



## Review

## Herbal drugs and natural bioactive products as potential therapeutics: A review on pro-cognitives and brain boosters perspectives

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## ABSTRACT

Memory, one of the most vital aspects of the human brain, is necessary for the effective survival of an individual. 'Memory' can be defined in various ways but in an overall view, memory is the retention of the information that the brain grasps. Different factors are responsible for the disbalance in the brain's hippocampus region and the acetylcholine level, which masters the memory and cognitive functions. Plants are a source of pharmacologically potent drug molecules of high efficacy. Recently herbal medicine has evolved rapidly, gaining great acceptance worldwide due to their natural origin and fewer side effects. In this review, the authors have discussed the mechanisms and pharmacological action of herbal bioactive compounds to boost memory. Moreover, this review presents an update of different herbs and natural products that could act as memory enhancers and how they can be potentially utilized in the near future for the treatment of severe brain disorders. In addition, the authors also discuss the differences in biological activity of the same herb and emphasize the requirement for a higher standardization in cultivation methods and plant processing. The demand for further studies evaluating the interactions of herbal drugs is mentioned.

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## 1. Introduction

### 1.1. Memory: Brief background

The human brain is the most complex organ in the body. One of its most impressive aspects is the ability to retain information, what is called memory (Christophel et al., 2017; Postle, 2016). Before this review work, we have to know the definition of what memory is. 'Memory' perhaps can be defined in various ways. An overall standard definition is: "Memory is the ability of an individual to record sensory stimuli, events, pieces of information etc. and retain them over short or long periods and recall the same whenever needed at a later date" (Zlotnik and Vansintjan, 2019). In short, memory is one of the most vital aspects for effective survival of human beings (Shiksharathi et al., 2011). But when we discuss memory, it is not only the retention of information, along with it we also consider some associated terms like- cognition, intelligence, attention, concentration, quality of life (QOL) etc. Intelligence is according to Ayurveda the combination of three capabilities of mind:

- **Acquisition:** Capacity to grasp any information and to analyze it.
- **Retention:** Retain the information inside the brain.
- **Recollection:** Recall the information later (Rathee et al., 2008).

Based on the different mechanisms and types, memory can be classified into 3 types (Camina and Güell, 2017):

- i) **Short-term memory (STM)**—rapidly formed memory that is retained for a short time (minutes to hours).
- ii) **Long-term memory (LTM)**—a memory that is retained for long periods, e.g.-from hours to days, weeks, months, even years. (Rho et al., 2005).
- iii) **Sensory Memory or Iconic Memory**—the potential to remember temporarily the huge amounts of information that people experience every day

The up mentioned 'retention' and 'recollection' deal with STM and LTM respectively (Rathee et al., 2008).

### 1.2. Storing of memory inside the brain

When we are discussing memory, we have to know the mechanism by which various kinds of information are stored inside our brains. There is a region in our brain, named 'Hippocampus', located in the medial temporal lobe of the brain. This hippocampus is the center of all these memory and cognitive functions. At first, our brain cells grasp whatever we see, hear or do; then the hippocampus decides whether the information we grasped is important to store or not; if hippocampus decides to store the information, it retains inside our brains and we can memorize it, otherwise, the information gets deleted from our brain automatically (Shiksharathi et al., 2011; Kandel et al., 2014). This mechanism involves the interaction between various neurotransmitters in the brain (Shiksharathi et al., 2011; Sheffler and Pillarisetty, 2019). Acetylcholine (ACh) is the most important neurotransmitter

involved in memory and cognitive functions apart from several neurodegenerative pathogenicities (Parle and Vasidevan, 2007; Akaïke et al., 2018). One important enzyme involved in this mechanism is Acetylcholinesterase (AChE). Estimation of this enzyme's activity is an important parameter to assess the central cholinergic function. Acetylcholinesterase (AChE) modulates proper levels of acetylcholine by breaking ACh into Choline (the building block of ACh). However, the excessive activity of AChE results in the deficiency of ACh, leading to memory impairment (Rathee et al., 2008; Shikshartha et al., 2011).

### 1.3. Memory impairment

Poor memory, low retention power, difficulty to recall, lack of concentration, weak analyzing ability—these are very much common problems of the modern world. Besides some of the conditions, such as stress, ageing and emotions may lead to memory impairment, amnesia, dementia etc., and sometimes to some serious threats like Alzheimer's disease (AD), Schizophrenia etc. (Gur and Gur, 2013; Hildebrandt, 2019). In AD, the function of the hippocampus is destroyed, so that the brain cannot manage to store different kinds of information, especially the new ones. Besides, the neurons start to get degenerated. This disease affects mostly the elderly population, ageing 65 years or more (Wortmann, 2015; Winblad et al., 2016; Alzheimer's Association, 2016). According to cholinergic hypothesis, memory impairs due to deficiency in the cholinergic function inside the brain. Cognitive dysfunction is correlated with this impaired cholinergic function (Dumas and Newhouse, 2011; Bohnen et al., 2018).

### 1.4. Memory enhancers

Functional foods, supplements and drugs that are able to improve memory, cognition intelligence and other mental functions are known as memory and cognitive enhancers (Lynch et al., 2014; Morè et al., 2020). There is another term that can be used to describe memory and cognitive enhancers: 'Nootropics' (Pieramico et al., 2014; Onaolapo et al., 2019).

**Nootropics.** The word 'nootropic' (Greek: *noos*-mind, *tropein*-to bend/turn or monitor) was first coined in 1972 by Dr Corneliu E Giurgea. Nootropics are referred to as 'smart drugs' that act upon our brain cells. A nootropic is extremely non-toxic neuroprotective substance and can be used as memory and cognitive enhancer and in AD treatment (Colucci et al., 2012; Chaudhari et al., 2017). The functions of nootropics are: (a) Improving Acetylcholine level in the brain, (b) Improving O<sub>2</sub> supply to the brain, (c) Supplying neurochemicals (e.g. neurotransmitters, enzymes, hormones) to the brain (Jeon, 2015; Suliman et al., 2016; Crespo-Bujosa and Rodríguez, 2019). To improve memory and mood several nootropic agents are generally used such as Aniracetam, Oxiracetam, Pramiracetam, Piracetam and Choline esterase inhibitors like Donepezil, but the side effects of these agents (Talib and Ajaltouni, 2015; Zaami et al., 2020) have made their applicability limited.

### 1.5. Herbal remedies for impaired memory and cognition: Mechanisms and pharmacological actions

Herbal remedies are traditionally used all over the world to enhance poor memory and related ailments (Giampieri et al., 2014; Liao and Lin 2012; Banerjee et al., 2021; Gregory et al., 2021). Several medicinal plants and their extracts have shown nootropic properties or memory-enhancing properties by suitable character of their medicinal components (Aguar and Borowski, 2013; Onaolapo et al., 2019; Banerjee et al., 2021; Tandon et al., 2021). The increasing demand for herbal remedies worldwide is because herbal compounds have lesser or no side effects than

any other chemical compound (Anand et al., 2019). Our very own Indian Ayurveda possesses a treasury of such medicinal plants that enhance memory, cognition and intelligence. These Ayurvedic herbs are now popular all over the world (Anand et al., 2019). Not only Indian Ayurveda, the Traditional Chinese Medicine (TCM), Japanese, Korean, African, American and European medicines also come with a huge number of medicinal plants helping in reversing memory impairment. The herbs acting upon brain cells are termed 'nootropic herbs/drugs' and their isolated compounds are called as 'smart drugs' or 'cognitive enhancers' or 'brain booster' (Hildt, 2013; Frati et al., 2015). According to Ayurveda, herbs that promote intelligence is known as 'Medhya herbs/ Rasayana' (Kulkarni et al., 2012; Reena et al., 2013) and includes 10 herbal drugs namely *Jatamansi*, *Ashwagandha*, *Vacha*, *Jyotishmati*, *Shankhapushpi*, *Amalaki*, *Yashtimadhu*, *Kavach Beej*, *Bramhi*, and *Mandukaparni* (Lele, 2010). All these medicinal herbs increase the neurotransmitter level (especially acetylcholine) in the brain by inhibiting excess AChE activity and also improve blood circulation inside the brain thus providing sufficient supply of O<sub>2</sub> to the brain cells (Colovic et al., 2013; Suliman et al., 2016). Some home remedies against poor memory are found in commonly known food plants, which we can have as oils and vegetables (Fernando et al., 2015; Hardman et al., 2016; Molz and Schröder, 2017). The World Health Organization (WHO) states that at present date 80% of the world populations are using herbal remedies for the improvement of health (Srivastava et al., 2019).

### 1.6. History of memory enhancers in Ayurveda and TCM

Ayurveda, the science of life is a long traditional alternative medicine system from the Indian subcontinent. This natural science is based on the fundamental laws of nature with therapeutic approach for treatment of innumerable human diseases. Aging represents a systematic involution of the human body and the brain is considered as the most vulnerable organ to this process. Therefore, to avoid this damage, the Rasayana therapy, a rejuvenation branch of Ayurvedic medicine was established. Various natural drugs that act as brain tonic, promote health of the brain, lead to the alleviation of behavioral disorders or improve memory impairment are utilized in Rasayana approach. Various memory enhancing and rejuvenating plants are used in Rasayana therapies, including: *Acorus calamus*, *Bacopa monniera*, *Clitoria ternatea*, *Nardostachys jatamansi*, *Terminalia chebula* and many others (Singh 2013).

Traditional Chinese medicine (TCM) is based on the balance between health and disease. According to theory of TCM, healthy body is the body in the balance, on the other hand disharmony is not the cause of disease. The disease is caused by life style, influence of pathogens and various negative effects. However, the balance can be restored by herbal treatment. For over thousands of years, Chinese people have accumulated experiences in treatment, diagnosis, and disease prevention to create a whole theoretical system of medicine therapy. Herbal medicines with memory enhancing properties are also encompassed in the TCM. Between the plants used in TCM for memory improvement belong: *Huperzia serrata*, *Ginkgo biloba*, *Panax ginseng*, *Camellia sinensis* and other (Yan et al., 2007). These and above-mentioned plants will be discussed in following sections.

## 2. List of herbs having memory and cognition-enhancing properties

### 2.1. Family *Acoraceae*

***Acorus calamus* L. / Sweet flag** is a medicinal valuable semi-aquatic herb that grows throughout India, Central Asia, Siberia,

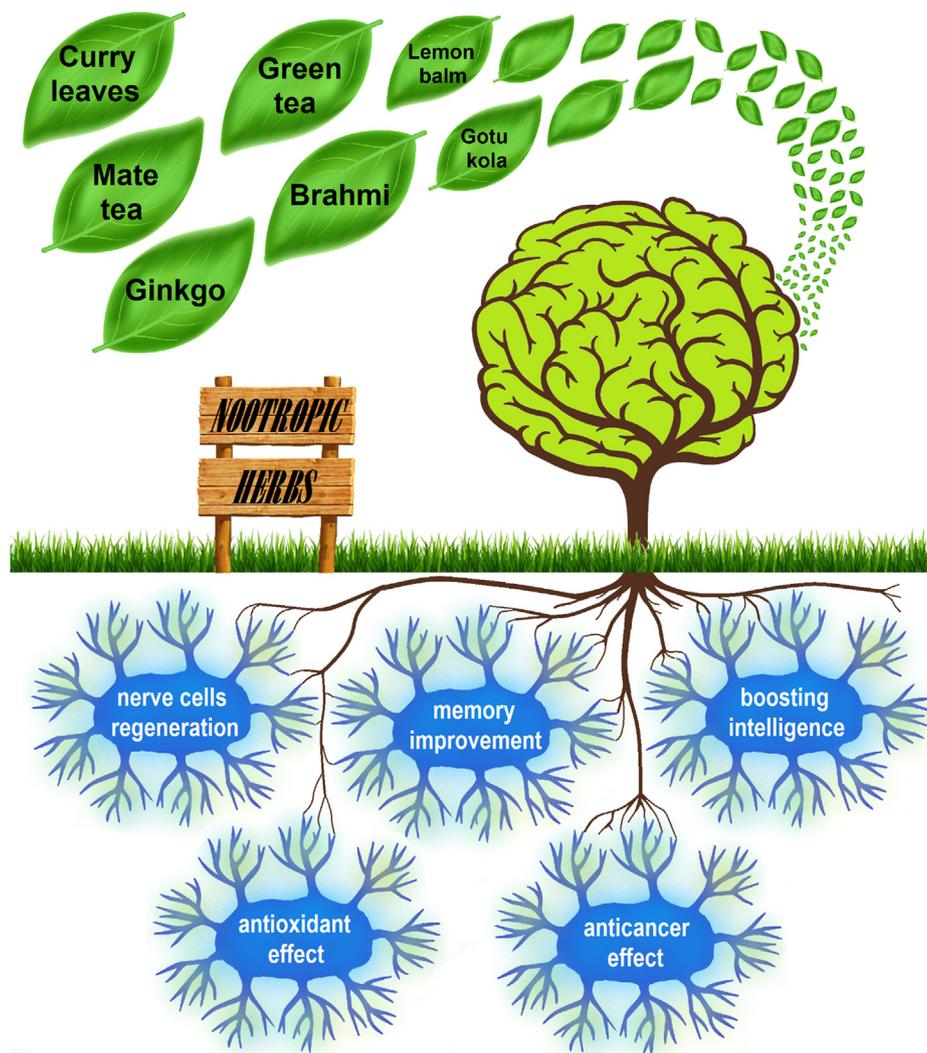


Fig. 1. Hallmarks of nootropic herbs.

Eastern Europe, Southern Russia, and could be found in gardens too. This perennial plant is not frost-tender and grows to a height of 1 m. It shows numerous therapeutic properties such as antiproliferative, antiulcerative, antibacterial, antioxidant, insecticidal, immunosuppressive, antifungal *etc.* (Pandit et al., 2011; Kumar et al., 2012; Parki et al., 2017). A plethora of bioactive chemical constituents like  $\beta$ -asarone (**40**) (AChE inhibitor) (Mukherjee et al., 2007a), phenylpropanoid, saponins, lectins, flavonoids, sesquiterpene, alkaloids,  $\alpha$ -asarone (**67**), phenols, monoterpene, and quinones, mucilages *etc.* are exhibited by this plant (Joshi, 2016). The rhizome of this plant 'Acori Calami Rhizoma', is mainly used to enhance/improve memory (May et al., 2016). Sweet flag is a very essential brain tonic as it shows a very short time results. Articles claiming this herb to cure AD are out (Nandakumar et al., 2013). Sweet flag strengthens the nervous system and increases the overall memory of the person. This is prescribed to patients who have epilepsy, amnesia, hysteria, insomnia, neurosis, remittent fevers, and melancholia (Huang et al., 2013; Sharma et al., 2014). The sweet flag contains essential oil in which **67** and **40** are present as the main components, which harbour anti-inflammatory properties to downregulate inflammatory cytokines (Shin et al., 2014; Lim et al., 2014).

## 2.2. Family *Apiaceae*

***Centella asiatica* (L.) Urban / Gotu kola** (also known as Than-kuni) is native to the wetlands in Asia and is widely scattered across the subtropical regions tropical geographical regions of India, Indonesia, Madagascar, China, Sri Lanka, and Nepal. This evergreen perennial plant is self-fertile, frost-tender, and grows to height of 20 cm. It is commonly used as a green leafy vegetable and as a medicinal herb in AM, Unani Medicine (UM), Traditional African Medicine (TAM) and TCM (Jahan et al., 2012). It contains a wide array of phytochemicals, which include flavonoids, tannins, triterpenoids (Asiatic acid, asiaticoside, madecassic acid, and madecassoside), glycosides, essential oils, alkaloids, and volatile fatty acids (Das, 2011). It effectively enhances the blood circulation in different body parts including the brain. Moreover, it helps to protect the brain from damage and improves concentration. The brain is more receptive to information and the memory is enhanced (Mannangatti and Naidu, 2016). The usage of this herb is documented over the centuries in Indian medicine system for the treatment and prevention of several diseases and health-related ailments including cancer, wound healing, dementia, diabetes, skin problems, ulcers, for regenerating the brain and nerve

cells, for combating ageing, asthma, (Singh et al., 2010; Sabaragamuwa et al., 2018) (Fig. 1). The positive results of *Centella asiatica* on the general ability, power of concentration and behaviour of mentally retarded children has been found in pharmacological and clinical trials. It is proposed that *Centella asiatica* and *Bacopa monnieri* have the similar medicinal value. A nervine tonic for treatment of various brain diseases or syrup to increase the memory of children are prepared from the whole plant. *C. asiatica* also inhibits scopolamine-induced memory impairment through the inhibition of AChE enzyme activity (Orhan et al., 2013). An animal study on mice model has shown asiaticoside as a neuroprotective agent and this effect could be linked with asiaticoside's anti-inflammatory activity by inhibition of the overactivated p38 MAPK pathway (Chen et al. 2014). In middle cerebral artery occlusion (MCAO) rats, the ethanolic extract of *C. asiatica* has demonstrated to be enhanced neurobehavioral activity, reduced infarction volume along with preserved brain neuroanatomy, increased the status of antioxidants and decreased the levels of free radicals (Tabassum et al., 2013). *In vitro* experiment of water extract of this herb preserved/protected human neuroblastoma MC65 cell line and SH-SY5Y cells from  $\beta$ -amyloid toxicity (Soumyanath et al., 2012). Recently, *in vitro* examination of *C. asiatica* leaf extract significantly suppressed  $\alpha$ -synuclein aggregation and prevented oligomer formation of aggregates that suggested the therapeutic potential of *C. asiatica* against Parkinson's disease (PD) (Ruben et al., 2014).

### 2.3. Family Aquifoliaceae

*Ilex paraguariensis* (A.) St.-Hil. / **Yerba mate** is plant typically growing and processing in South America, especially in northern Argentina, Paraguay, Uruguay and southern Brazil (Bracesco et al., 2011). This evergreen tree/shrub growing up to height of 15 m has simple obovate-oblong leaves, 4-membered small green-white flowers and small red drupe fruits with diameter of 4–6 mm. It is traditionally used for a preparation of the beverage called mate, which possesses high nutritional values. *I. paraguariensis* extract contains polyphenols (chlorogenic acids), tannins, xanthines (caffeine, theophylline and theobromine), flavonoids (quercetin (80), kaempferol), purine alkaloids (methyl xanthines), saponins, and vitamins (A, C, B1, B12, E) (Bracesco et al., 2011). Its entry into the body exhibit neuroprotective, diuretic, antimutagenic, anti-inflammatory, antioxidant, antidiabetic, anti-hyperglycemic, antidepressant, anticonvulsant, hypocholesterolaemic, antifungal, anti-obesity effects (Fernandes et al., 2017). The memory-enhancing activity of mate tea leaves are reported on different models of memory and learning (Prediger et al., 2008). The worthwhile effects of mate tea used for the enhancement of cognition, short- and long-term memory in animals were reported. It also has properties to treat dementia. More recently, several groups of researchers have demonstrated that *I. paraguariensis* derivatives are abundant with bioactive compounds which when enters CNS and produces significant therapeutic indices (Cittadini et al., 2019). Leaves aqueous extract of this medicinal herb has been shown to potentially inhibit scopolamine-induced memory loss in male Swiss mice (Santos et al., 2015).

### 2.4. Family Araliaceae

*Panax ginseng* C.A.Mey. / **Ginseng** grows only in the Northern Hemisphere, typically in cooler climates of North America and eastern Asia (northeast China, eastern Siberia, Korea and Bhutan). It is a perennial, hermaphrodite herb which grows to a height of 80 cm, has green-white small (3 mm) flowers and oval-shaped red drupe fruits, 6–7 mm long. This herb has a significant application in TCM for thousands of years. It is used mostly as a memory tonic and to improve memory and learning, especially in elderly

people. It contains saponins that enhance memory in the scopolamine-induced learning impairment. It is proposed that the main active components in Ginseng roots, Ginsenosides (Rg1 (20), Rg2 (21), Rg3 (30), Rh2 (22) etc), induce in the central cholinergic nervous system the enhancement of choline uptake, which is important for learning and memory. In rats, the cyproheptadine-induced recognition deficits were improved by a component of ginseng saponin.

### 2.5. Family Asteraceae

*Eclipta alba* (L.) Hassk. / **Bhringaraj** grows commonly in moist places and called as a weed by the farmers all over the world. This annual herb growing to a height of 30–40 cm, has cylindrical roots and white flowers 6–8 mm in diameter. It is widely distributed in tropical areas worldwide e.g. in India, China, Bangladesh, Thailand, and Brazil. Wedelolactone, luteolin, ursolic acid, apigenin, eclalbasaponins, and oleanolic acid are some of the potential bioactive constituents of this plant. *E. alba* possesses multifunctional pharmacological properties and has proven beneficial effects in the treatment of various disorders including cancer, gastrointestinal disorders, malaria, fever, snake bite, cuts and wounds, skin disorders, arthritis, respiratory tract disorders (like asthma), inflammation, graying of hair and hair loss, liver disorders (like jaundice), microbial diseases, and spleen development (Jahan et al., 2014). Bhringaraj is traditionally used for its memory enhancing quality, and thus it is not surprising that several studies were conducted for this purpose. Dose of 100 and 200 mg/kg of the Bhringaraj leaves aqueous extract was administered to rats. Then transfer latency (TL), which represents a measure of acquisition and retrieval learning was evaluated on an elevated plus-maze test. The spatial habitual learning revealed a relevant advancement in retrieval memory of tested rodents (Banji et al., 2007; Bhaskar and Chintamaneni, 2014). Notably, the antiepilepsy activity of *E. alba* phytoconstituents (wedelolactone,  $\beta$ -amyryn, and luteolin) have been widely reported by several groups of researchers (Shaikh et al., 2012; Shaikh et al., 2013).

### 2.6. Family Caprifoliaceae

*Nardostachys jatamansi* (D.Don) DC. / **Jatamansi** is well-reputed Medhya herb that has a place of respect in the Indian Ayurveda. This small perennial flowering herb grows to a height of 10–50 cm and has bell-shaped pink flowers. It commonly grows in the Himalayas of Nepal, China and India. Ayurveda says the roots of *Nardostachys jatamansi* have anti-ischemic, antioxidant, anticonvulsant and neuroprotective activities. The ethanolic extract of Jatamansi at a dose of 200 mg/kg b.w. significantly lead to the improvement in learning and memory power in young mice. Moreover, the scopolamine (0.4 mg/kg, i.p.) and diazepam (1 mg/kg, i.p.)-induced amnesia was considerably reversed. It also reversed the natural ageing-induced amnesia in mice. From these results, it can be said that Jatamansi might prove to be a useful remedy for the treatment of dementia in elderly persons.

### 2.7. Family Celastraceae

*Celastrus paniculatus* Willd. / **Jyotishmati** (also known as Kangani and Malkangni) belongs to the genus of woody, climbing shrubs. The stems are up to 10 m long and twine into the surrounding vegetation. Pale brown bark is covered with small elongated lenticles. The leaves are simple, broad and oval with toothed margins. Jyotishmati, one of the most widely explored medicinal plant and well known Medhya Rasayana' (nervine tonic) in Ayurvedic medicine (AM) (Malik et al., 2017). It is distributed in various geographical locations including Southeast Asian countries like

Thailand, Sri Lanka, Nepal, Japan, Myanmar, China, India, Malaysia, Taiwan, Indonesia, Vietnam and Australia (Mishra 2011) at elevations up to 10–18 m height. The seeds and seeds oil is the main part of this plant that contains a plethora of phytochemicals including triterpenoid pristimerin, sesquiterpenoid polyalcohols esters (celapnin, polyalcohol A–D, malkanguniol, malkangunin), polyalcohol (paniculatusdiol, malangunin, malkanguniol and malkanginnol), alkaloids celsastrine, paniculatin, calapagine, celapanine, calapanigine, sesquiterpenes, sterols ( $\beta$ -amyirin and  $\beta$ -sitosterol), saturated fatty acids (palmitic, stearic and lignoceric acid), unsaturated fatty acids (oleic, linoleic and linolenic), phenolic triterpenoids (paniculatadiol, celastrol), lipids etc. (Katekhaye et al., 2011). They have a bitter taste, an unpleasant odour and are regularly used as neuroprotective properties, cognitive disorders, and to sharpen/enhancing the memory and boosting intelligence (Bhanumathy et al., 2010; Arora and Pandey-Rai 2014). Whole plant extract of *C. paniculatus* has demonstrated anti-epileptic function (Atigari et al., 2012). The seeds and the seed oil are commonly used as a brain tonic, in many central nervous system (CNS) disorders and as neuro-protective agent (Bhagya et al., 2016; Malik et al., 2017). The seed oil improved learning and memory whereas the levels of dopamine, noradrenaline and serotonin were decreased in the brain of rats. The oil of this plant significantly decreases AChE activity (Bhagya et al., 2016; Malik et al., 2017). In addition to neurological benefits, different plant parts of *C. paniculatus* has potentially shown to exhibit potent activity in wound healing, hypolipidemic, antioxidant, analgesic, anti-inflammatory, stomach ulcers, dyspepsia (Palle et al., 2018).

## 2.8. Family *Combretaceae*

***Terminalia chebula* Retz. / Haritaki** is a deciduous tree, which grows in Southeastern Asia (India, China, Sri Lanka, Malaysia and Vietnam). The tree grows to a height of 30 m, the leaves are oval with opposite or alternate arrangement. The yellow flowers occur in terminal spikes or short panicles and emit unpleasant odor. The ovoid fruits are yellow to orange-brown. The ripe fruit of *Terminalia chebula* is valued due its beneficial health effects including memory and intellect enhancement. Further, it is believed that consumption of the fruit is efficient to prolong life, to improve eyesight and can delay ageing. To achieve the desired effects, consumption of one ripe fruit every morning is recommended.

## 2.9. Family *Convolvulaceae*

***Convolvulus pluricaulis* Choisy / Shankpushpi** (also known as Bindweed) is a well-reputed Medhya herb commonly found in southern India and Burma. This perennial herb has 10–40 cm long stems and small (5 mm) blue color flowers. In ancient times, it was a prominent memory-improving drug, a psychostimulant and tranquiliser in traditional Indian medicine (Shethiya and Mishra, 2010). A brain tonic is prepared from the whole plant and is used for memory and intellect improvements. Its consumption also claimed to prevent memory loss. The plant contains diverse phytochemicals including  $\beta$ -sitosterol, vitamin C or ascorbic acid (23), silane, decanoic acid, carbohydrates, vitamin E, valeric acid or pentanoic acid, cinnamic acid, squalene, linoleic acid, phthalic acid, gums, proteins, mucilages, several alkaloids (tropane), flavonoids (Kaempferol), and glycosides etc. as active chemicals that bring about its diverse beneficial pharmacological effects (Agarwa et al., 2014). Several groups of researches have shown that bioactive compounds of this herb displayed anti-ulcerogenic, neuroprotective, antimicrobial (anti-bacterial, antiviral), antioxidant, antianxiety, nootropic, anxiolytic, antiobsessive, anticonvulsant, antithyroid, hepatoprotective, antidepressant, hypotensive, anxiolytic, ameliorative property (Ravichandra et al., 2013; Rachitha

et al., 2018; Anupama et al., 2019). In a preclinical study, the ethanolic extract of *Convolvulus pluricaulis* (in two doses- 100 mg and 200 mg per kg b.w.) reversed scopolamine-induced amnesia in rats (Nahata et al., 2008). Clinical studies of its polyherbal formulation justified its potential for the ancient claim of brain tonic. The memory enhancing and learning behavior properties of Shankpushpi have become increasingly popular worldwide in recent years. Most recently, an aqueous extract of *C. pluricaulis* has demonstrated to the downregulated  $\tau$  protein level, enhances locomotor deficits and increases longevity in human microtubule-associated protein tau (hMAP $\tau$ ) induced *Drosophila* AD model (Anupama et al., 2019).

## 2.10. Family *Cornaceae*

***Cornus officinalis* Siebold & Zucc. / Japanese cornel** is a deciduous tree widely spread/occurs in China, Japan and Korea. The tree grows to a height of 10 m, has a brown-gray bark and ovate leaves are 5–12 cm long. The flowers are bright yellow on bare stems in late winter or early spring. Fruits are red edible berries about 1.5 cm long. This plant is usually used as a food or due to its medicinal properties (Ma et al., 2014). A plethora of phytoconstituents is exhibited by *C. officinalis* including anthocyanins, flavonoids (quercetin), and phenolic acids (*trans*-cinnamic acid, benzoic acid), triterpenoids, anthocyanin, carbohydrates (Rudrapaul et al., 2015). Furthermore, this herb is known to harbour neuroprotective, antitumor, antidiabetic, immunomodulatory, cardioprotective, anti-amnesic, antimicrobial, antioxidant, anti-inflammatory, renal and hepatic protective, antiosteoporotic and insecticidal property (Czerwińska and Melzig, 2018). Cornel iridoid glycoside (CIG) is the main component in this herb, which has the ability to promote neurogenesis and to improve neurological function after ischemia in rats. Iridoids of *C. officinalis* also protect hippocampal cells that have suffered from glutamate (Jeong et al., 2012). Further assays in rats proved, that CIG treatment significantly improved the memory deficits seen in Fimbria-fornix transection (FFT). It also reduced the loss of neurone in the mouse hippocampus (Zhao et al., 2010). Many polyphenolic compounds obtained from *C. officinalis* fruits, e.g. tellimagrandin I, tellimagrandin II and isoterchebin, are important regulators of certain enzymes and downregulate total enzymes implicated in the development of AD neurodegeneration (Bhakta et al., 2017). The documented neuroprotective and anti-amnesic property of *C. officinalis* is attributed because of antioxidant and radical scavenging effects (Cooper and Ma, 2017; Huang et al., 2018).

## 2.11. Family *Fabaceae*

***Desmodium gangeticum* (L.) DC. / Shalparni** is widely used in Ayurvedic medicine. This small shrub grows to a height of 1.2 m. The oblong leaves are simple with an alternative arrangement. The purple-white flowers have a bilateral symmetry. *D. gangeticum* has traditionally been used as astringent, anthelmintic, diuretic, laxative, antipyretic, and in the treatment and prevention of neurodegenerative diseases like dementia and mental disorders (Ma et al., 2011). Significant bioactive phytochemicals of this plant include flavonoids, alkaloids, terpenoids, phenolic compounds, and steroids. Furthermore, *D. gangeticum* has been documented to display immunomodulatory, antidiabetic, antioxidant, antimicrobial, anti-writhing, anti-inflammatory, renal-protective, anti-ulcer, hepatoprotective, antileishmanial, wound healing, and cardio-protective properties (Bhattacharjee et al., 2013). In laca mice, the alkaloid-rich fraction of *D. gangeticum* greatly reversed the scopolamine-induced amnesia at the dosage of 50 mg/kg (Mahajan et al., 2015). Shalparni in mice significantly improves learning and memory abilities and reverses the scopolamine or

natural ageing induced amnesia. It also decreases acetylcholinesterase activity in brain. Hence, *D. gangeticum* bears notable potential to its medicinal application for memory improving as well for the treatment of dementia and AD.

**Glycyrrhiza glabra L. / Licorice** is a legume that is native to Southern Russia and Asia, Mediterranean region and is broadly planted throughout the Middle East and Europe. It is a perennial plant which grows to a height of 1.2 m. The herb has a compound leaves about 7–15 cm long, purple to pale-blue flowers long about 0.8–1.2 cm and produces oblong pods with several seeds. This herb is known worldwide for its various curative properties. *G. glabra* contains diverse phytochemicals, which are of high medicinal value including flavonoids (liquiritin, liquiritigenin, rhamnoliquiritin, isoliquiritin, etc.), triterpenes (glycyrrhizin or glycyrrhizic acid, glycyrrhetic acid monoglucuronide), isoflavonoids (Dehydroglyasperin C), saponin, tannins, glycosides etc. (Batiha et al., 2020; Han et al., 2020). Various parts of this plant have been used in the treatment of various health-related disorders such as roots in diabetes, flatulence and Graves' disease, stem in tuberculosis, and leaves in wounds. Furthermore, this perennial herb has been widely acknowledged to treat various pathological conditions including epilepsy, stomach ulcers, jaundice, respiratory disorders, fever, hyperdipsia, hemorrhagic diseases, rheumatism, sexual debility, paralysis, skin diseases etc. Licorice, a root extract of *G. glabra* is generally used as a brain tonic and a brain re-vitalizer. This plant is termed in Ayurveda as 'Medhya dravya' and it was commonly utilized to improve memory and intellect. The assays on mice confirmed, that aqueous extract of liquorice at the dose of 150 mg/kg significantly boosts memory and learning skills. Furthermore, diazepam (1 mg/kg i.p.) and scopolamine (0.4 mg/kg i.p.) induced amnesia was significantly reduced by liquorice extracts. Liquiritigenin (LIQ), a bioactive compound of *G. glabra* root has shown to inhibit glutamate-induced hippocampal neuronal cell death by downregulating ROS production, Ca<sup>2+</sup> influx and lipid peroxidation, protected mitochondria from stress and MAPKs phosphorylation (p38) thereby LIO is attributed as a strong neuroprotective agent and could be a possibility to become a potent drug for AD and PD (Yang et al., 2013).

#### 2.12. Family Ginkgoaceae

**Ginkgo biloba L. / Ginkgo** is a living fossil, native to China and Japan. It is a large deciduous tree growing up to a height of 35 m. The leaves are fan-shaped with two lobes, in autumn turn yellow and fall sometimes within a short period of time (1–15 days). Seeds are edible. EGb761, *Ginkgo biloba* leaves extract is famous globally for its beneficial pharmacological effect on neurotransmitter systems particularly in treating neurological disorders. EGb761 contain terpenoids (e.g., bilobalide, ginkgolides (28)) and ginkgolides A (13), B (14) (Fig. 2), C, J, and M, flavonoids (e.g. kaempferol, quercetin (80) and polymeric flavonoids) (Yuan et al., 2010). Among these, ginkgolides, a bioactive constituent of EGb761 has proven to interact with the cholinergic system and have neuroprotective and neural stem cells (NSCs) regenerative potential (Wang and Han, 2015; Ren et al., 2019). Ginkgo improves circulation of blood into the central nervous system and increases the distribution of nutrients and oxygen into the brain. It also eliminates free radicals in the body thereby improves memory and alertness. The ginkgo extract is prescribed for the treatment of amnesia and AD. Ginkgo is used as one of the important compounds in several herbal nerve tonics. Recently, this plant has demonstrated a positive effect on many neurological related health ailments including depression, psychosis, anxiety, and schizophrenia (Kumar et al., 2017). In clinical practice, *Ginkgo biloba* extract (GBE) has proven to treat cognitive disorders, memory impairment, AD and coronary heart disease and showed therapeutic effects at the biochemical and pharmaco-

logical levels (Vellas et al., 2012; Jahanshahi et al., 2012; Zhang et al., 2013). The extract is widely used to treat AD and cerebrovascular disease (CD) (Zhang et al., 2017). Notably, during cerebral ischemia (CI) bilobalide (BB) has proven to exhibit neuroprotective effects (Huang et al., 2012). Hence, From the molecular point of view, EGb761 display antioxidant activity and downregulating tau hyperphosphorylation in addition to the protection against A $\beta$ -induced neurotoxicity and hence it could be a potential medication for treating AD.

#### 2.13. Family Hypericaceae

**Hypericum perforatum L. / St. John's wort** is native to subtropical and temperate geographical regions of Europe, western Asia, Middle-East India, northern Africa, Russia and China. This perennial self-fertile flowering plant grows up to a height of 1 m. It has woody stems near the base, the leaves are oblong, narrow, and about 1–2 cm long. The five petal flowers are about 2.5 cm wide and colored bright yellow. *H. perforatum* is approved for therapeutic intervention (Božin et al., 2013) and contains diverse phytochemicals such as flavonoids derivatives (rutin, amentoflavone, hyperoside, quercetin (80), biapigenin, isoquercitrin, kaempferol, etc.), phenolic compounds, acylated phloroglucinols (hyperforin and derivatives), and naphthodiantrones (hypericin and derivatives) (Russo et al., 2014; Oliveira et al., 2016). These phytochemicals confer an array of pharmacological properties such as antiviral, neuroprotective, antifungal, anti-ischemic, wound-healing, antibacterial, antioxidant, and antidepressant activity. In SH-SY5Y neuroblastoma cells, rutin prevents accumulation and cytotoxicity of  $\beta$ -amyloids, mitigates mitochondrial damage, ROS, oxidative stress, and reduces nitric oxide and proinflammatory cytokines production (Wang et al., 2012). It is an excellent tonic for brain damage and ameliorates spatial memory and learning behaviour against A $\beta$ <sub>25–35</sub>-induced toxicity (Liu et al., 2013). It helps to regenerate the nervous system, specifically the myelin sheath that surrounds nerves. Possibly, the usage of *Hypericum* extract could be more beneficial for the treatment of depression associated with dementia than other antidepressants that may cause sedation.

#### 2.14. Family Iridaceae

**Crocus sativus L. / Saffron** dried red–orange stigma (the only usable part of this plant) is well-known as a fruit colouring, flavoring agent, and exhibit beneficial biological/pharmacological effects. It is a flowering perennial plant which forms small brown compact corms that are flat on the base. The plant grows to a height of 10–25 cm. The purple flowers do not close during the night. The flowers consist of six petals, three stamens, and three stigmas. The red–orange stigmas are 2.5–3 cm long and using as a noble spice. Saffron is the world's most expensive regularly used dietary spice (Moore et al., 2012). It is a native herb in Southwest Asia (Iran). The main bioactive chemical constituents are  $\alpha$ -crocin (47) (C<sub>44</sub>H<sub>64</sub>O<sub>24</sub>), crocetin (70) (C<sub>20</sub>H<sub>24</sub>O<sub>4</sub>), picrocrocin (C<sub>16</sub>H<sub>26</sub>O<sub>7</sub>), safranal (81) (C<sub>10</sub>H<sub>14</sub>O), water-soluble carotenoids (crocin), vitamins (thiamine and riboflavin), carbohydrates, low concentration of monoterpene aldehydes and its glucosides (81 and picrocrocin), lipids, polypeptides, proteins, flavonoids (quercetin (80), kaempferol, isorhamnetin and anthocyanins e.g. petunidin, malvidin, and delphinidin), starch, amino acids, gums, and minerals (Goupy et al., 2013; Zeka et al., 2015). For centuries, saffron has been extensively used as anxiolytic activity, antitussive, antibacterial, antiinflammatory, hypolipidemic, antifungal, anti-diabetic, anti-convulsant, antityrosinase, anti-neuropathic pain, anticancer, antitussive, antioxidant, antiseptic, antidepressant, antinociceptive, anti-cancer, anti-tumor, liver and spleen enlargement prevention,

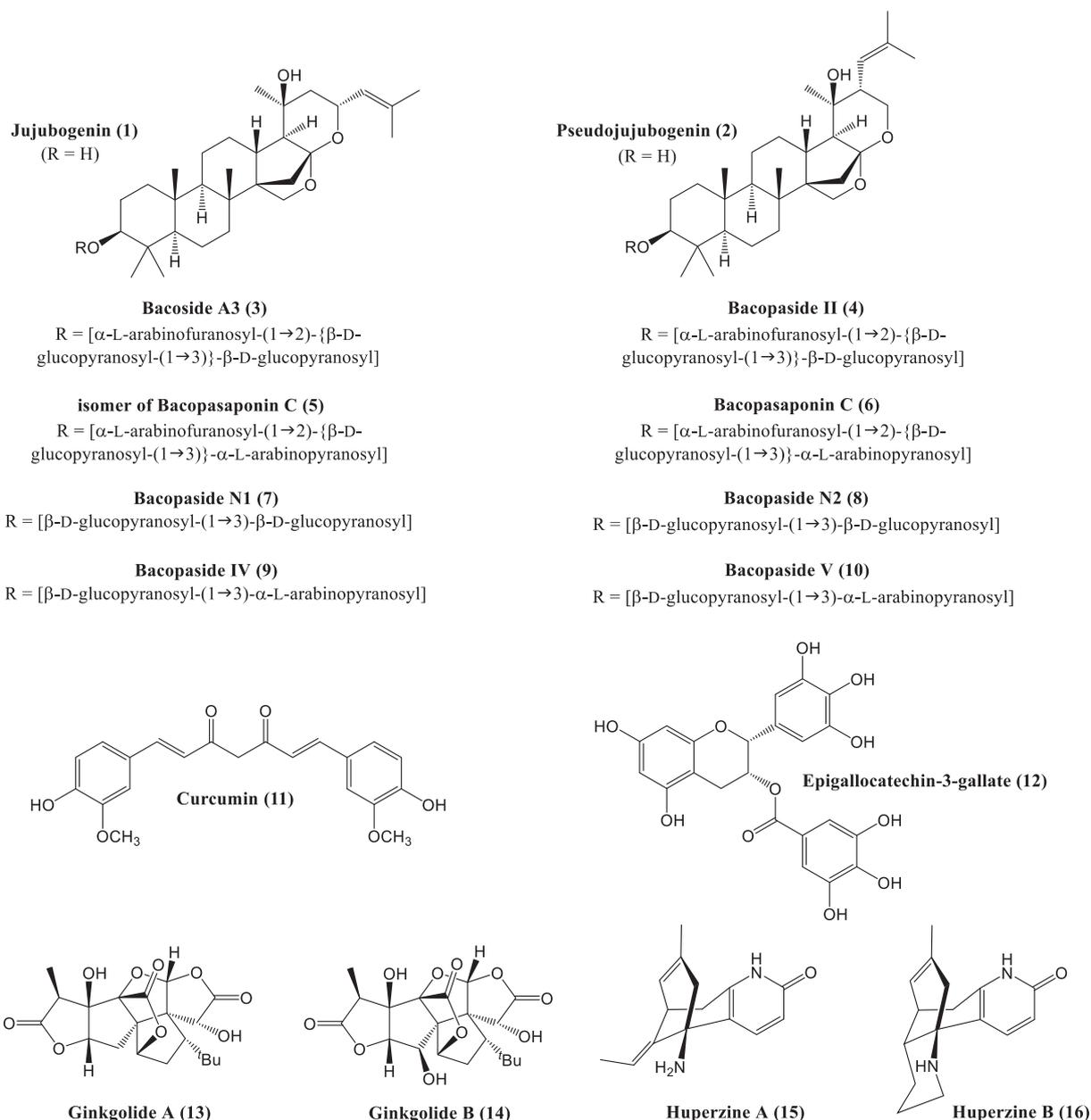


Fig. 2. Chemical structure of selected pro-cognitives and memory enhancers.

lumbar pain remedy, chemoprotective, renal ischemia–reperfusion prevention, anti-genotoxic, an aphrodisiac, antispasmodic, tension relieving, expectorant, cardiovascular protective, antidote against poisoning, dysentery, cataract, measles, pre-eclampsia treatment, withdrawal syndrome inhibition, wound healing, and abscesses (Hosseinzadeh, 2014; Moshiri et al., 2015; Ghasemi et al., 2015). In addition to its historical value as a food additive, several studies recently indicated its potential use as neuroprotective (anti-Alzheimer, anti-Parkinson), learning and memory enhancer, anxiolytic and hypnotic, against cerebral ischemia, memory deficits and brain damage, against morphine dependency mitigation (Hosseinzadeh et al., 2012; Tashakori-Sabzevar et al., 2013). Moreover, enhancing disease in adjuvant-induced arthritis, minimizing oxidative damage to the kidney (Zamani et al., 2015). These compounds significantly reverse scopolamine-induced amnesia. A study reveals that the treatment of mild-to-moderate AD with Saffron is safe and effective in adults ageing 55 years or more (Akhondzadeh et al., 2010). Recently, a study on adult male Wistar

rats administered with aqueous extract of saffron demonstrated that saffron significantly upregulated brain-derived neurotrophic factor (BDNF) (both transcriptomics and protein levels) and cyclic-AMP response element binding protein (CREB) (only protein levels) in the hippocampus which manifestate that saffron could be a potential lead molecule for AD treatment (Ghasemi et al., 2015).

#### 2.15. Family *Lamiaceae*

**Melissa officinalis L. / Lemon balm** is a perennial lemon-scented herb, which grows naturally in south-central Europe and the Mediterranean region. The herb is not frost tender and grows to a height of 70 cm. During summer, the white flowers appear. Although they are small and inconspicuous, honey bees love them. The tea prepared from this plant is used in TCM to calm nerves, for its spasmolytic effects (Kumar et al., 2013) and used in European medicine to improve senses and memory. It also strengthens brain cells and clears the head. Monoterpenes such as citral and citronel-

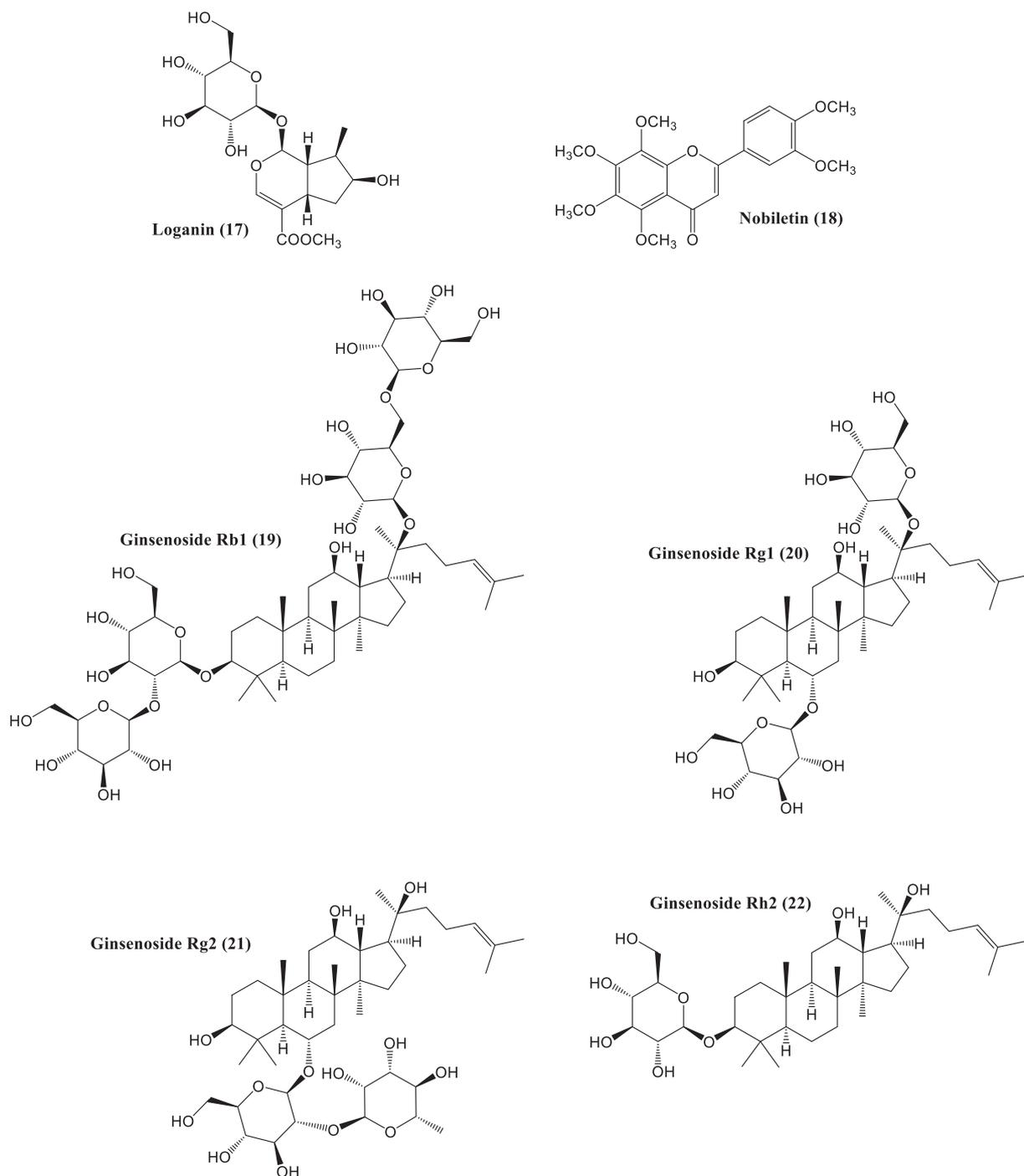


Fig. 2 (continued)

lul are included in the essential oil of *Melissa officinalis*, which inhibits the AChE in a dose-dependent manner. Randomized, placebo-controlled, balanced-crossover and double blind studies confirmed influence of acute administered lemon balm on the modulation of mood and cognitive performance. It also shows a significant effect on people having severe dementia. Different studies show that Lemon balm has the potentials to manage the AD and to control agitation in AD patients (Kumar et al., 2013).

***Ocimum tenuiflorum* L. / Tulsi** (also known as 'holy basil') is an aromatic plant belonging to the family Lamiaceae. This well-branched perennial herb grows up to a height of 1 m. The ovate, long and slightly toothed leaves are green or purple color. The

small purplish or white flowers are placed on terminal spikes. It is indigenous to the Indian Subcontinent and cultivated throughout the Southeast Asian tropics. Tulsi holds a place of respect since ancient times in India. The whole plant extract reverses the amnesia induced by scopolamine (0.4 mg/kg) and diazepam (1 mg/kg) in mice. It also reverses the memory deficits induced by ageing. The extract from *Ocimum tenuiflorum* decreases transfer latency and increases step-down latency in mice (in EPM test and PA paradigms as an exteroceptive behavioural model), in comparison with control (treated with piracetam), scopolamine and age groups.

***Salvia lavandulaefolia* Vahl / Spanish sage** is a perennial plant in family Lamiaceae. It is an evergreen shrub which grows to a

height of 30 cm. The leaves are in opposite arrangement and contain essential oil with fragrance similar to rosemary. The small flowers are purplish and very attractive to bees. This small woody herb grows typically in rocky soil in the Mediterranean region (Spain and southern France). This herb become popular due its worthwhile effects on depression, cerebral ischemia, memory disorders and anticholinesterase activity. The essential oil of *Salvia* contains 1,8-cineole, linalool, carvacrol and luteolin. Based on clinical data, the essential oil and extracts from *Salvia lavandulaefolia* suggested the potential for the therapy of AD and other memory-related disorders.

***Salvia officinalis* L. / Common sage** is evergreen, perennial herb growing to a height of 60 cm. The oblong leaves are rugose, 6.5 cm long, and are green-gray color. The flowers are placed in spike and can be purple, pink, white or red. The plant is native to the Mediterranean area, however due its popularity it is now cultivated in different places worldwide. It is one of our best-known herbs medicinally. It has a good reputation in British herbal encyclopaedias memory enhancing agents. The oil of Sage contains caryophyllene, camphor and borneol (54) etc. The sage proved the inhibition of acetylcholinesterase action. Further research exhibit that this herb may be useful in the treatment of mild-to-moderate AD.

***Salvia rosmarinus* Spenn. / Rosemary plant** (synonym: *Rosmarinus officinalis* L.) in the family Lamiaceae, is an evergreen, perennial shrub growing to a height of 1.5 m. The plant is not frost tender, and has the linear leaves about 2–4 cm long, but only 2–5 cm wide. The leaves are green on the top and gray on the bottom. The small flowers are purple, deep blue, pink or white color. Rosemary plant originated in the Mediterranean area. Since ancient times, rosemary has been used for improvement and strengthening of the memory. In ancient Greece, it was considered as a mind stimulator. Even at the present date, students in Greece are burning the plant when they are studying for exams. Indeed, it affects as a stimulator of the blood flow into the brain and enhancer of mental alertness.

#### 2.16. Family Magnoliaceae

***Magnolia officinalis* Rehder & Wilson / Magnolia tree** grows naturally in China typically in mountains and valleys at altitudes of 300–1500 m. It is a deciduous tree growing up to a height of 20 m. The tree has a brown and thick bark, ovate enormous green leaves about 20–40 cm long and 10–20 cm wide, and fragrant creamy-white to butter-yellow large flowers about 10–14 cm in diameter. The bark of *Magnolia officinalis* (Magnoliaceae) is traditionally used in China as a medicine for the memory enhancement and for the treatment of neurosis, anxiety, stroke, dementia etc. *Magnolia* is able to inhibit scopolamine-induced memory impairment through the inhibition of AChE. The active constituent of *Magnolia officinalis* is 4-O-methylhonokiol, honokiol and magnolol (61) (Lee et al., 2011). The polyphenolic compounds 61 and honokiol are used in the treatment of fever, headache, neurosis, anxiety and stroke (Woodbury et al., 2013) since ancient times. *In vivo* experiments showed that honokiol was found to promote the level of acetylcholine in rat hippocampus. Both 61 and honokiol show AChE inhibitory property. The water maze and step-down avoidance tests have shown that *Magnolia officinalis* increasing the power of memory and learning skills.

#### 2.17. Family Malvaceae

***Theobroma cacao* L. / Cacao tree** in the family Malvaceae, is a small evergreen tropical tree, growing to a height of about 8 m. The large leaves about 40 cm long are simple, in alternative arrangement and periodically and replaced by new leaves. The

small flowers are present at all times, however twice a year appear in abundance, their color can be white, yellow, reddish or pink. Flowers are clustered, odourless or foul-smelling and placed directly on the trunk and limbs. The fruits are elongated pods in various color from yellow to deep purple. The ovoid pod is up to 35 cm long, about 12 cm wide and contains 20–60 edible seeds, termed as beans. Cacao tree is native to Central and South America. *Theobroma cacao* contains different types of chemical compounds e.g. alkaloids (theobromine, theophylline and caffeine), glycosides, galactosides, tannins, polyphenols, triglycerides, coumarins, catechins, catechol, linoleic acids, rutin, vitexin etc. All these bring about its significant effect on the enhancement of memory.

#### 2.18. Family Menispermaceae

***Tinospora cordifolia* (Willd.) Miers / Giloy** is a deciduous climbing shrub. The simple heart-shaped leaves are in alternative arrangement. The species is dioecious, female flowers usually occur solitary, while male flowers are clustered. Red or orange ovoid fruits are clustered. The plant is native to the tropical regions (India, Sri Lanka and Myanmar). This multipurpose herb regenerates brain cells and the whole body. Memory enhancing properties of *Tinospora cordifolia* were observed on the memory and learning skills in normal and memory deficits animals. It increases the synthesis of Acetylcholine. The passive avoidance task and Hebb William maze proved its cognition enhancement property, when applied on normal and cognition deficits animals.

#### 2.19. Family Myristicaceae

***Myristica fragrans* Houtt. / Nutmeg tree** is an evergreen tree which usually grows up to a height of 20 m. The dark green leaves are in alternative arrangement, about 5–15 cm long and 2–7 cm wide. The species is dioecious, the bell-shaped female and male flowers are borne on different plants. The female flowers are in small groups (1–3 flowers) and longer than the male flowers that are aggregated in larger groups (1–10 flowers). The fruit, similar in appearance to an apricot is a pendulous drupe with an edible pulp. Inside the fruit is shiny purple-brown seed about 2 cm long, covered with a red aril. Nutmeg tree originated from Banda Islands, Indonesia. The *n*-hexane extract of *M. fragrans* seeds in three doses (5, 10 and 20 mg/kg p.o.) was administered to mice with scopolamine (0.4 mg/kg i.p.) and diazepam (1 mg/kg i.p.) induced memory deficit. The passive-avoidance task and elevated plus-maze test were used to evaluate learning and memory parameters. A significant improvement in learning skills and memory power was recognized after 3 successive days of *M. fragrans* extract administration at a dose of 5 mg/kg p.o. to young and aged mice. Scopolamine and diazepam-induced memory impairment in mice was also reversed with the extract.

#### 2.20. Family Orchidaceae

***Gastrodia elata* Blume** is a perennial herb growing up to a height of 1 m. The unique botanical character of the herb is that the whole plant is chlorophyll-free. Except for florescence, the main live-cycle stages of the plant running underground. The vertical, leafless stems are yellowish and fringed golden color inflorescence is about 13–30 cm long. The ovoid rhizome is about 8–12 cm long. *Gastrodia elata* is found in North Korea, Siberia, Nepal, Bhutan, India, Japan (Hokkaido, Honshu, Shikoku, Kyushu), Taiwan as well as mainland China. For centuries, the herb is used to treat various disorders including epilepsy, spasm, headache, amnesia, dizziness, stroke etc. (Chinese Pharmacopoeia Commission, 2015). Rhizome *Gastrodiae* (rhizome of *G. elata*) is the key part of this medicinal plant. Gastrodin (4-hydroxybenzyl alcohol-4-O-β-D-

glucopyranoside) is considered as the most important bioactive constituents of *Rhizoma Gastrodiae* which exhibit high pharmacological intervention. A plethora of research has been investigated for gastrodin (C<sub>13</sub>H<sub>18</sub>O<sub>7</sub>), medicinal importance which has demonstrated remarkable beneficial bioactive activity including memory-improving, hypnotic, sedative, anti-epileptic, anti-vertigo, preventing osteonecrosis, analgesic, antidepressant, anxiolytic, anti-aging, lowering blood pressure etc. (Zhan et al., 2016). In the light of AD, gastrodin extract or its bioactive constituents has demonstrated to enhance learning and memory performance in an AD mouse model (Liu and Wang 2012; Hu et al., 2014). *In vitro* investigation of gastrodin has shown to suppress intracellular and extracellular A $\beta$  levels in a dose-dependent manner (Zhu et al., 2014) and further investigation indicated that the cause of this reduction could be associated with the mitigation of  $\beta$  and  $\gamma$ -secretase activities (Zhou et al., 2016).

### 2.21. Family Phyllanthaceae

***Phyllanthus emblica* L. / Amla** (synonym: *Emblica officinalis* Gaertn.) is a tropical deciduous tree that grows up to a height of 18 m. It has green pinnately compound leaves with the greenish-yellow flowers. Edible globular fruits are greenish-yellow color. The tree grows in tropical Southeastern Asia, Southern China, Pakistan, and Bangladesh, particularly in central and southern India, Ceylon, Malaya and the Mascarene Islands. *P. emblica* contains diverse active constituents like different tannins, vitamin C, oils, polyphenols (gallic acid (75), punigluconin, ellagic acid (73), chebulinic acid, leutolin, aepigenin, quercetin (80), etc.), phyllembin, amino acids, 3,6-di-O-galloyl-D-glucose, 1-O-galloyl- $\beta$ -D-glucose, 3-ethylgallic acid (3-ethoxy-4,5-dihydroxybenzoic acid), 1,6-di-O-galloyl  $\beta$ -D-glucose, minerals, flavonoids (rutin and 80) etc (Variya et al., 2016, Yadav et al., 2017). Presence of vitamin-C, in the amla possesses beneficial calming effects on the memory improvement, cholesterol-lowering property and anti-cholinesterase activity. Amla shows positive results on memory enhancement in scopolamine (0.4 mg/kg, i.p.) and diazepam (1 mg/kg, i.p.) induced memory deficits. It also inhibits AChE activity (Reddy et al., 2010). A study in young and aged rats and mice model showed a dose-dependent improvement in memory scores after administration of *Anwalachurna* (50, 100, and 200 mg/kg, p. o.) (Parle and Vasudevan, 2007). Numerous studies have shown the neuropharmacological property of *P. emblica* in the treatment and prevention of dementia which is manifested by the multifunctional characteristic including anti-oxidant property, cholesterol-lowering property, anti-cholinesterase property, and potency to improve and reverse memory deficits (Ashwlayan and Singh, 2011; Perry and Howes, 2011; Golechha et al., 2012).

### 2.22. Family Plantaginaceae

***Bacopa monnieri* (L.) Pennel / Brahmi** (also known as water hyssop) is a perennial, non-aromatic herb which grows to a height of 30 cm. The herb is frost tender, has oblong, succulent, thick leaves in alternative arrangement, that are edible. The small, white flowers have 4–5 petals. Brahmi is native to India and Australia (Aguilar and Borowski, 2013) and also grows throughout the United States and East Asia. *Bacopa monnieri* (BM) has a long history of use in the AM tradition in the treatment of several ailments, including epilepsy, learning enhancer, lack of concentration, mental illnesses, sedative, stroke, anxiety etc. (Srivastava et al., 2019). All of the herbs investigated for their memory-enhancing properties Brahmi is likely the most studied. The usage of *Bacopa monnieri* for memory enhancement can be dated back to 800 BCE in India (Rathe et al., 2008). In modern India, Brahmi is used as a tonic for school-going children to improve their mental capacity. The grasp-

ing power of the brain and the power to analyze grasped information are also increased by (Singh, 2013). Studies show that the major nootropic bioactive constituents in this herb are alkaloids (such as brahmine, nicotine (62), and herpestine), steroidal saponins (like; D-mannitol and hersaponin, bacopasides I–XII, bacopasaponins, bacosides A (42) and B, acid A, and monnierin), (Aguilar and Borowski, 2013; Le et al., 2015), which have beneficial influence on enhancement of memory and cognitive function. *Bacopa monnieri* exhibits neuroprotective, anti-oxidant, and hepatoprotective properties (Rastogi et al., 2012). These bioactive components have promising results in normal rats e.g. learning and memory were facilitated whereas the amnesic effect induced by electroshock, scopolamine and immobilization stress was inhibited. Furthermore, the activity of protein kinase C (PKC) in hippocampus was enhanced by Brahmi, which contributes to its nootropic action. *Bacopa monnieri* has also been documented to shown AChE inhibitory activity in patients with AD (Goswami et al., 2011). There have also been preliminary clinical studies suggesting significant improvement of neurocognitive function in humans after treatment with *Bacopa monnieri* (Peth-Nui et al., 2012; Downey et al., 2013; Neale et al., 2013). Brahmi contributes to soothing and relaxing of the brain cells and restore them to a regular functioning state in adults. Hence, all these findings demand to take further research to know the real mechanism of action regulation these pathways/processes.

### 2.23. Family Rutaceae

***Murraya koenigii* (L.) Sprengel / Curry tree** in the family Rutaceae is an evergreen tree which grows to a height of 6 m. The odd-pinnate leaf usually consists of 11–21 green, ovate, leaflets about 2.5–5 cm long that are aromatic. The white, funnel-shaped flowers are small, arranged in clusters and have a sweet fragrance. Fruits are bluish-black, oblong drupes with a sweet, edible pulp and a single, large, non-edible seed. Curry tree grows in tropical to subtropical regions. This tree is native to Sri Lanka and India. *Murraya koenigii* leaves commonly known as 'curry patta', are used in Indian dishes as a very common food-additive. Reduction of brain cholinesterase activity as well as cholesterol-lowering effects were reported in diets added with curry leaves that may be attributed to the observed nootropic effect. Therefore, curry leaves can be investigated for use in the management of AD.

### 2.24. Family Solanaceae

***Withania somnifera* (L.) Dunal / Ashwagandha** is a perennial, evergreen shrub in the family Solanaceae which grows up to a height of 1 m. The species is hermaphrodite and frost tender. The green leaves are elliptic about 10–12.5 cm long. The small, green flowers are bell-shaped. The fruit, enclosed in the calyx is a spherical, orange-red to red berry about 5–8 mm in diameter. It is usually cultivated in the drier regions of India, but found also in Nepal. *Withania somnifera* belongs to one of the most researched Ayurvedic herbs and its roots are one of the most remarkable ingredients in AM, similar to the status of Ginseng in Chinese therapies. Therefore, it is not surprising that *Withania somnifera* is often termed as the 'Indian Ginseng'. The root extract from Ashwagandha (50, 100 and 200 mg/kg; p.o.) in mice led to improvement of retention of a passive avoidance task in a step-down paradigm. Ashwagandha further reversed disruption of acquisition and retention induced by scopolamine (0.3 mg/kg). Moreover, the amnesia produced by acute treatment with electroconvulsive shock (ECS) was attenuated by Ashwagandha immediately after training (Dhulley, 2001).

## 2.25. Family *Theaceae*

***Camellia sinensis* (L.) Kuntze / Green tea plant** is an evergreen shrub which grows up to a height of 4 m. The tree has a rough, gray bark and strong taproot. The dark green leaves are oval, in alternative arrangement and about 5–10 cm long. The white flowers are quite fragrant, solitary or arranged in small groups. The flower is about 4 cm in diameter with 5–9 petals. Green tea plant is native to South, East and Southeast Asia. However, nowadays, it is cultivated across the subtropical and tropical regions of the world including Japan and Sri Lanka. *Camellia sinensis* plant produces three types of teas: non-fermented (white and green tea), partially fermented (oolong and red tea) and completely fermented (black tea) (Suzuki et al., 2016; Hayat et al., 2015) and interestingly its bioactive constituents greatly depend on the degree and ease of fermentation process. Tea is globally the second most consumed beverage after the water and its pharmacological properties are extensively documented. It is having potent neuroprotective, free radical scavenging, antioxidative, antioncogenic, hepatoprotective, anti-diabetic, antiviral, and chemopreventive properties because of its diverse chemical constituents including amino acids, aluminum, proteins, phenolic acids (chlorogenic acid, gallic acid (**75**) or trihydroxybenzoic acid, and caffeic acid), alkaloids (theophylline, caffeine, and theobromine), caffeine, flavonoids (quercetin (**80**), kaempferol, and myricetin) and polyphenols (catechins such as epigallocatechin-3-gallate (EGCG, **12**), (–)-epicatechin gallate (ECG), (–)-epicatechin (EC, **49**), and (–)-epigallocatechin (EGC)), carbohydrates, minerals, theanine, volatile organic compounds, trace elements, and fluoride (Mahmood et al., 2010; Legeay et al., 2015) that are beneficial in preventing a plethora of health related ailments including neurodegeneration, hypotension, vomiting, memory loss, skin cancer, lung cancer, and breast cancer, obesity, atherosclerosis, headaches, type 2 diabetes, stomach disorders, gastrointestinal cancer, ovarian cancer, PD, diarrhea, kidney stones (Shivashankara et al., 2014; Yang et al., 2014; Yang and Wang, 2016; Yokogoshi, 2017; Baliga et al., 2018). Since, green tree exhibits a plethora of bioactive molecules especially catechins, it is a well-known source of neuroprotection (Flores et al., 2014; Schimidt et al., 2014; Fernando et al., 2017). It decreases the production of  $\beta$ -amyloid ( $A\beta$ ) monomers, the major cause of AD, which forms proteins that are able to create the amyloid plaques in the brains of patients with AD (Polito et al., 2018). Several recent studies have found that teas (reg and green) as dietary supplements have significant potential to reduce/protect memory and learning deficits and hippocampus oxidative stress in an Alzheimer disease model and ischemia–reperfusion (IR) (Martins et al., 2017; Schimidt et al., 2017). The ability of green tea to stop the degeneration in neuronal cells results from the presence of EGCG in the brain, meaning that it can impart its antioxidative effects on the free radicals causing the brain damage. A mouse study in China shows that EGCG from green tea supports the formation of brain cells, which are important to memory and spatial learning (Weatherby, 2012). Hence, bioactive teas might be a suitable potent therapeutic candidate against neurodegenerative disorder (Chen et al., 2018) which demands an evaluation of these chemicals in a clinical setting. Furthermore, in clinical studies and various animal models, green tea intake has been shown to reduce cardiovascular disease by reducing total and LDL cholesterol, blood pressure and CVD mortality (Onakpoya et al., 2014; Yarmolinsky et al., 2015; Zhang et al., 2015).

## 2.26. Family *Zingiberaceae*

***Curcuma longa* L. / Turmeric** is perennial, tropical, rhizomatous, herbaceous plant, which grows up to a height of 1.5 m. The leaves arise from the pseudostem, which is composed of long,

interlocked, succulent leaf petioles. The simple leaves are long and can be simple green color or variegated. The flower spikes arise from the top of the pseudostem. The florets can be white, yellow, orange or pink in color, and the bracts can be also in various colors. The rhizome has a strong orange–yellow color, pepper-like aroma and bitter taste. Turmeric is a traditional Chinese herbal plant and is native to tropical Tamilnadu in Southeast India. Turmeric, obtained from the rhizome of *C. longa* is known as the golden spice and is widely considered a medicine for the treatment of a plethora of diseases comprising inflammations, arthritic, diabetic wound healing, anorexia, microbial infections, muscular disorders, cancer, hepatic disorders, diabetes, biliary disorders, sinusitis and cough (Li et al., 2012; Kuete, 2017). The rhizomes are the reservoir of diverse compounds out of which curcuminoids (**25**) (curcumin, **11**), principal phenolic compound (Zhao et al., 2012) exhibit multifunction that is potent in the management of various diseases. Additionally, **11** also exhibited several pharmacological properties such as neuroprotective, hepatoprotective, cardiovascular protective, antidiabetic, anticoagulant, anti-inflammatory, antioxidant, antifungal, antiviral, antibacterial, antineoplastic, antifertility and immunostimulant activities in animals (Singh and Sharma, 2011). The pivotal potential of **11** has been well established in treating and preventing neurodegenerative disorders (Kim et al., 2012; Villaflores et al., 2012). In wistar rats, curcuma oil has been documented to minimize inflammation of the endothelial cells in post-myocardial ischemia/ reperfusion (Manhas et al., 2014). Curcumin prevents the accumulation of  $A\beta$  or facilitates its disaggregation at low concentration levels ( $IC_{50} = 0.81\text{--}1\ \mu\text{M}$ ) (Fang et al., 2014). Curcumin has also been shown to protect against  $A\beta$  neurotoxicity by downregulating  $A\beta$  synthesis via inhibition of the presenilin 1 (PS1) expression and glycogen synthase kinase-3beta (GSK3 $\beta$ ) expression (Caesar et al., 2012; Zhang et al., 2011). In SH-SY5Y neuroblastoma cells treated with 6-hydroxydopamine, **11** has been indicated to arbitrate neuroprotective activity by attenuating quinoprotein development, expression of p-p38 mitogen-activated protein kinases (MAPKs), and activation of caspase-3 (Meesarapee et al., 2014). Curcumin (**11**) substantially increased cognitive function in a streptozotocin (STZ) model of sporadic AD by restoring downregulated IGF-1 levels (Agrawal et al., 2010). Furthermore, another research found that **11** enhanced the neurotoxicity of 6-hydroxydopamine (6-OHDA) via its anti-inflammatory action and by restoring the expression of SOD-1 (Tripanichkul and Jaroensuppaperch, 2013). In mice, oral administered aqueous extract of *C. longa* led to the inhibition of brain monoamine oxidase-A. **11**, as the major bioactive compound from *C. longa* displays the neuroprotective properties against ethanol-induced brain injury. The **11** enhanced/increased locomotive function in a homocysteine rat model with PD (Mansouri et al., 2012). Concerning epilepsy, in the experimental seizure models, **11** has shown antiepileptic effects (Ahmad, 2013; Peng et al., 2012; Kiasalari et al., 2013) by its antioxidant activity (Choudhary et al., 2013; Noor et al., 2012). Furthermore, **11** is effective in preventing brain injury (cerebral stroke), in addition to antiepileptic effects (Lapchak, 2011; Liu et al., 2013; Yu et al., 2012; Zhao et al., 2010). **11** has boosted candesartan's neuroprotective activity on brain ischemia via the repression of blood flow and oxidative stress (Awad, 2011). **11** pretreatment decreased infarction and brain lesions, and increased neurological function in rats following Traumatic Brain Injury (TBI) (Samini et al., 2013). In rats experiencing TBI, curcumin derivatives administration enhanced locomotive and cognitive functioning (Wu et al., 2011).

***Zingiber officinale* Roscoe / Ginger** is a perennial, tropical, flowering plant, which grows up to a height of 1.5 m. The leaves are narrow and about 15–30 cm long. They are in alternative arrangement and arise from the pseudostem. Flowering heads are placed on short stems and the herb produces pale yellow, cone-shaped

flowers. The rhizomes are irregular in shape with variable color from light brown to dark yellow. Ginger was cultivated first in South Asia, but nowadays is also cultivated in the East Africa and the Caribbean region. Its rhizomes possess potent memory-enhancing properties. It improves memory power and the whole-body blood circulation including the supply of nutrients into the brain. Ginger significantly improved learning and memory by increasing whole-brain acetylcholinesterase inhibition activity in case of scopolamine-induced memory impairment. It is also reported to inhibit  $\beta$ -amyloid peptide accumulation. Gingerin, gingerol (56), shogaol and zingerone are the major active compounds in ginger.

### 3. Use of crude drugs from herbs in memory impairment

***Artemisia asiatica* Willd. (Asteraceae):** a Korean tea plant. Methanolic extract of this plant was administered to the beta-peptide infused rats. This  $\beta$ -peptide infusion caused toxicity in the PC12 cells in rats. Administration of *Artemisia* showed a significant result in reversing the toxicity in PC12 cells. A study demonstrated that an alkaloid of *Artemisia* appeared to be an acetylcholinesterase (AChE) inhibitor with a blocker of  $\beta$ -amyloid-induced neurotoxicity causing AD.

***Celastrus paniculatus* Willd. (Celastraceae):** the aqueous fraction of *C. paniculatus* seeds was administered to rats with sodium nitrite induced amnesia. The results show an increase in the brain's acetylcholine (ACh) level by decreasing AChE activity, thus improving memory in amnesic models of mice (Bihaji et al., 2011).

***Corydalis ternata* (Nakai) Nakai (Papaveraceae):** a total methanolic extract of the tuber of *Corydalis ternata* exhibits considerable inhibition of acetylcholinesterase (AChE). Protopine, an isolated alkaloid from *Corydalis* showed a dose-dependent inhibitory effect on the acetylcholinesterase activity with  $IC_{50} = 50 \mu M$ . This inhibitory activity was specific reversible and competitive in the manner.

***Foeniculum vulgare* Mill. (Apiaceae):** a whole plant methanolic extract significantly increases latency in step-down avoidance test as well as the inhibition of acetylcholinesterase in mice. Therefore, *Foeniculum vulgare* can be utilized in the therapy of cognitive disorders e.g. dementia and AD.

***Gastrodia elata* Blume (Orchidaceae):** the methanolic extract of the rhizomes of *Gastrodia elata* in the passive avoidance task results in significant prolongation of the shortened step-through latency, induced by scopolamine. Similarly, the *n*-butanol and ethyl acetate fractions prepared from crude methanolic extract of *Gastrodia elata*, administered at the dose of 50.0 mg/kg for one week prolonged the scopolamine-induced step-through latency in rats. Moreover, the shortened step-through latency on the passive avoidance task induced by scopolamine was prolonged by gastrodin, as the product isolated from the *n*-butanol fraction and by *p*-hydroxybenzyl alcohol, obtained from the ethyl acetate fraction of the methanolic extract.

***Glycyrrhiza glabra* L. (Fabaceae):** the aqueous extract of *Glycyrrhiza glabra* was administered to one-month-old male albino Wistar rats with Diazepam-induced memory impairments. The experiment showed a significant increase in learning and memory in the rats and reversed the effect of Diazepam toxicity (Chakravarthi and Avadhani, 2013).

***Ocimum tenuiflorum* L. (Lamiaceae):** a whole plant aqueous extract of dried *Ocimum tenuiflorum* were evaluated on the passive avoidance paradigm and elevated plus maze in mice. The step-down latency increasing and the transfer latency decreasing were evident in comparison to control group (treated with piracetam), scopolamine group and age group of mice. The results suggested

possible application of *Ocimum tenuiflorum* in the therapy of cognitive disorders (e.g. AD and dementia).

***Schisandra chinensis* (Turcz.) Baill. (Schisandraceae):** a deciduous climbing plant, which is native to Northern China and the Far Eastern Russia. The water fraction of this plant at the dose of 25 mg/kg after one-week administration on rats resulted in the prolongation of cycloheximide-induced step-through latency. Interestingly, the water fraction of *Schisandra chinensis* seems to be the major active fraction of this plant (Kopustinskiene and Bernatoniene, 2021; Szopa et al., 2017).

***Scutellaria baicalensis* Georgi (Lamiaceae):** a flowering plant native to China, Korea and Siberia. The extracts of its roots are utilized in the traditional Korean medicine and are beneficial in treatment of the brain diseases. Further, it was reported that the orally administered extracts of this plant improved the memory impairment, which was induced by chronic lipopolysaccharide (LPS) infusion or by chronic cerebral hypoperfusion (Hwang et al., 2011).

### 4. Effective herbal formulations for memory enhancement

**Abana** is an Indian Ayurvedic polyherbal formulation, contains 16 well-known herbs as composition. It significantly reduces the activity of cholinesterase, which results to increase of acetylcholine level in the brain of aged and young mice. The ingredients of Abana express the antioxidant property, which reduces oxidative stress of the brain cells. Thus, Abana helps to reduce brain impairment and improves neuronal function. The influence of orally administered Abana on cognitive functions was monitored on groups of aged and young mice. Testing of memory was evaluated by using exteroceptive behavioral models (passive avoidance apparatus and elevated plus-maze test) as well as interoceptive behavioral models (amnesia induced by diazepam, scopolamine and ageing). Abana improves the memory score in dose-dependent manner of both aged and young mice. Even, Abana reverses the scopolamine- and diazepam-induced amnesia. Therefore, the polyherbal formulation Abana bears promising potential for the treatment of Alzheimer's disease.

**BR-16A (Mentat)** is a herbal psychotropic preparation containing various indigenous plant extracts which are well-reputed in the AM. The compositional herbs are: *Bacopa monnieri*, *Acorus calamus*, *Asparagus racemosus*, *Evolvulus alsinoides*, *Withania somnifera*, *Phyllanthus emblica* and *Triphala*. Mentat on the elevated plus-maze test reduced transfer latency delay induced by scopolamine in mice. Moreover, evaluation of passive avoidance paradigm revealed that Mentat also reduces ECS-induced acute and chronic retrograde amnesia in rats. A combination of Mentat and a low dose of aniracetam (a well-known nootropic) in the passive avoidance task brings much better results in the reduction of mistakes. Clinical studies on different age groups with Mentat show improvement in memory quotient of tested subjects. In normal adults Mentat attenuates fluctuations of attention and increases memory span. In children with minimal brain damage or behavioural problems improves the ability to learn.

**Brain-o-brain** is capsule with a unique mixture of herbs like Shankhpushpi, Brahmi and Sweet flag to improve learning ability, memory power and naturally helps to avoid stress and depression. These herbal brain enhancer pills are made especially for all age groups to prevent or decrease forgetting. Indeed, regularly taken Brain-o-brain is effective to increase gasping power and natural ability of the brain. This fully natural remedy supports to overcome nervous exhaustion and mental fatigue.

**Bramhi ghrita** contains four Ayurvedic herbs including Brahmi (*Bacopa monnieri*) and cowmilk's ghee. The memory and learning improvement effect of Brahmi ghrita applied in different doses (30, 50 and 100 mg/kg, p.o.) was tested in rodents. The elevated

**Table 1**  
List of herbs having memory and cognition enhancing properties.

Sl. No.	Botanical name	Genus Family	Common name	Parts used	Active constituents	Reference
1	<i>Acorus calamus</i>	<i>Acorus</i> Araceae	Sweet flag	Rhizomes	1. $\alpha$ - and $\beta$ -Asarone 2. Methyl isougenol (S)-allyl-L-cysteine	Shiksharathi et al., 2011
2	<i>Allium sativum</i>	<i>Allium</i> Amaryllidaceae	Garlic	Bulb		Semwal et al., 2014
3	<i>Amberboa ramosa</i>	<i>Amberboa</i> Asteraceae			Sesquiterpene lactones: • Amberin • Amberbin A • Amberbin B • Amberbin C	Ibrahim et al., 2013
4	<i>Asparagus racemosus</i>	<i>Asparagus</i> Asparagaceae	Shatavari	Roots	Triterpene saponins: Shatavarin I-IV	Shiksharathi et al., 2011
5	<i>Bacopa monnieri</i>	<i>Bacopa</i> Plantaginaceae	Brahmi	Whole plant	Bacosides A and B	Shiksharathi et al., 2011
6	<i>Butea monosperma</i>	<i>Butea</i> Fabaceae	Palash	Leaves		Malik et al., 2013
7	<i>Camellia sinensis</i>	<i>Camellia</i> Theaceae	Green tea	Leaves	1. Flavanoids –Epigallocatechin-3-gallate (EGCG) 2. Isoflavone diadzein	Shiksharathi et al., 2011; Compas, 2006
8	<i>Celastrus paniculatus</i>	<i>Celastrus</i> Celastraceae	Jyotishmati	Seeds	Alkaloids: Celastrine, Paniclatin, Calapagone, Calapanigine etc	Shiksharathi et al., 2011
9	<i>Centella asiatica</i>	<i>Centella</i> Apiaceae	Thankuni	Whole plant	1. Triterpentic pentacyclic saponins: Madicacoside 2. Asiaticoside 3. Brahmoside	Shiksharathi et al., 2011
10	<i>Clitoria ternatea</i>	<i>Clitoria</i> Fabaceae	Aparajita	Roots	1. Histidine 2. Threonine 3. Tannin	Shiksharathi et al., 2011
11	<i>Coeloglossum viride</i>	<i>Coeloglossum</i> Orchidaceae	Frog orchid	Rhizomes		Martha, 2010
12	<i>Convolvulus pluricaulis</i>	<i>Convolvulus</i> Convolvulaceae	Shankh pushpin	Whole plant	Flavanoids	Shiksharathi et al., 2011
13	<i>Coriandrum sativum</i>	<i>Coriandrum</i> Apiaceae	Corriander	Leaves and Seeds		Parle and Vasudevan, 2009
14	<i>Cornus officinalis</i>	<i>Cornus</i> Cornaceae	Japanese cornel	Fruits	Cornel iridoid glycosides (CIG): • Loganin, • (7R)-O-methylmorroneiside • (7S)-O-methylmorroneiside	Zhao et al., 2010
15	<i>Corydalis ternata</i>	<i>Corydalis</i> Papaveraceae	Nakai	Tuber	Alkaloids: • Protopine • Protoberberin	Kim et al., 1999
16	<i>Crocus sativus</i>	<i>Crocus</i> Iridaceae	Saffron	Whole plant	1. Crocin 2. Crocetin	Shiksharathi et al., 2011
17	<i>Curcuma longa</i>	<i>Curcuma</i> Zingiberaceae	Turmeric	Rhizomes	1. Curcuminoids: Curcumin, Bisdemethoxycurcumin, Demethoxycurcumin 2. Calebin-A	Shiksharathi et al., 2011
18	<i>Cyperus rotundus</i>	<i>Cyperus</i> Cyperaceae	Java grass	Rhizomes		(Sunil et al., 2011; Kumar et al., 2012)
19	<i>Dendrobium moniliforme</i>	<i>Dendrobium</i> Orchidaceae	Sekkoku	Whole plant		
20	<i>Eclipta alba</i>	<i>Eclipta</i> Asteraceae	Bhringaraj	Leaves	1) $\alpha$ -Amyrin 2) Seclabatin 3) Urosilic acid 4) Oleonic acid 5) Ecliptasaponin	Bhaskar and Chintamaneni, 2014
21	<i>Embelia ribes</i>	<i>Embelia</i> Primulaceae	Black pepper	Roots		
22	<i>Euphrasia officinalis</i>	<i>Euphrasia</i> Orobanchaceae		Powdered herb	1. Iridoid glycosides: Aucubin, Catalpol, Euphosid 2. Tannins 3. Flavonoids	Sticher and Salama, 1981
23	<i>Foeniculum vulgare</i>	<i>Foeniculum</i> Apiaceae	Fennel	Whole plant		Joshi and Parle, 2006
24	<i>Gastrodia elata</i>	<i>Gastrodia</i> Orchidaceae	Gastrodia tuber	Root	1. P-hydroxybenzyl alcohol (HBA) 2. Gastrodins	Shiksharathi et al., 2011
25	<i>Ginkgo biloba</i>	<i>Ginkgo</i> Ginkgoaceae	Ginkgo	Leaves	1. Flavanoids 2. Terpenoids 3. Kaempferol 4. Quercetin 5. Terepene lactones- Ginkolides 6. Bilobalide	Shiksharathi et al., 2011
26	<i>Glycyrrhiza glabra</i>	<i>Glycyrrhiza</i> Fabaceae	Licorice	Roots	Glycyrrhizine	Shiksharathi et al., 2011
27	<i>Hibiscus asper</i>	<i>Hibiscus</i> Malvaceae	Hibiscus	Leaves		Foyet et al., 2011

Table 1 (continued)

Sl. No.	Botanical name	Genus Family	Common name	Parts used	Active constituents	Reference
28	<i>Huperzia serrata</i>	<i>Huperzia</i> Lycopodiaceae	Club moss	Moss	Huperzine A and B	Jesky et al., 2011
29	<i>Hypericum perforatum</i>	<i>Hypericum</i> Hypericaceae	St. John's wort	Roots	1. Naphthodianthrone: Hypericin 2. Prenylated phloroglucinol: Hyperforin	Shikshartha et al., 2011
30	<i>Ilex paraguariensis</i>	<i>Ilex</i> Aquifoliaceae	Mate tea	Leaves	1. Flavanoids: Quercetin, Kaempferol 2. Polyphenols: Chlorogenic acid, Xanthines (Theophylline, Theobromine, caffeine) 3. Vitamins: B1, B12	Shikshartha et al., 2011
31	<i>Illicium verum</i>	<i>Illicium</i> Schisandraceae	Star anise		Sesquiterpenoids: Veranisatins A, B, and C	
32	<i>Magnolia officinalis</i>	<i>Magnolia</i> Magnoliaceae	Houpu	Bark	1. Magnolol 2. Honokiol	Reddy et al., 2010
33	<i>Marsilea minuta</i>	<i>Marsilea</i> Marsileaceae	Marsilea	Leaves	Marsiline	Dwivedi et al., 2012
34	<i>Melissa officinalis</i>	<i>Melissa</i> Lamiaceae	Lemon balm	Leaves	Rosmarinic acid	Awad et al., 2009
35	<i>Murraya koenigii</i>	<i>Murraya</i> Rutaceae	Curry leaves	Leaves		Parle and Vasidevan, 2009
36	<i>Myristica fragrans</i>	<i>Myristica</i> Myristicaceae	Nutmeg	Seeds		Parle et al., 2004
37	<i>Narcissus confuses</i>	<i>Narcissus</i> Amaryllidaceae	Daffodil	Crude drug	Galanthamine	(Bastida and Viladomat, 2002)
38	<i>Nardostachys jatamansi</i>	<i>Nardostachys</i> Caprifoliaceae	Jatamansi	Whole plant	1. Jatamansone 2. Nardostachone	Shikshartha et al., 2011
39	<i>Nicotiana tabacum</i>	<i>Nicotiana</i> Solanaceae	Tobacco plant	Leaves	1. Nicotine 2. Choline	Dua et al., 2009
40	<i>Ocimum tenuiflorum</i>	<i>Ocimum</i> Lamiaceae	Holy basil	Whole plant		Joshi and Parle, 2006
41	<i>Panax ginseng</i>	<i>Panax</i> Araliaceae	Ginseng	Roots	1. Ginsenosides: Rg1, Rg2, Rg3 2. Saponins: Protopanaxdiol, Oleanoic acid, Protopantriol	Shikshartha et al., 2011
42	<i>Phyllanthus emblica</i> (synonym: <i>Emblica officinalis</i> )	<i>Phyllanthus</i> Phyllanthaceae	Amla	Fruit	1. L-Ascorbic acid (vitamin C) 2. Phyllembin 3. Hypophyllanthin 4. Phyllanthin	Shikshartha et al., 2011
43	<i>Piper betle</i>	<i>Piper</i> Piperaceae	Bittle leaf	Leaves	Arecoline	Shikshartha et al., 2011
44	<i>Piper nigrum</i>	<i>Piper</i> Piperaceae	Black pepper	Fruits	Piperine	Chonpathompikunlert et al., 2010
45	<i>Polygala tenuifolia</i>	<i>Polygala</i> Polygalaceae	Yuan zhi	Roots	Triterpenoid saponins	Kumar et al., 2013
46	<i>Polygonatum multiflorum</i>	<i>Polygonatum</i> Asperagaceae	Solomon's seal		Emodin	Lu et al., 2007
47	<i>Prunus amygdalus</i>	<i>Prunus</i> Rosaceae	Almond	Nuts	1. Total flavonoid content 2. Total phenolic content	Kumar and Seth
48	<i>Pueraria tuberosa</i>	<i>Pueraria</i> Fabaceae	Vidarikand	Tubers	Flavanoids	Shikshartha et al., 2011
49	<i>Punica granatum</i>	<i>Punica</i> Lythraceae	Pomegranate	Seeds	1. Tannin 2. Polyphenols: Gallocatechin, Catechin etc.	Kumar et al., 2009
50	<i>Rehmannia glutinosa</i>	<i>Rehmannia</i> Orobanchaceae	Sheng di huang	Roots	1. Iridoids 2. Glycosides 3. Catalpol	Zhang et al., 2008
51	<i>Ricinus communis</i>	<i>Ricinus</i> Euphorbiaceae	Castor oil plant	Beans	Ricinine	Dua et al., 2009
55	<i>Salvia lavandulaefolia</i>	<i>Salvia</i> Lamiaceae	Spanish sage		1. Essential oils 2. 8-cineole 3. Linalool 4. $\alpha$ - and $\beta$ -pinene 5. Carvacrol 6. Luteolin	Reddy et al., 2010
53	<i>Salvia officinalis</i>	<i>Salvia</i> Lamiaceae	Common sage	Leaves	1. Monoterpenoid 2. Carnosic acid 3. Rosemarinic acid	Shikshartha et al., 2011
54	<i>Salvia rosmarinus</i> (synonym: <i>Rosmarinus officinalis</i> )	<i>Salvia</i> Lamiaceae	Rosemary	Leaves	1. Carnosic acid 2. Carnosol	(Kosaka and Yokoi, 2003)
55	<i>Schisandra chinensis</i>	<i>Schisandra</i> Schisandraceae	Five flavor berries			(Hsieh et al., 1999)
56	<i>Scutellaria baicalensis</i>	<i>Scutellaria</i> Lamiaceae		Roots	Flavonoid: Oroxylin A	(Hwang et al., 2011)
57	<i>Sphaeranthus indicus</i>	<i>Sphaeranthus</i> Asteraceae		Flowers		(Patel and Amin, 2012)
58	<i>Solanum indicum</i>	<i>Solanum</i> Solanaceae	Brinjal	Fruit		Gunawardena J
59	<i>Solanum melongana</i>	<i>Solanum</i> Solanaceae	Eggplant	Fruit		Gunawardena J

(continued on next page)

Table 1 (continued)

Sl. No.	Botanical name	Genus Family	Common name	Parts used	Active constituents	Reference
60	<i>Taverniera cunefolia</i>	<i>Taverniera</i> Fabaceae				Jamdhade and Surwase, 2013
61	<i>Terminalia chebula</i>	<i>Terminalia</i> Combretaceae	Haritaki	Rhizomes	Chebulic acid	Shikshartha et al., 2011
62	<i>Theobroma cacao</i>	<i>Theobroma</i> Malvaceae	Cocoa	Seeds	1. Catechin 2. Catechol 3. Polyphenols 4. Glycosides 5. Alkaloids	Adams et al., 2007
63	<i>Tinospora cordifolia</i>	<i>Tinospora</i> Menispermaceae	Giloy	Whole plant	1. Tinosporine 2. Tinosporide	Shikshartha et al., 2011
64	<i>Uncaria tomentosa</i>	<i>Uncaria</i> Rubiaceae		Bulbs	Alkaloids: • uncarine E • uncarine C • mitraphylline • rhynchophylline • isorhynchophylline	Heitzman et al., 2005
65	<i>Vitis vinifera</i>	<i>Vitis</i> Vitaceae	Grapes	Seeds	Resveretrol	Shikshartha et al., 2011
66	<i>Withania somnifera</i>	<i>Withania</i> Solanaceae	Ashwagandha	Roots	1. Withanolides 2. Sitiindosites- VII, VIII, IX, X 3. Withaferin	Shikshartha et al., 2011
67	<i>Zingiber officinale</i>	<i>Zingiber</i> Zingiberaceae	Ginger	Rhizome	1. Gingerin 2. Gingerol 3. Shogaol 4. Zingerone	Shikshartha et al., 2011

plus-maze test was used for evaluation of memory acquisition and retention in rats. Morris water maze test was used to interpret spatial memory in mice. The elevated plus-maze transfer latency and Morris water maze escape latency were significantly reduced after administration of Bramhi ghrita (50 and 100 mg/kg, p.o.).

**Chyawanprash (Chy)** is an Ayurvedic tonic, which contains almost 50 herbs and herbal extracts. One of its basic ingredients is Amla (*Phyllanthus emblica*) a rich natural source of vitamin C. Consumption of Chy is popular in Indian households. Animal studies confirmed significant influence of Chy in the memory impairment protection effect. Furthermore, administration of Chy (2% w/w) decreases thiobarbituric acid reactive substances (TBARS) in the brain and increases the levels of glutathione. Results indicate a decrease in the free radical generation and an increase in the protection from free radical. Thus, Chy could be an efficient remedy for the therapy of AD.

**Memorin** is comprised of 21 kinds of herbal extracts. The experimental studies of Memorin were made upon rats using passive avoidance learning paradigm in a shuttle box. Memorin at the dose of 200 mg/kg b.w./day was administered for a fortnight to animals. Administration of ECS produced significant retrograde amnesia in rats. Memorin was found to attenuate the ECS-induced amnesia. In clinical studies, when applied on human, Memorin was found to reverse poor memory, age-related dementia and mental fatigue.

**Optimized-Sopung Sunkiwon (OSS)** is a polyherbal formula comprising of six medicinal herbs from SopungSunkiwon. SopungSunkiwon is a traditional medicine usually prescribed for people suffering from neurodegenerative disorders. OSS significantly improves the memory functions via inhibition of AChE activity. Latency time in the passive avoidance test was significantly longer for mice treated with OSS compared with control group or group treated with scopolamine. Besides, mice treated with OSS exhibited increase of synaptic proteins that facilitate acetylcholine release and synaptic growth (e.g. PSD-95 and synaptophysin). These results show that OSS may act upon memory impairment and increase synaptophysin and PSD-95 in the brain (Choi et al., 2011).

**Shimotsu-to** literally mean 'four substance decoction'. This TCM formula consists of following four crude herbal extracts: Japanese angelica root, peony root, rehmannia root and cnidium rhizome. Shimotsu-to have beneficial effects on spatial memory improvement in rats. Moreover, the study in rat models suggests importance of paeoniflorin (extracted from peony root) and tetramethylpyrazine (extracted from cnidium rhizome) as the enhancers of cognitive functions.

**Yukmijihwang-tang derivatives** is a Chinese polyherbal formulation used as memory or cognition enhancer. It consists of six different herbal medicines. Chinese herbal textbook refers to YMJD as an anti-ageing prescription. Besides, it also helps to prevent memory and learning impairment in mice. Studies reported that YMJD in stressed rats could increase neurogenesis in the dentate gyrus (hippocampus) along with improvement of cognitive functions and memory retention.

## 5. Other advantageous compounds

**Ascorbic acid (23)** is found mainly in citrus fruits (e.g. lemon). Studies in aged mice have shown that **23** increased step-down latency and decreased transfer-latency, which indicated its ability to improve learning and memory. Moreover, memory impairment induced by diazepam and scopolamine was significantly reduced in young mice treated with **23**.

**Bacosides (24)** (bacoside A (**42**) and bacoside B) are derived from the well-reputed *Bacopa monnieri*. However, recent study identified bacoside A (**42**) as the mixture of four different saponins, termed as: bacoside A3 (**3**), bacoside II (**4**), bacosaponin C (**6**) and isomer of bacosaponin C (**5**) (Fig. 2). Similarly, bacoside B represents the mixture of saponins, which exact constitution is not clearly identified to date. To the best of our knowledge, bacoside B consists of four following saponins: bacoside N1 (**7**), bacoside N2 (**8**), bacoside IV (**9**) and bacoside V (**10**) (Fig. 2) (Deepak et al., 2013). In a clinical trial, **24** were administered to elderly people (65 years or older) without a clinical sign of dementia in a double blind and placebo-controlled study (Table 4). The

**Table 2**  
Crude drugs to improve memory.

Sl no.	Plant	Genus Family	Extracted in	Study model	Biological effects	Reference
1	<i>Andrographis paniculata</i>	<i>Andrographis</i> Acanthaceae	Methanol	Rats with streptozotocin and nicotinamide induced typell diabetes	1. Increased cognitive function in typell diabetic rats 2. Decreased latency period	Radhika et al., 2012
2	<i>Artemisia asiatica</i>	<i>Artemisia</i> Asteraceae	Methanol	<i>In vitro</i> : Abeta-induced toxicity in rat PC12 cells	1. Reduced Abeta induced toxicity, 2. appeared as an AChE inhibitor	Heo et al., 2000
3	<i>Butea frondosa</i>	<i>Butea</i> Fabaceae	Hydro alcohol	Rats with scopolamine-induced amnesia	1. Decreased escape latency in MWM test 2. decreased AChE activity	Malik et al., 2012
4	<i>Celastrus paniculatus</i>	<i>Celastrus</i> Celastraceae	Water	Rats with sodium nitrite induced amnesia	1. Increase acetylcholine level inside the brain by reducing AChE activity 2. Improves memory	Bhanumathy et al., 2010
5	<i>Clitoria ternatea</i>	<i>Clitoria</i> Fabaceae	Water	Young and adult rats	1. Singificantly increased ACh content inrat hippocampus	Rai et al., 2002
6	<i>Convolvulus pluricaulis</i>	<i>Convolvulus</i> Convolvulaceae	Water	Male Wistar rats with scopolamine induced neurotoxicity	1. Decreased scopolamine induced increase in transfer latency in EPM test 2. In MWM test, increased spatial memory 3. AChE activity inhibited in cortex and hippocampus	Bihaqi et al., 2011
7	<i>Cornus officinalis</i>	<i>Cornus</i> Cornaceae	Methanol	HT22 hippocampal cell with glutamate toxicity	1. Reversed glutamate toxicity in HT22 hippocampal cells	Jeong et al., 2011
8	<i>Corydalis ternate</i>	<i>Corydalis</i> Papaveraceae	Methanol	Mice with scopolamine-induced memory deficit	1. Protopine present in the extract chowed AChE inhibitory activity 2. Reversed scopolamine-induced memory impairment	Kim et al., 1999
9	<i>Desmodium gangeticum</i>	<i>Desmodium</i> Fabaceae	Water	Mice with scopolamine and ageing induced amnesia	1. Reversed both scopolamine and ageing induced amnesia 2. Decreased whole brain AChE activity	Joshi and Parle, 2006
10	<i>Eclipta alba</i>	<i>Eclipta</i> Asteraceae	Distilled water	Mice	1. Decreased transfer latency in EPM test	Banji et al., 2007
11	<i>Foeniculum vulgare</i>	<i>Foeniculum</i> Apiaceae	Methanol	Mice	1. Increased step-down latency 2. inhibited AChE activity	Joshi and Parle, 2006
12	<i>Gastrodia elata</i>	<i>Gastrodia</i> Orchidaceae	Methanol	Rats	1. Increased shortened step through latency induced by scopolamine	Wu et al., 1996
13	<i>Glycyrrhiza glabra</i>	<i>Glycyrrhiza</i> Fabaceae	Water	1 month old male Wistar albino rats with Diazepam induced amnesia	1. Enhanced learning and memory 2. reversed the effect of diazepam	Chakravarthi and Avadhani, 2013
14	<i>Hibiscus asper</i>	<i>Hibiscus</i> Malvaceae	Methanol	Male Wistar rats with 6-hydroxydopamine-lesion	1. Showed antioxidant and free-radical scavenging activity 2. Improved spatial memory in Y-maze, improved arm-maze task	Foyet et al., 2011
15	<i>Hypericum perforatum</i>	<i>Hypericum</i> Hypericaceae	Ethanol	Albino rats with scopolamine and sodium nitrite induced amnesia	1. Decreased transfer latency in EPM 2. Reversed scopolamine and SA induced memory impairment	Kumar et al., 2000
16	<i>Marsilea minuta</i>	<i>Marsilea</i> Marsileaceae	Ethanol	Rats with ECS treated and scopolamine induced amnesia	1. Reversed amnesia 2. Inhibited AChE activity in the frontal cortex and hippocampus	Bhattamisra et al., 2012
17	<i>Nardostachys jatamansi</i>	<i>Nardostachys</i> Caprifoliaceae	Ethanol	Young and aged mice with scopolamine and diazepam induced amnesia	1. Reversed both scopolamine and diazepam induced amnesia 2. Reduced ageing related amnesia	Joshi and Parle, 2006
18	<i>Nepeta menthoides</i>	<i>Nepeta</i> Lamiaceae	Water	Rats with ECS induced amnesia	1. Increased memory retention and retrieval	Sarahroodi et al., 2012
19	<i>Ocimum sanctum</i>	<i>Ocimum</i> Lamiaceae	Water	Rats with scopolamine and ageing induced amnesia	1. Decreased transfer latency in EPM model 2. Increased step-down latency	Joshi and Parle, 2006
20	<i>Schisandra chinensis</i>	<i>Schisandra</i> Schisandraceae	Water	Rats	1. Increased shortened step through latency induced by scopolamine	(Hsieh et al., 1999)
21	<i>Scutellaria baicalensis</i>	<i>Scutellaria</i> Lamiaceae			1. Rescued memory impairment caused by chronic LPS infusion	Hwang et al., 2011
22	<i>Sphaeranthus indicus</i>	<i>Sphaeranthus</i> Asteraceae	Petroleum ether	Mice with scopolamine-induced memory impairment	1. Reversed cognitive impairment by PA test, 2. Reduced escape-latency in water maze task, 3. Has anti-cholinesterase activity may be due to presence of sesquiterpene lactones	Patel and Amin, 2012

results showed significant enhancement in their auditory verbal learning and word recall. There are possibilities that the **24** can help to manage AD too (Kumar et al., 2012).

**Curcuminoids (25)** represent major chemical components present in turmeric (*Curcuma longa*). Specifically, it is a mixture consisting of: curcumin (**11**), demethoxycurcumin (**71**) and bisdemethoxycurcumin (**68**) (Table 4). Effective on rats showing AD-like neuronal loss caused by a  $\beta$ -peptide infusion. **25** also

increased PSD-95 and synaptophysin expression in the rat hippocampus.

**Epigallocatechin-3-gallate (EGCG, 12)** is the major catechin derivative found in green tea (*Camellia sinensis*). EGCG represents the most effective therapeutic component of green tea. EGCG possesses antioxidant properties and reduces lipid peroxidation in biological systems caused by free radicals (Kumar et al., 2012). A study in rats revealed the ability of EGCG to increase neurogenesis in hip-

**Table 3**

Different herbal formulations for memory enhancement.

Sl no.	Hebal formuation	Components	Study model	Biological effects and targets	Reference
1	Abana	<ol style="list-style-type: none"> <li>1. <i>Acorus calamus</i></li> <li>2. <i>Asparagus racemosus</i></li> <li>3. <i>Celastrus paniculatus</i></li> <li>4. <i>Centella asiatica</i></li> <li>5. <i>Crocus sativus</i></li> <li>6. <i>Cyperus rotundus</i></li> <li>7. <i>Elettaria cardamomum</i></li> <li>8. <i>Foeniculum vulgare</i></li> <li>9. <i>Glycyrrhiza gabra</i></li> <li>10. <i>Nardostachys jatamansi</i></li> <li>11. <i>Ocimum sanctum</i></li> <li>12. <i>Phyllanthus emblica</i></li> <li>13. <i>Piper betel</i></li> <li>14. <i>Terminalia chebula</i></li> <li>15. <i>Withania somnifera</i></li> <li>16. <i>Zingiber officinale</i></li> </ol>	<i>In vivo</i> -young and aged mice	<ul style="list-style-type: none"> <li>• Abana elevates acetylcholine level in the brain through significant decrease in cholinesterase activity</li> <li>• Improves memory of both young and aged mice</li> <li>• Has the potentiality to manage Alzheimer's disease</li> </ul>	<a href="#">Parle and Vasudevan, 2007</a>
2	Brahmi-ghrita	<ol style="list-style-type: none"> <li>1. <i>Acorus calamus</i></li> <li>2. <i>Bacopa monnieri</i></li> <li>3. <i>Evolvulus alsinoides</i></li> <li>4. <i>Saussurea lappa</i></li> <li>5. Cow's ghee</li> </ol>	<i>In vivo</i> -mice	<ul style="list-style-type: none"> <li>• May act as a memory enhancer</li> <li>• May be useful for the treatment of impaired memory function</li> </ul>	<a href="#">Girish et al., 2004</a>
3	Brain-o-Brain	<ol style="list-style-type: none"> <li>1. <i>Acorus calamus</i></li> <li>2. <i>Agati grandiflora</i></li> <li>3. <i>Asparagus racemosus</i></li> <li>4. <i>Bacopa monnieri</i></li> <li>5. <i>Bauhinia tomentosa</i></li> <li>6. <i>Brunella vulgaris</i></li> <li>7. <i>Celastrus paniculatus</i></li> <li>8. <i>Clitoria ternatea</i></li> <li>9. <i>Convolvulus pluricaulis</i></li> <li>10. <i>Hibiscus rosa-sinensis</i></li> <li>11. <i>Lepidium sativum</i></li> <li>12. <i>Nardostachys jatamansi</i></li> <li>13. <i>Orchis mascula</i></li> <li>14. <i>Poley germander</i></li> <li>15. <i>Richolepsis claberrima</i></li> <li>16. <i>Rourea santiloides</i></li> <li>17. <i>Sphaeranthus indicus</i></li> <li>18. <i>Zizypus vulgaris</i></li> <li>19. Gold</li> <li>20. Silver</li> </ol>	<i>In vivo</i> -human (Children, adults and elderly people)	<ul style="list-style-type: none"> <li>• Promotes brain function</li> <li>• Improves memory, learning ability, and concentration</li> <li>• Co-ordinates between mind and body</li> <li>• Reduces mental and physical stress</li> <li>• Reduce nervous exhaustion and mental fatigue</li> <li>• Reduce tension and anxiety</li> </ul>	
4	YMJD	<ol style="list-style-type: none"> <li>1. <i>Rehmannia radix</i></li> <li>2. <i>Discoreae radix</i></li> <li>3. <i>Alismatis radix</i></li> <li>4. <i>Corni fructus</i></li> <li>5. <i>Mountain cortex radices</i></li> <li>6. <i>Holen</i></li> </ol>	<i>In vivo</i> - stressed rats	<ul style="list-style-type: none"> <li>• YMJD increases neurogenesis in the dentate gyrus of the hippocampus in stressed rats, while enhances memory retention and cognitive activities</li> <li>• Reverses scopolamine-induced and p-chloroamphetamine-induced amnesia in rats</li> <li>• YMJD including <i>Lycii fructus</i> enhances memory retention b protecting neuronal cells from attack by reactive oxygen</li> </ul>	<a href="#">Rho et al., 2005</a>
5	Chyawanprash	50 herbs employing <i>Phyllanthus emblica</i>	<i>In vivo</i> -mice with memory deficit	<ul style="list-style-type: none"> <li>• Protects form memory impairment</li> <li>• Decrease free radical generation and increase scavenging of free radicals</li> </ul>	<a href="#">Parle and Bansal, 2011</a>

Table 3 (continued)

Sl no.	Herbal formulation	Components	Study model	Biological effects and targets	Reference
6	Memofit	1. <i>Achyranthus aspera</i> 2. <i>Acorus calamus</i> 3. <i>Asparagus racemosus</i> 4. <i>Bacopa monnieri</i> 5. <i>Convolvulus pluricaulis</i> 6. <i>Embelia ribes</i> 7. <i>Terminalia chebula</i> 8. <i>Tinospora cordifolia</i> 9. <i>Withania somnifera</i>	<i>In vivo</i> - human	<ul style="list-style-type: none"> <li>• May be a useful remedy for management of Alzheimer's disease</li> <li>• Enhances memory</li> <li>• Reduces stress and fatigue</li> </ul>	
7	Memorin	1. <i>Acorus calamus</i> 2. <i>Caryophyllus aromaticus</i> 3. <i>Celastrus paniculatus</i> 4. <i>Centella asiatica</i> 5. <i>Convolvulus pluricaulis</i> 6. <i>Elettaria cardamomum</i> 7. <i>Embelia ribes</i> 8. <i>Foeniculum vulgare</i> 9. <i>Herpestis monniera</i> 10. <i>Mucuna prurita</i> 11. <i>Myristica fragrance</i> 12. <i>Nardostachys jatamansi</i> 13. <i>Oroxylum tuberosum</i> 14. <i>Prunus amygdalus</i> 15. <i>Pueraria tuberosa</i> 16. <i>Terminalia arjuna</i> 17. <i>T. belerica</i> 18. <i>T. chebula</i> 19. <i>Tinospora cordifolia</i> 20. <i>Withania somnifera</i> 21. <i>Zingiber officinale</i> 22. Pearl paste 23. Salab mishri	<i>In vivo</i> -rats with ECS-induced retrograde amnesia	<ul style="list-style-type: none"> <li>• Reversed ECS-induced retrograde amnesia successfully</li> </ul>	Vinekar et al., 1998
8	Shimotsu-to	1. Japanese angelica root 2. Cnidium rhizomes 3. Peony root 4. Rehmannia root	<i>In vivo</i> -rats	<ul style="list-style-type: none"> <li>• Improve spatial working memory</li> <li>• Paeoniflorin and Tetramethylpyrazine (TMP) extracted from Peony root and Cnidium rhizome are the cognitive enhancers</li> </ul>	Watanabe, 1997
9	OSS		<i>In vivo</i> - mice with scopalamine induced memory impairments	<ul style="list-style-type: none"> <li>• Affect impairment and enhancement of memory</li> <li>• Increase synaptophysin and PSD-95 facilitating acetylcholine release and synaptic growth</li> </ul>	Choi JG et al, 2011
10	Mentat	1. <i>Acorus calamus</i> 2. <i>Asparagus racemosus</i> 3. <i>Centella asiatica</i> 4. <i>Evolvulus alsinoides</i> 5. <i>Phyllanthus emblica</i> 6. <i>Withania somnifera</i> 7. <i>Triphala</i>	<i>In vivo</i> - mice with ECS induced amnesia and Clinical trial on human (adults and children)	<ul style="list-style-type: none"> <li>• Reduced scopalamine-induced transfer latency in mice</li> <li>• Attenuated acute and chronic retrograde amnesia induced by ECS</li> <li>• Improves memory quotient in different age group</li> <li>• Increases memory span</li> <li>• Enhances learning ability in children</li> </ul>	Kulkarni and Verma,1992
11	PMCMT	1. <i>Ginseng radix</i> 2. <i>Atractylodis Macrocephalae Rhizoma</i> 3. <i>Poria</i> 4. <i>Glycyrrhizae radix</i>	<i>In vivo</i> - rats with ischemia-induced memory and cognitive impairment	<ul style="list-style-type: none"> <li>• Significant improvement in escape latency in MWM test</li> <li>• Protection against ischemia-induced neuronal and cognitive impairments</li> </ul>	Yun et al., 2007

(continued on next page)

Table 3 (continued)

Sl no.	Herbal formulation	Components	Study model	Biological effects and targets	Reference
12	PJBH	5. <i>Angelicae Gigantis Radix</i> 6. <i>Ligusticum rhizome</i> 7. <i>Rehmanniae radix</i> 8. <i>Paeoniae radix</i> 9. <i>Acori graminei rhizome</i> 10. <i>Polygalae radix</i> 1. <i>Dendrobium moniliforme</i> 2. <i>Thuja oreintalis</i> 3. <i>Torilis japonica</i> 4. <i>Rubus coreanus</i> 5. <i>Cornus officinalis</i> 6. <i>Schizandra chinensis</i> 7. <i>Morinda officinalis</i> 8. <i>Asparagus cochinchinensis</i> 9. <i>Polygala tenuifolia</i> 10. <i>Phlomis ambrosia</i> 11. <i>Panax ginseng</i> 12. <i>Rehmannia glutinosa</i> 13. <i>Cinamomum cassia</i> 14. <i>Acorus calamus</i> 15. <i>Alisma canaliculatum</i> 16. <i>Dioscorea japonica</i> 17. <i>Cistanche salsa</i>		<ul style="list-style-type: none"> <li>Promote brain function and memory</li> <li>Increase life span</li> <li>Elevated catalase and glutathione peroxidase activities in H<sub>2</sub>O<sub>2</sub> induced injury in PC12 cells</li> </ul>	Adams et al., 2007

pocampus. Moreover, dietary EGCG study in mice proved enhancement of spatial memory and object recognition (see Tables 1, 2, 3, 5, 6).

**Ginkgolides (28)**, a kind of terpene lactones, are derived from the living fossil tree *Ginkgo biloba*. Extract from *Ginkgo biloba* enhances the rate of acetylcholine turnover. Further, the stimulation of ligands binding to muscarinic receptors in the hippocampus was observed after application of the extract. It improves dementia and cognitive deficits. The extract also proves significant antioxidant activity via reduction of free radicals in animals. In a study, patients with dementia of AD type and multi-infract dementia were administrated with **28** supplement. The results showed improvement in their task-assessing speed for processing ability (Kumar et al., 2012).

**Ginsenosides** are extracted from the plant *Panax ginseng*. There is about 30 major members of ginsenosides, including Rb1 (**19**) and Rg1 (**20**) (Fig. 2), as the most active compounds. Other active ingredients are Rg2 (**20**), Rg3 (**30**) etc. Both major active ginsenosides **20** and **19** can increase the neuroplasticity in efficacy and structure. A study in normal adult mice proved that small molecular drug **20** is able to improve proliferation and differentiation of neural progenitor cells in hippocampus. Moreover, it also improved a global ischemia model in gerbils. Further beneficial effects of **20** include following results: enhancement of the deteriorated immune system, improvement of motor and behavior response caused by age-related alterations, promoting activity of the hippocampal neuronal function in aged rats and partial protection against the glutamate-induced excitotoxicity. The structure of **20** consists of panaxatriol and two sugar moieties, while the structure of **19** is composed of panaxatriol with four sugar moieties. Another study revealed potential of ginsenoside Rh2 (**22**) to reverse suppression of long-term potentiation induced by scopolamine in the CA1 hippocampal region (Kumar et al., 2012). Standardized ginseng extract (G115) significantly improved retention, improves learning, greatly increased the locomotor activity of mice.

**Loganin (17)** was used in oral treatment of mice in passive avoidance test with *Cornus officinalis* fruits (100 mg/kg b.w.) as one of its major constituent (1 and 2 mg/kg b.w.). Loganin (Fig. 2) considerably reversed memory deficits induced by scopolamine. Further, orally treated mice with **17** in the Morris water maze test significantly improved memory deficits induced by scopolamine, which showed the formation of long-term and/or short-term spatial memory. Moreover, considerable inhibition of AChE activity was observed after administration of **17** (2 mg/kg b.w.) (Lee et al., 2009).

**Nobiletin (18)** is derived from herb *Aurantii nobilis*, a component of TCM. Nobiletin (Fig. 2) administered daily within four months avoided to the memory impairment in fear conditioning. Immunohistochemical analysis in transgenic mice shows hippocampal decrease of the Aβ deposi (Yamakuni et al., 2010).

**Pseudocoptisine (34)** is a hexacyclic quaternary alkaloid found in tubers of *Corydalis turtchaninovii*, which showed a dose-dependent inhibitory activity of AChE with IC<sub>50</sub> = 12.8 μM. The oral administration of **34** at the dose of 2.0 mg/kg in mice reversed the cognitive impairment in passive avoidance test and decreased the escape latencies in training trials. According to these results, it is assumed that **34** can be a useful remedy for treatment of cognitive impairment (Huang et al., 2008).

6. Quality and safety of herbal drugs

Phytochemical profile of plants is significantly affected by the environment. In the same species, levels of bioactive constituents can vary according to geographical location, weather condition, soil composition and other aspects. Even on the same location, the

**Table 4**  
Different phytochemicals for memory improvement.

Sl no.	Chemical compound	Source plant	In vivo study model	Biological effect and target	Reference
1	L-Ascorbic acid (23)	Citrus fruits	Scopolamine and Diazepam-induced young animals, Aged mice	<ul style="list-style-type: none"> <li>• Improve learning ability in aged mice</li> <li>• Reduce transfer-latency and increase step-down latency</li> <li>• Protect against scopolamine- and diazepam-induced memory impairments</li> </ul>	(Parle and Dhingra, 2003)
2	Bacosides (24)	<i>Bacopa monnieri</i>	Elderly people (65 years or older) without clinical sign of dementia in double-blind, placebo-controlled clinical trial	<ul style="list-style-type: none"> <li>• Enhanced auditory verbal learning and word recall</li> <li>• Effective in patients with AD</li> </ul>	Kumar et al., 2012
3	Curcuminoids (25)	<i>Curcuma longa</i>	Abeta-peptide infused rat models of AD	<ul style="list-style-type: none"> <li>• Positive effect on rats displaying AD-like neuronal loss</li> <li>• Increased PSD-95 expression in hippocampus</li> <li>• Increased synaptophysin expression</li> <li>• Inhibited acetylcholinesterase activity</li> <li>• Reversed scopolamine-induced memory impairments</li> </ul>	Ahmed et al., 2010
4	Dehydroevodiamine (26)	<i>Evodia rutaecarpa</i>	Rats with Scopolamine-induced memory deficit	<ul style="list-style-type: none"> <li>• Improved neurobehavioral performance</li> <li>• Protection against LPS-induced memory impairments</li> </ul>	Park et al., 1996
5	Dendrobium alkaloids (27)	<i>Dendrobium moniliforme</i>	Rats with LPS-induced memory deficit	<ul style="list-style-type: none"> <li>• Boosts neurogenesis in brain areas important for memory (e.g., hippocampus)</li> </ul>	Li et al., 2010
6	Epigallocatechin-3-gallate (EGCG, 12)	<i>Camellia sinensis</i>	Mice	<ul style="list-style-type: none"> <li>• Improved task assessing speed for processing ability</li> <li>• Might improve cognitive process in older adults</li> </ul>	Weatherby, 2012
7	Ginkgolides (28)	<i>Ginkgo biloba</i>	Patients with dementia of AD type and multi-infract dementia	<ul style="list-style-type: none"> <li>• Improvement in speed of performing memory task and accuracy of attentional task</li> </ul>	Kumar et al., 2012
8	Ginsenosides (29):Rg1 (20), Rg2 (21), Rg3 (30), Rb1 (19), Rh2 (22), etc.	<i>Panax ginseng</i>	Healthy and young volunteers	<ul style="list-style-type: none"> <li>• Improved cognition, mood and behaviour of patients with AD</li> </ul>	Kumar et al., 2012
9	Huperzine A (15)	<i>Huperzia serrata</i>	Individuals with AD	<ul style="list-style-type: none"> <li>• Significant mitigation in scopolamine-induced memory deficits in passive avoidance test</li> </ul>	Kumar et al., 2012
10	Loganin (17)	<i>Cornus officinalis</i>	Scopolamine-induced amnesic mice	<ul style="list-style-type: none"> <li>• Inhibition of acetylcholinesterase activity in mouse hippocampus</li> </ul>	Lee K.Y et al.,
11	Nobiletin (18)	<i>Aurantii nobilis</i>	Mice	<ul style="list-style-type: none"> <li>• Reduced memory impairment in fear conditioning</li> <li>• Reduced Abeta deposit in mice hippocampus</li> </ul>	Yamakuni et al., 2010
12	Phosphatidyl choline (31)	<ul style="list-style-type: none"> <li>• <i>Allium sativum</i></li> <li>• Soy bean</li> <li>• Lettuce</li> <li>• Whole grain</li> <li>• Cauliflower</li> </ul>	Human	<ul style="list-style-type: none"> <li>• Enhance healing of brain tissue and nerves</li> <li>• Increase level of acetylcholine in brain</li> <li>• Useful for AD and bipolar depression</li> </ul>	Rathee et al., 2008
13	Piperine (32)	<i>Piper nigrum</i>	Adult male Wistar rats	<ul style="list-style-type: none"> <li>• Improve memory impairment</li> <li>• Reduced neurodegeneration in hippocampus</li> <li>• Showed neurotrophic effect in hippocampus</li> </ul>	Chonpathompikunlert et al., 2010
14	Polygala saponins XXXII (PGS32, 33)	<i>Polygala tenuifolia</i>	Mice with scopolamine-induced cognitive impairment	<ul style="list-style-type: none"> <li>• Reverse Abeta-induced memory impairment through its anti-oxidative property</li> <li>• Reversed scopolamine effect by improving synaptic transmission</li> <li>• Enhancement of brain derived neurotrophic factor level</li> </ul>	Kumar et al., 2012
15	Pseudocoptisin (34)	<i>Corydalis tuber</i>	Mice with scopolamine-induced memory impairment	<ul style="list-style-type: none"> <li>• Has anti-cholinesterase and anti-amnesic activity</li> <li>• Reversed cognitive impairments in PA test</li> <li>• Reduced escape latencies</li> </ul>	Hung et al., 2008
16	Oroxylin A (35)	<i>Scutellaria bicalensis</i>	Rats with 2VO-induced memory impairments	<ul style="list-style-type: none"> <li>• Reversed 2VO-induced memory impairments</li> <li>• Reduction in activated microglia</li> <li>• Increased BDNF expression and CREB phosphorylation</li> </ul>	Kim et al., 2006
17	Sauroine (36)	<i>Huperzia squarurus</i>	Male Wistar rats	<ul style="list-style-type: none"> <li>• Improved memory retention in step-down test</li> <li>• Increased hippocampal plasticity</li> </ul>	Vallejo et al., 2009
18	Sesquiterpene lactone (37)	<i>Amberboa ramosa</i>		<ul style="list-style-type: none"> <li>• Inhibits acetyl-cholinesterase and butyl-cholinesterase enzymes</li> </ul>	Ibrahim et al., 2013

**Table 5**  
Compound level in the natural sources.

No.	Bioactive compound	Content	Source (part)	Reference
1	(S)-Allyl-L-cysteine ( <b>38</b> )	2.0–2.4 mg/100 g	<i>Allium sativum</i> (bulb)	Ryu and Kang, 2017
2	Arecoline ( <b>39</b> )	1.5 ± 0.008%	<i>Areca catechu</i> (raw nuts)	Dutta et al., 2017
3	β-Asarone ( <b>40</b> )	4.4% w/w	<i>Acorus calamus</i> (rhizome)	Hanson et al., 2005
4	L-Ascorbic acid ( <b>23</b> )	34–38 mg/100 g	<i>Phyllanthus emblica</i> (fruit)	Raghu et al., 2007
5	Bacopaside I ( <b>41</b> )	0.29–1.36%	<i>Bacopa monnieri</i> (whole plant)	Christopher et al., 2017
6	Bacoside A ( <b>42</b> )	1.44–5.40%	<i>Bacopa monnieri</i> (whole plant)	Christopher et al., 2017
7	Baicalin ( <b>43</b> )	8.1–15.6%	<i>Scutellaria baicalensis</i> (roots)	Zheljazkov et al., 2007
	Baicalein ( <b>44</b> )	0.2–1.2%		
8	Carnosic acid ( <b>45</b> )	18.2–35.1 mg/g	<i>Salvia rosmarinus</i> (leaves)	Hidalgo et al., 1998
9	Chebulic acid ( <b>46</b> )	7.99 g/kg	<i>Terminalia chebula</i> (dry fruit)	Pfundstein et al., 2010
10	α-Crocin ( <b>47</b> )	>10%	<i>Crocus sativus</i> (dry saffron's mass)	Shahdadi et al., 2016
11	Curcumin ( <b>11</b> )	3–5%	<i>Curcuma longa</i> (rhizome)	Guimarães et al., 2020
12	Emodin ( <b>48</b> )	156.37 ± 0.179 µg/g	<i>Polygonum multiflorum</i> (dried tuberous root)	Yang et al., 2018
13	(-)-Epicatechin (EC, <b>49</b> )	270–1235 mg/100 g	<i>Theobroma cacao</i> (beans)	Othman et al., 2010
14	Epigallocatechin-3-gallate (EGCG, <b>12</b> )	7380 mg/100 g	<i>Camellia sinensis</i> (dried leaves)	Sharifi-Rad et al., 2020
15	Essential oil	0.93%	- <i>Salvia officinalis</i> (aerial parts)	Damyanova et al., 2016
	- α-Thujone ( <b>50</b> )	- 26.68%	(of essential oil)	
	- β-Thujone ( <b>51</b> )	- 5.35%	(of essential oil)	
	- α-Pinene ( <b>52</b> )	- 3.58%	(of essential oil)	
	- β-Pinene ( <b>53</b> )	- 5.44%	(of essential oil)	
	- Borneol ( <b>54</b> )	- 3.69%	(of essential oil)	
16	Flavonoids ( <b>55</b> ) (total content)	14.30 mg/g	<i>Ginkgo biloba</i> (fresh leaves)	Shi et al., 2012
17	Gingerol ( <b>56</b> )	75.25 ± 2.03 mg/100 g	<i>Zingiber officinale</i> (fresh rhizome)	Saensouk and Chumroenphat, 2018
18	Ginsenoside Rg1 ( <b>20</b> )	3.3 mg/g	<i>Panax ginseng</i> (roots)	Lee et al., 2015
	Ginsenoside Re ( <b>57</b> )	2.0 mg/g		
	Ginsenoside Rb1 ( <b>19</b> )	5.8 mg/g		
	Ginsenoside Rc ( <b>58</b> )	1.7 mg/g		
	Ginsenoside Rb2 ( <b>59</b> )	2.3 mg/g		
	Ginsenoside Rd ( <b>60</b> )	0.4 mg/g		
19	Huperzine A ( <b>15</b> )	182.55 ± 0.18 µg/g	<i>Huperzia serrata</i> (moss)	Ma et al., 2005
20	Loganin ( <b>17</b> )	10.4 µg/mg	<i>Cornus officinalis</i> (dried fruit)	Ahn et al., 2017
21	Magnolol ( <b>61</b> )	2–10%	<i>Magnolia officinalis</i> (bark)	Patocka et al., 2006
22	Nicotine ( <b>62</b> )	0.3–3.5%	<i>Nicotiana tabacum</i> (dried leaves)	Fatica et al., 2019
23	Piperine ( <b>32</b> )	2–7.4%	<i>Piper nigrum</i> (fruits)	Gorgani et al., 2017
24	Resveratrol ( <b>63</b> )	50–100 µg/g	<i>Vitis vinifera</i> (grape skin)	Singh et al., 2015
25	Ricinine ( <b>64</b> )	0.13–0.26%	<i>Ricinus communis</i> (fresh leaves)	Burgess et al., 1988
26	Rosmarinic acid ( <b>65</b> )	3.67–8.07%	<i>Melissa officinalis</i> (leaves)	Kittler et al., 2018
27	Tannic acid ( <b>66</b> )	0.16–0.77 mg/g	<i>Clitoria ternatea</i> (raw mature seeds)	Al-Snafi, 2016
28	Tannic acid ( <b>66</b> )	4.1 g/100 g	<i>Punica granatum</i> (dry seeds)	S. Mohammed, 2008

**Table 6**  
Summarized biological assays of active compounds.

No.	Compound	Effective concentration/dose	Biological activity	Reference
1	α-Asarone ( <b>67</b> )	IC <sub>50</sub> = 46.38 ± 2.69 µM	<i>In vitro</i> AChE inhibitory potential	Mukherjee et al., 2007b
2	β-Asarone ( <b>40</b> )	IC <sub>50</sub> = 3.33 ± 0.02 µM	<i>In vitro</i> AChE inhibitory potential	Mukherjee et al., 2007b
3	Bisdemethoxycurcumin ( <b>68</b> )	IC <sub>50</sub> = 16.84 µM	<i>In vitro</i> inhibition of AChE	Ahmed and Gilani, 2009
4	(+)-Catechin ( <b>69</b> )	1–10 µM	Attenuation of hippocampal cell death	Bastianetto et al., 2000
5	Croctin ( <b>70</b> )	IC <sub>50</sub> = 96.33 ± 0.11 µM	Inhibition of AChE	Geromichalos et al., 2012
6	Curcumin ( <b>11</b> )	IC <sub>50</sub> = 67.69 µM	<i>In vitro</i> inhibition of AChE	Ahmed and Gilani, 2009
7	Curcumin ( <b>11</b> )	IC <sub>50</sub> = 0.81–1 µM	Inhibition of Aβ aggregation or its disaggregation promotion	Yang et al., 2005
8	Curcuminoids ( <b>25</b> )	IC <sub>50</sub> = 19.67 µM	<i>In vitro</i> inhibition of AChE	Ahmed and Gilani, 2009
9	Demethoxycurcumin ( <b>71</b> )	IC <sub>50</sub> = 33.14 µM	<i>In vitro</i> inhibition of AChE	Ahmed and Gilani, 2009
10	Dimethylcroctin ( <b>72</b> )	IC <sub>50</sub> = 107.1 ± 1.9 µM	Inhibition of AChE	Geromichalos et al., 2012
11	Ellagic acid ( <b>73</b> )	IC <sub>50</sub> = 45.63 µM	Inhibition of AChE	G and De, 2011
12	Epigallocatechin-3-gallate (EGCG, <b>12</b> )	Daily oral dose of 9 mg/kg of EGCG given for 12 months	Improvement of visual recognition memory	de la Torre et al., 2016
13	Galanthamine ( <b>74</b> )	IC <sub>50</sub> = 1.995 µM	Inhibition of AChE (rat cortex)	Tang and Han, 1999
14	Gallic acid ( <b>75</b> )	IC <sub>50</sub> = 5.85 µM	Inhibition of AChE	G and De, 2011
15	Ginsenoside Rg5 ( <b>76</b> )	IC <sub>50</sub> = 18.4 µM	Inhibition of AChE	Kim et al., 2013
16	Ginsenoside Rh3 ( <b>77</b> )	IC <sub>50</sub> = 10.2 µM	Inhibition of AChE	Kim et al., 2013
17	Huperzine A ( <b>15</b> )	IC <sub>50</sub> = 0.082 µM	Inhibition of AChE (rat cortex)	Tang and Han, 1999
18	Loganin ( <b>17</b> )	IC <sub>50</sub> = 0.33 ± 0.05 µM	Inhibition of AChE	Bhakta et al., 2016
19	Physostigmine ( <b>78</b> )	IC <sub>50</sub> = 1.42 µM	Inhibition of AChE	G and De, 2011
20	Protopine ( <b>79</b> )	IC <sub>50</sub> = 50 µM	Inhibition of AChE	Kim et al., 1999
21	Quercetin ( <b>80</b> )	5–25 µM	Attenuation of hippocampal cell death	Bastianetto et al., 2000
22	Resveratrol ( <b>63</b> )	5–25 µM	Attenuation of hippocampal cell death	Bastianetto et al., 2000
23	Safranal ( <b>81</b> )	IC <sub>50</sub> = 21.09 ± 0.17 µM	Inhibition of AChE	Geromichalos et al., 2012

chemical composition in plants varies from year to year due to local weather divergency (temperature, drought, flood, etc.). The constituent levels in wild plants are in general more variable. These negative effects in commercial plants can be reduced by standardization of cultivation techniques. Indeed, plants that originate from characterized and uniform genetic source and that grown under controlled conditions contain more stable levels of bioactive compounds.

The concentration of nootropics depends on the mechanism of plant processing. The whole plant, essential oil, roots, leaves, fruits, etc. contain various levels of desired compounds, therefore it is important to use parts of plant with higher concentration of drugs. Diverse extraction methods produce mixture of substances in various levels. Solvents, temperature, time of extraction, etc. significantly affect composition of the final mixture. In addition, some of the natural products containing bioactive compounds are prepared without standardization, therefore the composition of the products may vary between producers and even batches. Detailed standardization in plant processing is needed for a higher quality of final products.

An application of the same nootropic may result in various biological effects. The major advantage of herbal drugs is presence of several active or supporting compounds compared to a single-component drugs. This fact represents a unique challenge for the identification of active constituents and further evaluation of their bioactivity. It is further important to detect and separate any potential hazardous compounds. Inadequate separation techniques may reduce the levels of active compound and lead to reduced bioactivity. Further, the application of nootropics plays a crucial role in the bioavailability. Natural products are applied in different forms such as tablets, capsules, dried plant, raw herb, tinctures (alcoholic extracts), tisanes (hot water extracts) and others. This also impacts on the biological activity of drug.

Another interesting point to consider represents assumptions and expectations of customers in extraordinary effects of natural products. The customers usually believe that natural products on the markets are high-quality products only. However, even if the herb has been reported to have a remarkable bioactivity, there can be a significant difference in the levels of active constituents. Moreover, it is generally believed that natural products are inherently safe without adverse effects and without any chance of overdosing. Although natural products may also have adverse effects and interactions type herb-herb or herb-drug are possible. Therefore, further studies are needed for a deeper insight into the interactions of nootropics (Wachtel-Galor and Benzie 2011).

## 7. Conclusions and future directions

From this study, it is clear that plants, in the forms of herb foods and spices, play a vital role in enhancing poor memory (Eufoliye et al., 2012). Various medicinal plants are used worldwide (i.e. in Indian Ayurveda, TCM, Korean medicine, African medicine, American medicine etc.) and they have shown significant memory and cognition improving activity on animal models. These medicinal plants contain a variety of phytochemicals that are proven to improve cognition, intelligence, attention and concentration by maintaining the proper level of neurotransmitter Acetylcholine (ACh) inside the brain by providing a controlled activity of the enzyme Acetylcholinesterase (AChE). The different kinds of polyherbal formulations also work well on the central nervous system. Besides preclinical studies, some clinical trials are also being made which have also given positive results. As these medicinal plants show significant results on animal models of amnesia, dementia and AD-type dementia, it can be said that there is a possibility that

these herbs can be used for the treatment of some serious brain disorders in humans (e.g. AD) in near future.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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