1) **A:** Plaque inhibition assay and *in vivo* assessment in Balb/C mice following cutaneous wild type strain 7401H HSV-1 infection. **B:** Reduction in replication of HCMV.				Acute toxicity: LD_{50} ≤5000 mg/kg; subchronic toxicity: mildly nephrotoxic and hepatotoxic.
36	*Toddalia asiatica*[275,276,278]	Influenza Type A virus **A:** 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium (MTS) assay for viral-induced cytopathic effect (CPE) and qPCR to assay for the depletion of viral RNA.			**A:** Carrageenan-induced paw edema test.		Acute toxicity: No mortality observed, but induced liver enzymes, elevated total cholesterol and nephrotoxicity observed.
37	*Aloe ferox*[279,280,428,429]		Herpes simplex virus Type 1 **A:** Effect on HSV-1 cultured on monolayers of Vero cells.		**A:** Carrageenan, histamine and formaldehyde-induced rat paw edema tests.		Acute toxicity: LD_{50} > 5000 mg/kg.
38	*Nigella sativa*[284,430,441]	Avian influenza virus (H9N2) **A:** Murine BALB/c cytomegalovirus infection model.		**A:** Effect on human immune system in normal volunteers; assays using human lymphocytes and macrophages; evaluation of effect on cellular and humoral adaptive immune responses; investigation in BALB/c mice and C57/BL6 primary cells. **B:** Increase in the ratio of helper to suppressor T cells; enhancement of natural killer cell activity; increased production of IL-3 by	**A:** Carrageenan-induced paw edema test. **B:** Radical scavenging activity and interaction with molecular targets involved in inflammation (pro-inflammatory enzymes and cytokines).	Spasmolytic and broncho-dilatory effects. **A:** Respiratory system of Guinea-pig model and histamine release from rat peritoneal mast cells *in vitro* assay. **B:** Amelioration of histamine-induced broncho-spasm; spasmolytic and broncho-dilatory	Acute and chronic toxicity: No death observed; LD_{50} of *N sativa* seed fixed oil was 29 mL/kg.

(Continued)

Table 2. Continued

S/no	Botanical name	Antiviral activity		Immunomodulatory activity	Anti-inflammatory activity	Symptoms relieving activity	Toxicity profile
		Respiratory	Nonrespiratory				
				human lymphocytes and stimulatory effect on macrophages, enhancement of splenocyte proliferation; and suppression of secretion of IL-6, TNF-α, and NO by primary macrophages.		activities via calcium channel blockade; and inhibition of histamine release from rat peritoneal mast cells *in vitro* via decreased intracellular calcium through inhibition of protein kinase C and oxidative energy metabolism. Antithrombotic effect. **A:** Arachidonic acid-induced platelet aggregation and blood coagulation; adenosine diphosphate-induced platelet aggregation; and fibrinolysis assay. **B:** Inhibitory effects on platelet aggregation and blood coagulation; fibrinolysis promotive action; and inhibitory effects on adenosine diphosphate-induced platelet aggregation.	

A: Method; **B:** Mechanism(s).

the formalin-induced rat paw edema test.[196] Some authors have reported that BCG through the inflammatory pathway causes the release of pro-inflammatory markers, including TNF, IL-1β, IL-6, and C-reactive protein.[378,379] In a reported study, the stem-bark methanol extract of *A digitata* ameliorated BCG-induced fever and depression suggesting possible involvement of anti-inflammatory mechanisms.[209]

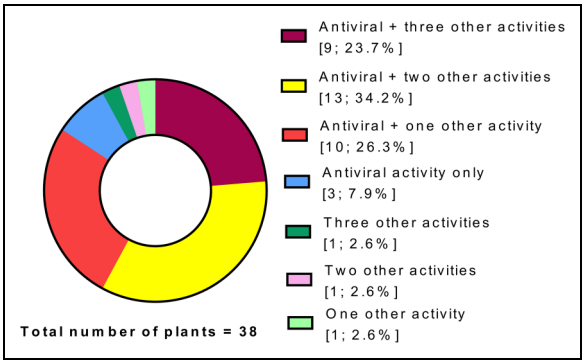

Figure 1. Distribution of plant activities. Values in parenthesis represent number of plants demonstrating specified activities and corresponding percentage.

The methanol leaf, root-bark, and fruit pulp extracts of the plant have been reported to increase the delayed-type hypersensitivity reaction significantly.[205] This suggests the capability to stimulate T-cells. Likewise, the extracts increased sheep red blood cell count (SRBC) induced antibody titer in immune-suppressed rats. Also, there was a significant increase in the phagocytic index.

The root-bark methanol extract showed activity against herpes simplex, sindbis, and polioviruses. Similar effects were elicited by the leaf methanol extract of *A digitata*.[197] Virucidal actions on herpes simplex of the leaf and root-bark methanol extracts have been established.[198] The inhibitory effect of the methanol fruit pulp, leaf, and root-bark extracts in HIV-1 reverse transcriptase (RT) and HIV-protease assays was also reported.[200,206] The root-bark methanol extract demonstrated antiviral activity in respect of Newcastle disease virus in-ovo.[201] Methanol, DMSO, and water extracts of the leaves were reported as having the most potent effect on influenza virus. The leaf extracts were also active as cytokine modulators.[199]

In the phytochemical investigation of the plant, procyanidin B2, feruloylquinic acid, catechin, epicatechin and their oligomers, procyanidin dimer I and II, procyanidin trimer I and II, quercetin 3-*O*-glucoside, kaempferol 3-*O*-galactoside, kaempferol

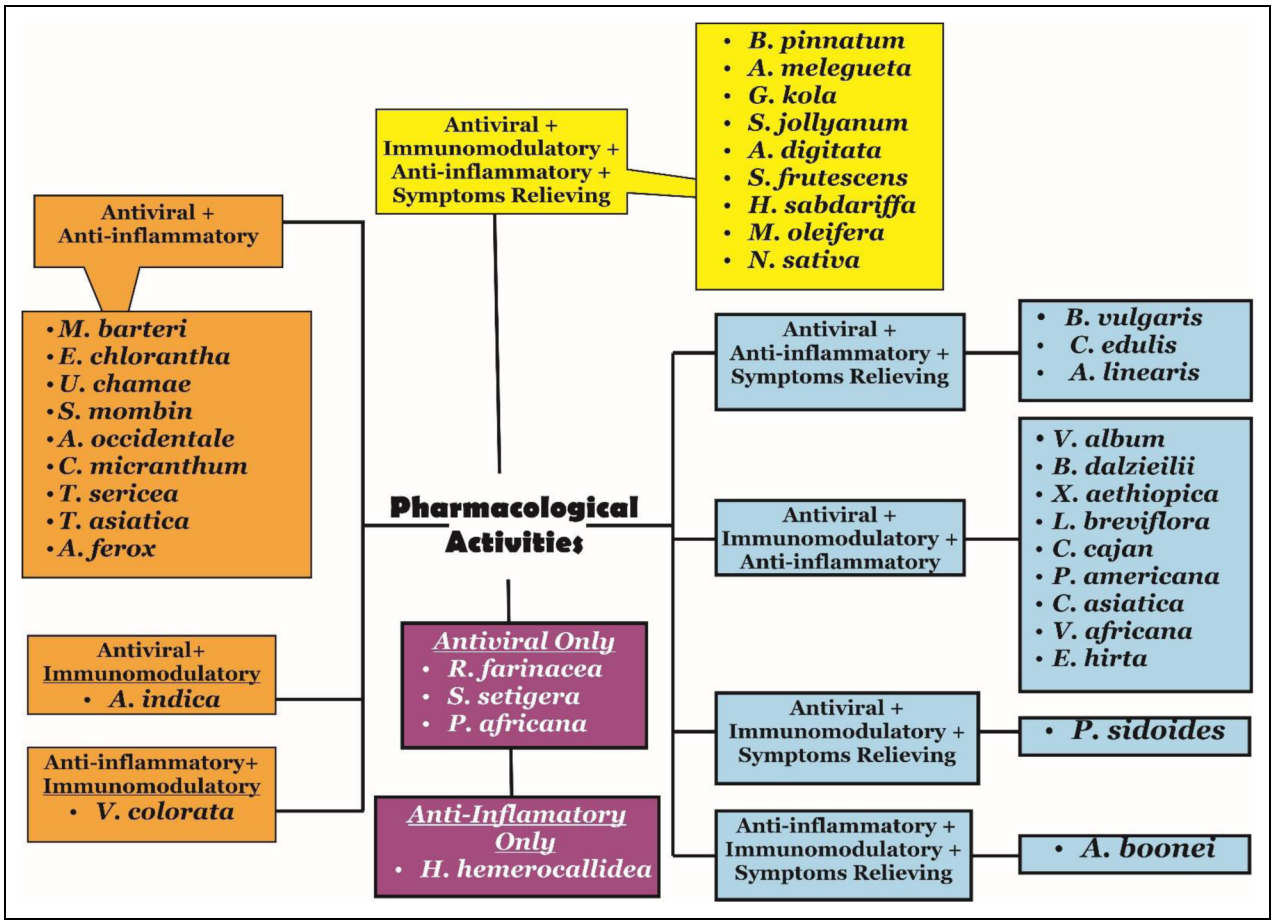

Figure 2. Specific activities distribution of plants.

3-*O*-glucoside, tiliroside I and II, and kaempferol were isolated.[202,208]

In the toxicity study, the oral LD_{50} of the stem-bark methanol extract of the plant was reported to be ≥5000 mg/kg,[209] while the i.p. LD_{50} of the fruit pulp aqueous extract was 8000 mg/kg, underlining its safety.[196]

Aframomum melegueta K Schum. (Zingiberaceae) is native to tropical regions of Africa as a perennial spice. The plant has reddish, brown, hard seeds, commonly known as Guinea pepper/grains, alligator pepper, melegueta pepper, or grains of paradise. The seeds are extensively used as a common ingredient in many traditional medicines, including for the treatment of skin and throat infections.[452] It is also used for the treatment of intestinal infections, inflammatory conditions, measles, and diarrhea.[99,453] The ethanol extract of the plant inhibited yellow fever and measles viruses. MICs were respectively 250 and 125 μg/mL. Poliovirus type 1 was not susceptible to the extract.[96] The antiadhesive effect of the methanol extract, fractions, and major phenolics on lower respiratory tract pathogens has also been reported.[103]

The significant inhibitory effect of the methanol extract and light petroleum fraction of the plant on ear edema induced with xylene and paw edema induced with egg albumin in rodents has been established,[329] as well as the acute and chronic inflammatory responses inhibition in rats reported for the seed extract.[328] The authors further reported the effects of the aqueous seed extract on leukocyte migration.[330] Report of the anti-inflammatory activity associated with COX-2 enzyme activity and expression of pro-inflammatory genes inhibition for the ethanolic extract of the seeds of the plant has been documented.[334] The spasmolytic activities of the aqueous seed extracts of the plant and *Citrus aurantifolia* mixture were investigated on isolated rat trachea and an EC_{50} of 1.80 ± 0.48 mg/mL was obtained.[332]

The immunomodulatory property of the extract on the activation of RAW 264.7 macrophages showed remarkable inhibition in the generation of NO and TNF-α with CC_{50} of 169.89 ± 6.89 μg/mL and 144.59 ± 7.89 μg/mL, respectively.[335]

An i.p. LD_{50} of 2154 mg/kg for the methanol extract of the seed in an acute toxicity test in mice has been reported, while an LD_{50} of 273.86 mg/kg was recorded for the seed oil, indicating mild toxicity.[329,333] A dose-dependent liver enlargement and elevation in alkaline phosphatase was observed in a 28-day subchronic toxicity study in rats.[331] In another study, the methanolic seed extract of the plant demonstrated potential hepatotoxicity at 300 mg/kg.[454]

Several compounds have been isolated from *A melegueta* seeds, including 3-(S)-acetyl-1-(4′,5′-dihydroxy-3′-methoxyphenyl)-7-(3″,4″-dihydroxyphenyl) heptane; dihydrogingerenone A; dihydrogingerenone C; 3,5-diacetoxy-1-(3′,4′-dihydroxylphenyl)-7-(3″,4″-dihydroxy-5″-methoxyphenyl) heptane; 6-paradol; [6]-gingerol; [6]-shogaol; [8]-gingerol; dihydro[6]paradol; (S)-9-hydroxy-[6]-paradol; (9S)-3,9-dihydroxydihydro-[6]-paradol; and (3S,5S)-3,5-dihydroxy-1-(4-hydroxy3-methoxyphenyl)decane.[99,104]

Bryophyllum pinnatum (Lam.) Oken is a fleshy herbaceous perennial plant with an erect stem. It can be widely found in tropical and subtropical areas. The plant is applied in ethnomedicine to manage pathologies such as abdominal discomforts, sepsis, asthma, blisters, burns, chest colds, chicken pox, cholera, constipation, cough, cuts, eczema, edema, epilepsy, fever, menstrual disorders, piles, psychiatric disorders, and rheumatoid arthritis. Specifically, the leaf extracts are applied in the management of diabetes, hypertension, infections, jaundice, and renal stones, while the leaves, when slightly heated, can be applied to dermal infections, fever, gout, abscesses, and palpitations.[29,31]

A review has documented many studies that have been carried out on the medicinal value of *B pinnatum*.[455] This plant has several studies that reported on the anti-inflammatory activity of the different parts. The aqueous root extract has been reported to be active as an anti-inflammatory agent in an *in vitro* investigation using a protein denaturation method, with an IC_{50} value of 570.24 μg/mL.[34] Single topical application of the ethanol extract inhibited mice ear edema induced by croton oil (57%, inhibition), arachidonic acid (67%, inhibition), phenol (80%, inhibition), capsaicin (72%, inhibition), and EPP (75%, inhibition).[291] The methanolic extract of the leaves has also been reported to inhibit formaldehyde-induced paw edema in rats.[33] The aqueous leaf extract (25-800 mg/kg p.o. or i.p.) also inhibited fresh egg albumin-induced acute inflammation.[32] The anti-inflammatory activity of the fluid extract of the leaves against edema caused by carrageenan in rats has been reported.[456] Stigmast-4, 20 (21), 23-trien-3-one from the aqueous leaf extract of *B pinnatum* was reported to reduce inflammation in the carrageenan-induced inflammation model.[289] Antiviral activity was reported for *B pinnatum* leaf extract as it inhibited the measles virus and Herpes Simplex Virus-1 at 0.016 μg/μL.[41]

The extract of *B pinnatum* reduced the percentages of Th1, Th2, Th17, and mature B cells in a dose-dependent manner in an experiment to modulate the immune response and pregnancy outcomes in gravid mice.[292] The ethanol extract of the leaves had modulatory propensity on hematological parameters.[293] The extract was reported to increase the PCV and hemoglobin levels. No significant variation was observed between white blood cell proliferation of the experimental animals and the control group. Reports showed that there was significant inhibition of cell-mediated and humoral immune responses from the application of the aqueous extract of leaves in mice.[286] Moreover, leaf extracts of the plant inhibited *in vitro* lymphocyte proliferation and exhibited *in vivo* immunosuppressive activity.[287] A purified fraction (KP12SA) from the ethanolic extract of *B pinnatum* was observed as having twenty-fold better potency toward the blocking of murine lymphocyte proliferation than the crude extract.[286]

An *ex vivo* SYBR Green I fluorescence assay was used to investigate the antimalarial activity of the ethanol extract of *B pinnatum* in another study. This investigated antiplasmodial activity against both chloroquine-sensitive Pf3D7 and chloroquine-resistant PfINDO strains of *Plasmodium falciparum* both grown in human red blood cell cultures. The plant

extract showed an IC_{50} value of 11 to 20 μg/mL.[457] A combination of *Aloe barbadensis* and *B pinnatum* administered orally to *Plasmodium berghei* infected albino mice resulted in a significant reduction in malaria density at 10^{-1} and 10^{-3} mg/mL concentrations.[458] The antiasthmatic effect of the aqueous extract of the leaves of *B pinnatum* (400 mg/kg/d) was reported as it inhibited histamine-induced bronchospasm in Guinea pig.[290] Several authors reported the antioxidant potentials of different parts of the plant.[459,460]

Literature on phytochemical studies on *B pinnatum* is extensive. There have been reports of the isolation of 3,8-dimethoxy-45,7 trihydroxyflavone, astragalin, epigallocatechin-3-*O*-syringate, friedelin, kaempferol, luteolin, rutin,[461] quercetin-3L-rhamonsido-L-arabino furanoside,[462] and kaempferol-3-*O*-α-L-arabinopyranosyl (1→2) α-L-rhamnopyranoside from the plant.[463] Compounds such as 18-α-oleanane, α-amyrin, β-amyrin, α-amyrinacetate, β-amyrinacetate, bryophollenone, bryophyllol, bryophynol, bryophillin A and B, cardienolide, friedelin, glutinol, β-sitosterol, taaxerol, and pseudo taraxasterol were all reported to have been isolated from this plant.[461] The presence of the following compounds in *B pinnatum*: anthocyanins, bufadienolides, bryophyllol, bryophynol, bryophyllin derivatives, bersaldegenin-3-acetate, bryotoxin A, bryotoxin B, coumarins, kaempferol, kaempferol-3-glucoside, kaempferol-3-*O*-α-L-arabinopyranosyl(1,2) α-L-rhamnopyranoside, lectins, luteolin, malic acid, quercetin, quercetin-3L-rhamonsido-L-arabino furanoside, quercetin-3-*O*-diarabinoside, quercetin-3-*O*-α-L-arabinopyranosyl (1,2) α-L-rhamnopyranoside, quinines, sitosterol, syringic acid, rutin, and tocopherol have also been documented in the plant.[289,464] The plant also contains bryophollone,[462] taraxerol, Ψ-taraxasterol,[465] pseudo taraxasterol, 18-αoleanane, friedelin, glutinol, bryotoxin C,[466] campesterol,[467] 24-ethyl-25-hydroxycholesterol, isofucosterol,[468] clionasterol,[462] codisterol, peposterol, 22dihydrobrassicasterol,[469] clerosterol, 24-epiclerosterol, 24ethyl-desmosterol,[470] 5α-stigmast-24-en-3β-ol, 25-methyl-ergosta-5-24(28)-dien3-β-ol, 25-methyl-5α-ergost-24(28)-en-3β-ol, ergosta-5-24(28)-dien-3-β-ol, (24 s)-stigmast-25-en-3-β-ol, (24r)-5α-stigmasta-7-25-dien-3-β-ol, (24 s)-5α-stigmasta-7,25dien-3-β-ol, 24(R)-stigmasta-5,25-dien-3β-ol, stigmasterol,[471] patuletin,[472] 3-*O*-(4-*O*-acetyl-α-L-rhamnopyranosyl)-7-*O*-(2-*O*-acetyl-α-L-rhamnopyranoside) patuletin, 3-*O*-α-L-rhamno pyranosyl-7-*O*-(2-*O*-acetyl-α-L-rhamnopyranoside) patuletin, and 3-*O*-(4-*O*-acetyl-α-L-rhamnopyranosyl)-7-*O*-rhamno pyranosidepatuletin.[67,473,474] The ethyl acetate fraction of the whole plant extract also yielded afzelin, kaempferol 3-*O*-α-L-(2-acetyl)rhamnopyranoside-7-*O*-α-L-rhamnopyranoside, kaempferol 3-*O*-α-L-(3-acetyl)rhamnopyranoside-7-*O*-α-L-rhamnopyranoside, kaempferol 3-*O*-α-L-(4-acetyl) rhamnopyranoside-7-*O*-α-L-rhamnopyranoside, kaempferol 3-*O*-α-D-glucopyranoside-7-*O*-α-L-rhamnopyranoside, kaempferitrin, and α-rhamnoisorobin.[459]

Furthermore, the intraperitoneal LD_{50} was reported to show acute toxicity of the leaf extract at 1.8 g/kg body weight. The subacute treatment of 35 days was reported not to significantly alter animal organ-to-body weight ratios; fluid intake; weights; hematological indices and the levels of AST; ALP and albumin.[288] It was also reported that the subacute treatment of the aqueous extract of *B pinnatum* leaf on Wistar rats' hematological, renal, and testicular functions elicited elevation of white blood cell count; reduction in neutrophil count without affecting lymphocyte count and packed cell volume.[294] Another study conducted on the testes of rats treated with ethanolic fractions of the leaves of *B pinnatum* suggested increased intercellular spaces within the seminiferous epithelium, shrunken, and increased lumen resulting in cells disintegration and adverse effect on the testes of treated rats.[295]

Garcinia kola is obtainable in the rain forest of some countries of Central and West Africa, such as Benin, Cameroon, Cote d'Ivoire, Democratic Republic of Congo, Gabon, Ghana, Liberia, Nigeria, Senegal, and Sierra Leone.[475] The plant has no obvious sign of acute intoxication after a 48-h observation period at an LD_{50} above 5000 mg/kg in both mice and rats.[141,142] The bioactive constituents are apigenin, benzophenone, coumarin, kolaviron, garciniabiflavonoid (GB)-1a-glucoside, GB-1a, GB-1, GB-2, kolaflavonone, xanthone, quercetin, garcinoic acid,[145] amentoflavone, apigenin 5,7,4,-trimethyl ether, apigenin-4-methylether, fisetin, and kolaflavanone.[476] Traditional medicine practitioners apply extracts of the bark and seed for the management of some diseases such as bronchitis, liver cirrhosis, hepatitis, liver disorder, diarrhea, laryngitis, and gonorrhea.[139] Kolaviron has been identified to be an antiviral bioflavonoid in both *in vitro* and *in vivo* studies.[140] Drawing from the antiviral potentials of *Garcinia kola*, specific investigation of this medicinal plant on SARS-CoV-2 is advocated toward drug development for COVID-19.

Moringa oleifera (Moringaceae) is a pan-tropical species commonly grown in Africa and Asia. Preparations made from *M oleifera* (leaves and roots) are being used by traditional medicine practitioners as antiviral, antibacterial, antioxidant, antihypertensive, antitrypanosomal, antiulcer, antidiabetic, antipyretic, anti-inflammatory, anthelmintic, antispasmodic, anticonvulsant, anticancer, diuretic, hepatoprotective, hypoglycemic, and hypocholesterolemic drugs. Due to its numerous health benefits, *M oleifera* is popularly regarded as a "miracle tree."[477]

Effect of the anti-inflammatory effect of *M oleifera* leaves on albino rats has been reported.[267] Using the cotton pellet induced granuloma method, carrageenan-induced paw edema model, and formaldehyde-induced paw edema method, the investigators recorded a significant anti-inflammatory activity at a dose of 200 mg/kg/d. The protease activity of *M oleifera* aqueous extracts against the blood coagulation cascade (procoagulation activity) has been reported.[265] The researcher assayed for protease activity using human plasma clot, human fibrinogen, and casein as substrates; zymographic techniques were used to detect the presence of proteolytic enzymes. The result from this study showed a significantly higher caseinolytic activity of the leaf extract compared to that of the root extract. Similarly, human plasma clot hydrolyzing activity was significantly higher in the leaf when compared to root extract. A

significant procoagulant activity determined by a notable decrease in recalcification time, followed by fibrinogenolytic and fibrinolytic activities was observed with both extracts. At a concentration of 2.5 mg/mL, a significant decrease in clotting time from 180 ± 10 s to 119 ± 8 s and 143 ± 10 s was observed for both the leaf and root extract, respectively. Both extracts were shown to selectively hydrolyze Aα and Bβ subunits of fibrinogen to fibrin clot. However, prolonged exposure to these extracts resulted in degradation of the previously formed fibrin clot, signifying possible fibrinolytic activity.

The antiviral potential of *M oleifera* leaf against Herpes simplex virus type 1 and type 2 cultured on Vero cells has been evaluated.[266] Findings from this study revealed 43.2% and 21.4% inhibition of HSV-1 and HSV-2, respectively, at 200 μg/mL of the leaf extract. The antiviral property of *M oleifera* against hepatitis B virus (genotype C and H) was also reported.[427] In the study, hepatitis B virus genome was successively cloned in pGEM-T EASY (Promega) and pHY-106 vectors. pHY-106 contains the minimum HBV sequence required for viral replication and transcription after insertion of a full-length HBV genome. Selected clones (pHY-H) were transiently transfected into Huh7 cells. The transfected cells were subsequently treated with various concentrations of *M oleifera* extract. Findings from this study revealed a decrease in the expression of hepatitis B virus surface antigen (for both genotypes), regardless of the extract's concentration. Conversely, a slight reduction was only observed in replication of the HBV genotype C, but not in genotype H.

The presence has been reported of constituents of *M oleifera* such as gallic tannins, steroids and triterpenoids, catechol tannins, anthraquinones, saponins, reducing sugars, and alkaloids.[477] A report of some phytochemicals in *M oleifera* leaf extract have been documented such as: 2,2,3,3,5,6,,6-heptamethyl, dibutyl phthalate, 4-dodecanol, hexanedioic acid, bis (2-ethylhexyl); Z6, Z9-pentadecadien-1-ol, heptane, 1,2-benzenedicarboxylic acid, mono(2-ethylhexyl) ester, hentriacontane, 1-nonene, 46,8-trimethyl, 1-hexanol, 2-ethyl-2-propyl, squalene, trimethyl (4-tert-butyphenoxy) silane, tetracontane-1,40-diol, tetrapentacontane and dotriacontane, D.L. alpha–tocopherol, oxirane, hexadecyl, beta-amyrin, and 24,6-cycloheptatrien-1-one,3,5-bis-trimethylsilyl.[266]

Due to its consideration as a "miracle tree," *M oleifera* is widely consumed by all. In order to ascertain the safety index of this plant, the toxicological effect of the aqueous leaf extract of *M oleifera* on male Wistar albino mice was investigated.[264] For acute toxicity assay, the extract was administered orally and intraperitoneally with a respective dosage of ≤6400 mg/kg and ≤2000 mg/kg. For subchronic toxicity effect, a second group of the test animals was given daily oral doses of 250, 500, and 1500 mg/kg for a period of 60 days. Findings from this study revealed no significant difference ($P \geq .05$) in hematological, sperm quality, and biochemical parameters. The LD_{50} of the aqueous extract was estimated to be 1585 mg/kg. Prolonged use of *M oleifera* leaves exhibited significant ($P < .05$) increases in serum AST, BUN, ALT, and creatinine, which pointed to hepatic and kidney damage.[478]

Nigella sativa (Ranunculaceae), commonly known as black cumin, is a native herbaceous plant of Southwest Asia and is cultivated in the Middle East, Southern Europe, and North Africa.

The seeds are used in the treatment of asthma, bronchitis, rheumatism, and other inflammatory diseases. They are also reported to be used for the treatment of paralysis, dyspepsia, jaundice, intermittent fever, piles, and skin diseases.[479] Various pharmacological properties ranging from anti-inflammatory, spasmolytic, antihypertensive, antidiabetic, anticancer, immunomodulatory, analgesic, bronchodilator, gastroprotective, antimicrobial, anthelmintic, and hepatoprotective to renal protective properties have been reported for the plant.

Thymoquinone from the seed fixed oil has been reported to have antiviral activity against avian influenza virus (H9N2)[440] and murine BALB/c cytomegalovirus infection. The seed oil has also been reported to exhibit anti-inflammatory activity by reduction in edema and granuloma weight in carrageenan-induced paw edema and cottonseed pellet granuloma, respectively.[441,480] Inhibition of cyclooxygenase and 5-lipoxygenase pathways has also been reported in peritoneal leukocytes of rats.[481] The essential oil from *N sativa* has been reported to have an analgesic effect when investigated using acetic acid-induced writhing, formalin, and light tail flick assays.[482] Spasmolytic and bronchodilatory activities of the crude extracts of the seeds have also been shown.[435]

The protective ability of the oil of *N sativa* against histamine-induced bronchospasm in Guinea pigs has been reported.[430,437] *N sativa* seed crude extract elicited spasmolytic and bronchodilatory activity through calcium channel blockade.[435] Nigellone from *N sativa* has also been reported to inhibit histamine release from rat peritoneal mast cells *in vitro*.[432] This effect has been associated with a reduction in intracellular calcium through inhibition of protein kinase C and oxidative energy metabolism.[437]

The antithrombotic effects of components of *N sativa* oil have been demonstrated, as well as inhibitory actions on arachidonic acid-induced platelet aggregation and blood coagulation.[284,483] The oil obtained from *N sativa* seeds also enhanced fibrinolysis and exhibited inhibitory activity on adenosine diphosphate-induced platelet aggregation.[284]

The immunomodulatory properties of *N sativa* and its major active ingredient, thymoquinone, and the ability to modulate cellular and humoral adaptive immune responses have been documented.[439] In the investigation of the immunomodulatory effect with respect to splenocyte proliferation, macrophage function, and antitumor activity in BALB/c mice and C57/BL6 primary cells, the aqueous extract of *N sativa* showed potential immunomodulatory effect with enhanced splenocyte proliferation.[438]

Aqueous extract of *N sativa* was reported to have an anti-inflammatory effect *in vitro* as suppression of the secretion of key pro-inflammatory mediators (IL-6, TNF-α, and NO) by primary macrophages was observed. Based on another report, the extract of *N sativa* seeds elicited an increased ratio

of helper to suppressor T cells and enhanced the functionality of natural killer cells.[431] Boosting of the production of IL-3 by human lymphocytes, as well as stimulation of macrophages by *N sativa* has also been reported.[433]

Alkaloids (nigellone, nigellidine, nigellimine, and nigellicine), triterpenoids (cycloart-23-methyl-7,20,22-triene-3b, 30-diol and cycloart-3-one-7,22-diene-24-ol) and aliphatic compounds (4-hydroxy undecyl nonanoate, 14,20-dimethyl heptacosanol) have been isolated from the seeds of *N sativa*.[282,484]

The volatile oil from the seeds has been reported to contain thymoquinone as the main active constituent, as well as nigellone, thymohydroquinone, dithymoquinone, thymol, carvacrol, α-pinene, β-pinene, carvacrol, t-anethole, 4-terpineol, longifoline d-limonene, d-citronellol, and *p*-cymene.[283,284] The contents of the fixed oil include arachidonic, eicosadienoic, linoleic, linolenic, oleic, almitoleic, palmitic, stearic, and myristic acids, β-sitosterol, cycloeucalenol, and cycloartenol.[283]

Toxicological evaluation of the fixed oil from the seed of the plant fed to rats for 8 and 12 weeks showed no significant changes in vital organs, red and white blood cells, cardiac enzymes, liver enzymes, urea, creatinine, albumin, and total protein.[483,485] Another study carried out on the oil at 200 mg/kg/d for 14 weeks showed no histopathological changes in liver, kidney, spleen, lungs, stomach, intestine, testes, and thyroid gland.[486] An LD_{50} of 29 mL/kg was reported for the fixed oil from the seed in mice and rats.[483]

Sphenocentrum jollyanum Pierre (Menispermaceae) is known by diverse local names, including Akerejupon (South west Nigeria), Aduro koko/Okraman Kote/Krakoo (Ghana), Oban abe (Benin Republic), and Ouse-abe (Cote d'Ivoire). It is a perennial undergrowth of dense forest found in deep shade and is widely cultivated in Cameroun, Sierra Leone, Nigeria, Ghana, and Côte d'Ivoire. Traditionally, *S jollyanum* is used to treat wounds, fever, coughs, high blood pressure, and constipation.[158]

Higher anti-inflammatory activity of the fruit extract was reported when compared with the root extract in the carrageenan-induced hind paw edema model.[156] The activity of the leaf and root extracts against poliovirus Type 2 has also been reported.[154] The light petroleum and methanol leaf extracts have also been reported to have *in vitro* antipyretic activity.[369] Anti-allergic activity of the ethanolic fruit extract in milk-induced leukocytosis and eosinophilia mice with a decrease in absolute eosinophils has also been reported.[159]

Phytochemical investigations revealed the presence of sphenocentroside A, sphenocentroside B, polypodoaurein, polypodine B, ecdysterone and 20, 26-dihydroxyecdysone in the root, as well as isocolumbin, fibleucin in the fruit.[156,487] The ethyl acetate and n-butanol fractions of the seed yielded pinnatasterone, polypodine B, 20-hydroxyecdysone, 20, 26-dihydroxyecdysone and atrotosterone A.[488] Columbin has been isolated from the seed and root extracts.[156,489] The methanol extract of the stem bark was reported to contain saponins, tannins, alkaloids, and terpenes.[490] α-Eudesmol, α-pinene, isocaryophyllene, 1,8-cineole, β-pinene, camphene, B-pinene, d3-carene, p-cymene, 1,8-cineol, γ-terpinene, α-ylangene, aromadendrene, γ-humulene, epi zonarene, δ-amorphene, guaia-6,9-diene-4α-ol, globulol, and 5-guaiene-11-ol were identified in the root oil.[491]

In respect of toxicological studies, *S. jollyanum* root oil was reported to be moderately toxic to brine shrimp with an LC_{50} of 84.87 ppm.[491] The hepatoprotective potential has been documented of the stem bark extract in CCl_4-induced liver damage in rats with reversal of elevated aspartate aminotransferase, alkaline phosphatase, alanine aminotransferase, total bilirubin, and decrease in the level of total serum protein.[157] No adverse toxicological effect was reported for the ethanolic extract of the root at 100 to 1000 mg/kg for 90 days of treatment. Also, no mutagenic potential was observed in the reverse mutation test using several strains of *Salmonella typhimurium*.[492] No mortality or morbidity for the leaves of the plant was reported in acute and subchronic toxicity studies.[370]

Sutherlandia frutescens R.Br. (Fabaceae) is indigenous to Southern Africa, including South Africa, Lesotho, southern Namibia, and southeastern Botswana.[248] It is a medium-sized shrub, with fine grayish-green leaves and red butterfly-shaped flowers.[406]

In South Africa, *Sutherlandia* is used by traditional medicine practitioners to wash wounds and bring down fevers. The infusions from the leaves and stems are used to treat cancers, fever, diabetes, kidney and liver problems, rheumatism, and stomach ailments. *Sutherlandia* is available in various dosage forms; the tablets being popularly used for the treatment of muscle-wasting effects in patients with HIV/AIDS.[248]

The leaf extract has been reported to stimulate reverse transcriptase activity in the presence of tannin[406] and modulate cytokine secretion in unstimulated normal PBMCs *in vitro*.[405] In addition, *S frutescens* shoot aqueous extract possesses antiinflammatory activity in the fresh egg albumin-induced edema model.[397]

A large number of compounds that may be responsible for the medicinal activity of *Sutherlandia* have been reported. Pinitol has been found to possess insulin-like properties while L-canavanine (2-amino-4-guanidinooxybutyric acid) is reported to abate pancreatic cancer.[493] There have not been any serious adverse effects on the use of *S. frutescens*, although symptoms such as occasional dry mouth, mild diuresis, and slight dizziness have been observed in weak patients when the herb is administered on an empty stomach. A scientific study recommended a daily dose of *Sutherlandia* leaf powder as 9.0 mg/kg body weight, which is equivalent to 2 *Sutherlandia* tablets per day, each containing 300 mg of *Sutherlandia* dried leaf powder each.[403] In phase I clinical trial in healthy adults, no side effects were reported during or 3 months after the trial period.[402]

Hibiscus sabdariffa L. (Malvaceae), commonly known as roselle, hibiscus, and red sorrel in English, is widely cultivated in both tropical and subtropical regions. It is an annual, erect shrub with a red stem and simple, toothed margin leaves. Fresh or dried calyces of *H. sabdariffa* are used in the preparation of herbal drinks known by different names in many countries. In Egypt, the fleshy calyces are used in making "cacody tea," while in Sudan and Nigeria, the calyces are boiled with sugar to produce a drink known as "Karkade" or "Zoborodo."[494,495]

Traditionally, the plant is used for its diuretic, choleretic, febrifugal, and hypotensive effects, in many parts of Africa and China.[260] In India, a decoction from the seeds is used to relieve pain in urination and indigestion. In Brazil, the roots are believed to have stomachic and emollient properties.[260] In Iran, sour hibiscus tea is reportedly a traditional treatment for hypertension, while in Nigeria the decoction of the seeds is used to enhance or induce lactation in cases of poor milk production, poor let-down, and maternal mortality.[261]

Pharmacological studies documented for the plant include its antiviral activity against Measles Virus (MV) and Hep-2 cells.[424] The study reported that the extract exhibited antiviral activities only at 10 and 15 mg/mL on MV in pre-inoculative treatment. *H. sabdariffa* tea extract was applied against Influenza A virus (IAV) using an animal model.[496] The study evaluated the influence of pH on the effective activities of the plant extract and reported that the pH of hibiscus tea extract is acidic, and its rapid and potent antiviral activity relied largely on the acidic pH. The authors concluded that the low-pH-independent activity had no effect on the conformation of immunodominant hemagglutinin protein. There was a report on the immunomodulatory effect of water and alcohol extracts *H. sabdariffa* in a mouse model.[421] The authors evaluated the ability of the extracts to inhibit or enhance the production of 2 cytokines (tumor necrosis factor-α and interleukin-10) compared to levamisole. The authors reported a low production of tumor necrosis factor-α in all the extract groups tested, while the production of interleukin 10 was high compared with the control. Moreover, anti-inflammatory activities have been reported for the leaves[420,497] and the calyx of *H. sabdariffa*.[498] The effect of the extract, which resulted in a dose-dependent reduction in LPS-induced NO production in RAW 264.7 cells, has also been reported.[497] The extract possessed anti-inflammatory properties against carrageenan-induced inflammation similar to the action of diclofenac.[420] The effect of *H. sabdariffa* calyces on nociceptive response and antipyretic activity in yeast-induced fever in rats has also been reported.[499] The extract decreased only the yeast-induced fever at 200 to 800 mg/kg, p.o., and the authors concluded that *H. sabdariffa* calyces possess antipyretic action through mechanisms that are different from that of aspirin.

The phytochemical investigations on *H. sabdariffa* are vast, as corroborated by various review reports.[263,500,501] The bioactive constituents reported include organic acids (hydroxycitric acid and hibiscus acid), anthocyanins (delphinidin-3-sambubioside and cyanidin-3-sambubioside), and polyphenols (hibiscitrin, sabdaritrin, gossypitrin, gossytrin, gossypetin glucosides, quercetin, luteolin, chlorogenic acid, protocatechuic acid, pelargonidic acid, quercetin, and luteolin).[262,502]

As regards the toxicity studies, there have been several reports on the acute and chronic toxicities of different extracts from the leaves and calyces of *H sabdariffa*.[425,500,503] Overall, these reports indicated that the administration of the extracts could be considered safe at various tested doses.

Ghidoli et al[504] made a case for diet as a veritable means of COVID-19 prevention and/or mitigation. The position of these authors, as reported, is based on the presence of secondary metabolites mainly of the flavonoids class which possess antiviral, immunostimulatory, and anti-inflammatory properties. Such compounds include quercetin, kaempferol, naringenin, hesperetin (flavonoids), curcumin, phloretin, epigallocatechin gallate (other aromatic compounds), and sulforaphane (sulfur compounds) derived from various food sources. Associated mechanisms adduced include blocking the enzymatic activities of viral proteases (3CLpro and PLpro), interfering with spike glycoproteins, suppressing the activity of ACE2 receptors, inhibition of NF-kB, activation Nrf2 pathway, and epigenetic regulation.[504,507]

Anacardium occidentale has been reported in this review to possess antiviral and anti-inflammatory activities. Isa et al[508] screened 29 compounds obtained from the extracts of *Zingiber officinale* and the leaves of *A. occidentale* for physicochemical, Pan-assay interference structure, and pharmacokinetic properties to determine the pharmaceutical active ingredients. Nineteen of the compounds demonstrated drug-likeness properties with efficient oral bioavailability and less toxicity. Through molecular docking analysis to determine their binding energies with 3CLpro, phytochemicals CID_9910474, and CID_10503282 are highly stable and robustly bound to the target receptor 3CLpro. This finding, along with results of molecular dynamics simulation (MDS) and interaction analysis, suggests the stable complexes CID_9910474 and CID_10503282 are promising for clinical validation against novel coronavirus (nCoV-19) target receptors.[508]

Jan et al,[509] using a cell-based infection assay, enzymatic assays, molecular modeling, and *in vivo* assay reported mefloquine, nelfinavir, and extracts of *Ganoderma lucidum*, *Perilla frutescens*, and *Mentha haplocalyx* as effective in a challenge study using hamsters as a disease model. Liu et al[510] investigated the anti-SARS-CoV-2 effect of *Scutellaria baicalensis* and its main component, baicalein. Findings by the authors revealed that *S. baicalensis* ethanol extract and baicalein inhibited SARS-CoV-2 3CLpro activity *in vitro* and replication of SARS-CoV-2 in Vero cells. The ethanol extract of the plant inhibited viral entry, while baicalein was mainly active at the viral post-entry stage. Nair et al[511] investigated the effect of *Artemisia annua* L. extracts on *in vitro* replication of SARS-CoV-2 and 2 of its variants. The authors reported that *A. annua* extracts inhibited SARS-CoV-2 infection, blocking virus infection at a step downstream of virus entry.

Limitations

This review was limited to African medicinal plants with antiviral, immunomodulatory, anti-inflammatory, and symptoms relieving properties, thereby leaving out potential anti-COVID-19 plants of non-African origin. However, there may be more medicinal plants of African origin that this paper did not consider.

Implications and Future Direction

The findings from this review paper further established the use of medicinal plants in the treatment and prevention of diseases as adduced by World Health Organization and some experts in

the field of ethnomedicine. To date, there is no specific orthodox treatment for COVID-19 with an attendant increase in morbidity and mortality all over the world. It is interesting to note that our findings bring to the fore medicinal plants with strong antiviral, anti-inflammatory, immunomodulatory and symptom-relieving potentials with remarkable safety profile that will be useful in the treatment of COVID-19. The future line of action is to obtain active phytomolecules from the identified medicinal plants that will be used for anti-COVID-19 drug development from African flora. The aforementioned will not only be beneficial for Africans but for the entire globe that is currently ravaged by COVID-19.

Conclusion

The study highlights the rich diversity of African medicinal plants and their chemical compounds with antiviral, anti-inflammatory, and immunomodulatory activities, and COVID-19 symptoms relieving effects with potential for the treatment of COVID-19. Baseline information on the pharmacological profile, toxicity, and chemical components of 9 African medicinal plants with the stated activities are provided, thereby making the plants candidates of interest for further investigation for effectiveness against COVID-19. Further, in-depth studies are needed to investigate the therapeutic potential of the plants against COVID-19 in preclinical and clinical trials. Isolation and characterization of the bioactive compounds responsible for their activities are also required.

Authors' Contributions

A.J.A., A.S., F.O.A., M.O.S., O.A, O.A.A., I.O., I.O.I., C.I.A., O.B.S., M.O.A., I.A.O. - conceived the review and wrote the manuscript; all authors read and approved the manuscript.

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