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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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 ethnomedical 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 foodstuffs were identified. Of the 101 identified plant species, 50 species serve as functional foodstuffs. Twenty-three (23) of the ethnomedical 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 aggre-
gation 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 micro-
biota and HSV-1 infection as contributing factors to the de-
velopment 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 mainly 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 thy-
midine 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 neuroinflammation33 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 agent36,37 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 essen-
tial 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 ethno-
pharmaceutical 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 ethnomedi-
cinal knowhow and it is now more important than ever to profile ethnomedicinal plants that can attenuate AD-related pathophys-
ology. 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 categori-
ized 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)** | Memory enhancer | | Bulb\(^{47}\) |
| **Compounds/Phytochemicals:** | Hamayne Lycorine | | |
| **Mechanism:** | Active against AChE | | |
| **Crinum jagus C. (Amaryllidaceae)** | Memory enhancer | | Bulb\(^{47}\) |
| **Compounds/Phytochemicals:** | Hamayne Lycorine | | |
| **Mechanism:** | Active against AChE | | |
| **Hydrolea glabra Schum. (Hydrophilaceae)** | Memory enhancer and alleviates anxiety in mice | | Leaves\(^{48,49}\) |
| **Compounds/Phytochemicals:** | Steroids | | |
| **Mechanism:** | Acts on GABA receptor | | |
| **Pistia stratiotes L. (Araceae)** | Relieves dementia | | Roots / Leaves\(^{50,51}\) |
| **Compounds/Phytochemicals:** | Stratioid II | | |
| **Mechanism:** | Anti-inflammatory and nociceptor sensitization | | |
| **Boophone disticha (L.f.) Herb.** | Inhibits AChE and potentially neuroprotective | | Leaves / Bulb\(^{52,53}\) |
| (Amaryllidaceae) | 6-hydroxyestrainine | | |
| **Compounds/Phytochemicals:** | 6-hydroxyestrainine | | |
| **Mechanism:** | Inhibits AChE | | |
| **Croton sylvaticus Hochst. (Euphorbiaceae)** | Inhibits AChE and potentially neuroprotective | | Leaves\(^{54}\) |
| **Compounds/Phytochemicals:** | Quercetin Kaempferol | | |
| **Mechanism:** | Inhibits AChE | | |
| **Ziziphus mucronata Willd. (Rhamnaceae)** | Inhibits Aβ in SH-SY5Y cells | | Leaves\(^{55,56}\) |
| **Compounds/Phytochemicals:** | Galantamine | | |
| **Mechanism:** | Inhibits AChE | | |
| **Cola nitida (Vent.) Schott & Endl.** | CNS stimulant/anti-depressant | | Seed\(^{57,58}\) |
| (Sterculiaceae) | 9-Octadeconenamide | | |
| **Compounds/Phytochemicals:** | 9-Octadeconenamide | | |
| **Mechanism:** | Inhibits AChE and BuChE | | |
| **Lannea schweinfurthii (Engl.) Engl.** | Inhibits A-beta in SH-SY5Y cells | | Roots\(^{55,59}\) |
| (Anacardiaceae) | Epicatechin Sitossterol | | |
| **Compounds/Phytochemicals:** | Epicatechin Sitossterol | | |
| **Mechanism:** | Inhibits AChE | | |
| **Terminalia sericea Burch. ex DC.** | Inhibits A-beta in SH-SY5Y cells | | Roots\(^{55,60}\) |
| (Combretaceae) | Seric acid Sericoside | | |
| **Compounds/Phytochemicals:** | Seric acid Sericoside | | |
| **Mechanism:** | Inhibits AChE and A-beta | | |
| **Piper capense Lf. (Piperaceae)** | Inhibits AChE and potentially neuroprotective | | Roots\(^{56}\) |
| **Compounds/Phytochemicals:** | Piperine 4,5-dihydropiperine | | |
| **Mechanism:** | Inhibits AChE, and antioxidant activity | | |
| **Piper nigrum L (Piperaceae)** | Enhanced memory in Wistar rat | | Fruits\(^{61,62}\) |
| **Compounds/Phytochemicals:** | Allyl isothiocyanate Zingerone | | |
| **Mechanism:** | Inhibits cellular production of TNF-α and nitric oxide | | |
| **Terminalia sericea Burch. ex DC.** | Enhanced memory in Wistar rat | | Roots\(^{56,63,64}\) |

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

(continued)
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.

| Botanical name (Family) | in vivo | in vitro | Part(s) used/references |
|-------------------------|--------|----------|------------------------|
| **Mechanism**: Anti-neuroinflammatory and anti-AChE | | | |
| Agnaecum echlerianum Bory. (Orchidaceae) | Memory enhancer | | Leaves<sup>90</sup> |
| **Compounds/Phytochemicals**: Alkaloids Flavonoids | | | |
| **Mechanism**: Antioxidant effect | | | |
| Aframomum melegueta K. Schum. (Zingiberaceae) | Memory enhancer | | Seeds<sup>80,81</sup> |
| **Compounds/Phytochemicals**: Gingerols Paradols | | | |
| **Mechanism**: Antioxidant effect and anti-neuroinflammatory | | | |
| Moringa Oleifera (Moringaceae) | Memory enhancer | | Leaves<sup>57,72,82</sup> |
| **Compounds/Phytochemicals**: Alkaloids Flavonoids | | | |
| **Mechanism**: Antioxidant effect | | | |
| Ecklonia maxima (Lessoniaceae) | | | Whole plant<sup>83–85</sup> |
| **Compounds/Phytochemicals**: Dibenzo [1,4]dioxine-2,4,7,9-tetral Eckmaxol | | | |
| **Mechanism**: Anti-AChE effect, and decreases Reactive Oxygen Species | | | |
| Gelidium pristoides (Gelidiaceae) | | | Whole plant<sup>83</sup> |
| **Compounds/Phytochemicals**: 35,7-trimethoxy flavone Biochanin A | | | |
| **Mechanism**: Anti-BChE, anti-AChE, and anti-amyloidogenic | | | |
| Gracilaria gracilis (Gracilariaeae) | | | Whole plant<sup>83</sup> |
| **Compounds/Phytochemicals**: Alpha-tocopherol Beta-sitosterol | | | |
| **Mechanism**: Anti-BChE, anti-AChE, and anti-amyloidogenic | | | |
| Ulva lactuca (Ulvaceae) | | | Whole plant<sup>83</sup> |
| **Compounds/Phytochemicals**: Beta-D-Galactofuranoside Arabinose | | | |
| **Mechanism**: Anti-BChE, anti-AChE, and anti-amyloidogenic | | | |
| Zingiber officinale (Zingiberaceae) | | | Rhizomes<sup>86,87</sup> |
| **Compounds/Phytochemicals**: α-Zingiberene Camphene | | | |
| **Mechanism**: Antioxidant effect, and anti-inflammatory | | | |

*** 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).
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.\(^7^4\) 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*.\(^7^8\) The bulb extract of *Crinum glaucum* (Figure 1C),\(^4^7\) *Crinum jagus* (Figure 1D),\(^4^7\) and *Crinum macowanii* (Figure 1E)\(^7^3\) 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.\(^5^2\) Furthermore, the bulb extract of *Ammocharis coranica* (Figure 1G), which is used ethnomedically as an antipsychotic, has also been reported to have neuroprotective capacity and ability to inhibit AChE *in vitro*.\(^7^0\) The root extract of *Rauwolfia vomitoria* (family: 

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*Figure 1.* Photographs of some of the plants listed in Table 1. (continued)
Figure 1. Continued.
Apocynaceae) (Figure 1I) was reported to be a potent anti- 
psychotic 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 demen-
tia 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* 
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 
sylvestris* (Figure 1N), were identified from the Euphorbiaceae 
family. While the fruits of *Jatropha curcas* has antipsychotic 
properties,\(^67\) the leaf extract of *Croton sylvestris* 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 pris-
toides* (Figure 1P), *Gracilaria gracilis* (Figure 1K), *Ecklonia 
maxima* (Figure 1Q), and *Ulva lactuca* (Figure 1R) were iden-
tified from *Gelidiaceae*, *Gracilariaceae*, *Lessoniaceae*, and 
*Ulvaaceae* 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 eichleri-
anum*) (Figure 1T), *Scrophulariaceae* (*Aptosimum decumbens*) 
(Figure 1U), and *Zingiberaceae* (*Aframomum melegueta*) 
(Figure 1V). The leave extracts of *Moringa oleifera*\(^57,72\) and 
*Angraecum eichleri*\(^80\) 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 offici-
 nale* had been identified as having neuroprotective capacity 
and the ability to inhibit AChE in vitro.\(^86\) *Pycnanthus angolen-
sis* 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 
*Polygonaceae* had successfully demonstrated cognition 
enhancement in CD1 mice.\(^79\)

The leave extract of *Hydrolea glabra* (Figure 1Z) of the 
family *Hydrophylaceae* 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 neuro-
protective 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 antidepres-
sonal 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 cyto-
megalovirus (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 through-
out 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 ethnomedi-
cinal plants affecting various stages of viral growth.\(^92\) Herbal 
preparations are widely used as antiviral drugs,\(^92–94\) and ethno-
pharmacological preparations are currently being classified for 
their activity against viral infections.\(^92,95\)

Table 2 below shows the compiled list of some African eth-
nomedicinal 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*, 
*Euphorbiaceae*, *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) | Aerial | Aqueous ethanol | Vero cells | Plaque reduction/inhibition assay<sup>96.97</sup> |
| **Compounds/Phytochemicals:** Quercetin, Quercetin-7-O-rutinoside, Luteolin, Kaempferol-3-galactoside, and Quercetin-7-O-glucoside | | | | |
| Cypus rotundus L. (Capparaceae) | Tuber | Aqueous ethanol | Vero cells | Plaque reduction/inhibition assay<sup>96.98</sup> |
| **Compounds/Phytochemicals:** Luteolin-7-O-glucoside, Tricin, (+)-catechin, quercetin, (--)-cypera-2,4-diene, 4α,5α-oxidoedem-sem-11-en-30-ol, and Rotundane A | | | | |
| Ephedra alata Deccne. (Ephedraceae) | Aerial | Aqueous ethanol | Vero cells | Plaque reduction/inhibition assay<sup>96.99</sup> |
| **Compounds/Phytochemicals:** Phedrine, Pseudoephedrine, Trans-cinnamic acid, Catechin, Syringin, Epicatechin, Symplcoside, Kaempferol 3-O-rhamnoside 7-O-glucoside, Isovitexin 2-O-rhamnosid, and Luteolin-7-O-glucuronic acid flavonoid | | | | |
| *Moringa peregrina* (Forsk.) Fiori. (Moringaceae) | Seed | Aqueous ethanol | Vero cells | Plaque reduction/inhibition assay<sup>96.100</sup> |
| **Compounds/Phytochemicals:** Lupeol acetate, β-amyrin, α-amyrin, β-sitosterol, and β-sitosterol-3-O-β-D-glucoside | | | | |
| Tammarix nilotica (Ehrenb.) Bunge. (Tamaricaceae) | Aerial | Aqueous ethanol | Vero cells | Plaque reduction/inhibition assay<sup>96.101</sup> |
| **Compounds/Phytochemicals:** Gallic acid, Quercetin, Kaempferol, di-Galloylglucose, Kaempferol glucuronide, and Methyl-queretin | | | | |
| Erica multiflora L. (Ericaceae) | Aerial | Methanolic | Vero cells | Plaque reduction/inhibition assay<sup>96.102</sup> |
| **Compounds/Phytochemicals:** Quercetin, Kaempferol, Myricetin, Uvic acid, Caffeic acid hexiside, 3-O-caffeoylquinic acid, P-coumaric acid hexiside, Syringic acid hexiside | | | | |
| *Frankenia pulverulenta* L. (Frankeniaceae) | Whole plant | Methanolic/acetonic | Vero cells | Plaque reduction/inhibition assay<sup>93.103</sup> |
| **Compounds/Phytochemicals:** Dihydeotocamanine, 5,7-Dodecadien-1,12-diol, 6-Acetyl-β-D-mannose, Gamolenic acid, and Giberrellac acid | | | | |
| *Zygophyllum album* L. (Zygophyllaceae) | Whole plant | Acetonic | Vero cells | Plaque reduction/inhibition assay<sup>93.104,105</sup> |
| **Compounds/Phytochemicals:** Hyacantine, 1-Nonen-4-ol, Nonanal, 1,2-Dihydro-14,6-trimethyl napththalene, Bis(2-ethyl hexyl) phthalate, Quercetin 3-sulfate, Isoharmanetin-3-O-rutinoside, and Quinovicacid 3-O-rhamnoside | | | | |
| Pelargonium sidoides DC. (Geraniaceae) | Roots | Aqueous-ethanolic | RC-37 cells | Plaque reduction/inhibition assay<sup>94.106,107</sup> |
| **Compounds/Phytochemicals:** 7-hydroxy-5,6-di-methoxycoumarin, 6,8-dihydroxy-5,7-dimethoxycoumarin, 6-Methoxy-7-(sulfoxyl)-2H-1-benzopyran-2-one, and 6,8-Bis(sulfoxyl)-7-methoxy-2H-1-benzopyran-2-one | | | | |
| Helichrysum aureonitens Sch. Bip. (Asteraceae) | Shoots | Aqueous | Human lung fibroblast | Plaque reduction/inhibition assay<sup>95.108,109</sup> |
| **Compounds/Phytochemicals:** 35,3'-Dihydroxyflavone, 3'-Caffeoylquinic acid, 5-Caffeoylquinic acid, 4,5-Dicaffeoylquinic acid, Ferulic acid, and 13S-Hydroxy-9Z,11E,15Z-octadecatrienoic acid | | | | |
| Combretum micranthum (Combretaceae) | Leaves | Methanolic | Vero cells | Plaque reduction/inhibition assay<sup>96.110</sup> |
| **Compounds/Phytochemicals:** C-glycosylflavones, vitexin, isovitexin, orientin, and homoaractin, m-inositol and sorbitol, myricetin-3-O-glucoside, and myricetin-3-O-rutinoside | | | | |
| Bauhinia thonningii (Schum.) (Leguminosae) | Leaves | Methanolic | Human colonic cancer cells (HT-29) | Plaque reduction/inhibition assay<sup>111,112</sup> |
| **Compounds/Phytochemicals:** C-methylflavanones, 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-methylkaempferol 3-methyl ether, 6,8-di-C-methylkaempferol 3,7-dimethyl ether, and quercitrin | | | | |
| Anacardium occidentale L. (Anacardiaceae) | Bark | Methanolic | Human colonic cancer cells (HT-29) | Plaque reduction/inhibition assay<sup>111,113</sup> |
| **Compounds/Phytochemicals:** 2-(10Z,13′Z-nonadecadienyl)-6-(8′Z,11′Z-pentadecadienyl) salicylic acid, (+)-catechin, (-)-epicatechin, epigallocatechin, protocatechuic, cinnamic acid, 5,7-Dodecadiyn-1,12-diol, 6-Acetyl-β-D-mannose, Gamolenic acid, and Giberrellac acid | | | | |

(continued)
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 infection 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 infection.94

Mechanistic studies conducted on the antiviral activity of functional foods have been limited.93

Some African Plants and Traditional Foodstuff Used as Functional Foods

Functional Food

The gut microecology is the physiologic base for the consequence of probiotics and prebiotics 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.\textsuperscript{124,125} However, in 2001, probiotics were further defined by the Food and Agriculture Organization (FAO)/World Health Organization (WHO) (2001).\textsuperscript{126} This definition described probiotics as “live microorganisms that when administered in adequate amounts confer health benefit effects on the host”.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{133} Only fermented foodstuffs that meet the following conditions can be considered as probiotic foodstuffs.\textsuperscript{134}

A probiotic foodstuff must meet the following conditions:

- Have live organisms (10\textsuperscript{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.\textsuperscript{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. Adolescens.
- Other organisms: Lactococcus lactis, Enterococcus faecium, Enterococcus faecalis, Pediococcus acidilactici, Streptococcus salivarus var. thermophilus, Saccharomyces boulardi).\textsuperscript{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.\textsuperscript{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.\textsuperscript{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\textsuperscript{137,138} |
| Ogi (maize) and Kunuzaki (millet) | Nigeria\textsuperscript{138} |
| Mawe (maize) | Benin\textsuperscript{138} |
| Mbege (millet) | Tanzania\textsuperscript{138} |
| Ben-saalga (millet) | Burkina Faso\textsuperscript{138} |
| Bogobe (sorghum) | Botswana\textsuperscript{138} |
| Humular and Hussuwa (sorghum) | Sudan\textsuperscript{138} |
| Bouza and kishk (wheat) | Egypt\textsuperscript{139} |
| Uji (maize) and Kule naoto (milk) | Kenya\textsuperscript{139} |
| Amasi (mil), Mahewu (maize) and Munkoyo (maize) | SA/ Zimbabwe\textsuperscript{134,139} |
| Ergo (milk) and Ititu (milk) | Ethiopia\textsuperscript{139} |

\textsuperscript{44}SA = South Africa.
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 the attributes of functional foods (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 bio-compounds 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

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**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) | Tanzania\(^{140}\) |
| *Kappaphycus alvarezii* (Solieriaceae) | Morocco\(^{140}\) |
| *Gelidium abbotiorum* (Gelidiaceae) | |
| *Gelidium canariense* (Gelidiaceae) | |
| *Gelidium cornum* (Gelidiaceae) | |
| *Gelidium crinale* (Gelidiaceae) | |
| *Gelidium latifolium* (Gelidiaceae) | |
| *Gelidium microdon* (Gelidiaceae) | |
| *Gelidium pulchellum* (Gelidiaceae) | |
| *Gelidium pusillum* (Gelidiaceae) | |
| *Gelidium spinosum* (Gelidiaceae) | |
| *Pterocladia Caerulescens* (Pterocladiaceae) | |
| *Pterocladia capillacea* (Pterocladiaceae) | South Africa\(^{140,141}\) |
| *Gigartina acicularis* (Gigartinaeaceae) | |
| *Gigartina teidii* (Gigartinaeaceae) | |
| *Spirulina platensis* (Spirulinaeaceae) | |
| *Chlorococcum littorale* (Chlorococcaceae) | |
| *Dunaliea salina* (Dunalielleaceae) | |
| *Scenedesmus magnus* (Scenedesmaceae) | |
| *Chlorella pyrenoidosa* (Chlorellaceae) | |
| *Chlorella ellipsoidea* (Chlorellaceae) | |
| *Gelidium abbotiorum* (Gelidiaceae) | |
| *Gelidium microdon* (Gelidiaceae) | |
| *Gelidium pteridifolium* (Gelidiaceae) | |

**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 cuneiformis* | Ripe fruit | Lesotho, Swaziland and South Africa\(^{128}\) |
| Rosehip     | *Rosa rubiginosa* | Ripe fruit | Leaves |
| Thistle      | *Sanchus dregeanus* | | Leaves |
| Red pigweed  | *Amaranthus retroflexus* | | Leaves |
| Wild spinach | *Chenopodium album* | | Leaves |
| Sting nettle  | *Urtica dioica* | | Leaves |
| Hare-bell    | *Wahlengeria andrascanceae* | | Leaves |
| Cape pepper  | *Lepidium capense* | | Leaves |
| Wild nesemia | *Nemesia fruticans* | | Leaves |
| Purples      | *Berkheya purpurea* | | Africa\(^{128,143}\) |
| Wild mustard | *Sisymbrium thelungi* | | Leaves |
| Sedge        | *Cyperus esculentus* | | Leaves |
| Thistle      | *Sonchas integrifolius* | | Leaves |
| Wonderberry  | *Solanum retroflexum* | | Leaves |
| Wild jute plant | *Cochurus 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 |
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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