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Indian Herbs and their Therapeutic Potential against Alzheimer's Disease and other Neurological Disorders

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4.1 Introduction

The history of medicine dates back several thousand years – perhaps to the dawn of human civilization. Different thoughts and schools of medicine have developed through the years in different parts of the world, many relying on the use of natural plants and herbs for the treatment of a plethora of diseases. One such is the Indian system of medicine, "Ayurveda." The Ayurvedic system is considered to be among the oldest systems of medicine still in use. The ancient masters are thought to have understood the delicate physiological mechanisms occurring in the body and the disruption of balance and coordination among these systems that leads to the development of disease. Thus, they developed certain dietary regimes and therapeutic formulations for the alleviation of disease in a holistic manner. Based on traditional knowledge, many herbal plants are still being used in exactly the same way today for many diseases in India, with great therapeutic benefit. Many registered medical Indian practitioners propagate the science of Ayurveda even today. Although modern science did not recognize Ayurveda for a long time, this system is now gaining popularity in the West. In recent years, many scientists have focused their research on understanding the mode of action of traditional Indian herbs in different diseases. This has helped in lending robust scientific evidence to the use of these plants. This review summarizes some of the common traditional Indian plants of relevance to the treatment of dementia, Alzheimer's disease (AD), and other neurological disorders.

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4.2 Ayurveda

It is believed that the traditional system of health care in India originated around 4500–1600 BC, dating to the period of the Indus Valley Civilization [1–3]. Knowledge about health and the use of various herbs and therapeutic interventions was believed to be received through sages and passed on orally to subsequent generations, before being transcribed into books. This system was well established by around 2500–600 BC, when it evolved into the science now known as "Ayurveda." "Ayurveda" comes from Sanskrit *ayu* (longevity) and *ved* (knowledge). It is discussed at great length in the four ancient books of spiritual knowledge – Rigveda, Yajurveda, Samaveda, and Artharvaveda – written between the 12th and 7th centuries BC [1,4]. Two of the greatest physicians of ancient India, Shushrutha and Charaka, worked during this time, composing texts known as Samhitas [5,6].

Ayurveda is divided into two schools – the School of Physicians and the School of Surgeons – which laid the foundation for its practice and discarded superstitions regarding its divine origins. According to Ayurveda, our body is composed of three doshas: vata (nervous system), pitta (enzymes), and kapha (mucus). Balance between these doshas is required for a healthy life. This traditional system makes mention of organ transplants, plastic surgery, artificial limbs, and processes that prolong health; geriatrics, rejuvenation, immunology, genetics, and higher consciousness are also much described. "Rasayana chikitsa," which focuses on the preservation and promotion of health, has a special place in Ayurveda; this involves taking special rejuvenation therapies and following a dietary regimen in order to improve the functioning of the whole body. It is preceded by "Panchakarma therapy," wherein the body is thoroughly cleansed [7].

Rasayana drugs are rich in antioxidants and immunomodulatory agents. Traditionally, they were used against a wide variety of diseases. The strong antioxidant potential of some of these drugs has already been proven. As a majority of diseases are linked to disruption of the delicate balance between oxidants and antioxidants, the ability to scavenge free radicals or to activate antioxidant defenses in the cell can be thought of as their main mechanism of action. Many plants have been categorized as Rasayana plants: ashwagandha, brahmi, mandukaparni, shankapushpi, vacha, jatamansi, and jyotishmati. These are referred to as "Medhya Rasayanas," meaning plants specific to brain tissues and classed as brain tonics or rejuvenators [8,9].

For a long time, medical practitioners in the West did not fully understand Ayurveda, but today it is recognized across the world. The US National Institutes of Health (NIH) consider it a complementary and alternative medicine [4].

4.3 Therapeutic Intervention in AD

Even with the tremendous advances made in medical science in recent decades, dementia and age-related disorders remain untreatable. The occurrence of age-related disorders rises as life expectancy increases. Of all the neurodegenerative diseases, AD is the most common. AD is a complex, multifactorial, progressive, neurodegenerative disease

affecting people over 65 years of age, accounting for 50–60% of dementia cases. It is characterized by the loss of memory and impairment of cognitive functions. Pathologically, it is characterized by the presence of amyloid beta (Aβ) plaques and neurofibrillary tangles [10].

Various models have been proposed to describe the pathological sequential events in AD progression and development. The most accepted is "amyloid cascade hypothesis," which views the accumulation of Aβ as an early event in AD development. Some scientists also view mitochondrial dysfunction, synaptic damage, and neuronal and cytoskeletal alterations as early events that occur before Aβ accumulation. There is significant debate over whether the fibrillary or the soluble oligomeric forms of Aβ are the most toxic species in AD development and progression.

The autosomal-dominant forms of AD have been proposed to occur as a result of abnormal processing of the amyloid precursor protein (APP) gene. The apolipoprotein E (APOE) gene has been identified as a potential risk factor for AD. Aging and oxidative stress has also been implicated in its development. It is believed that the pathological processes begin very early, before the development of dementia and cognitive damage. Thus, it is this stage which needs to be targeted for therapeutic intervention, to prevent progression from normal cognition to mild cognitive impairment (MCI) and finally AD. Biomarkers have helped remarkably in detecting the pathological accumulation of Aβ deposits and tracking the preclinical stages of AD. These include a reduction in the levels of Aβ1–42 in the cerebrospinal fluid (CSF) and increased retention of amyloid tracer on positron emission tomography (PET). For detection of synaptic dysfunction, decreased uptake of fluorodeoxyglucose 18 F is viewed as a biomarker. The study of brain atrophy via magnetic resonance imaging (MRI) is also used as a validated biomarker [11]. More progress needs to be made in the field of biomarker discovery, however, if we are to identify AD patients even before symptoms or cognitive decline occurs. Developments need to be made in identifying potential epidemiological and neuropsychological factors, and more cognitive studies must be conducted to assess the risk of progression of AD if we are to clearly detect subtle cognitive decline [11].

Before the advent of technological procedures, herbal formulations served to treat neurological disorders. Successful clinical trials are being conducted using herbs and their constituent phytochemicals to treat various neurodegenerative diseases, including AD. Phytochemicals that cause upregulation of antioxidants and a decrease in oxidative stress are seen to be effective in AD [12]. α-tocopherol and ascorbic acid have also been shown to be beneficial. Phytocompounds such as withanone (from ashwagandha: *Withania somnifera*), which has the capability to induce neurite outgrowth and differentiation, have the potential to repair the neuronal damage seen in AD [13,14]. Plants with antioxidant activity and the capacity to improve cognition act as therapeutic agents for AD (e.g., *Ginkgo biloba*, GB). Plants with antiacetylcholinesterase (anti-AChE) activity (e.g., *Hemidesmus indicus*) provide a useful therapeutic target for AD [15] (Figure 4.1). Plants that display antisecretase activity and block the formation of Aβ fibrillization and oligomerization may serve as effective therapeutic agents for AD. Thus, understanding the molecular mechanism(s) of the pathogenesis and progression of AD may lead to the discovery of effective therapeutic targets for its treatment.

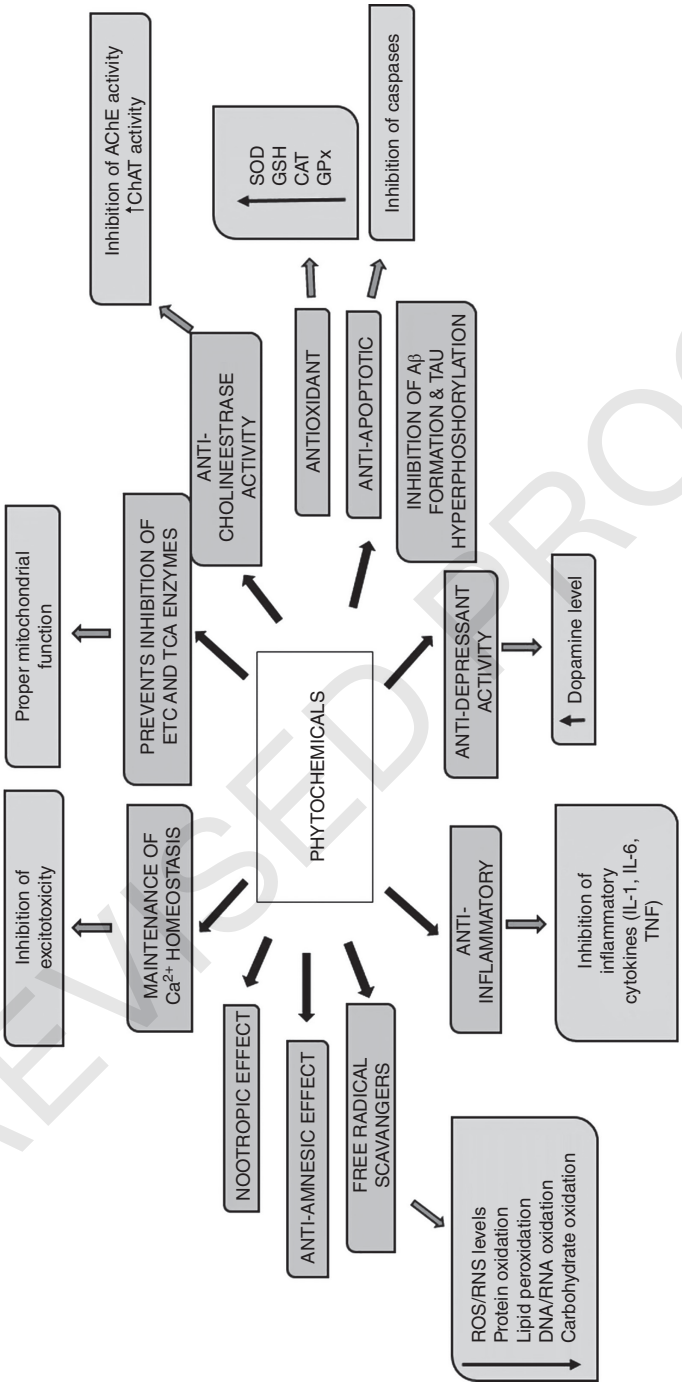

Figure 4.1 Basic mechanisms by which different phytochemicals act at the cellular level: (i) through an increase in the activity of antioxidant enzymes (e.g., SOD, GSH, CAT, GPx); (ii) through maintenance of Ca^{2+} homeostasis; (iii) through inhibition of inflammatory cytokines; (iv) through inhibition of AChE activity and increasing the activity of choline acetyltransferase activity; (v) through prevention of the inhibition of ETC and TCA enzymes; and (vi) through inhibition of the activity of caspases. (*See insert for color representation of the figure.*)

4.4 Medicinal Plants

India has 45 000 plant species, making up 33% of the world's total plant diversity. The formulations and uses of a variety of Indian herbs are well documented in the Indian Ayurvedic texts [16]. In recent years, studies have been conducted to validate and elucidate the mechanistic mode of action of these herbs in different diseases. In this section, we describe some of the common traditional Indian herbs in the light of recent scientific findings relating to their *in vitro* and *in vivo* activities of relevance to dementia and AD (Table 4.1).

Table 4.1 Indian plants and their modes of action.

Name	Constituent	Effect
Safed bach *(Acorus calamus)*	α- and β-asarone	Antioxidant activity and sedative effects
Ashwagandha (*Withania somnifera)*	Ergostane-type steroidal lactones, phytosterols, sitoindosides VII–X, β-sitosterol, alkaloids	Anti-AD agent, increases cholinergic activity, increases ACh content and ChAT activity, stimulates neurite outgrowth, prevents fibril formation [121]
Brahmi (*Bacopa monnieri*)	Saponins and triterpenoid bacosaponins that include bacopasides III–V, bacosides A and B, and bacosaponins A, B, and C	Improves memory and cognitive function, nootropic action, reverses the depletion of ACh, reduces ChAT activity, protects neurons from Aβ-induced cell death by suppressing cellular AChE activity, restrain intracellular oxidative stress [121]
Aparajita (*Clitoria ternatea*)	Kaempferol and quercetin glycosides and myricetin glycosides	Increases levels of ACh and ChAT [31]
Shankhapushpi (*Convolvulus pluricaulis*)	Ascorbic acid, Piracetam, Rivastigmine tartrate, triterpenoids, flavonolglycosids, anthrocyanins and steroids.	Free radical-scavenging effect, memory-enhancing effect, maintains the muscarinic receptor's mRNA levels, ChAT, and NGF-TrkA [122,123]; nootropic and memory-enhancing properties, calms the nerves by regulating the body's production of the stress hormones adrenaline, cortisol, ethanolic extract, and aqueous fractions, significantly improves learning and memory in rats [124]
Chandan (*Santalum album*)	Sesquiterpenoids, triterpenoids, phenylpropanoids, α- and β-santalols	Antioxidant action, anti-inflammatory, NO-scavenging properties, improves memory and cognition [36,38]
Gotu kola (*Centella asiatica*)	Monoterpenes (bornyl acetate, α- and β-pinene, γ-terpinene), triterpene asiatic acid	Sedative, antidepressant, and potentially cholinomimetic *in vivo*, protects cortical neurons from glutamate-induced excitotoxicity *in vitro*, reverses Aβ pathology in the brain [31,121]

(Continued)

Table 4.1 (Continued)

Name	Constituent	Effect
Guggulu (*Commiphora wightii*)	Commiphoric acids, commiphorinic acid, heerabomyrrhols, terpenes, sesquiterpenoids, cuminic aldehyde, eugenol, the ketone steroids Z- and E-guggulsterone, guggulsterols I, II, and III, ferulic acids, phenols, guggulipid	Scavenges superoxide radicals, decreases neuronal cholesterol levels, inhibits the Aβ-forming amyloidogenic pathway, protects against the streptozotocin-induced memory-deficit model of dementia, lowers cholesterol, shows antioxidant and antiacetylcholine esterase activity [121]
Ananthamoola (*Hemidesmus indicus*)	Coumarino-lignoids, flavonoids	Antioxidant and nootropic properties [84]
Jatamansi (*Nardostachys jatamansi*)	Crocetin	Reduces the level of TBARS and elevates the content of GSH and the activities of antioxidant enzymes (GPx, glutathione-S-transferase, CAT) [125]
Yastimadhu (*Glycyrrhiza glabra*)	Glycyrrhizin, flavanones, isoflavones, glycyrrhetenic acid	Antioxidant action, antituberculosis activity, balances sugar levels in the blood, increases blood circulation [43,126]
Tulsi (*Ocimum sanctum*)	Sesquiterpene, carvacrol, flavonoids, monoterpenes, urosolic acid, apigenin, luteolin, orientin, molludistin	Increases the antioxidant enzymes CAT, SOD, and GPx and decreases MDA levels, oxidative stress, and calcium levels [97,98]
Bhilawa (*Semecarpus anacardium*)	Biflavonoids, phenolic compounds, bhilawanols, minerals, vitamins, amino acids	Neuroprotective and antioxidant activity, nootropic actions [127]
Haldi (*Curcuma longa)*	Curcuminoids	Antioxidant activity, reduces lipid peroxidation and enhances of GSH in rat brain, antidepressant activity, inhibits brain MAO-A, modulates eicosanoid biosynthesis and inhibits COX-1, COX-2, and LOX [31]
Ber (*Ziziphus jujube*)	Phenolics, terpenoids, flavonoids	Protects against ischemic damage, upregulates SOD activity, reduces lipid peroxidation, increases GPx activity, inhibits caspase-3 activation [103,104]
Pudina (*Melissa officinalis*)	Citral, Citronellal, caryophyllene, α- and β-pinene	Decreases MDA levels, inhibits MAO-A activity, increases antioxidant capacity, act as chelating agent, inhibits AChE activity [107,108]
Til (*Sesamun indicum*)	Flavonoids, phenolics, alkanoids, tannins, saponins, terpenoids, sesamin, sesaminol, cephalin, lecithin	Increases GR, GPx, CAT activity, and GSH levels, decreases TBARS and caspase-3 activation, inhibits MAPK and COX-2 in neuronal cells [112,113]

AD, Alzheimer's disease; Ach, acetylcholine; ChAT, choline acetyltransferase; AChE, acetylcholinesterase; Aβ, amyloid beta; NGF-TrkA, nerve growth factor–tyrosine kinase A receptor; NO, nitric oxide; TBARS, thiobarbituric acid reactive substances; GSH, glutathione; GPx, glutathione peroxidase; CAT, catalase; SOD, superoxide dismutase; MDA, malondialdehyde; MAO, monoamine oxidase; COX, cyclooxygenase; LOX, lipoxygenase; GR, glutathione reductase; MAPK, mitogen-activated protein kinase.

4.4.1 Ashwagandha

Ashwagandha (*Withania somnifera*) (Figure 4.2) is a shrub, part of the Solanaceae family. It is prevalent in India and several South Asian countries. It is commonly referred to as "winter cherry" or "Indian ginseng." In Sanskrit, "ashwagandha" means "odor of the horse." Although its roots and leaves are used most commonly, other parts – including the shoots, seeds, and berries – have also traditionally been used in a variety of diseases. It is considered an adaptogen – a nontoxic medication that normalizes physiological functions against chronic stress by engaging the endocrinal and immune systems [5].

Alkaloid and steroidal lactones (commonly known as withanolides) form the major constituents of ashwagandha leaves. Using an alcoholic extract of ashwagandha leaves (i-Extract) (made up of a variety of constituents, including withaferin A, withanone, and withanolides A), marked inhibition of the proliferation of glioma cells (C6 and YKG1) was seen in a dose-dependent manner. In addition, enhanced differentiation of glial cells was seen on treatment with i-Extract components [17]. In line with this, another study showed that low doses of the leaf extracts of ashwagandha led to neuroprotection against oxidative stress and glutamate toxicity. Further, the leaf extracts led to differentiation of both glioblastoma (C6) and neuroblastoma (IMR-32) cells against H_2O_2 stress, thus serving as potent natural neurotherapeutic drugs [13].

Another study by Konar et al. [18] showed downregulation of brain-derived neurotrophic factor (BDNF) and glial fibrillary acidic protein (GFAP) in a dose-dependent manner when the neuronal (IMR-32) and glioma (C6) cells were given treatment with scopolamine. These effects were attenuated by treatment with i-Extract or its purified component, withanone [18]. An earlier study showed that methanolic extract of roots of ashwagandha increased the percentage of cells with neurites in human neuroblastoma SK-N-SH cells. Also, the mRNA levels of dendrite markers such as microtubule-associated protein 2 (MAP2) and postsynaptic density 95 (PSD-95) also increased on treatment with the extract [14]. Yet another study showed that when exposed to

Figure 4.2 Ashwagandha (*Withania somnifera*). *Source:* Adapted from the ENVIS Centre on Medicinal Plants (www.envis.frlht.org), Bengaluru, Karnataka, India, under the Ministry of Environment and Forests (MoEF), Govt. of India. Photos credit Dr. K. Ravikumar, Dr. Ganesh Babu, Ms. Suma TS, Mr. MV Sumanth, Mr. Patchaimal of FRLHT and Dr. D. Narasimhan, MCC, Chennai. 2016. (envis.frlht.org). FRLHT's ENVIS Centre on Medicinal Plants, Bangalore. Copyright FRLHT, Bangalore and MoEF, GoI. (*See insert for color representation of the figure*.)

methanolic root extracts of ashwagandha, axons are extended by withanolides, whereas withanoside induced extensions of dendrites studied by double immunostaining using an antibody to axonal marker neurofilament-H (NF-H) and dendritic marker MAP2 in rat cortical neurons [19]. This shows that ashwagandha may help restore damaged neuronal circuits by extending its neurite outgrowth. In regard to the antioxidant potential of ashwagandha, it was shown that the lipid peroxidation and activity of glutathione peroxidase (GPx), which was decreased in the spinal cord of adult Wistar rats and copper-induced stress, was attenuated by treatment with the plant extract [20]. Taken together, these results point toward the preventive and therapeutic potential of leaf extracts of ashwagandha in age-related neurodegenerative diseases such as AD.

4.4.2 Brahmi

Brahmi (*Bacopa monniera*; Family: Scrophulariaceae) (Figure 4.3) is an indigenous creeping annual plant seen in wet, damp, and marshy areas of India, Sri Lanka, Nepal, Pakistan, Afghanistan, subtropical regions of the United States, tropical Asia, Africa, and Australia [21].

B. monniera has been described as one of the most popular Medhya drugs (nootropic agents). Its therapeutic efficacy is extensively recounted in the Ayurvedic and Indian Vedic literature, such as the Artharvaved, Carak Samhita, and Susrutu Samhita. It is used for the treatment of insomnia, anxiety, and epilepsy, as an antipyretic and antiepileptic agent, and as a mild sedative [22]. In Ayurveda, *B. monniera* has been used for centuries as a well-valued brain tonic for rejuvenating intellect (Medhya), an antistress agent in anxiety, and for a means of enhancing cognitive ability (Rasayana) [23]. Several studies have reported that this medicinal herb acts as a mental tonic and a nervine and can be used for the treatment of mental and neurological disorders [24].

B. monniera contains alkaloids, flavonoids, glycosides, and saponins. Saponins are considered to be the active constituents of the plant, consisting of numerous components designated as bacosides, bacopasides, and bacopasaponins. Bacoside A is the major active

Figure 4.3 Brahmi (*Bacopa monniera*). *Source:* Adapted from the ENVIS Centre on Medicinal Plants (www.envis.frlht.org), Bengaluru, Karnataka, India, under the Ministry of Environment and Forests (MoEF), Govt. of India. Photos credit Dr. K. Ravikumar, Dr. Ganesh Babu, Ms. Suma TS, Mr. MV Sumanth, Mr. Patchaimal of FRLHT and Dr. D. Narasimhan, MCC, Chennai. 2016. (envis.frlht.org). FRLHT's ENVIS Centre on Medicinal Plants, Bangalore. Copyright FRLHT, Bangalore and MoEF, GoI.

constituent of the plant. Various studies have confirmed the neuropharmacological and nootropic (memory-enhancing) action of bacosides extracted from *B. monniera* [21].

Bacosides A and B, the two active components of *B. monniera*, have shown a cognition-facilitating effect. Bacoside A has also been reported to possess antioxidant activity. Additionally, the triterpenoid- and bacoside-enriched fractions of *B. monniera* have anti-inflammatory and antiapoptotic activity and enhance nerve impulse transmission [21]. The bacosides have also been found to enhance kinase activity and to aid in the repair of damaged neurons, neuronal synthesis, and synaptic activity. Dysfunction of cholinergic neuronal activity in the hippocampus is the primary feature of AD. *B. monniera* has been shown to decrease whole-brain AChE activity, suggesting that it may act as useful memory restorative agent in the treatment of AD and dementia. A clinical study in human subjects demonstrated the potential of *B. monniera* in the treatment of neuritis [24].

B. monniera extract has been reported to rehabilitate the activity of antioxidant enzymes (reduced glutathione (GSH), superoxide dismutase (SOD), catalase (CAT), etc.) against neurotoxicity-causing agents, and further enhances the capacity of the brain to fight against hydroxyl radicals [21,25]. *B. monniera* has been also reported to inhibit lipid peroxidation in the frontal cortex, striatum, and hippocampus [26].

B. monniera has an important protective effect against several models of cognitive impairment, and its neuroprotective role has been studied in various AD models. Extract of *B. monniera* also attenuated the levels of Aβ in PSAPP mice. *B. monniera* is a powerful antioxidant that prevents cognitive impairment, oxidative damage, and morphological changes in streptozotocin-infused rats [21]. It has been postulated to improve memory dysfunction, for example by decreasing neuronal oxidative stress, neuroinflammation, and neuronal loss; it achieves this by increasing AChE inhibition in the brain and enhancing synaptic plasticity-related signaling (neural firing) within hippocampal regions [27].

4.4.3 Gotu Kola

Gotu kola or mandookaparni (*Centella asiatica*) (Figure 4.4) is a stoloniferous perennial herb root belonging to the parsley family Apiaceae (Umbelliferae). It is widely dispersed

Figure 4.4 Gotu kola (*Centella asiatica*). *Source:* Adapted from the ENVIS Centre on Medicinal Plants (www.envis.frlht.org), Bengaluru, Karnataka, India, under the Ministry of Environment and Forests (MoEF), Govt. of India. Photos credit Dr. K. Ravikumar, Dr. Ganesh Babu, Ms. Suma TS, Mr. MV Sumanth, Mr. Patchaimal of FRLHT and Dr. D. Narasimhan, MCC, Chennai. 2016. (envis.frlht.org). FRLHT's ENVIS Centre on Medicinal Plants, Bangalore. Copyright FRLHT, Bangalore and MoEF, GoI.

throughout the tropical and subtropical regions of India, as it grows lavishly as a weed. It has been used for centuries in Indian systems of medicine, commonly as a brain food, due to its antistress and revitalizing properties [22,28]. In Ayurveda, *C. asiatica* is highly prized as a Medhya (memory- and intellect-promoting) and Vayasst hapana (antiaging) drug. In Bhavaprakasha, it has been stated that gotu kola and brahmi have very similar pharmacological activities against AD [29].

For the last 3000 years of Ayurvedic medicine, *C. asiatica* has been used to increase concentration, boost memory, and provide altertness, as a mild diuretic, a tonic for poor digestion, and an anti-inflammatory, and to prevent rheumatism and promote wound healing. Being a psychoactive medicinal plant, it is also used to treat anxiety and stress. Since ancient Ayurvedic times, it has been used as a revitalizing herb to restore youth and memory and to strengthen the nervous system [30]. *C. asiatica* leaves are given with milk to improve memory against dementia and aging [31]. Various pharmacological and clinical trials have found that *C. asiatica* extract improves the cognitive function, behavior, and general ability of mentally retarded children [32]. *C. asiatica* is found to improve short-term memory and learning performance, perhaps due to its possible nootropic action, involving cholinergic and gamma-aminobutyric acid (GABA) ergic modulation. *C. asiatica* causes an overall decrease in the turnover of central monoamines, implicating the involvement of the norepinephrine, dopamine, and 5-HT systems in learning and memory process [22].

The major bioactive components of *C. asiatica* are triterpenoid saponins, including asiaticoside, brahmoside, brahminoside, isothankunoside, oxyasiaticoside, thankunoside, and other sapogenins; they possess central nervous system (CNS)-depressant and mild sedative, tranquilizer, anxiolytic, and antioxidant properties. Triterpenoid acids in the plant contain asiatic acid, madecassic acid, brahmic acid, isobrahmic acid, and betulic acid, among others. However, the exact mechanism of action of *C. asiatica* in the treatment and management of neurodisorders is not yet fully understood [33].

Asiatic acid, the principal triterpenoid constituent of *C. asiatica*, has shown to possess antioxidant properties, as it lowers intracellular free-radical concentration and minimizes H_2O_2-induced neuronal cell death [34]. Asiatic acid, along with some similar synthetic derivatives, has shown to protect cultured cortical neurons from neurotoxic glutamate. Derivatives of asiatic acid have shown to possess significant neuroprotective effects, along with their potentiation of the cellular oxidative defense mechanism [34]. Asiatic and betulinic acid possess AChE-inhibiting activity, so *C. asiatica* may be a potential lead in enhancing memory and the symptomatic treatment of AD [29].

C. asiatica has a unique neuritogenic ability (nerve growth). It has shown to be able to actually stimulate neurite outgrowth in human neuroblastoma cells. Its neuroprotective properties may be attributable to its phospholipase A2-blocking actions, acting as an anti-inflammatory within cortical neurons. This would be helpful for people who are suffering from memory loss due to a variety of different physiological circumstances [27].

A recent study was conducted in a transgenic animal model to prove the efficacy of *C. asiatica* extract in the management of AD [24,30]. It found *C. asiatica* to possess neuroprotective properties, showing that it can put down the amyloid cascade-changing Aβ pathology in the brains of APP/PS mice and alter components of the oxidative stress response implicated in the neurodegenerative changes occurring in AD [24,30]. *C. asiatica* has been reported to be an efficient drug detoxifying agent: it is used to clear the mind

after cocaine abuse. In addition to improving memory, it prevents adrenal hyperfunctioning and works as an "antistress" herb [22].

One study demonstrated that extract of fresh leaves from *C. asiatica* enhances the neuronal dendrites in stressed conditions and various other neurodegenerative disorders [35]. It is clear, therefore, that *C. asiatica* possesses neuronal dendritic growth-stimulating and nervous system-revitalizing properties [35]. *C. asiatica* extract also inhibited the neuronal damage caused by cerebral ischemia. This all indicates that *C. asiatica* has potential in preventing neuronal damage in stroke. Asiaticoside present in the water extract of this plant was also found to inhibit the cPLA2 and sPLA2 activities responsible for neurodegenerative conditions [35].

4.4.4 Chandan

Chandan (*Santalum album*) (Figure 4.5), or the East Indian sandalwood tree, belongs to the taxonomic group Santalaceae. *S. album* is an obligate hemiparasite plant on various hosts, including *Cassia siamea*, *Pongamia glabra*, and *Lantana acuminata* [36]. Due to illegal poaching and spike disease, this tree has been inducted into the International Union for Conservation of Nature (IUCN) and Natural Resources Red List of Threatened Species. *S. album* is regarded as a royal tree. It yields sandalwood oil containing over 90% santalols (α- and β-santalols and their isomers) [37]. Sandalwood oil has a sweet, powerful odor and is used in making perfumes. Sandalwood is used as a coolant, but it also has a sedative effect and astringent activity, making it is useful as a disinfectant in the genitourinary and bronchial tracts, a diuretic, an expectorant, and a stimulant. It is also used as an antipoison, anti-inflammatory, blood purifier, and liver, heart, and stomach tonic, as well as in improving memory [36].

Among the many plants investigated for their antioxidant properties, *S. album* seems to play an important role in fighting against free radicals. The potential of this plant to increase memory and cognitive function is described in one of the siddha systems,

Figure 4.5 East Indian sandalwood tree (*Santalum album*). *Source:* Adapted from the ENVIS Centre on Medicinal Plants (www.envis.frlht.org), Bengaluru, Karnataka, India, under the Ministry of Environment and Forests (MoEF), Govt. of India. Photos credit Dr. K. Ravikumar, Dr. Ganesh Babu, Ms. Suma TS, Mr. MV Sumanth, Mr. Patchaimal of FRLHT and Dr. D. Narasimhan, MCC, Chennai. 2016. (envis.frlht.org). FRLHT's ENVIS Centre on Medicinal Plants, Bangalore. Copyright FRLHT, Bangalore and MoEF, GoI.

while *Smruthi leha*, an Ayurvedic formulation, describes how *S. album* has the potential to decrease dementia in older people [38,39].

S. album essential oil contains sesquiterpenoids, triterpenoids, and phenylpropanoids. The sesquiterpene alcohols cis-α-santalol, cis-β-santalol, α-trans-bergamotol, and epi-cis-β-santalol are its primary components, while trans-β-santalol and cis-lanceol, hydrocarbons, α-santalene, β-santalene, α-bergamotene, epi-β-santalene, α-curcumene, β-curcumene, γ-curcumene, β-bisabolene, and α-bisabolol are its minor constituents. α-santalol is the primary component of sandalwood oil and is responsible for most of its biological activities [37].

Alongside its antixodant properties, *S. album* has been found to possess nitric oxide (NO) scavenging activity [36]. Cyanidin-3-glucoside, an anthocyanic pigment in *S. album*, possesses antioxidant activity and is nutritionally essential. Studies in mice have shown that the methanolic extracts of *S. album* possesses analgesic and anti-inflammatory properties [37].

S. album reduces stress, anxiety, depression, and nervous exhaustion. It has calming and relaxation effects and enhances meditation. α-santalol, the major constituent of the oil, has relaxing and sedative effects and is an active inhibitor of both cholinesterase (CHe) and tyrosinase *in vitro*, and hence it has a high potential for use in the treatment of AD [37].

Various extracts of *S. album* have been shown to quench 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals and superoxide radicals, but the methanolic extract shows a significant total antioxidant capacity and has been found to hold higher phenolic fractions than other extracts [39]. In a study in Aβ-treated male albino mice, treatment with the alcoholic extract of *S. album* demonstrated memory-enhancing properties [38].

4.4.5 Shankhapushpi

Shankhapushpi (*Convolvulus pluricaulis*) (Figure 4.6), also known as nilpushpi, is a prostrate, perennial herb belonging to family Convolvulaceae. It is found on sandy or

Figure 4.6 Shankhapushpi (*Convolvulus pluricaulis*). *Source:* Adapted from the Indian Medicinal Plants Database (www.medicinalplants.in). Photos credit Dr. K. Ravikumar (envis.frlht.org). FRLHT's ENVIS Centre on Medicinal Plants, Bangalore. Copyright FRLHT, Bangalore and MoEF, GoI.

rocky ground under xerophytic conditions in northern India [22,40]. It has woody rootstock and its flowering time is from July to November. On the basis of flower colors, three types of shankhpushpi are described in the reference literature: red, white, and blue [22].

The major bioactive components of *C. pluricaulis* are the glycosides, flavonoids, coumarins, and alkaloids. Sitosterol glycoside, octacosanol tetracosane, hydroxy cinnamic acid, and glucose have been isolated from the plant [22].

In Ayurveda, *C. pluricaulis* is mentioned as a Medha Rasayana. It is bitter in taste and pungent, and clinically it has been used as a memory-enhancer, anxiolytic, alexiteric, and anthelmintic, to increase appetite, and in the treatment of bronchitis, biliousness, epilepsy, leucoderma and teething troubles of infants [22]. Since ancient times, different parts of *C. pluricaulis* have been used to treat different diseases; for example, the flowers and leaves were used to treat hypertension and anxiety neurosis, oil from the roots was used for hair growth and fever reduction, and the leaves were used to treat chronic bronchitis and asthma [40]. *C. pluricaulis* is also used to cure respiratory diseases. Herbal cigarettes made from *C. pluricaulis* plus other herbs such as adhatoda, datura, and blemea are used to cure asthma, bronchitis, and chronic cases of insanity and epilepsy [22]. *C. pluricaulis* also possesses diuretic, antioxidant, antimicrobial, antidiabetic, antiulcer, hypolipidemic, antipyretic, analgesic, anti-inflammatory, hypotensive, tranquilizing and insecticidal properties [40]. In combination with other herbs (mainly bach (*Acorus calamus*) and shatavari (*Asparagus racemosus*), shankhapushpi is also used to treat neurotic disorders [22].

4.4.6 Yastimadhu

Yastimadhu (*Glycyrrhiza glabra*) (Figure 4.7) is a hardy herb and undershrub belonging to the Leguminosae family. Also known as mulathi, it is a common Indian subtropical plant and is distributed marginally worldwide.

The active ingredients of yastimadhu are glycyrrhizin, flavanones, isoflavones, glycyrrhetenic acid, and six phenolic compounds. Its multidimensional activities may be attributed to glycyrrhizin and flavanones. A fine powder of its dried root mixed with milk is used for therapeutic purposes. Almost every part of the plant is used for

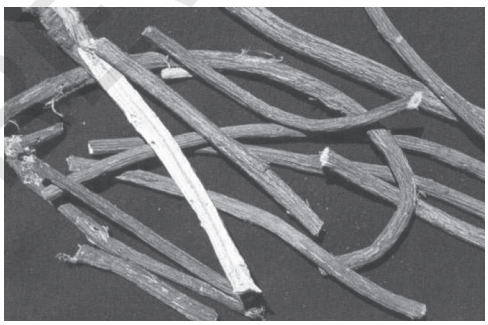

Figure 4.7 Yastimadhu (*Glycyrrhiza glabra*). *Source:* Adapted from the Indian Medicinal Plants Database (www.medicinalplants.in). Photos credit Dr. K. Ravikumar (envis.frlht.org). FRLHT's ENVIS Centre on Medicinal Plants, Bangalore. Copyright FRLHT, Bangalore and MoEF, GoI.

household remedies and in the mainstream Ayurvedic system: it features in approximately 1250 Ayurvedic preparations.

Ethanol extract of *G. glabra* possesses a cerebroprotective effect in hypoxic rats, which is mediated by its antioxidant effects [41]. It is very effective against the side effects of radiation and chemotherapy in head and neck cancer, including mucositis [42]. Its roots (licorice) have antituberculosis activity and help to combat the problem of drug-resistant *Mycobacterium tuberculosis* strains [43]. The roots and rhizomes are a powerful brain tonic, increasing the blood circulation into the CNS and balancing the sugar levels in the blood [44]. Licorice has significant action on memory-enhancing activity and significantly improves learning and memory in scopolamine-induced dementia [45].

4.4.7 Bhilawa

Bhilawa (*Semecarpus anacardium*) (family: Anacardiace) (Figure 4.8), also commonly known as "marking nut" or "ballataka," is used in many human ailments, and is described in all three Ayurvedic treatises (Charka, Sushruta, and Vagbhata) [46]. It also acts as a brain tonic and is a potent antioxidant agent. It has allergic properties, due to the presence of alkyl catechols, phenols, quinols, and resorcinols [47].

Chemical and phytochemical analyses reveal the presence of biflavonoid, phenolic compounds, bhilawanols, minerals, vitamins, and amino acids [48]. The active compounds in *S. anacardium* are 1′,2′-dihydroxy-3′-pentadec-8-enylbenzene (A) and 1′,2′-dihydroxy-3′-pentadeca-8,11-dienylbenzene (B). *In silico* docking experiments showed a similar bioactivity for compounds A and B [49].

S. anacardium nut extract possesses anticancer properties [50]. In the human breast cancer cell line (T47D), *S. anacardium* extract shows an inhibitory effect, documented as a decrease in Bcl2 and an increase in Bax, cytochrome c, caspases, and PARP cleavage [47,51]. The effect of *S. anacardium* nut extract on the level of lipid peroxides (LPOs) and on the activities of SOD, CAT, GPx, and GSH in the lymphocytes and lymphoid organs has been investigated in adjuvant-induced arthritic rats [52]. A significant increase in the level of LPO and ROS and decrease in the levels of antioxidant enzymes

Figure 4.8 Bhilawa (*Semecarpus anacardium*). *Source:* Adapted from the ENVIS Centre on Medicinal Plants (www.envis.frlht.org), Bengaluru, Karnataka, India, under the Ministry of Environment and Forests (MoEF), Govt. of India. Photos credit Dr. K. Ravikumar, Dr. Ganesh Babu, Ms. Suma TS, Mr. MV Sumanth, Mr. Patchaimal of FRLHT and Dr. D. Narasimhan, MCC, Chennai. 2016. (envis.frlht.org). FRLHT's ENVIS Centre on Medicinal Plants, Bangalore. Copyright FRLHT, Bangalore and MoEF, GoI.

were observed in arthritic rats: upon treatment with the *S. anacardium* nut extract, these changes reverted to near-normal levels [52]. *S. anacardium* (stem bark) has shown AChE-inhibitory activity *in vitro*; methanolic extracts were found to be more active than aqueous extracts. This partly substantiates the traditional use of these herbs to improve cognition [53].

4.4.8 Haldi

Haldi (*Curcuma longa*) (Figure 4.9) is native to South East Asia. On the Indian subcontinent, it is used as a spice and coloring agent. Turmeric is derived from the rhizome of this plant. In turmeric, the active compounds are the curcuminoids: curcumin (75–80%), deoxycurcumin (15–20%), and bisdemethoxycurcumin (3–5%). These are responsible for most of its medicinal properties. Curcumin has been reported to have antioxidant, anti-inflammatory, chemopreventive, and chemotherapeutic properties. Curcumin has been shown to regulate numerous transcription factors, cytokines, protein kinases, adhesion molecules, redox status, and enzymes linked to inflammation [54]. The process of inflammation has been shown to play a major role in most chronic illnesses, including neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune, and neoplastic diseases. Curcumin inhibits Aβ40 aggregation and prevents aggregation of Aβ42 oligomer formation and toxicity [55]. Curcumin is quite stable at acidic pH, and almost 40–80% of the compound is unaltered in the gastrointestinal tract. This makes curcumin a less bioavailable compound, but coadministration of curcumin with piperine or another lipophilic compound may increase its bioavailability.

Curcumin possesses positive effects on neurodegenerative diseases such as AD, Parkinson's disease (PD), Huntington's disease (HD), epilepsy, cerebral injury, age-associated neurodegeneration, and schizopherenia [56–59]. Rao et al. [60] performed a computer simulation study and found that curcumin binds to Aβ aggregates and forms a nontoxic Aβ. Ono et al. [61] showed that curcumin destabilizes the fibrillary Aβ1–40

Figure 4.9 Haldi (*Curcuma longa*). *Source:* Adapted from the ENVIS Centre on Medicinal Plants (www.envis.frlht.org), Bengaluru, Karnataka, India, under the Ministry of Environment and Forests (MoEF), Govt. of India. Photos credit Dr. K. Ravikumar, Dr. Ganesh Babu, Ms. Suma TS, Mr. MV Sumanth, Mr. Patchaimal of FRLHT and Dr. D. Narasimhan, MCC, Chennai. 2016. (envis.frlht.org). FRLHT's ENVIS Centre on Medicinal Plants, Bangalore. Copyright FRLHT, Bangalore and MoEF, GoI.

and Aβ1–42, as well as their extensions. In the mononuclear cells of some AD patients, the curcuminoid compound bisdemethoxycurcumin enhances the defective phagocytosis of Aβ, transcription of mannosyl-glycoprotein N-acetylglucosaminyltransferase 3 (MGAT3) and toll-like receptor (TLRs), and translation of TLR2–4. Thus, bisdemethoxycurcumin may correct the immune defects of AD patients, providing a previously uncharacterized approach to AD immunotherapy [62].

4.4.9 Safed Bach

Safed bach (*Acorus calamus*) (Figure 4.10) belongs to the family Araceae. Other common species of this genus are *A. tatarinowii* and *A. gramineus*, which are widely studied for their pharmaceutical properties. *A. calamus* is a perennial, semiaquatic plant found in the northern temperate, subtropical, and warm regions of the Indian Himalayan Regions (IHR): the southern part of Shiwaliks, Trans-Himalaya, Jammu & Kashmir, and Himachal Pradesh.

A number of phytochemically active constituents are found in *A. calamus*, including polyphenols, terpenoids, flavonoids, alkaloids, glycosides, and volatile acids. Upon extensive investigation, the roots, leaves, and rhizomes are found to have a variety of chemical constituents, including α- and β-asarone. β-asarone is present in particularly high levels and displays multiple pharmaceutical actions.

Various studies have reported that ethanolic extract of *A. calamus* possesses antioxidative, anti-inflammatory, and neuroprotective properties against ischemic and oxidative stress in neurons. The methanolic and oil extracts of *A. graminei* show inhibitory actions in primary cultured rat cortical cells against N-methyl-D-aspartate (NMDA) and glutamate-induced excitotoxicity, suggesting an asarones-mediated barrier against the function of NMDA receptors [63]. Shukla et al. [64] demonstrated the neuroprotective action of *A. calamus* in middle cerebral artery occlusion (MCAO)-induced ischemia

Figure 4.10 Safed bach (*Acorus calamus*). *Source:* Adapted from the ENVIS Centre on Medicinal Plants (www.envis.frlht.org), Bengaluru, Karnataka, India, under the Ministry of Environment and Forests (MoEF), Govt. of India. Photos credit Dr. K. Ravikumar, Dr. Ganesh Babu, Ms. Suma TS, Mr. MV Sumanth, Mr. Patchaimal of FRLHT and Dr. D. Narasimhan, MCC, Chennai. 2016. (envis.frlht.org). FRLHT's ENVIS Centre on Medicinal Plants, Bangalore. Copyright FRLHT, Bangalore and MoEF, GoI.

in rat models. They observed that the treatment of *A. calamus* in these rats significantly decreased the lipid peroxidation levels and increased the levels of SOD and GSH. This study also advocated for a neuroprotective role of *A. calamus* in rat models of ischemia [64]. It has been demonstrated that *A. calamus* has a protective role against chronic constriction injury (CCI) through attenuation of total Ca^{2+} levels and axonal degeneration [65]. *A. calamus* also blocks the activated calcium channels and maintains Ca^{2+} levels [66].

A study found that *A. tatarinowii* has a potential role in the treatment of AD [67]. Administration of the β-asarone component of *A. tatarinowii* lowered caspase-3 activity by modifying the amount of Aβ1–42 in rat hippocampal neuronal cells. It was concluded that *A. tatarinowii* extracts have a neuroprotective effect in AD. β-asarone also elevates the expression of *Bcl-2* and *Bcl-w* in rat hippocampal neuronal cells; these are otherwise decreased by Aβ1–42 [67].

A. calamus has been found to have a neuroprotective role against PD. Dopamine levels were decreased in the presence of 6-hydroxydopamine (6-OHDA), and *A. calamus* treatment significantly enhanced neuronal functioning against 6-OHDA-induced neurotoxicity *in vivo*. *A. calamus* treatment further increased the dopamine content in 6-OHDA-induced rats. Also, it was confirmed that *A. calamus* reduced α-synuclein in the PD rat models [68,69]. A hydroalcoholic extract of rhizome and other essential oils was tested to check its action on AChE, and *A. calamus* was found to have a significant inhibitory potential against AChE activity [70]. Another study also confirmed that *A. calamus* has an inhibitory effect on AChE activity [71].

4.4.10 Guggulu

Guggulu (*Commiphora wightii*) (Figure 4.11) belongs to the family Burseraceae. It grows slowly, mainly on arid rocks, and is a highly branched plant. It is widely distributed in

Figure 4.11 Guggulu (*Commiphora wightii*). *Source:* Adapted from the ENVIS Centre on Medicinal Plants (www.envis.frlht.org), Bengaluru, Karnataka, India, under the Ministry of Environment and Forests (MoEF), Govt. of India. Photos credit Dr. K. Ravikumar, Dr. Ganesh Babu, Ms. Suma TS, Mr. MV Sumanth, Mr. Patchaimal of FRLHT and Dr. D. Narasimhan, MCC, Chennai. 2016. (envis.frlht.org). FRLHT's ENVIS Centre on Medicinal Plants, Bangalore. Copyright FRLHT, Bangalore and MoEF, GoI.

India, mainly being found in Rajasthan, Gujarat, Madhya Pradesh, Karnataka, and Kalat [72]. Its constituents are flavonoids, ellagic acid, camphorene, cembrene, diterpene hydrocarbon, diterpene alcohol, and guggulipids such as Z-guggulsterone, E-guggulsterone, and guggulsterol-I, II, and III.

Guggulipid, a bioactive component of *C. wightii*, is found to act as a neuroprotective agent against neuronal damage and memory deficits. It plays a beneficial role in neurons by acting as a free-radical scavenger and inhibiting the formation of LPOs. Another component of *C. wightii*, guggulsterone, is also found to be neuroprotective. It inhibits lipid peroxidation during oxidative stress in neurodegenerative diseases [73].

A study showed that guggulipid increased GSH levels and inhibited oxidative stress in mice with streptozotocin-induced oxidative stress. A neuroprotective effect of ethanolic extract of *C. wightii* against streptozotocin-induced oxidative stress in rats was also observed, and the level of antioxidants (GSH, SOD, and GPx) was found to be decreased. However, ethanolic extract of *C. wightii* was also found to attenuate the lipid and protein damage in streptozotocin-treated rats, although improved levels of antioxidants were seen in these rats [74].

Guggulsterone exerts an anti-inflammatory effect by inhibiting the activity of nuclear factor kappa B (NF-κB), a key regulator of inflammatory processes [75]. It also shows anti-AChE activity [21]. Guggulipid is found to decrease cholesterol levels, resulting in the inhibition of Aβ formation [76]. These results suggest that *C. wightii* could play a potential role in the treatment of AD pathogenesis.

4.4.11 Jatamansi

Jatamansi (*Nardostachys jatamansi*) (Figure 4.12), an endangered, perennial flowering plant of the family Valerianaceae, is widely used in Ayurveda. It is widely distributed in Jammu and Kashmir, Himachal Pradesh, Uttarakhand, and Sikkim in India [77]. Jatamansi is used in the treatment of mental disorders, insomnia, hyperlipidemia,

Figure 4.12 Jatamansi (*Nardostachys jatamansi*). *Source:* Adapted from the ENVIS Centre on Medicinal Plants (www.envis.frlht.org), Bengaluru, Karnataka, India, under the Ministry of Environment and Forests (MoEF), Govt. of India. Photos credit Dr. K. Ravikumar, Dr. Ganesh Babu, Ms. Suma TS, Mr. MV Sumanth, Mr. Patchaimal of FRLHT and Dr. D. Narasimhan, MCC, Chennai. 2016. (envis.frlht.org). FRLHT's ENVIS Centre on Medicinal Plants, Bangalore. Copyright FRLHT, Bangalore and MoEF, GoI.

hypertension, and heart disease. It is also found to be protective against various neurodegenerative disorders, such as AD, PD, epilepsy, and cerebral ischemia. It has the ability to lower the levels of norepinephrine and serotonin in the brain [78].

The bioactive components of *N. jatamansi* are mainly found in its rhizomes and roots. It contains both volatile and nonvolatile components (terpenoids, sesquiterpenes, coumarins, lignans, neolignans and alkaloids) [79].

A protective role has been demonstrated for *N. jatamansi* against cerebral ischemia in rats. The study showed that levels of GSH and other thiols were significantly decreased in ischemic rats. Elevated levels of thiobarbituric acid reactive species (TBARS) (i.e., lipid peroxidation) were also observed, and Na^+/K^+ ATPase activity and CAT activity were decreased. Pretreatment with *N. jatamansi* significantly restored the antioxidant levels. *N. jatamansi* was also found to be effective against lipid damage, lowering the TBARS content and lipid peroxidation [80].

Another study examined the neuroprotective role of *N. jatamansi* in a 6-OHDA-induced oxidative stress model of PD. 6-OHDA significantly decreased the dopamine content, while pretreatment with *N. jatamansi* significantly increased it. It was also demonstrated that 6-OHDA affected the biomolecules and antioxidants of the brain (i.e., increasing lipid peroxidation and decreasing GSH) and decreased the activities of CAT and SOD. The reduction in GSH content and elevation of lipid peroxidation caused degeneration of nigrostriatal neurons. *N. jatamansi* was found to attenuate lipid peroxidation and improve GSH content and antioxidant enzyme activities with pretreatment [81].

N. jatamansi showed a protective role against haloperidol-induced catalepsy in a rat model. Administration of haloperidol increased lipid peroxidation by increasing the generation of TBARS and caused a considerable reduction in GSH, SOD, and CAT, while pretreatment with *N. jatamansi* significantly normalized GSH, SOD, and CAT activities in the brain. In this way, *N. jatamansi* showed a neuroprotective role against haloperidol-induced catalepsy in rats [82].

Rahman et al. [83] found a significant protective role for *N. jatamansi* in a sleep-deprived AD mouse model. It showed antioxidant effects by increasing the levels of antioxidants such as SOD an GPx, and showed an inhibitory effect on AChE activity [83].

4.4.12 Ananthamoola

Ananthamoola (*Hemidesmus indicus*) (Figure 4.13) is a common Indian medicinal plant, whose usage has been featured in the Indian and British Pharmacopoeias. It is found and used mostly in the tropical and subtropical parts of India (also known as "Indian Sarsaparilla"). It has been a part of traditional Indian systems of medicine such as Ayurveda, Unani, and Siddha. Root extracts of this flavoring plant are used to prepare a cool drink called "nannari syrup" in South India [15,84]. It is a wonder herb with a variety of actions including antipyretic, antidiarrheal, astringent, blood purifying, diaphoretic, and diuretic, as well as refrigerant properties against common summer ailments [84].

A recent study showed that root extracts of *H. indicus* have potent inhibitory potential against AChE *in vitro* [via secretion of the phenolic compound 2-hydroxy-4-methoxybenzaldehyde (MBALD)], indicating that ananthamoola has potential as a

Figure 4.13 Ananthamoola (*Hemidesmus indicus*). *Source:* Adapted from the ENVIS Centre on Medicinal Plants (www.envis.frlht.org), Bengaluru, Karnataka, India, under the Ministry of Environment and Forests (MoEF), Govt. of India. Photos credit Dr. K. Ravikumar, Dr. Ganesh Babu, Ms. Suma TS, Mr. MV Sumanth, Mr. Patchaimal of FRLHT and Dr. D. Narasimhan, MCC, Chennai. 2016. (envis.frlht.org). FRLHT's ENVIS Centre on Medicinal Plants, Bangalore. Copyright FRLHT, Bangalore and MoEF, GoI.

therapeutic agent against AD [15]. Another study on similar lines showed that *H. indicus* treatment leads to an inhibition of both AChE and butyrylcholinesterase (BChE) *in vitro*, pointing to some new drug candidates for AD therapeutics [85]. Root extracts of *H. indicus* have also been shown to have antioxidant and nootropic properties *in vitro* and *in vivo* [86,87]. Similarly, a study showed that a butanolic extract of *H. indicus* improved memory and cognition in mice, indicating its nootropic potential [86]. Another paper pointed to a neuroprotective effect of *H. indicus,* showing that a methanolic root extract of *H. indicus* improved neuromuscular, vestibulomotor, and neuromotor functions in mice. Further, the antioxidant levels of the enzymes SOD, CAT, GPx, and glutathione reductase (GR) increased upon treatment with the root extract in mice with cerebral ischemia [84]. Thus, the methanolic root extract of *H. indicus* may have potential in improving/treating neurological disorders. These observations point toward a neuroprotective and, thus, memory-enhancing role for *H. indicus*, which could serve in protecting against AD.

4.4.13 Aparajita

Aparajita (*Clitoria ternatea*) (Figure 4.14) is a herbal Medhya drug. It is traditionally known as "sankupushpam" (Sanskrit) and has been used as a brain tonic. Although the Indian Pharmacopoeia considers shankhpushpi to be *Convolvulus pluricaulis* (Convolvulaceae) (see Section 4.4.5), traditional Ayurvedic practitioners refer to three plants by this name: *Evolvulus alsinoides* Linn. (Convolvulaceae), *Canscora decussata* Schult. (Gentianaceae), and *C. ternatea* Linn. (Papilionaceae) [88].

As antioxidant defense is an important factor in age-related neurodegenerative diseases such as AD, plants showing antioxidant properties against a variety of oxidative stresses have a potential role in treating these diseases. *C. ternatea* has been shown to have antioxidant properties against CCl_4-induced hepatotoxicity in Wistar rats. Levels of antioxidant enzymes, which decreased significantly in the presence of CCl_4-induced oxidative stress, increased upon treatment with leaf extracts of *C. ternatea* [89]. Jayachitra et al. [90] showed that enzymatic antioxidant activity increased on treatment with leaf

Figure 4.14 Aparajita (*Clitoria ternatea*). *Source:* Adapted from the ENVIS Centre on Medicinal Plants (www.envis.frlht.org), Bengaluru, Karnataka, India, under the Ministry of Environment and Forests (MoEF), Govt. of India. Photos credit Dr. K. Ravikumar, Dr. Ganesh Babu, Ms. Suma TS, Mr. MV Sumanth, Mr. Patchaimal of FRLHT and Dr. D. Narasimhan, MCC, Chennai. 2016. (envis.frlht.org). FRLHT's ENVIS Centre on Medicinal Plants, Bangalore. Copyright FRLHT, Bangalore and MoEF, GoI.

extracts of *C. ternatea* in the presence of H_2O_2-induced oxidative stress *in vitro*. Further, they showed a higher antioxidant content in white-flowered leaves than in blue-flowered leaves [90]. An earlier study showed that root extracts of *C. ternatea* produced antiamnesic effects in mice by increasing AChE activity and the content of acetylcholine (ACh) in the brain [91]. In line with this result, another study showed that *C. ternatea* caused memory enhancement and improved retention and spatial-learning performance in neonatal mice pups [92]. In a recent study, phytocompounds ((*Z*)-9,17-octadecadienal and n-hexadecanoic acid) from *C. ternatea* were extracted and used as potent monoamine oxidase (MAO) inhibitors in molecular docking studies [88]. Thus, *C. ternatea* has a potential role in targeting MAO inhibition in neurodegenerative diseases like AD. In yet another study, it was shown that hydroalcoholic extract of *C. ternatea* reduced oxidative stress, ChE activity, and rho kinase (ROCK II) expression in the presence of streptozotocin-induced cognitive impairment *in vitro* and *in vivo*, indicating its role in treating cognitive function in neurological disorders [93]. Improved dendritic arborization of amygdaloid neurons was seen on treating young Wistar rats with aqueous root extract of *C. ternatea,* increasing memory function, as shown by increased passive avoidance learning and memory [94]. These results point toward the neuroprotective role of *C. ternatea*, which can act as a potent therapeutic agent for the treatment of neurodegenerative diseases like AD by increasing cognitive function and decreasing oxidative stress in the brain.

4.4.14 Tulsi

Tulsi (*Ocimum sanctum*) (Figure 4.15) is a perennial shrub belonging to the family Lamiaceae. Its name means "matchless one" in Sanskrit and it is found throughout India. *O. sanctum* has great importance in Hindu culture. It has been well known since the Vedic period for its important medicinal properties [95].

O. sanctum contains a volatile oil that further contains sesquiterpene and carvacrol. The phytochemicals found in *O. sanctum* are some phenolic compounds, flavonoids,

Figure 4.15 Tulsi (*Ocimum sanctum*). *Source:* Adapted from the ENVIS Centre on Medicinal Plants (www.envis.frlht.org), Bengaluru, Karnataka, India, under the Ministry of Environment and Forests (MoEF), Govt. of India. Photos credit Dr. K. Ravikumar, Dr. Ganesh Babu, Ms. Suma TS, Mr. MV Sumanth, Mr. Patchaimal of FRLHT and Dr. D. Narasimhan, MCC, Chennai. 2016. (envis.frlht.org). FRLHT's ENVIS Centre on Medicinal Plants, Bangalore. Copyright FRLHT, Bangalore and MoEF, GoI.

monoterpenes and sesquiterpenes, ursolic acid, apigenin, luteolin, apigenin-7-O-glucuronide, orientin, and molludistin [96].

In a study, the effect of *O. sanctum* was checked against ibotenic acid (IB)- and colchicine (Col)-induced oxidative stress in rat models of AD [97]. Rats treated with IB and Col showed impaired memory, which was improved with pretreatment by *O. sanctum*. IB- and Col-induced oxidative stress increased lipid peroxidation by increasing the activity of enzyme-lipid peroxidase, and this activity was significantly altered by *O. sanctum*, lowering the MDA levels in rats. In the same study, *O. sanctum* upregulated the activity of SOD [97]. These findings suggest that *O. sanctum* could prove a powerful agent in the treatment of AD in future.

A significant neuroprotective potential of *O. sanctum* and its saponin has been studied in vincristine-induced neuropathic pain in rats. The effect of vincristine was checked by measuring TBARS and superoxide anion content and total Ca^{2+} levels. Vincristine administration increased free radical production and raised intracellular Ca^{2+} levels. However, pretreatment with *O. sanctum* significantly decreased TBARS content and Ca^{2+} levels. This investigation points toward the role of *O. sanctum* in attenuating oxidative stress in a painful neuropathic state [98].

Zonisamide is an antiepileptic drug that causes significant memory loss in mice models [99]. This memory loss can be attributed to the reduction of ACh levels by zonisamide. Results show that prior administration of *O. sanctum* significantly increased ACh levels in zonisamide-treated mice. The same results support the neuroprotective role of *O. sanctum* [99].

4.4.15 Ber

Ber (*Ziziphus jujube*) (Figure 4.16) belongs to the family Rhamnaceae. It shows anti-inflammatory, antioxidant, and immunostimulant properties. Its key bioactive components are phenolic compounds, terpenoids, and flavonoids [100].

Figure 4.16 Ber (*Ziziphus jujube*). *Source:* Adapted from the ENVIS Centre on Medicinal Plants (www.envis.frlht.org), Bengaluru, Karnataka, India, under the Ministry of Environment and Forests (MoEF), Govt. of India. Photos credit Dr. K. Ravikumar, Dr. Ganesh Babu, Ms. Suma TS, Mr. MV Sumanth, Mr. Patchaimal of FRLHT and Dr. D. Narasimhan, MCC, Chennai. 2016. (envis.frlht.org). FRLHT's ENVIS Centre on Medicinal Plants, Bangalore. Copyright FRLHT, Bangalore and MoEF, GoI.

It has been shown that *Z. jujube* induces neuronal differentiation in PC12 cells and performs a similar action to that of nerve growth factor (NGF) [101]. *Z. jujube* also has antioxidant activity against ethanol-induced oxidative stress in rats [102]. It protects neuronal cells from ischemic damage by upregulating SOD activity and reduces the levels of lipid peroxidation in ischemic gerbil brains [103]. It lowers the levels of lipid peroxidation in the presence of ethanol-induced oxidative stress. Similarly, it increases GPx activity against ethanol-induced oxidative stress [102].

A study showed that *Z. jujube* has a protective role against the high-glucose-induced cell toxicity in PC12 cells [104]. The high glucose concentration induces an increase in ROS levels and the activation of caspase-3, which causes the death of neurons. However, the administration of *Z. jujube* inhibits the ROS generation and caspase-3 activation in these cells [104]. These findings indicate that *Z. jujube* may play a significant role in the prevention of neurodegenerative diseases such as AD.

4.4.16 Pudina

Pudina (*Melissa officinalis*) (Figure 4.17) is a perennial herb that belongs to the family Lamiaceae. Its main bioactive components are citral, citronellal, caryophyllene α-pinene, and β-pinene, among others [105].

M. officinalis showed a protective role in PC12 cells against H_2O_2-induced neurotoxicity. It displayed a free radical-scavenging effect and inhibited MAO-A activity in PC12 cells treated with H_2O_2 [106]. It also decreased MDA levels and caspaase-3 activity in hypoxic-ischemic injury. Subsequently, it led to the production of proinflammatory cytokines and increased antioxidant capacity in the presence of hypoxic-ischemic injury [107]. *M. officinalis* was shown to act as a chelating agent and to maintain Fe^{2+} in a Fe^{3+} state, pointing toward its role in neurotherapeutic interventions [108]. Moreover, it inhibited the activity of AChE in the neurons, which is important in the treatment of AD-like neurodegenerative disorders [109].

Figure 4.17 Pudina (*Melissa officinalis*). *Source:* Adapted from the ENVIS Centre on Medicinal Plants (www.envis.frlht.org), Bengaluru, Karnataka, India, under the Ministry of Environment and Forests (MoEF), Govt. of India. Photos credit Dr. K. Ravikumar, Dr. Ganesh Babu, Ms. Suma TS, Mr. MV Sumanth, Mr. Patchaimal of FRLHT and Dr. D. Narasimhan, MCC, Chennai. 2016. (envis.frlht.org). FRLHT's ENVIS Centre on Medicinal Plants, Bangalore. Copyright FRLHT, Bangalore and MoEF, GoI.

Figure 4.18 Til (*Sesamum indicum*). *Source:* Adapted from the ENVIS Centre on Medicinal Plants (www.envis.frlht.org), Bengaluru, Karnataka, India, under the Ministry of Environment and Forests (MoEF), Govt. of India. Photos credit Dr. K. Ravikumar, Dr. Ganesh Babu, Ms. Suma TS, Mr. MV Sumanth, Mr. Patchaimal of FRLHT and Dr. D. Narasimhan, MCC, Chennai. 2016. (envis.frlht.org). FRLHT's ENVIS Centre on Medicinal Plants, Bangalore. Copyright FRLHT, Bangalore and MoEF, GoI.

4.4.17 Til

Til (*Sesamum indicum*) (Figure 4.18) is a medicinal and sacred plant in India. It is an annual herb that belongs to the family Pedaliaceae [110]. The main phytochemicals found in *S. indicum* are flavonoids, phenolic compounds, alkaloids, tannins, saponins, terpenoids, sesamin, sesaminol, gamma tocopherol, cephalin and lecithin [111].

S. indicum showed a protective role against ischemic neuronal damage in HT22 cells that were induced by oxygen–glucose deprivation and reoxygenation [112]. Increased LPO- and cell death-like events were found during ischemic neuronal

damage, but the pretreatment of defatted seeds of *S. indicum* significantly reduced the LPO levels and increased the cell viability. In another report, the neuroprotective effect of *S. indicum* were seen in kainic acid-induced brain damage in PC12 cells [113]. The kainic acid increased the MDA levels, lactate dehydrogenase (LDH) activity, and caspase-3 activation in PC12 cells. However, the administration of sesamin (a component of *S. indicum*) in kainic acid-treated PC12 cells reduced all three. Further, sesamin increased the cell viability in kainic acid-treated PC12 cells by suppressing ROS and Ca^{2+} levels. Kainic acid also showed its harmful effect by causing the activation of MAP kinases and COX-2, which normally leads to the death of neurons, but the sesamin protected the neurons by inhibiting the MAPK and COX-2 [113].

Another study suggested that *S. indicum* shows broad potential to cure the AD-like neurodegenerative disorders. In the study, mice were pretreated with *S. indicum* oil and then induced by 6-OHDA. The GR, GPx, and CAT activities and total GSH levels were significantly increased by *S. indicum* oil but were decreased in the control 6-OHDA-treated mice. *S. indicum* oil further decreased TBARS content and exhibited an inhibitory role in Nox2 and COX2 activation [114].

4.5 Herbs and Drug Interactions

Traditionally plants have been used to cure many diseases. Although therapeutic drugs produced by pharmaceutical companies have largely replaced these medicinal herbs, the last 2 decades have seen a revival of ancient systems of medicine such as Ayurveda. People suffering from cancers and other debilitating diseases, including dementia and neurodegenerative diseases such as AD, make use of traditional herbs alongside their prescribed drugs to relieve the symptoms and side effects associated with their treatment therapies. In the case of neurological disorders, older people are often prescribed a number of herbs for the treatment of dementia or memory impairment. These herbs interfere with the metabolism of drugs by either inhibiting or inducing cytochrome P450 (CYP) enzymes (according to their different pharmacodynamics and pharmacokinetic properties), causing herb–drug interactions in the body.

Evaluation of different herbs showed that St. John's wort (*Hypericum perforatum*) causes the most herb–drug interactions, followed by GB and kava kava. Among the drugs, warfarin caused most of these interactions, followed by insulin and aspirin [115]. Patients who mixed St. John's wort with selective serotonin reuptake inhibitors (SSRIs) developed mild serotonin syndrome [116]. GB caused bleeding when combined with warfarin or aspirin (acetylsalicylic acid) and raised blood pressure when combined with a thiazide diuretic [117,118]. *Panax ginseng* reduced the blood concentrations of alcohol and warfarin, and induced mania when used in combination with phenelzine [119]. Bleeding occurred when *Salvia miltiorrhiza* was taken along with warfarin [120]. Patients with parkinsonism who took levodopa had an increase in "off" periods when taking *Piper methysticum* (kava) and fell into a semicomatose state when taking with alprazolam [117].

Medical practitioner should inform their patients about the recommended doses when taking herbs alongside prescribed drugs, in order to avoid any adverse reactions in the body. More research needs to be conducted in order to see the effects and safety profiles of different herbs when used alongside currently available pharmaceutical drugs.

4.6 Conclusion

Ayurveda, the traditional Indian medicine system, has evolved gradually since its conception 5000 years ago. It has a very important place in Indian culture and society. Although initially not so popular in the West, Ayurveda has now developed into a holistic and comprehensive system of medicine that is recognized worldwide. It has established itself as a well-developed and systematic branch of medicine dealing with a variety of ailments. In relation to neurological disorders, various herbs and phytochemicals have been documented in Ayurveda as improving cognitive functioning in AD patients. These plants are known as "Rasayanas" or "rejuvenators." Many investigators are now working to understand the mechanistic action of these Indian herbs and their phytoconstituents in AD and to identify targets for therapeutic intervention. Further, successful clinical trials using these phytocompounds will be an important milestone in AD treatment.

Drug discovery is emerging as an important research arena. Based on our traditional knowledge, new research should be focused on studying the mechanistic mode of action of Indian herbs and on identifying the therapeutic targets in different diseases. Clinical trials can then be carried out to study the use of these natural plant-based products in both the prevention and the cure of AD and other neurological diseases.

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