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A Review of African Medicinal Plants and Functional Foods for the Management of Alzheimer's Disease-related Phenotypes, Treatment of HSV-1 Infection and/or Improvement of Gut Microbiota

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Abstract

Alzheimer's disease (AD), which is a progressive neurodegenerative disorder is the most common form of dementia globally. Several studies have suggested alteration in the gut microbiota and HSV-1 infection as contributing factors to the development of the disease. As at now, there are no AD attenuating agents and AD pharmacotherapy is focused on managing symptoms while plants used in ethnomedicine remain potential sources of drugs for the treatment of the condition. Here, we reviewed published databases for African ethnomedicinal plants and functional foods of African origin that are used in the management of AD-related phenotypes, treatment of herpes simplex virus −1 (HSV-1) and/or improvement of gut microbiota. A total of 101 unique plant species and 24 different types of traditionally prepared African functional foodstuff were identified. Of the 101 identified plant species, 50 species serve as functional foodstuffs. Twenty-three (23) of the ethnomedicinal plant families were successfully identified for the treatment and management of AD-related phenotypes and age-related dementia. Eighteen (18) African plant species from 15 families were also identified as potent remedies for HSV-1; while many African wild fruits (3 species), roots and tubers (7 species), leafy vegetables (14 species), and seaweeds (26 species) were functional foods for modifying AD-related phenotypes. It was concluded that African medicinal plants are potential sources of both AD attenuating agents and phytocompounds that may be used against HSV-1 infection and alteration of gut microbiota. Additionally, a number of African functional foods are important sources of prebiotics and probiotics.

Keywords

Alzheimer's disease, HSV-1 infection, ethnomedicinal plants and functional foods

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Introduction

Alzheimer's disease (AD) described by Alois Alzheimer in 1906,[1] is now the most common form of dementia globally.[2] AD results in memory loss and erosion of several cognitive and emotional functions. Age is often considered the most central risk factor for AD, with an estimated 14-fold increase in risk in people over 85 years of age compared to people between the ages of 65 and 69.[1–7] Globally, it is estimated that between 7–10% of individuals over 65 years of age and approximately 50–60% of persons over 85 years of age suffer from AD.[5] The disease condition occurs as a result of the aggregation of misfolded β-amyloid and hyperphosphorylated tau peptides in selective regions of the central nervous system (CNS).[8–14]

Several studies have suggested alteration of the gut microbiota and HSV-1 infection as contributing factors to the development of the disease,[15–17] while other studies have implicated dysbiosis in the intestinal microbiota and neurotropic infectious agents as triggers.[18–20] Using polymerase chain reaction (PCR) in the studies of the human brain of elderly normal and AD patients have led to the detection of the viral DNA signal of human simplex virus type 1 (HSV-1) in the regions that are mostly affected by AD.[21–23] These findings were confirmed by other studies that have also detected viral DNA signals in the brain.[24–26] A study by Itzhaki et al (1993) has demonstrated by reverse transcription (RT) PCR that the infection was latent by the presence of latency-associated transcripts in favor of thymidine kinase transcripts.[23,27] According to Jamieson and colleagues (1992), the viral DNA of HSV-1 was detected in only a very small percentage of brains in younger people compared to the aged,[22] suggesting that the virus is able to cross the blood-brain barrier in the aged possibly as a result of declined immunity.[23,28] From both cell culture and brain studies, it is evident that HSV-1 cause neuronal damage directly or through inflammation when reactivated.[29]

Gut microbiota induced immuno-modulation has emerged as an important pathway in the pathogenesis of AD.[30] The human gut microbiota is diverse, large, dynamic and made up of more than 100 trillion microorganisms that come from more than 1000 different bacteria species with evidence of the interplay between the intestinal mucosal immune system and intestinal microbiota.[31,32] Numerous studies have generated compelling evidence suggesting that the human gut microbiota may play a key role in AD neuroinflammation[33] such that the gut flora can influence the brain in several ways through the immune system. Thus, signifying that the gut and the CNS engage in crosstalk.[18,33–35]

Currently, there is no AD attenuating agent[36,37] and AD pharmacotherapy is focused on managing symptoms without disease attenuation.[38] The neuroprotective capabilities of natural phenolic compounds from plants used in ethnomedicine have been reported and they remain the preferred primary treatment choice. It is estimated that over 60% of the global population and approximately 80% of the population in developing countries rely on herbal medicine.[37,39,40] According to Fabricant and Farnsworth (2001), a total of some 122 isolated compounds from 94 plant species have been identified.[41] Of these, 80% were employed for the same or related ethnomedicinal uses.[41] Considering the fact that these isolated plant compounds were derived from only 94 plant species out of an estimated 250 000 plant species, Mahapatra and colleagues argued that the plethora of active drug compounds that remains to be identified in plants is unlimited.[42] The use of prebiotics and probiotics has also been shown to help restore or at least improve the density and diversity of healthy human gut flora. This is achieved by consuming probiotic foodstuffs that provide healthy food microbes to the gut or indigestible polysaccharides known as prebiotics that are essential for the growth of healthy gut flora.[43] This study therefore reviewed published records on African ethnomedicinal plants that are used in the management of the above-stated disease conditions and those that are used as functional foodstuffs.

Methodology

This study reviewed electronic databases (Science Direct, Google Scholar, ResearchGate, and PubMed) and the Ghana Herbal Pharmacopoeia for African ethnomedicinal plants that have been used in the treatment of AD-related phenotypes, the treatment of HSV-1, and the enhancement and restoration of the gut microbiota, to determine their therapeutic efficacy and functional food use. The search was performed using specific search terms for the various disease conditions, and functional food usage.

Traditional Use of Plants

Ethnomedicinal Plants for the Management of AD-Related Phenotypes

The current AD management therapeutics are only focused on slowing disease progression and alleviating the symptoms.[38,44] However, since time immemorial, mankind has always relied on ethnomedicine for the treatment and management of diseases related to the CNS.[37,44] One plant from which successful ethnopharmaceutical have been developed for the treatment of dementia is *Ginkgo biloba* with a good safety profile.[44,45] One of such efficacious remedies from *Ginkgo biloba* is EGb 761 (a standardized extract marketed by Wilmar Schwabe GmbH), which is very effective in the treatment of AD-related dementia in clinical trials.[44,46] The drug discovery and development pipeline have always started with ethnomedicinal knowhow and it is now more important than ever to profile ethnomedicinal plants that can attenuate AD-related pathophysiology. This section is a compilation of some African ethnomedicinal plants that are traditionally used in the treatment and management of AD-related phenotypes. The compilation considers the (i) traditional use of the plants in humans; (ii) its uses on animals:—of which both (i) and (ii) are categorized as *in vivo* use; and (iii) its uses on cell-line(s), which is categorized as *in vitro* use.

The list of ethnomedicinal plants credited with attenuating capacity in AD-related phenotypes consists of plants belonging

Table 1. List of African Medicinal Plants Used for Memory and Cognition Enhancement, and Management of Other Alzheimer's Disease Related Phenotypes.

Botanical name (Family)	*in vivo*	*in vitro*	Part(s) used/ reference
Crinum glaucum A. Chev. (**Amaryllidaceae**) ***Compounds/Phytochemicals**: Hamayne* *Lycorine* ***Mechanism**: Active against AChE*	Memory enhancer		Bulb[47]
Crinum jagus C. (**Amaryllidaceae**) ***Compounds/Phytochemicals**: Hamayne* *Lycorine* ***Mechanism**: Active against AChE*	Memory enhancer		Bulb[47]
Hydrolea glabra Schum. (**Hydrophilaceae**) ***Compounds/Phytochemicals**: Steroids* ***Mechanism**: Acts on GABA receptor*	Memory enhancer and alleviates anxiety in mice		Leaves[48,49]
Pistia stratiotes L. (**Araceae**) ***Compounds/Phytochemicals**: Stratioside II* ***Mechanism**: Anti-inflammatory and nociceptor sensitization*	Relieves dementia		Roots / Leaves[50,51]
Boophone disticha (L.f.) Herb. (**Amaryllidaceae**) ***Compounds/Phytochemicals**:* *6-hydroxycrinamine* ***Mechanism**: Inhibits AChE*		Inhibits AChE and potentially neuroprotective	Leaves / Bulb[52,53]
Croton sylvaticus Hochst. (**Euphorbiaceae**) ***Compounds/Phytochemicals**: Quercetin* *Kaempferol* ***Mechanism**: Inhibits AChE*		Inhibits AChE and potentially neuroprotective	Leaves[54]
Ziziphus mucronata Willd. (**Rhamnaceae**) ***Compounds/Phytochemicals**: Galantamine* ***Mechanism**: Inhibits AChE*		Inhibits Aβ in SH-SY5Y cells	Leaves[55,56]
Cola nitida (Vent.) Schott & Endl. (**Sterculiaceae**) ***Compounds/Phytochemicals**:* *9-Octadecenamide* *Augustamine* *Undulatine* ***Mechanism**: Inhibits AChE and BuChE*	CNS stimulant/anti-depressant		Seed[57,58]
Lannea schweinfurthii (Engl.) Engl. (**Anacardiaceae**) ***Compounds/Phytochemicals**: Epicatechin* *Sitosterol* ***Mechanism**: Inhibits AChE*		Inhibits A-beta in SH-SY5Y cells	Roots[55,59]
Terminalia sericea Burch. ex DC. (**Combretaceae**) ***Compounds/Phytochemicals**: Sericic acid* *Sericoside* ***Mechanism**: Inhibits AChE and A-beta*		Inhibits A-beta in SH-SY5Y cells	Roots[55,60]
Piper capense L.f. (**Piperaceae**) ***Compounds/Phytochemicals**: Piperine* *4,5-dihydropiperine* ***Mechanism**: Inhibits AChE, and antioxidant activity*		Inhibits AChE and potentially neuroprotective	Roots[56]
Piper nigrum L (**Piperaceae**) ***Compounds/Phytochemicals**: Allyl isothiocyanate* *Zingerone* ***Mechanism**: Inhibits cellular production of TNF-α and nitric oxide*		Enhanced memory in Wistar rat	Fruits[61,62]
Terminalia sericea Burch. ex DC.			Roots[56,63,64]

(continued)

Table 1. (continued)

Botanical name (Family)	*in vivo*	*in vitro*	Part(s) used/ reference
(**Combretaceae**) ***Compounds/Phytochemicals***: *Anolignan B* *Sericic acid* ***Mechanism***: *Anti-inflammatory, and inhibits AChE*		Inhibits AChE and potentially neuroprotective	
Ziziphus mucronate Willd. (**Rhamnaceae**) ***Compounds/Phytochemicals***: *Sanjoinine A* *Sanjoinine B* ***Mechanism***: *Inhibits AChE, and antioxidant activity*		Inhibits AChE and potentially neuroprotective	Roots[56,65]
Rauwolfia vomitoria Afz. (**Apocynaceae**) ***Compounds/Phytochemicals***: *Yohimbine* *Ajmaline* *Reserpine* ***Mechanism***: *Inhibits AChE*	Antipsychotic		Roots[57,66]
Jatropha curcas L. (**Euphorbiaceae**) ***Compounds/Phytochemicals***: *Curcin* *Sitosterol* ***Mechanism***: *Anti-inflammatory effect*	Antipsychotic		Fruits[67,68]
Peltophoru africanum Sond. (**Fabaceae**) ***Compounds/Phytochemicals***: *Coumarins* *Gallic acid* ***Mechanism***: *Anti-depressant, anti-inflammatory effect*		Anti-oxidant and potentially neuroprotective	Roots/Bark[69]
Ammocharis coranica (Ker-Gawl.) Herb. (**Amaryllidaceae**) ***Compounds/Phytochemicals***: *Lycorine* ***Mechanism***: *Inhibits AChE*	Antipsychotic	Inhibits AChE and potentially neuroprotective	Bulb[70]
Carpolobia lutea G. Don (**Polygalaceae**) ***Compounds/Phytochemicals***: *Flavones* *Isoflavones* ***Mechanism***: *Antioxidant and anti-AChE effect*	Enhanced cognition in mice (CD 1)		Roots[71,72]
Crinum macowanii (**Amaryllidaceae**) ***Compounds/Phytochemicals***: *Lycorine* ***Mechanism***: *Anti-AChE effect*	Enhanced memory in BALB/c mice		Bulb[73]
Agapanthus africanus (**Agapanthaceae**) ***Compounds/Phytochemicals***: *Alkaloids* *Flavonoids* ***Mechanism***: *Anti-AChE effect*	Memory enhancer		Whole plant[74]
Aptosimum decumbens Schinz (**Scrophulariaceae**) ***Compounds/Phytochemicals***: *Alkaloids* *Flavonoids* ***Mechanism***: *Anti-AChE effect*	Memory enhancer		Whole plant[74,75]
Tithonia diversifolia (Hemsl.) (**Asteraceae**) ***Compounds/Phytochemicals***: *Gallic acid* *Chlorogenic acid* ***Mechanism***: *Antioxidant and anti-cholinesterase*		Inhibits AChE and potentially neuroprotective	Leaves[76]
Pycnanthus angolensis (Welw) Warb. (**Myristicaceae**) ***Compounds/Phytochemicals***: *Omifoate A* ***Mechanism***: *Anti-cholinesterase*	Enhanced memory in mice		Bark[77,78]
Carpobrotus edulis L. (**Aizoaceae**) ***Compounds/Phytochemicals***: *Coumaric acid* *Epicatechin*		Inhibits AChE and BuChE and potentially neuroprotective	Leaves[79]

(continued)

Table 1. (continued)

Botanical name (Family)	*in vivo*	*in vitro*	Part(s) used/ reference
***Mechanism**: Anti-neuroinflammatory and anti-AChE*			
Angraecum eichlerianum Bory. (***Orchidaceae***) ***Compounds/Phytochemicals**: Alkaloids Flavonoids* ***Mechanism**: Antioxidant effect*	Memory enhancer		Leaves[80]
Aframomum melegueta K. Schum. (**Zingiberaceae**) ***Compounds/Phytochemicals**: Gingerols Paradols* ***Mechanism**: Antioxidant effect and anti-neuroinflammatory*	Memory enhancer		Seeds[80,81]
Moringa Oleifera (**Moringaceae**) ***Compounds/Phytochemicals**: Alkaloids Flavonoids* ***Mechanism**: Antioxidant effect*	Memory enhancer		Leaves[57,72,82]
Ecklonia maxima (**Lessoniaceae**) ***Compounds/Phytochemicals**: Dibenzo [1,4]dioxine-2,4,7,9-tetratol Eckmaxol* ***Mechanism**: Anti-AChE effect, and decreases Reactive Oxygen Species*		Inhibits Cholin., β-sec., Aβ aggregation and potentially neuroprotective	Whole plant[83–85]
Gelidium pristoides (**Gelidiaceae**) ***Compounds/Phytochemicals**: 35,7-trimethoxy flavone Biochanin A* ***Mechanism**: Anti-BChE, anti-AChE, and anti-amyloidogenic*		Inhibits Cholin., β-sec., Aβ aggregation and potentially neuroprotective	Whole plant[83]
Gracilaria gracilis (**Gracilariaceae**) ***Compounds/Phytochemicals**: Alpha-tocopherol Beta-sitosterol* ***Mechanism**: Anti-BChE, anti-AChE, and anti-amyloidogenic*		Inhibits Cholin., β-sec., Aβ aggregation and potentially neuroprotective	Whole plant[83]
Ulva lactuca (**Ulvaceae**) ***Compounds/Phytochemicals**: Beta-D-Galactofuranoside Arabinose* ***Mechanism**: Anti-BChE, anti-AChE, and anti-amyloidogenic*		Inhibits Cholin., β-sec., Aβ aggregation and potentially neuroprotective	Whole plant[83]
Zingiber officinale (**Zingiberaceae**) ***Compounds/Phytochemicals**: α-Zingiberene Camphene* ***Mechanism**: Antioxidant effect, and anti-inflammatory*		Inhibits AChE andpotentially neuroprotective	Rhizomes[86,87]

*** Cholin. = Cholinesterases; β-sec. = β-secretase; ***BuChE = Butyrylcholinesterase; *** AChE = Acetylcholinesterase; Aβ = β-amyloid; CNS = Central Nervous System; Compounds/Phytochemicals = Already identified plant compounds or phytochemicals; Mechanism = Mechanism of action of the plant extract(s).

to the family *Agapanthaceae* to family *Zingiberaceae* (Table 1). Plants from the following families were identified *Agapanthaceae, Aizoaceae, Amaryllidaceae, Apocynaceae, Araceae, Asteraceae, Combretaceae, Euphorbiaceae, Fabaceae, Gelidiaceae, Gracilariaceae, Hydrophilaceae, Lessoniaceae, Moringaceae, Myristicaceae, Orchidaceae, Piperaceae, Polygalaceae, Rhamnaceae, Scrophulariaceae, Sterculiaceae*, *Ulvaceae* and *Zingiberaceae,* making a total of 23 plant families in all. Majority of the plants were from the family *Amaryllidaceae,* followed by an equal proportion of members from the following families:—*Combretaceae, Euphorbiaceae, Piperaceae, Rhamnaceae* and *Zingiberaceae*. Photographs of some of the members of plants listed in Table 1 are provided.

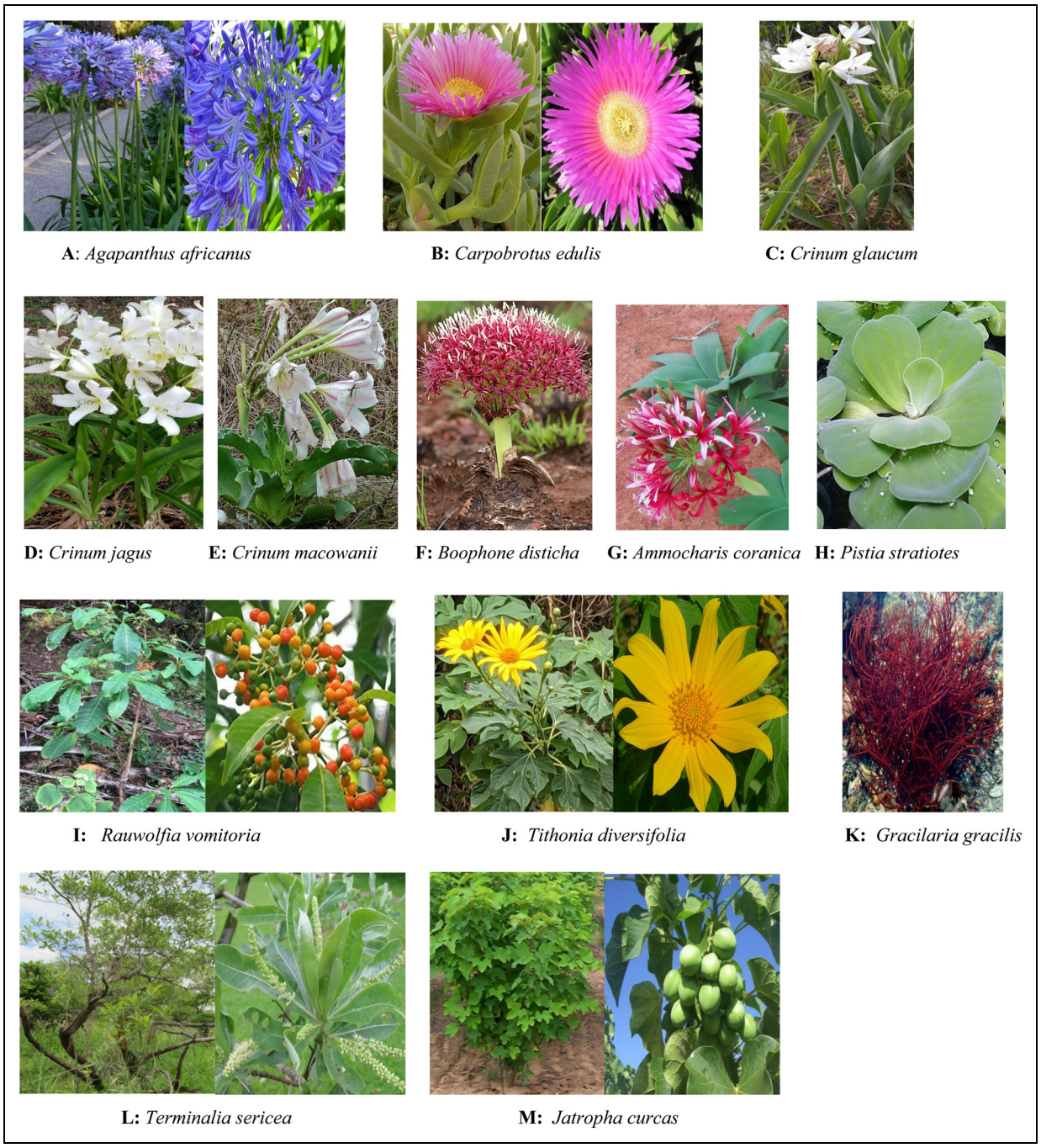

Figure 1. Photographs of some of the plants listed in Table 1. (continued)

Whole plant extract of *Agapanthus africanus* (Figure 1A) belonging to the *Agapanthaceae* family is known to have memory-enhancing capability and has been used to enhance memory in ethnomedicine.[74] The leaf extract of *Carpobrotus edulis* (Figure 1B) from the family *Aizoaceae* has been reported to have neuroprotective capacity and shown to inhibit AChE and BuChE *in vitro*.[79] The bulb extract of *Crinum glaucum* (Figure 1C),[47] *Crinum jagus* (Figure 1D),[47] and *Crinum macowanii* (Figure 1E)[73] have all demonstrated their capacity as memory enhancers *in vivo* whiles the *in vitro* assessment of the leaves and bulb extracts of *Boophone disticha* (Figure 1F) have both demonstrated the plant's neuroprotective potential and the capacity to inhibit AChE.[52] Furthermore, the bulb extract of *Ammocharis coranica* (Figure 1G), which is used ethnomedicinally as an antipsychotic, has also been reported to have neuroprotective capacity and ability to inhibit AChE *in vitro*.[70] The root extract of *Rauwolfia vomitoria* (family:

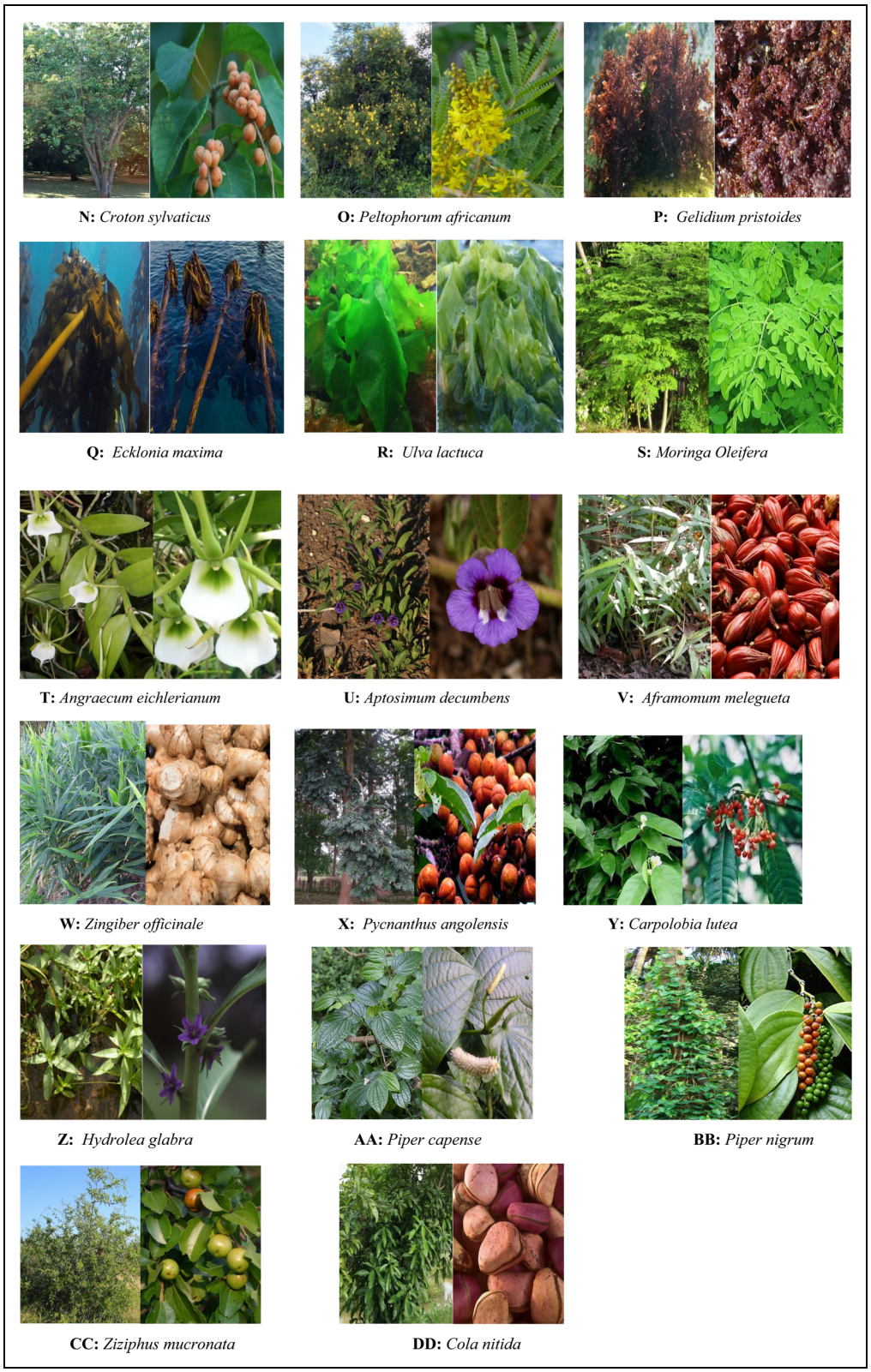

Figure 1. Continued.

Apocynaceae) (Figure 1I) was reported to be a potent antipsychotic agent used in ethnomedicine around the African continent.[57,66]

Leave and root extracts of *Pistia stratiotes* (family: *Araceae*) (Figure 1H) are known to exhibit the capacity to relieve dementia in ethnomedicine.[50] The leaf extract of *Tithonia diversifolia* (family: *Asteraceae*) (Figure 1J) has demonstrated the capacity as both a neuroprotective agent and an inhibitor of AChE *in vitro*,[76] whereas root extract of *Terminalia sericea* (Figure 1L) belonging to the Family *Combretaceae* exhibited neuroprotective capacity and the ability to inhibit AChE *in vitro*.[56] The capacity of the root extract of *Terminalia sericea* to inhibit the formation of beta-amyloid was also demonstrated in the SH-SY5Y cell line.[56]

Two plant species *Jatropha curcas* (Figure 1M) and *Croton sylvaticus* (Figure 1N), were identified from the *Euphorbiaceae* family. While the fruits of *Jatropha curcas* has antipsychotic properties,[67] the leaf extract of *Croton sylvaticus* have been reported to both inhibit AChE and protect neuron cells.[54] The root and bark extracts of *Peltophorum africanum* (family: *Fabaceae*) (Figure 1O) demonstrated a strong antioxidant capacity and neuroprotective potential *in vitro*.[69] *Gelidium pristoides* (Figure 1P), *Gracilaria gracilis* (Figure 1K), *Ecklonia maxima* (Figure 1Q), and *Ulva lactuca* (Figure 1R) were identified from *Gelidiaceae, Gracilariaceae, Lessoniaceae, and Ulvaceae* families respectively. Whole plant extracts from these plants have demonstrated their neuroprotective capacity, as well as their ability to inhibit cholinesterase, beta-secretase, and beta-amyloid aggregation *in vitro*.[83]

Ethnomedicinal plants with the capacity to enhance memory were identified from the plant families: *Moringaceae* (*Moringa Oleifera*) (Figure 1S), *Orchidaceae* (*Angraecum eichlerianum*) (Figure 1T), *Scrophulariaceae* (*Aptosimum decumbens*) (Figure 1U), *and Zingiberaceae* (*Aframomum melegueta*) (Figure 1V). The leave extracts of *Moringa Oleifera*[57,72] and *Angraecum eichlerianum*[80] have been shown to demonstrate the capacity to enhance memory, while the whole plant extract of *Aptosimum decumbens* demonstrated its ability to enhance memory.[74] Also, the seeds of *Aframomum melegueta* have been traditionally reported to enhance memory.[80] Another member identified from the *Zingiberaceae* family is *Zingiber officinale* (Figure 1W). The rhizome of *Zingiber officinale* had been identified as having neuroprotective capacity and the ability to inhibit AChE *in vitro*.[86] *Pycnanthus angolensis* is the plant that was identified as representative of the family *Myristicaceae. Pycnanthus angolensis* (Figure 1X) bark extract demonstrated its ability to enhance memory in mice.[77] The root extract of *Carpolobia lutea* (Figure 1Y) of the family *Polygalaceae* had successfully demonstrated cognition enhancement in CD1 mice.[79]

The leave extract of *Hydrolea glabra* (Figure 1Z) of the family *Hydrophilaceae* has been shown to be a potent memory enhancer with the capacity to alleviate anxiety in mice.[48,49] From the family *Piperaceae* were identified plant species; *Piper capense* (Figure 1AA) and *Piper nigrum* (Figure 1BB). The roots of *Piper capense* are known to be neuroprotective with the ability to inhibit AChE *in vitro*,[56] while the fruits of *Piper nigrum* have demonstrated memory enhancing capacity in the Wistar rat.[61]

The root extract of *Ziziphus mucronata* (family: *Rhamnaceae*) (Figure 1CC) has been shown to possess neuroprotective capacity and AChE inhibitory effect,[56] while the leaf extract has been shown to inhibit beta-amyloid.[55] The seeds of *Cola nitida* (Figure 1DD) belonging to the *Sterculiaceae* family have been identified as having antidepressant properties and the ability to stimulate the CNS.[57]

Ethnomedicinal Plants for the Treatment of Herpes Simplex Virus Type 1 (HSV-1)

The Herpes Simplex Virus

In essence, there are eight types of herpesviruses in a large family called Herpesviridae, which consist of viral particles made up of a single double-stranded DNA molecule contained in a viral envelope.[88] The large family of herpesviruses has been classified into 3 basic groups, (i) group alpha: made up of herpes simplex virus type-1 and −2 (HSV-1/HSV-2), and varicella-zoster virus (VZV); (ii) group beta: includes human herpesvirus type-6 and −7 (HHV-6/HHV-7), and human cytomegalovirus (HCMV); as well as (iii) group gamma: which has human herpesvirus type-8 (HHV-8) and Epstein-Barr virus (EBV) as members of the group.

Herpesviruses have the characteristic of persisting throughout the host's lifetime and can be reactivated from latency.[89] Herpesviruses are common pathogens that cause varying types of diseases ranging from infections of the skin, oral cavity, eye, esophagus, pharynx up to the genitalia.[90] HSV-1 is a neurotropic virus that causes lifelong infection and can enter latency in infected neuronal cells[91] with the possibility of reactivation resulting in recurrent and acute infections.[90]

Current Trends in Antiviral Ethnopharmacology

Studies have shown the antiviral efficacy of several ethnomedicinal plants affecting various stages of viral growth.[92] Herbal preparations are widely used as antiviral drugs,[92–94] and ethnopharmacological preparations are currently being classified for their activity against viral infections.[92,95]

Table 2 below shows the compiled list of some African ethnomedicinal plants that have been used and are still in use for the treatment and management of HSV-1 infection for several centuries. Plants with efficacy against HSV-1 infection were identified across several plant families (from family *Anacardiaceae* to *Zygophyllaceae*). The total number of plant families from which specific plants were identified is 15 in all, and these families are as follows: *Anacardiaceae, Apocynaceae, Asteraceae, Capparaceae, Combretaceae, Ephedraceae, Ericaceae, Frankeniaceae, Geraniaceae, Leguminosae, Mimosaceae, Moringaceae, Sterculiaceae, Tamaricaceae,* and *Zygophyllaceae.* The same family size

Table 2. List of African Medicinal Plants That Have Demonstrated Inhibitory Activity Against HSV-1 Infection.

Scientific Name (Family)	Part used	Extract	*in vivo/in vitro*	Assay/reference
Capparis sinaica Veill. in Duh. (**Capparaceae**) ***Compounds/Phytochemicals**: Quercetin, Quercetin-7-o-rutinoside, Luteolin, Kaempferol-3-galactose, and Quercetin-7-O-glucoside*	Aerial	Aqueous ethanol	Vero cells	Plaque reduction/ inhibition assay[96,97]
Cyperus rotundus L. (**Capparaceae**) ***Compounds/Phytochemicals**: Luteolin-7-O-*glucoside, Tricin, (+)-catechin, quercetin, (−)-cypera-2,4-diene, 4α,5β-oxidoeudesm-11-*en*-3α-ol, and Rotundine A	Tuber	Aqueous ethanol	Vero cells	Plaque reduction/ inhibition assay[96,98]
Ephedra alata Decne. (**Ephedraceae**) ***Compounds/Phytochemicals**: Phedrine, Pseudoephedrine, Trans-cinnamic acid, Catechin, Syringin, Epicatechin, Symplocoside, Kaempferol 3-O-rhamnoside 7-O-glucoside, Isovitexin 2-O-rhamnosid, and Luteolin-7-O-glucuronide flavonoid*	Aerial	Aqueous ethanol	Vero cells	Plaque reduction/ inhibition assay[96,99]
Moringa peregrina (Forssk.) Fiori. (**Moringaceae**) ***Compounds/Phytochemicals**: Lupeol acetate, β-amyrin, α-amyrin, β-sitosterol, and β-sitosterol-3-O-β-D-glucoside*	Seed	Aqueous ethanol	Vero cells	Plaque reduction/ inhibition assay[96,100]
Tamarix nilotica (Ehrenb.) Bunge. (**Tamaricaceae**) ***Compounds/Phytochemicals**: Gallic acid, Quercetin, Kaempferol, di-Galloylglucose, Kaempferol glucuronide, and Methyl-quercetin*	Aerial	Aqueous ethanol	Vero cells	Plaque reduction/ inhibition assay[96,101]
Erica multiflora L. (**Ericaceae**) ***Compounds/Phytochemicals**: Quercetin, Kaempferol, Myricetin, Uinic acid, Caffeic acid hexoside, 3-O-caffeoylquinic acid, P-coumaric acid hexoside, and Syringic acid hexoside*	Aerial	Methanolic	Vero cells	Plaque reduction/ inhibition assay[93,102]
Frankenia pulverulenta L. (**Frankeniaceae**) ***Compounds/Phytochemicals**: Dihydrotecomanine, 5,7-Dodecadiyn-1,12-diol, 6-Acetyl-β-d-mannose, Gamolenic acid, And Gibberellic acid*	Whole plant	Methanolic/ acetonic	Vero cells	Plaque reduction/ inhibition assay[93,103]
Zygophyllum album L. (**Zygophyllaceae**) ***Compounds/Phytochemicals**: Hyacinthine, 1-Nonen-4-ol, Nonanal, 1,2-Dihydro-14,6-trimethyl naphthalene, Bis(2-ethyl hexyl) phthalate, Quercetin 3-sulfate, Isorhamnetin-3-O-rutinoside, and Quinovicacid 3-0-rhamnoside*	Whole plant	Acetonic	Vero cells	Plaque reduction/ inhibition assay[93,104,105]
Pelargonium sidoides DC. (**Geraniaceae**) ***Compounds/Phytochemicals**: 7-hydroxy-5,6-di-methoxycoumarin, 6,8-dihydroxy-5,7-dimethoxycoumarin, 6-Methoxy-7-(sulfooxy)-2H-1-benzopyran-2-one, and 6,8-Bis(sulfooxy)-7-methoxy-2H-1-benzopyran-2-one*	Roots	Aqueous-ethanolic	RC-37 cells	Plaque reduction/ inhibition assay[94,106,107]
Helichrysum aureonitens Sch. Bip. (**Asteraceae**) ***Compounds/Phytochemicals:** 35,7-trihydroxyflavone, 3-Caffeoylquinic acid, 5-Caffeoylquinic acid, 4,5-Dicaffeoylquinic acid, Ferulic acid, and 13S-Hydroxy-9Z,11E,15Z-octadecatrienoic acid*	Shoots	Aqueous	Human lung fibroblast	Plaque reduction/ inhibition assay[95,108,109]
Combretum micranthum (**Combretaceae**) ***Compounds/Phytochemicals**: C-glycosylflavones, vitexin, isovitexin, orientin, and homoorientin, m-inositol and sorbitol, myricetin-3-O-glucoside, and myricetin-3-O-rutinoside*	Leaves	Methanolic	Vero cells	Plaque reduction/ inhibition assay[96,110]
Bauhinia thonningii (Schum.) (**Leguminosae**) ***Compounds/Phytochemicals**: C-methylflavonols, quercetin, 6,8-di-C-methylquercetin 3-methyl ether, 6-C-methylquercetin 3,7-dimethyl ether, 6,8-di-C-methylquercetin 3,7-dimethyl ether, 6-C-methylquercetin 3-methyl ether, 6-C-methylquercetin 37,3′-trimethyl ether, 6,8-di-C-methyl-kaempferol 3-methyl ether, 6,8-di-C-methylkaempferol 3,7-dimethyl ether, and quercitrin*	Leaves	Methanolic	Human colonic cancer cells (HT-29)	Plaque reduction/ inhibition assay[111,112]
Anacardium occidentale L. (**Anacardiaceae**) ***Compounds/Phytochemicals**: 2-(10″Z, 13″Z-nonadecadienoyl)-6-(8′Z, 11′Z-pentadecadienyl) salicylic acid, (+)-catechin, (-)-epicatechin, epigallocatechin, protocatechuic, cinnamic*	Bark	Methanolic	Human colonic cancer cells (HT-29)	Plaque reduction/ inhibition assay[111,113]

(continued)

Table 2. (continued)

Scientific Name (Family)	Part used	Extract	*in vivo/in vitro*	Assay/reference
acids, syringic, p-coumaric acids,5-hydroxymethylfurfural, catechin, epicatechin, epigallocatechin and gallic acid, and 2-(8″Z-eicosenoyl)-6-(8′Z-pentadecenyl) salicylic acid				
Dichrostachys glomerate (Chiev.) (**Mimosaceae**) ***Compounds/Phytochemicals**: flavonoids, phenolic compounds, alkaloids, tannins, saponins, quinones, glycosides, and terpenoids*	Leaves	Methanolic	Human colonic cancer cells (HT-29)	Plaque reduction/ inhibition assay[111]
Sterculia setigera (Del.) (**Sterculiaceae**) ***Compounds/Phytochemicals**: Procyanidin dimer B, Procyanidin trimer C1, Procyandin tetramer, (+)- Catechin, and 3,4-Dimethoxyphenol b-D-apiofuranosyl(1″ → 6″)-b-D-glucopyranoside*	Bark	Methanolic	Human colonic cancer cells (HT-29)	Plaque reduction/ inhibition assay[111,114]
Detarium senegalensis (**Leguminosae**) ***Compounds/Phytochemicals**: 34,5-tri-O-galloylquinic acid, caffeoylquinic acids, caffeic acid, synapoic acid, and 34,5-tri-O-caffeoylquinic acid*	Leaves	Methanolic	Human colonic cancer cells (HT-29)	Plaque reduction/ inhibition assay[111,115]
Guiera senegalensis (J.F. Gmelin) (**Combretaceae**) ***Compounds/Phytochemicals**: 3-O-Galloylquinic acid, 4-O-Galloylquinic acid, 1,3-Di-O-galloylquinic acid, 3,4- Di-O-galloylquinic acid,* and *4,5- Di-O-galloylquinic acid*	Leaves	Methanolic	Human colonic cancer cells (HT-29)	Plaque reduction/ inhibition assay[111,116]
Carissa edulis (Forssk.) Vahl (**Apocynaceae**) ***Compounds/Phytochemicals**: Ursolic acid, carissone, caredulis, -{1-[2-(2 hydroxypropoxy) propoxy] propan-2-yloxy}, carissanol, β-sitosterol, scopoletin, butyl-O-α-l-rhamnoside, kaempferol, rutin, and quercetin-3-O-glucoside-7,3′,4′-trimethyl ether*	Roots	Aqueous	Vero Cells and Balb/C mice	Plaque reduction/ inhibition assay[117–119]

dominance was observed for *Capparaceae, Combretaceae,* and *Leguminosae* (Table 2).

The aqueous ethanol extracts of *Capparis sinaica* (plant part: Aerial) (Figure 2A), *Cyperus rotundus* (plant part: Tuber) (Figure 2B), *Ephedra alata* (plant part: Aerial) (Figure 2C), *Moringa peregrina* (plant part: Seed) (Figure 2D), and *Tamarix nilotica* (plant part: Aerial) (Figure 2E) were found to possess anti-viral capacity against HSV-1 invasion of Vero cells in plaque reduction assay.[96] The aqueous ethanol root extract of *Pelargonium sidoides* (Figure 2F), when investigated using RC-37 cells, demonstrated its capacity as an inhibitor of HSV-1 invasion.[94]

Methanolic extracts of *Erica multiflora* (plant part: Aerial) (Figure 2G),[93] *Combretum micranthum* (plant part: Leaves) (Figure 2H),[96] and *Bauhinia thonningii (*plant part: Leaves) (Figure 2I)[111] have been identified as potent anti-HSV-1 agents using plaque reduction assay. However, both methanolic and acetonic extracts of the whole *Frankenia pulverulenta* (Figure 2J) plant demonstrated their ability to inhibit and reduce HSV-1 infection, when tested on Vero cells using a plaque reduction assay.[93] Also, the whole plant acetonic extract of *Zygophyllum album* (Figure 2K) reduced and inhibited HSV-1 invasion when investigated in Vero cells using plaque reduction assay.[93]

Anti-HSV-1 inhibition and reduction potential were observed for the aqueous shoots and roots extract of *Helichrysum aureonitens* (Figure 2L) and *Carissa edulis* respectively. The extract from *Helichrysum aureonitens* inhibited and reduced HSV-1 invasion of Human lung fibroblast cells,[95] whiles the extract of *Carissa edulis* (Figure 2M) demonstrated its anti-HSV-1 capacity in both in Vero cells and Balb/C mice.[74]

Many other plants have also demonstrated their capacity to inhibit and reduce HSV-1 infection when their methanolic extracts were investigated in human colonic cancer cells (HT-29).[111] The bark extracts of *Anacardium occidentale* (Figure 2N) and *Sterculia setigera* (Figure 2O) were identified as potential HSV-1 inhibitors. Furthermore, the methanolic leaves extracts of *Dichrostachys glomerate*, *Detarium senegalensis* (Figure 2P), and *Guiera senegalensis* (Figure 2Q) have been observed to reduce and inhibit HSV-1 infection *in vivo*.[111]

Some African Plants and Traditional Foodstuff Used as Functional Foods

Functional Food

The gut microecology is the physiologic base for the consequence of prebiotics and probiotics on the host.[108,120,121] Generally, probiotics and prebiotics are used in the production of functional foodstuff; containing healthy food microbes that are important for the biological processes of the human gut when ingested. And this is achieved by adding healthy microorganisms (probiotics) or indigestible polysaccharides (prebiotics) that artificially impact the host by selectively stimulating the growth of intestinal flora.[118,122,123]

In 1989, Fuller (1989) gave the first generally accepted definition of probiotics, which states that probiotics are "A live

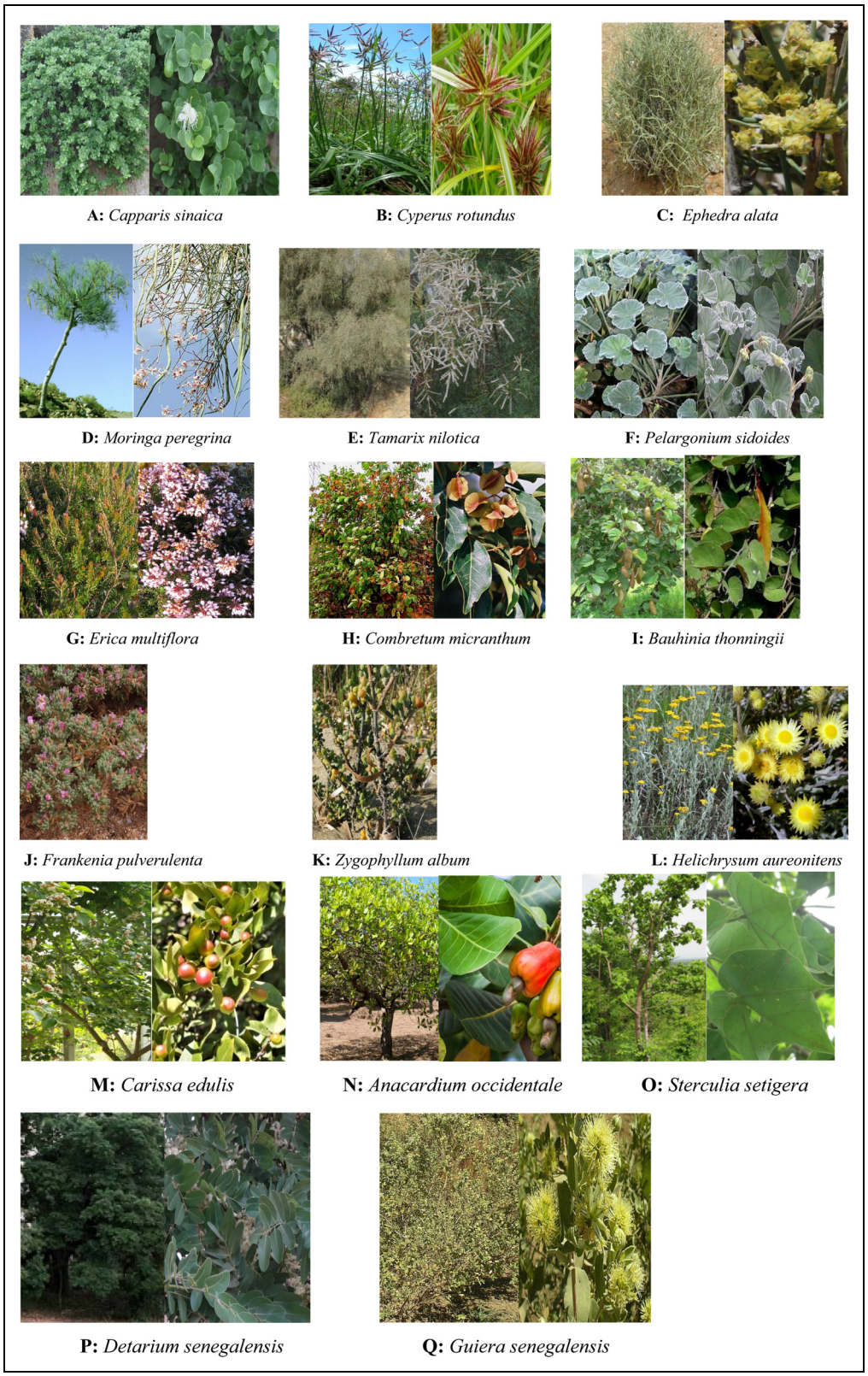

Figure 2. Photographs of some of the plants listed in Table 2.

microbial feed supplement that beneficially affects the host animal by improving its intestinal microbial balance".[124,125] However, in 2001, probiotics were further defined by the Food and Agriculture Organization (FAO)/World Health Organization (WHO) (2001).[126] This definition described probiotics as "live microorganisms that when administered in adequate amounts confer health benefit effects on the host".[127] It should be noted that some of these beneficial microorganisms for the health of the human gut originate from fermented foodstuffs or the environment.[128] The sole purpose of consuming foodstuff produced with probiotics is to prevent the thriving of pathogenic bacteria and their metabolites and to enhance the immune system in its response to infection and maintain proper intestinal function. Whiles, on the other hand, prebiotics are food items that promote the propagation and persistence of probiotic bacteria and beneficial pro-health microbes in the human gut.[122,126]

Some African Functional Foodstuffs

In recent times, several traditional African foods have been given functional food roles. These include traditional meals prepared either by way of fermentation, roots and tubers as well as some edible seaweeds, based on their ability to alter the colonic microbiome; either by contributing to its composition directly or by serving as a growth medium for the flora thereby directly contributing to human health.[129–132]

Probiotic Foodstuff

Several indigenous African traditional fermented foodstuff qualify as probiotic, however, not all fermented foodstuff can be classified as probiotic until some basic conditions are met.[133] Only fermented foodstuffs that meet the following conditions can be considered as probiotic foodstuffs.[134]

A probiotic foodstuff must meet the following conditions:

- Have live organisms (10^6 cfu / ml).
- The organisms must be members of the lactic acid bacteria (LAB) family.
- Organisms must be resistant to gastric acidity and bile salts.
- Must have no negative nutritional effects on the human body.

Probiotic Microorganisms

Probiotic organisms are largely functionally beneficial microbes that are able to convert the chemical components of raw plant and/or animal materials through fermentation. Which basically, augments the sensory quality of food and nutrients bio-availability, thus enhancing human health by contributing to the gut microflora equilibrium. These microbes also degrade mycotoxins and phytic acid among others, whiles producing compounds with antimicrobial and antioxidant properties.[133,135]

Microorganisms that qualify as probiotics:

- Lactobacillus species: Lactobacillus casei, L. acidophilus, L. brevis, L. lactis, L. plantarum, L. fermentum, L. delbrueckii var. Bulgaricus.
- Bifidobacterium species: Bifidobacterium breve, Bf. animalis, Bf. Lactis, Bf. bifidum, Bf. longum, Bf. Adolescentis.
- Other organisms: Lactococcus lactis, Enterococcus faecium, Enterococcuc faecalis, Pediococcus acidolactici, Streptococcus salivarus var. thermophilus, Saccharomyces boulardi).[134]

Prebiotics Foodstuff

Generally, prebiotics are indigestible foodstuff that beneficially affect the host health. Prebiotics are able to selectively stimulating the activity and/or growth of a particular or a group of gut-microorganisms which subsequently enhance host health.[136] For a foodstuff to qualify as prebiotic, the following under listed criteria must be met.

Prebiotic Classification Criteria

A prebiotic foodstuff must meet the following criteria:

- Be resistant to the upper gut tract.
- Undergo fermentation by the intestinal microbiota.
- It should be beneficial to the host's health.
- Selectively stimulate probiotics.
- Have stability to food processing treatment.[132]

Listed in Table 3 below are several traditional probiotic foodstuffs produced by random fermentation in some African countries. These African functional foods are produced from

Table 3. Some Traditional African Probiotic non-Alcoholic Foodstuffs Produced by Spontaneous Fermentation.

Traditional Food (Raw material)	Country and reference
Fura (millet), Nunu (milk), Koko (maize), Pito (millet / sorghum), Kenkey (maize), Agbelima (cassava) and Bonome (fish)	Ghana[137,138]
Ogi (maize) and Kunuzaki (millet)	Nigeria[138]
Mawe (maize)	Benin[138]
Mbege (millet)	Tanzania[138]
Ben-saalga (millet)	Burkina Faso[138]
Bogobe (soghum)	Botswana[138]
Humulur and Hussuwa (soghum)	Sudan[138]
Bouza and kishk (wheat)	Egypt[138]
Uji (maize) and Kule naoto (milk)	Kenya[139]
Amasi (milk), Mahewu (maize) and Munkoyo (maize)	SA/ Zimbabwe[134,139]
Ergo (milk) and Ititu (milk)	Ethiopia[139]

***SA = South Africa.

Table 4. Some African Seaweeds/Macroalgae with Prebiotic Capacity.

Scientific name(s) of Algae/Seaweed	Country and reference
Meristotheca senegalensis (**Solieriaceae**)	Senegal[140]
Hypnea musciformis (**Cystocloniaceae**)	
Kappaphycus alvarezii (**Solieriaceae**)	Tanzania[140]
Gelidium abbotiorum (**Gelidiaceae**)	Morocco[140]
Gelidium canariense (**Gelidiaceae**)	
Gelidium corneum (**Gelidiaceae**)	
Gelidium crinale (**Gelidiaceae**)	
Gelidium latifolium (**Gelidiaceae**)	
Gelidium microdon (**Gelidiaceae**)	
Gelidium pulchellum (**Gelidiaceae**)	
Gelidium pusillum (**Gelidiaceae**)	
Gelidium spinosum (**Gelidiaceae**)	
Pterocladiella Caerulescens **(Pterocladiaceae)**	
Pterocladiella capillacea **(Pterocladiaceae)**	
Gigartina acicularis **(Gigartinaceae)**	
Gigartina pistillata **(Gigartinaceae)**	
Gigartina teedii **(Gigartinaceae)**	
Spirulina platensis **(Spirulinaceae)**	South Africa[140,141]
Chlorococcum littorale **(Chlorococcaceae)**	
Dunaliella salina **(Dunaliellaceae)**	
Scenedesmus magnus **(Scenedesmaceae)**	
Chlorella pyrenoidosa **(Chlorellaceae)**	
Chlorella ellipsoidea **(Chlorellaceae)**	
Gelidium abbotiorum (**Gelidiaceae**)	
Gelidium pristoides (**Gelidiaceae**)	
Gelidium pteridifolium (**Gelidiaceae**)	

Note: Plant family names were retrieved form World Register of Marine Species (WoRMS); https://www.marinespecies.org/index.php.[142]

Table 5. Some Prebiotic African Wild Fruits, Leafy Vegetables, and Roots and Tubers.

Common name	Scientific name	Part used	Country and Reference
Baobab	*Adansonia digitata* L.	Ripe Fruit	Africa[128,143]
Wild berries	*Rubus cuneifolius*	Ripe Fruit	Lesotho, Swazilandand South Africa[128]
Rosehip	*Rosa rubiginosa*	Ripe Fruit	
Thistle	*Sonchus dregeanus*	Leaves	
Red pigweed	*Amaranthus retroflexus*	Leaves	
Wild spinach	*Chenopodium album*	Leaves	
Sting nettle plant	*Urtica dioica*	Leaves	
Hare-bell	*Wahlengergia androsacea*	Leaves	
Cape pepper cress	*Lepidium capense*	Leaves	
Wild nemesia	*Nemesia fruticans*	Leaves	
Purples	*Berkheya purpurea*	Leaves	Africa[128,143]
Wild mustard	*Sisymbrium thelungii*	Leaves	Lesotho, Swaziland and South Africa[128]
Sedge	*Cyperus esculentus*	Leaves	
Thistle	*Sonchas integrifolius*	Leaves	
Wonderberry	*Solanum retroflexum*	Leaves	
Wild jute plant	*Corchorus tridens*	Leaves	
Pigweed	*Amaranthus hybridus*	Leaves	
Sweet potato	*Ipomoea batatas*	Roots	Africa[140]
Yam	*Dioscorea alata*	Roots	
Carrot	*Daucus carota L.*	Roots	
Ginger	*Zingiber officinale*	Roots	
Cassava	*Manihot esculenta*	Roots	
Cocoyam	*Xanthosoma sagittifolium*	Roots	
Taro	*Colocasia esculenta*	Roots	

different kinds of raw materials. The raw materials may include, among others, cereals, legumes, milk, and fish.

Several African seaweeds that are traditionally used as food have also been credited with the attributes of functional foods (Table 4). Most of these prebiotic seaweeds can be found in South Africa and Morocco (based on available publications). Not many such plants have been described from other countries on the continent. However, some of these gut-friendly and healthy seaweeds can also be found in East and West Africa.

Some leafy vegetables and wild African fruits (such as baobab, wild berries, and rosehip) have also been credited with prebiotic properties (Table 5). The membership of prebiotic plants doesn't go without the inclusion of roots and tubers. A good number of roots and tubers found throughout the continent have also been categorized as prebiotic plants. These include yam, cassava, potato and ginger among many others.

Conclusion

Irrespective of the large use of ethnomedicinal plants in Africa, not much scientific studies have been done on the use of ethnomedicine for the treatment and management of age-related dementia, viz-a-viz AD. However, both *in vivo* use and *in vitro* assessment of African ethnomedicinal plants have demonstrated the potential of these plants in the treatment of dementia and AD-related phenotypes, suggesting that they contain biocompounds that are effective in the prevention and stalling of the progression of AD. Thus, we might be able to find potential plant sources for a novel class of anti-age-related dementia drugs. The ethnomedicinal use of plants as antiviral agents has existed on the African continent for many years. The use of these ethnomedicinal plants by traditional healers, coupled with current research findings, has demonstrated the potential of ethnomedicine as a source for the development of new anti-HSV-1 drugs and possibly a cure. There is therefore the

need to conduct further studies on plants that are traditionally used in the treatment of HSV-1 or in the botanical classes of those already identified in order to possibly carry them along the drug development pipeline. Finally, considering the general benefit of prebiotics and probiotics on overall human health, it is certainly of utmost importance to include prebiotics and probiotics in daily food intake. When a good balance is struck between prebiotics and probiotics, optimal synergy is likely to be achieved between prebiotics and probiotics, which will be beneficial to overall host health. This can be achieved by regulating the gut flora using functional food as therapy.

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Authors' Contributions

E.J.T. did the literature search prepared initial draft. M.Y.O.A reviewed the initial draft and included Table 3, D.L.S. conducted literature search and made inputs into Tables 1–3, M.M. conducted literature search and made inputs into tables Table 3 and A.O. generated the idea and reviewed the final draft.

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Consent for Publication

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Availability of Data and Materials

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