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Ethnopharmacological Approaches for Dementia Therapy and Significance of Natural Products and Herbal Drugs

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Dementia is a clinical syndrome wherein gradual decline of mental and cognitive capabilities of an afflicted person takes place. Dementia is associated with various risk factors and conditions such as insufficient cerebral blood supply, toxin exposure, mitochondrial dysfunction, oxidative damage, and often coexisting with some neurodegenerative disorders such as Alzheimer's disease (AD), Huntington's disease (HD), and Parkinson's disease (PD). Although there are well-established (semi-)synthetic drugs currently used for the management of AD and AD-associated dementia, most of them have several adverse effects. Thus, traditional medicine provides various plant-derived lead molecules that may be useful for further medical research. Herein we review the worldwide use of ethnomedicinal plants in dementia treatment. We have explored a number of recognized databases by using keywords and phrases such as "dementia", "Alzheimer's," "traditional medicine," "ethnopharmacology," "ethnobotany," "herbs," "medicinal plants" or other relevant terms, and summarized 90 medicinal plants that are traditionally used to treat dementia. Moreover, we highlight five medicinal plants or plant genera of prime importance and discuss the physiological effects, as well as the mechanism of action of their major bioactive compounds. Furthermore, the link between mitochondrial dysfunction and dementia is also discussed. We conclude that several drugs of plant origin may serve as promising therapeutics for the treatment of dementia, however, pivotal evidence for their therapeutic efficacy in advanced clinical studies is still lacking.

Keywords: Alzheimer's disease, amyloid fibrils, β-amyloid, dementia, ethnopharmacology, herbal drugs

INTRODUCTION

Dementia is a clinical syndrome wherein gradual decline of mental and cognitive capabilities of an afflicted person takes place. As the disease progresses, the ability to function independently of an affected individual deteriorates due to memory loss (Burgess et al., 2002; Damasio and Gabrowski, 2004; Grand et al., 2011). The causes of dementia can be either reversible or irreversible. The reversible causes include, for example, substance abuse, subdural hematoma, removable tumors, and central nervous system (CNS) infections (Tripathi and Vibha, 2009). Some of the irreversible causes of dementia are neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) (Mehan et al., 2012).

Thus, dementia is associated with multiple predisposing conditions and risk factors, among which aging is the greatest and most obvious one (Blennow et al., 2006; Corrada et al., 2010). The most widespread group of dementias is related to neurodegenerative disorders, including AD, PD, and HD, or amyotrophic lateral sclerosis (ALS). Another important group of dementias are vascular cognitive impairments. These pathologies often coexist with neurodegenerative dementias (Iadecola, 2013). Vascular cognitive impairments arise due to various cerebrovascular pathologies, such as hypoperfusions or hemorrhages causing disruption of the blood-brain barrier (BBB) and neurovascular units, usually in hemispheric white matter (Iadecola, 2013). Other diseases may also contribute to development of dementia. Such diseases include metabolic disorders, which participate in the pathology via dysregulation of energy management (Cai et al., 2012), AIDS, which causes indirect damage to the brain through immune activated macrophages (Navia and Rostasy, 2005), or even systemic infections (Lim et al., 2015). Various environmental factors also increase the risk of developing dementia. For example toxins contained in abused substances (Ridley et al., 2013), pesticides (Yan et al., 2016), or air pollution (Rivas-Arancibia et al., 2013; Power et al., 2016) may cause oxidative stress and subsequent neuronal cell death. In addition to the above factors, the etiology of dementia includes a genetic component. The occurrence of dementia is connected with numerous gene polymorphisms and other mutations (Weksler et al., 2013). For example, mutations in three deterministic autosomal dominant genes, i.e., presenilin 1 (PSEN1) on chromosome 14q, presenilin 2 (PSEN2) on 1q, and amyloid precursor protein (APP) on 21q, are associated with early-onset AD (EOAD) (Giri et al., 2016). The apolipoprotein E (APOE) gene, located at locus 19q13.2, is the strongest genetic risk factor for sporadic lead-onset AD (LOAD) (Corder et al., 1993; Giri et al., 2016; Swerdlow et al., 2017). There are three common APOE alleles, namely APOE ε2, ε3, and ε4 alleles, among which the APOE ε4 genotype is mainly associated with the higher risk of AD development (Mahley and Rall, 2000; Giri et al., 2016; Swerdlow et al., 2017). The link between the APOE ε4 genotype and development of AD pathology is complex (Giri et al., 2016). Studies suggest that APOE ε4 is associated with 3- up to 12-fold increased risk of LOAD and earlier onset of dementia in individuals with PSEN1 mutation, whereas APOE ε2 decreases the risk of LOAD (Pastor et al., 2003; Giri et al., 2016). In addition, APOE ε4 contributes to AD pathogenesis by Aβ-independent mechanisms involving neurovascular functions, synaptic plasticity, cholesterol homeostasis, and neuroinflammation (Giri et al., 2016). Thus, the presence of APOE4 ε4 allele is considered one of the risk factors for AD; more specifically, it is associated with increased risk of cerebral amyloid angiopathy and age-related cognitive decline during aging (Liu et al., 2013).

Dementia is a highly prevalent syndrome. Despite its prevalence, some evidence suggest that only 10% (low-middle-income countries) to 50% (high-income countries) of all dementia cases are diagnosed (Prince et al., 2016). In addition, the number of dementia cases will grow in consecutive years, as dementia mostly affects the elderly, and the number of people with advanced age is rising rapidly due to the global increase in life expectancy. Quaglio et al. (2016) approximate, that 1.5–2% of the Europeans are currently affected by dementia. On a similar note, Prince et al. (2016) estimated that in 2015 around 47 million people globally suffered from dementia. This number may reach roughly 131 million in 2050 (Prince et al., 2016). In the year 2021, one million people will be affected by dementia in the UK alone (Knapp et al., 2007). The importance of developing novel dementia treatments was recognized by the G7 summit in December 2014. The forum participants recommended that dementia should be treated as a global priority with the main objective to introduce effective therapy by 2025 (Cummings et al., 2016).

Dementia is a significant burden on society both by eliciting human suffering and financially. Dementia is the fifth most frequent cause of death in high-income countries (Dolgin, 2016). Their caregivers were also negatively affected by the health conditions of the patients and showed moderately high levels of depressive symptoms (Schulz et al., 2008). According to the World Alzheimer Report 2016 (Prince et al., 2016), not only in the low-income countries, but also in the high-income countries people with dementia have poor access to healthcare due to its high cost and ineffective diagnostic systems. Dementia management is very expensive due to long-lasting and costly care that the patients receive (Hurd et al., 2013). Various costs related to dementia, including health services, social services, unpaid careers, and others reach around €23 billion per year alone in the UK (Luengo-Fernandez et al., 2010). This economic burden can be further illustrated by the fact that, in the UK, the current annual cost of dementia is higher than current annual costs of heart disease and cancer combined (Luengo-Fernandez et al., 2010). Another prediction suggests that by 2050 dementia and Alzheimer's disease may cost the United States alone around USD 1 trillion (Dolgin, 2016).

In this review, we present a global overview on the worldwide use of ethnomedicine for the management of dementia. Moreover, we also focus on five prominent plants traditionally used for dementia treatment and highlight the constituents, which may be responsible for plant's bioactivity.

Currently, there is no highly effective medicine that stops the progressive course of dementia (Abbott, 2011). We propose that learning about the active substances produced by some plants and

TABLE 1 | Most common forms of dementia (according to Abbott, 2011).

Dementia form	Neuropathology	Symptoms	Dementia cases (%)
AD-related dementia	Aβ plaques, neurofibrillary tangles	Memory deficits, depression, poor judgment or evidence of mental confusion	50–80
Vascular dementia	Decreased or interrupted blood flow to the brain, hypoperfusion, oxidative stress	Similar to AD, but less affected memory	20–30
Dementia with Lewy bodies	α-Synuclein aggregates in neurons and glial cells (cortical Lewy bodies)	Similar to AD and less to PD, hallucinations, tremors, impaired attention	<5
Frontotemporal dementia	Accumulation of MAP tau, atrophy of frontal and temporal lobes	Changes in social behavior, difficulties with language	5–10

their mechanism of action may lead to the development of novel therapies for dementia. The natural products pool represents a continuous major source for drug discovery (Atanasov et al., 2015). In this context, the present review could serve as a useful resource for the development of ethnomedicine-derived pharmaceuticals for the dementia therapy.

FREQUENT FORMS OF DEMENTIA

The most common types of dementia are AD-related dementia (approximately 50–80% of all dementia cases) (Qiu et al., 2009; Abbott, 2011), vascular dementia (approximately 20–30%) (Abbott, 2011; Iadecola, 2013), dementia with Lewy bodies (between 15 and 35% according to Zupancic et al., 2011, or less than 5% according to Abbott, 2011) and the frontotemporal dementia (FTD), which is the fourth most frequent form of presenile dementia (between 5 and 10%) (Abbott, 2011; **Table 1**).

Common to these dysfunctions is a presence of abnormal accumulated proteins in the brains of patients. For example, in AD amyloid beta (Aβ) peptides aggregate into amyloid plaques (Hardy and Higgins, 1992), while TDP-43 protein accumulates in the human brain during the course of FTD (Baloh, 2011). Brains of FTD patients show gross atrophy of frontal and anterior temporal lobes (Brun, 1987; McKhann et al., 2001), and their histopathology reveals microvacuolar degeneration and loss of pyramidal neurons in the frontal and temporal cortex (Rabinovici and Miller, 2010). Furthermore, pathologic accumulation of microtubule-associated protein (MAP) tau is a process also common for AD and FTD (Iqbal et al., 2016). Abnormal hyperphosphorylation of tau protein leads to its aggregation into intraneuronal neurofibrillary tangles (Iqbal et al., 2010). Vascular dementia is a heterogeneous group of brain disorders associated with a cognitive impairment that is attributed to multifactorial cerebrovascular pathologies, such as hypoperfusion, oxidative stress, and inflammation (Iadecola, 2013). Dementia with Lewy bodies is characterized by the presence of α-synuclein aggregates in neurons and glial cells (Zupancic et al., 2011), and also associated with cholinergic as well as glutamate transmission deficiencies (Zupancic et al., 2011). It may also be concluded, that there is a great deal of overlap between the symptoms of different types of dementia (Abbott, 2011).

Naturally, the pathology of these diseases is more complicated (Blennow et al., 2006). Various markers of AD can be found in the brains of afflicted patients (Blennow et al., 2006). These markers include, e.g., dysregulation of signaling of memory-related neurotransmitter acetylcholine (ACh) (Kihara and Shimohama, 2004), vascular damage (Franzblau et al., 2013), loss of neurons (Niikura et al., 2006) and synapses (Shankar and Walsh, 2009). Mitochondrial dysfunction is another pathology, which was recognized as an important early event in the AD progression and, therefore, may be considered as promising target for the treatment of AD and AD-related dementia (Kumar and Singh, 2015). We briefly describe the mitochondrial dysfunction in the context of dementia in section Mitochondrial Dysfunction and Neurodegeneration.

MITOCHONDRIAL DYSFUNCTION AND NEURODEGENERATION

Mitochondria are double membrane-enclosed organelles that are responsible to exert a broad range of cellular functions that include the most important adenosine triphosphate (ATP) production (energy conversion), but also involvement in several homeostatic processes, such as regulation of cell cycle and cell growth, calcium handling, and apoptosis-programmed cell death (van Horssen et al., 2017). Moreover, mitochondria play a crucial role in many other essential metabolic processes (van Horssen et al., 2017). Thus, mitochondrial diseases often have an associated metabolic component and, therefore, mitochondrial defects are predictable in energy-dependent disturbances, inflammation, and aging (Chan, 2006; Banasch et al., 2011). Hence, mitochondrial dysfunction is one of the key pathological features in various age-related neurodegenerative diseases including AD-associated dementia due to the pivotal role of mitochondria in neuronal cell survival or death (Moreira et al., 2010). For example, it has been proposed that mitochondrial network remodeling plays a prominent role in neurodegeneration (Zhu et al., 2013; Burte et al., 2015). The mitochondrial cascade hypothesis proposed the mitochondrial dysfunction as a principal episode in AD pathology (Moreira et al., 2010; Swerdlow et al., 2010). Moreover, mitochondrial dysfunction, which is also described as an impairment of electron transport chain, is responsible to increase the production of reactive oxagen species (ROS) and change mitochondrial dynamics (Beal, 2005; Lin and Beal, 2006; Hung et al., 2018). A recent study has shown the reciprocal relationship between ROS and mitochondrial dynamics during early stages

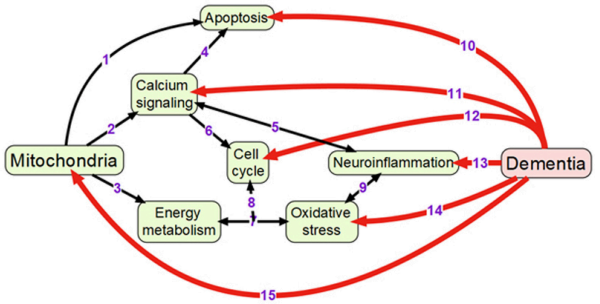


FIGURE 1 | Overview of mechanisms linking mitochondrial activity with dementia: (1) Mitochondria are crucially important for activating apoptosis (Wang and Youle, 2009); (2) Mitochondria regulate calcium signaling pathway (Walsh et al., 2009); (3) Oxidative phosphorylation occurs in electron transport chain of mitochondria; (4) Calcium signaling induces apoptosis (Hajnoczky et al., 2003); (5) Calcium and neuroinflammatory signaling pathways interact with each other (Sama and Norris, 2013); (6) Cell cycle requires calcium signaling (Berridge, 1995); (7) Mitochondrial oxidative phosphorylation is one of the main sources of reactive oxygen species (Dai et al., 2014); (8) Oxidative phosphorylation and reactive oxygen species regulate cell cycle (Antico Arciuch et al., 2012); (9) Oxidative stress and neuroinflammation are highly interconnected processes (Gao et al., 2014); (10) Neuronal apoptosis (LeBlanc, 2005; Favaloro et al., 2012); (11) Impaired calcium signaling (Berridge, 2011; Nimmrich and Eckert, 2013); (12) Changes in cell cycle (Raina et al., 2000; Katsel et al., 2013); (13) Presence of neuroinflammation (Pasqualetti et al., 2015); (14) Increased oxidative stress (Bennett et al., 2009; Kumar and Singh, 2015); (15) Changes in mitochondrial morphology and functions (Spano et al., 2015; Hung et al., 2018).

of neurodegeneration (Hung et al., 2018). It has also been found that the cause for mitochondria-mediated toxicity is the progressive accumulation of Aβ in mitochondria (Chen and Yan, 2010). Recent studies provided the crucial role of mitochondrial dysfunction in regulating the ROS and intracellular calcium levels in neuronal cells (Aminzadeh et al., 2018). In addition, Lee et al. investigated the relationship between the NAD-dependent deacetylase sirtuin-3 (SIRT3) protein and mitochondrial function using AD human brain samples, demonstrating that dysfunction of SIRT3 leads to mitochondrial and neuronal damage, and may improve the mitochondrial pathology and neurodegeneration in AD (Lee et al., 2017). Therefore, mitochondrial dysfunction is considered as a cardinal pathological hallmark for neurodegenerative diseases including AD and AD-related dementia (Lin and Beal, 2006; van Horssen et al., 2017). Detailed information of mitochondrial activities that may be associated with dementia is presented in **Figure 1**.

Summarizing the above, the oxidative stress and mitochondrial dysfunction are of high importance in the pathology and pathogenesis of AD and dementia. Therefore, natural antioxidants and mitochondria targeting molecules can be important strategies to treat elderly individuals with AD (Reddy and Reddy, 2017). Several naturally occurring antioxidants, such as *Ginkgo biloba* (Gb) and curcumin, showed blocking effect on the age-dependent spatial cognitive behavior and also increased the Aβ-degrading enzymes in transgenic mouse models (Stackman et al., 2003; Wang et al., 2014). Moreover, several other antioxidants, including ferulic acid, α-lipoic acid, R-lipoic acid, vitamin E, vitamin C, melatonin, CoQ10, *N*-acetyl-L-cysteine, pyrrolyl-alpha-nitronyl nitroxide, and zeolite supplementation, also showed beneficial effects on AD in different transgenic mouse models (Reddy and Reddy, 2017). Most of these naturally occurring compounds revealed reduction in Aβ levels, mitochondrial dysfunction, phosphorylated tau, and microglial activation, and also increased the synaptic activity (Reddy and Reddy, 2017). Therefore, many of them are available as supplements or can be used as alternative treatment strategies that may help certain neurological conditions, such as PD, AD, some dementia types, and other clinical conditions.

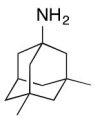
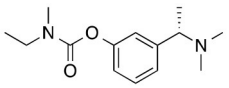
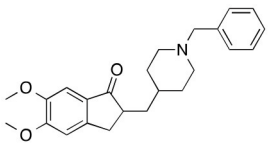
CURRENT PHARMACEUTICAL TREATMENTS OF DEMENTIA

Approved (Semi-)Synthetic Drugs

Several (semi-)synthetic drugs are available worldwide for the treatment of AD and some dementia types. The selective, reversible acetylcholinesterase (AChE) inhibitor donepezil, the non-selective butyrylcholinetserase (BuChE) and AChE inhibitor rivastigmine, as well as the *N*-methyl-D-aspartate (NMDA) receptor antagonist memantine are some of the most widely used therapeutics for AD-associated dementia (Blennow et al., 2006; Winblad et al., 2016). Some of these drugs, like the (semi-)synthetic drug rivastigmine, are also approved for treating other dementia types like PD-related dementia (Winblad et al., 2016). Most prominent drugs approved for clinical use in AD and different forms of dementia are present in **Table 2**. A combined donepezil–memantine drug with the brand name Namzaric® was approved by the FDA in 2014 for the treatment of moderate-to-severe AD in people who are taking donepezil hydrochloride at the recommended clinically efficient dose of 10 mg/day (http://www.alz.org AD report). However, this combinative medicine may cause various side effects, including muscle problems, slow heartbeat and fainting, increased stomach acid levels, nausea, vomiting, and seizures. In addition, some findings suggest that abovementioned drugs do not provide therapeutic benefits for agitation present in patients with severe behavioral symptoms (Howard et al., 2007; Fox et al., 2012). Some neuroleptic/antipsychotic drugs, such as haloperidol, risperidone, and olanzapine, are currently being used to treat behavioral and psychological symptoms of dementia (BPSD), however, their use is controversial (Ballard and Howard, 2006). Therefore, such drugs are not approved by FDA for the treatment of BPSD. Nevertheless, they are still often prescribed off-label as no better treatment for BPSD exists currently (Ibrahim et al., 2012).

The (semi-)synthetic drugs that are currently used for the treatment of dementia have an impact on several symptoms in different disease stages, but do not stop the progressive course of the disease (Tzvetkov and Antonov, 2017). Therefore, the investigation of naturally occurring compounds with potential therapeutic properties for the treatment of different dementia forms is of great medical and socioeconomic importance.

TABLE 2 | Approved (semi-)synthetic drugs used for the treatment of dementia.

	Memantine	**Rivastigmine**	**Donepezil**
Brand name	Namenda® (USA) Axura® (Europe) Ebixa® (Europe) Memando® (Ger)	Exelon® (USA, Europe)	Aricept® (USA, Europe)
Chemical structure	 Chem. formula: $C_{12}H_{21}N$ Mol. wt.: 179.3 g/mol	 Chem. formula: $C_{14}H_{22}N_2O_2$ Mol. wt.: 250.3	 Chem. formula: $C_{24}H_{29}NO_3$ Mol. wt.: 379.5 g/mol
Indications	Moderate-to-severe AD, AD-related dementia	Mild-to-moderate AD, AD-related dementia	Mild-to-moderate AD, early-to-mid AD dementia
Mode of action	Non-competitive NMDA-receptor antagonist	Slowly reversible, non-selective AChE and BuChE inhibitor	Reversible, selective AChE inhibitor
Side effects (http://www.alz.org)	Confusion, dizziness, constipation, and headache	Nausea, vomiting, loss of appetite, increased frequency of bowel movements	Nausea, vomiting, loss of appetite, increased frequency of bowel movements
Half-life (Blennow et al., 2006)	60–100 h (long)	1 h (very short)	70 h (long)
Doses per day (Blennow et al., 2006)	One (first week)	Two	One
Initial dose (Blennow et al., 2006)	5 mg/day	3 mg/day (2 × 1.5 mg)	5 mg/day
Recommended clinically efficient dose (Blennow et al., 2006)	20 mg/day	6–12 mg/day	10 mg/day

Galantamine—the Only Current Drug of Plant Origin against Dementia

Galantamine is an important drug of plant origin that is widely prescribed for the treatment of mild-to-moderate AD and AD-related dementia (Lilienfeld, 2002). Efficacy of galantamine has been confirmed in several clinical trials (Olin and Schneider, 2002). Galantamine, also known as galanthamine (for structure, see **Figure 2**), is an isoquinoline alkaloid produced by plants from *Amaryllidaceae* family. It was first discovered and isolated from bulbs of *Galanthus nivalis* (common snowdrop) by the Bulgarian chemist D. Paskov and his team in 1956 (Paskov, 1958). The original industrial phytopreparation of the pure galantamine extract (named Nivalin®) was prepared in late 1950s by the same research group (Chrusciel and Varagić, 1966). Galantamine was first applied to treat poliomyelitis and later, for the treatment of neuropathic pain and as an anesthetic (Ng et al., 2015). Today, galantamine is mainly obtained from *Galanthus woronowi* Losinsk and *Galanthus alpines* Sosn. (Caucasian snowdrop) daffodil bulbs and also synthesized artificially (Loy and Schneider, 2006).

Galantamine has a unique dual mode of action affecting the brain's cholinergic system (**Figure 2**). It is a reversible, competitive inhibitor of the AChE enzyme and an allosteric enhancer of the nicotinic acetylcholine receptor (nAChR) (Albuquerque et al., 2001).

Galantamine also prevents mitochondrial dysfunction, as shown by its capability to rescue changes in mitochondrial membrane potential (MMP) and morphology induced by Aβ25/35 or hydrogen peroxide treatment (Ezoulin et al., 2008; Liu et al., 2010). Oxidative stress is caused by toxic reactive oxygen species (ROS), which are generated mainly during the electron transport in mitochondria. By protecting the mitochondria and inhibiting AChE activity galantamine decreases oxidative damage to cells and thus mediates neuroprotection (Tsvetkova et al., 2013).

Furthermore, galantamine may interact with other brain-targeted drugs by decreasing activity of P-glycoprotein, a multi-drug resistance transporter present in brain's vascular endothelium (Namanja et al., 2009). It is responsible for actively effluxing drugs back into the bloodstream, thus preventing them from crossing into the brain (Namanja et al., 2009). Hence, galantamine may allow drugs that were co-administered with it to reach the brain more easily. Galantamine also enhances the protective effect of rofecoxib (an anti-inflammatory COX-2 inhibitor) and caffeic acid (a plant-derived phenol) against neurotoxicity-induced mitochondrial dysfunction, oxidative damage, and cognitive impairment in rats (Kumar et al., 2011). Similarly, galantamine potentiates antioxidative activity of melatonin, a brain sleep hormone (Romero et al., 2010). Combined galantamine and memantine treatment is also hypothesized to be a potential novel therapy for schizophrenia (Koola et al., 2014).

Treatment with galantamine has shown to consistently delay the onset of different behavioral symptoms of dementia, such as anxiety, euphoria, depression, irritability, delusions, and unusual motor behavior (Monsch and Giannakopoulos, 2004). A review by Loy and Schneider (2006) described in detail 10 clinical trials comprising the total of 6,805 demented patients, who were submitted to galantamine treatment. The results revealed that the galantamine is well-tolerated by the majority of patients. Some

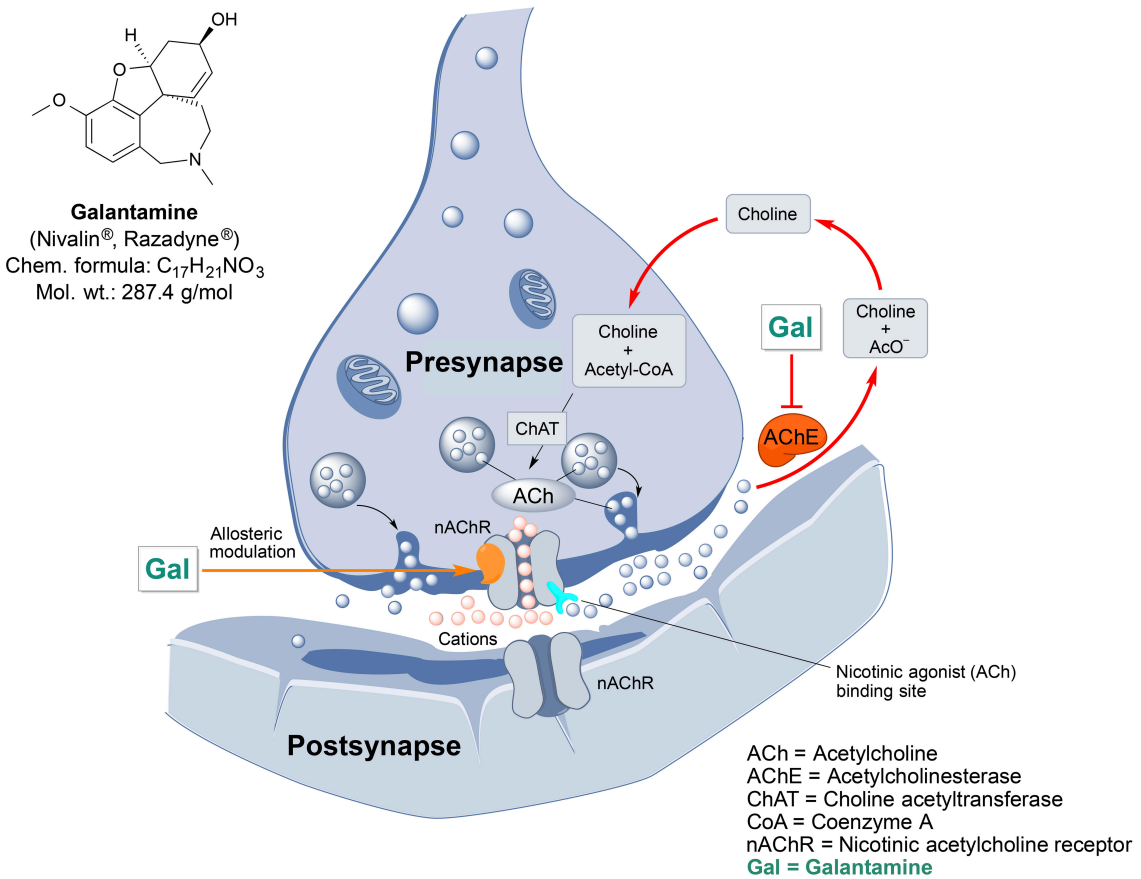


FIGURE 2 | Chemical structure and targeted mechanisms of galantamine (Gal) against AD and dementia. The major biological effects of Gal lead to significant neuroprotection via dual AChE inhibition and allosteric stimulation of nAChRs.

common side effects were observed in the treatment groups in a dose-dependent manner (Loy and Schneider, 2006).

Because of its efficacy, the drug is recommended by Alzheimer's disease/dementia treatment guidelines of the USA and Europe (Doody et al., 2001; Waldemar et al., 2007). The drug is also approved for use in roughly 29 countries including Canada, in the European Union (except for The Netherlands, under the name Nivalin® in 2000), Japan, Korea, Mexico, Singapore, South Africa, Thailand, etc. The FDA approved galantamine in the United States under the brand name Razadyne® in 2001 for the treatment of AD and AD-related dementia. In summary, the plant-derived galantamine is a well-established medicine for dementia treatment, which acts via modulation of acetylcholine signaling and inhibition of oxidative damage.

GENERAL OVERVIEW OF THE DIVERSITY OF PLANTS USED IN DEMENTIA TREATMENT

Modern research on dementias showed that they are complex diseases with multiple molecular mechanisms involved in their pathogenesis. With this realization emerged the new paradigm for treating these pathologies: therapies for dementia should target multiple underling molecular targets, instead of concentrating on any single one. Correspondingly, plant and plant extracts are composed of many substances that are hypothesized to act on multiple molecular targets in an additive or even synergistic manner (Long et al., 2015). Many herbal medicines are already being used for dementia treatment. Unfortunately, active ingredients of these herbs are poorly described. Similarly, we still know very little on how this myriad of substances interact with each other and with prescription medications (Zhou et al., 2016b). The research on these topics will be essential for developing therapeutics, comprised of substances that amplify each other activity and which are devoid of harmful side effects.

In this work, we attempted to collect and document scattered information from various ethnopharmacological reports. We searched several web databases namely, ScienceDirect, Pubmed, Scopus, and Google Scholar using keywords such as "dementia," "Alzheimer's," "traditional medicine," "ethnopharmacology," and "ethnobotany." Web hits from Google scholar were gathered through Boolean information retrieval method using plant name with "AND" operator (Pohl et al., 2010) followed by "dementia"

or "Alzheimer's." An overview of the identified medicinal plants used for treating dementia or AD is presented in **Table 3.**

SELECTED PROMINENT MEDICINAL PLANTS AND PLANT GENERA USED FOR THE TREATMENT OF DEMENTIA

After the extensive web-search for medicinal plants used for dementia treatment in various regions worldwide, the following five plants or plant genera described below were selected for detailed discussion according to the highest observed number of web hits.

Ginkgo biloba L.

Ginkgo is among the most unique plants on earth and belongs to world's oldest tree species (IARC Working Group, 2016). It is a living fossil which gross morphology did not change for around 200 million years (Guan et al., 2016). Gingko is the last living member of the *Ginkgoaceae* family, which appeared during the Mesozoic era. Gb was cultivated in ancient China due to its diverse medicinal properties. Extracts from this plant were utilized for the treatment of various ailments and symptoms viz. poor circulation, fatigue, vertigo, and tinnitus (Sun et al., 2013). Gingko extract is available on market in some countries (e.g., China) as a herbal supplement named Gingium. It is intended for use in certain age-related cognitive disorders including memory impairment and it alleviates the symptoms of dementias and AD (Zhou et al., 2016a). There are two main categories of chemical phytoconstituents likely responsible for the neuro-therapeutic potential of Gingko: terpene lactones (ginkgolides and bilobalide) and flavonoids (flavonols and flavone glycosides) (**Figure 3**; Solfrizzi and Panza, 2015; IARC Working Group, 2016).

The triterpene ginkgolides A, B, and C are unique to Gb (Solfrizzi and Panza, 2015). However, there are some other constituents such as the ginkgotoxin (found in Gb seeds) and the phenolic type lipid bilobol (found in Gb fruits) that possess some specific biological effects (IARC Working Group, 2016). For example, ginkgotoxin exhibit neurotoxic activity (induce the epileptic seizures) (IARC Working Group, 2016), whereas bilobol and its derivatives show cytotoxic and antibacterial activity (Tanaka et al., 2011).

Ginkgo leaf extract was first developed for therapeutic purposes in Germany in 1965 (Isah, 2015). The first commercially available extract was registered in France in 1974 under the name EGb761; it contains about 24% flavonoids and 6% terpene lactones (Isah, 2015). The standardized Gb extract (EGb761) belongs to the most widely tested in clinical trials herbal medications worldwide for cognitive impairment, AD, and AD-related dementia (Solfrizzi and Panza, 2015). EGb761 affects a multitude of mechanisms associated with proper brain functions (Zhou et al., 2016a; **Figure 4**).

It was reported to mediate neuroprotection by modulating circulating glucocorticoid levels, as well as Aβ aggregation, ion homeostasis and growth factors synthesis (Amri et al., 1996; Ahlemeyer and Krieglstein, 2003). These processes are likely involved in regulation of oxidative stress (Butterfield et al., 2013; Ruttkay-Nedecky et al., 2013; Dávila et al., 2016; Alam et al., 2017; Gómez-Sámano et al., 2017) which is in agreement with various reports showing antioxidative activity of Gb extract (Bridi et al., 2001; Chandrasekaran et al., 2003). Moreover, the influence of Ginkgo constituents on mitochondrial function is well recognized. Multiple *in vitro* studies show that Ginkgo constituents protect MMP from various toxicants and oxidative stress (Eckert et al., 2005; Abdel-Kader et al., 2007; Wang and Wang, 2016). Gingko extract affects many aspects of mitochondrial morphology such as fission (Zhou et al., 2017), swelling (Schwarzkopf et al., 2013), and coupling (Rhein et al., 2010). Gingko extract also interacts with mitochondrial electron transport chain (Abdel-Kader et al., 2007). Interestingly, it was found that improvement of the oxidative phosphorylation efficiency was more pronounced in cells overexpressing APP than in control cells (Rhein et al., 2010). This suggests that Ginkgo extract may be effective specifically in AD therapy. The extract also protected rodent neurons and glial cells against cerebral ischemia/reperfusion or scopolamine-induced toxicity (Chandrasekaran et al., 2003; Domoráková et al., 2006; Paganelli et al., 2006; Jahanshahi et al., 2012, 2013). Moreover, EGb761 enhanced the functional integrity and protected cerebral microvascular endothelial cells cultured *in vitro* from damage (Yan et al., 2008; Wan et al., 2014). These effects may be related to a known antiplatelet activity of Gingko extract (Kim et al., 2011). Antiplatelet agents are proposed as a possible therapeutics for vascular syndromes (Geeganage et al., 2010; Heim et al., 2017). Thus, EGb761 may counteract dysfunction of neurovascular unit, which is one of the pathologies associated with AD (Farkas and Luiten, 2001; Zlokovic, 2011).

The use of Ginkgo for the treatment of several cerebral dysfunctions connected to neurodegenerative dementia and brain aging has a long history (Abdou et al., 2016). Studies performed on several animal models suggest that Gingko extract may enhance the cognitive and behavioral functions in aged individuals and Parkinson's disease patients (Kim et al., 2004; Takuma et al., 2007; Ribeiro et al., 2016). Apart from the animal studies, several clinical trials also reported the lack of significant adverse effects and effectiveness of EGb 761 in the therapy of AD and vascular dementia (Kanowski et al., 1996; Napryeyenko et al., 2009; Ihl et al., 2012). Although the gingko extract seems to be beneficial for the treatment of cognitive impairments, further studies are required to assess its possible interaction with other drugs. Such studies may translate to better efficacy and safety of gingko extract therapy. Few important interactions between Ginkgo constituents and drugs are currently known (Izzo, 2012). Nevertheless, there are reports of single patients, which suffered serious neurological side effects after administering Ginkgo herb along with risperidone, valproic acid/phenytoin or trazodone (Izzo, 2012). In summary, Ginkgo extract shows neuroprotective effect, which may be underlined by its antioxidative and/or antiplatelet activities. Clinical studies confirm the effectiveness of Ginkgo extract for dementia treatment. Thus, we speculate that some Ginkgo-based drugs may reach the market in near future.

TABLE 3 | Overview of medicinal plants used to treat dementia worldwide.

Plant (Plant family)	References for the use of the plants for dementia treatment in ethnomedicine	Number of google scholar hits for keyword "dementia"	Number of google scholar hits for keyword "Alzheimer's"
Acorus calamus L. (Acoraceae)	Howes and Houghton, 2003	492	730
Aframomum melegueta (Roskoe) K. Schum. (Zingiberaceae)	Fatumbi, 1995	46	104
Agapanthus africanus (Agapanthaceae)	Stafford et al., 2008	06	06
Ammocharis coranica (Ker-Gawl.) Herb. (Amaryllidaceae)	Stafford et al., 2008	13	26
Ananas comosus (Bromeliaceae)	Wolters, 1994; Adams et al., 2007	129	414
Angelica sinensis (Oliv.) Diels (Apiaceae)	Mantle et al., 2000	1,010	1,660
Angelica archangelica (Apiaceae)	Ross, 2001; Howes and Houghton, 2003	196	318
Angelica species (Apiaceae)	Perry and Howes, 2011	4,670	3,140
Annona senegalensis Pers. (Annonaceae)	Stafford et al., 2008	139	80
Artemisia absinthium L. (Asteraceae)	Howes and Houghton, 2003; Adams et al., 2007	242	439
Asparagus africanus Lam. (Asparagaceae)	Stafford et al., 2008	26	34
Asparagus concinnus (Baker) Kies (Asparagaceae)	Stafford et al., 2008	01	01
Bacopa monnieri (L.) Wettst. (Plantaginaceae)	Manyam, 1999	1,370	1,990
Barbieria pinnata (Pers.) Baill. (Fabacea)	Schultes, 1993, 1994; Adams et al., 2007	04	06
Platycladus orientalis (L.) Franco (Syn. *Biota orientalis* (L.)Endl.) (Cupressaceae)	Nishiyama et al., 1995; Howes et al., 2003	150	236
Boophone disticha (L.f.) Herb. (Amaryllidaceae)	Stafford et al., 2008	39	78
Brugmansia ×*candida* Pers. (Solanaceae)	González Ayala, 1994; Adams et al., 2007	12	55
Bupleurum species (Apiaceae)	Perry and Howes, 2011	518	717
Camellia sinensis Kuntze (Theaceae)	Perry and Howes, 2011	1,420	3,910
Cannabis sativa L. (Cannabaceae)	Perry and Howes, 2011	1,740	3,260
Carum carvi L. (Apiaceae)	Adsersen et al., 2006	163	340
Caryophyllus spp. (Caryophyllaceae)	Tabernaemontanus, 1987; Adams et al., 2007	161	292
Cassia lucens Vog. (Fabaceae)	Schultes, 1993, 1994; Adams et al., 2007	28	93
Celastrus paniculatus Willd. (Celastraceae)	Howes and Houghton, 2003	189	274
Centella asiatica (L.) Urb (Apiaceae)	Stafford et al., 2008	1,060	1,970
Dysphania ambrosioides (L.) Mosyakin&Clemants (Amaranthaceae) {Syn. *Chenopodium ambrosioides* L.(Chenopodiaceae)}	de Barradas, 1957; CESA, 1992, 1993; Adams et al., 2007	94	154
Clitoria ternatea L. (Fabaceae)	Howes and Houghton, 2003	185	294
Codonopsis pilulosa (Franch.) Nannf. (Campanulaceae)	Howes and Houghton, 2003	198	245
Coffea arabica L. (Rubiaceae)	Perry and Howes, 2011	484	1,180
Convallaria majalis L. (Convallariaceae)	Tabernaemontanus, 1987; Adams et al., 2007	82	95
Coriandrum sativum L. (Apiaceae)	Tabernaemontanus, 1987; Adams et al., 2007	310	765
Corydalis cava (L.) Schw. et K. (Papaveraceae)	Adsersen et al., 2006; Adams et al., 2007	65	86
Corydalis intermedia (L.) M'erat (Papaveraceae)	Adsersen et al., 2006; Adams et al., 2007	71	141
Corydalis solida (L.) Swartz ssp. *laxa* (Papaveraceae)	Adsersen et al., 2006; Adams et al., 2007	21	30
Corydalis solida (L.) Swartz ssp. *slivenensis* (Papaveraceae)	Adsersen et al., 2006; Adams et al., 2007	04	04
Crinum bulbispermum (Burm.f.) Milne-Redh. & Schweick. (Amaryllidaceae)	Stafford et al., 2008	47	97
Crinum moorei Hook.f (Syn.*Crinum imbricatum* Baker) (Amaryllidaceae)	Stafford et al., 2008	20	54
Crinum macowanii Baker (Amaryllidaceae)	Stafford et al., 2008	41	93
Crocus sativus L. (Iridaceae)	Perry and Howes, 2011	678	1,310
Curcuma longa L. (Zingiberaceae)	Howes and Houghton, 2003; Perry and Howes, 2011	2,130	6,270
Euphrasia nemorosa (Pers.) Wallr. (Scrophulariaceae)	Adsersen et al., 2006	09	16

(Continued)

TABLE 3 | Continued

Plant (Plant family)	References for the use of the plants for dementia treatment in ethnomedicine	Number of google scholar hits for keyword "dementia"	Number of google scholar hits for keyword "Alzheimer's"
Tetradium ruticarpum (A.Juss.) T.G.Hartley (Syn. *Evodia rutaecarpa* Hook.f.&Thoms.) (Rutaceae)	Mantle et al., 2000; Howes and Perry, 2011	366	367
Ferula gummosa Boiss. (Apiaceae)	Tabernaemontanus, 1987; Adams et al., 2007	22	32
Galanthus woronowii Losinsk. (Amaryllidaceae)	Perry and Howes, 2011	155	286
Galanthus alpinus Sosn. (Syn. *Galanthus caucasicus*) (Amaryllidaceae)	Perry and Howes, 2011	27	55
Ginkgo biloba L. (Ginkgoaceae)	Gurib-Fakim, 2006; Perry and Howes, 2011	14,000	17,300
Glycyrrhiza species (Leguminosae)	Perry and Howes, 2011	2,410	4,050
Huperzia serrate (Thunb.) Trevis. (Lycopodiaceae)	Howes et al., 2003; Adams et al., 2007; Perry and Howes, 2011	1,130	1,710
Hydrolea glabra Schum. and Thonn. (Hydrophilaceae)	Fatumbi, 1995; Adams et al., 2007	01	03
Hypericum perforatum L. (Clusiaceae)	Perry and Howes, 2011	2,500	3,180
Lactuca sativa L. (Asteraceae)	Schweitzer de Palacios, 1994; Adams et al., 2007	287	895
Lannea schweinfurthii Engl. (Anacardiaceae)	Stafford et al., 2008	12	22
Lantana camara L. (Verbenaceae)	Müller-Ebeling and Rätsch, 1989; Adams et al., 2007	97	262
Lavandula angustifolia Miller (Lamiaceae)	Adsersen et al., 2006; Perry and Howes, 2011	800	981
Leucojum aestivum L. (Amaryllidaceae)	Perry and Howes, 2011	133	447
Lycoris radiata Herb. (Amaryllidaceae)	Howes and Houghton, 2003	227	273
Magnolia officinalis Rehder and Wilson (Magnoliaceae)	Howes and Houghton, 2003	389	715
Matricaria recutita L. (Asteraceae)	Tabernaemontanus, 1987; Adams et al., 2007	575	1,150
Medicago sativa L. (Fabaceae)	Finkler, 1985; Adams et al., 2007	390	1,180
Melissa officinalis L. (Lamiaceae)	Lonicerus, 1679; Mills, 1991; Perry et al., 1998; Mantle et al., 2000; Adsersen et al., 2006; Adams et al., 2007; Perry and Howes, 2011	1,140	1,920
Mentha spicata L. (Lamiaceae)	Adsersen et al., 2006	223	537
Narcissus spp. (Amaryllidaceae)	Perry and Howes, 2011	1,480	745
Nicotiana species (Solanaceae)	Perry and Howes, 2011	900	3,060
Ocimum basilicum L. (Lamiaceae)	Fuchs, 1543; Sfikas, 1980; Adams et al., 2007	407	997
Origanum majorana Moench (Lamiaceae)	Fuchs, 1543; Adams et al., 2007	675	1,550
Origanum vulgare L. (Lamiaceae)	Adsersen et al., 2006	358	978
Paeonia ×suffruticosa Andrews (Paeoniaceae)	Mantle et al., 2000	189	345
Panax ginseng C.A.Mey. (Araliaceae)	Perry and Howes, 2011	4,790	6,950
Paullinia cupana Kunth ex. H. B. K (Sapindaceae)	Taylor, 1998; Adams et al., 2007	248	515
Petroselinum crispum (Mil.) Nym.exA.W.Hill. (Apiaceae)	Adsersen et al., 2006	308	562
Physostigma venenosa Balf.f. (Leguminosae)	Mantle et al., 2000	08	11
Pimpinella anisum L. (Apiaceae)	Adsersen et al., 2006	214	493
Piper methysticum G.Forst. (Piperaceae)	Perry and Howes, 2011	768	953
Polygala tenuifolia Willd. (Polygalaceae)	Duke and Ayensu, 1985; Chang et al., 1986; Howes and Houghton, 2003	549	679
Pteroselinum vulgare (Mill.) Nym. and A.W. Hill (Apiaceae)	Adams et al., 2007	82	221
Rosmarinus officinalis L. (Lamiaceae)	Price and Price, 1995; Chevallier, 1996; Perry et al., 1998; Mantle et al., 2000; Adams et al., 2007	1,140	2,440
Rosmarinus officinalis L. (Lamiaceae)	Adsersen et al., 2006	1,140	2,440
Ruta graveolens L. (Rutaceae)	Adsersen et al., 2006	351	420
Salvia lavandulifolia Vahl. (Lamiaceae)	Perry and Howes, 2011	103	190
Salvia miltiorrhiza Bung. (Lamiaceae)	Howes and Houghton, 2003	1,430	2,090

(Continued)

TABLE 3 | Continued

Plant (Plant family)	References for the use of the plants for dementia treatment in ethnomedicine	Number of google scholar hits for keyword "dementia"	Number of google scholar hits for keyword "Alzheimer's"
Salvia officinalis L. (Lamiaceae)	Sfikas 1980; Tabernaemontanus, 1987; Akhondzadeh et al., 2003; Howes et al., 2003; Savelev et al., 2004; Adams et al., 2007	1,610	2,960
Scadoxus multiflorus (Martyn) Raf. (Amaryllidaceae)	Stafford et al., 2008	06	31
Syzygium aromaticum (L.) Merrill and Perry (Myrtaceae)	Tabernaemontanus, 1987; Adams et al., 2007	248	647
Tagetes lucida Cav. (Asteraceae)	Ortiz de Montellano, 1990; Adams et al., 2007	25	54
Terminalia chebula Retz. (Combretaceae)	Misra, 1998; Manyam, 1999; Howes and Houghton, 2003	545	938
Theobroma cacao L. (Sterculiaceae)	Roeder, 1988; Adams et al., 2007	535	1,400
Thymus vulgaris L. (Lamiaceae)	Adsersen et al., 2006	1,440	2,760
Valeriana officinalis L. (Valerianaceae)	Perry and Howes, 2011	973	1,340
Vinca minor L. (Apocynaceae)	Perry and Howes, 2011	1,520	2,070
Vitis vinifera L. (Vitaceae)	Perry and Howes, 2011	994	3,010

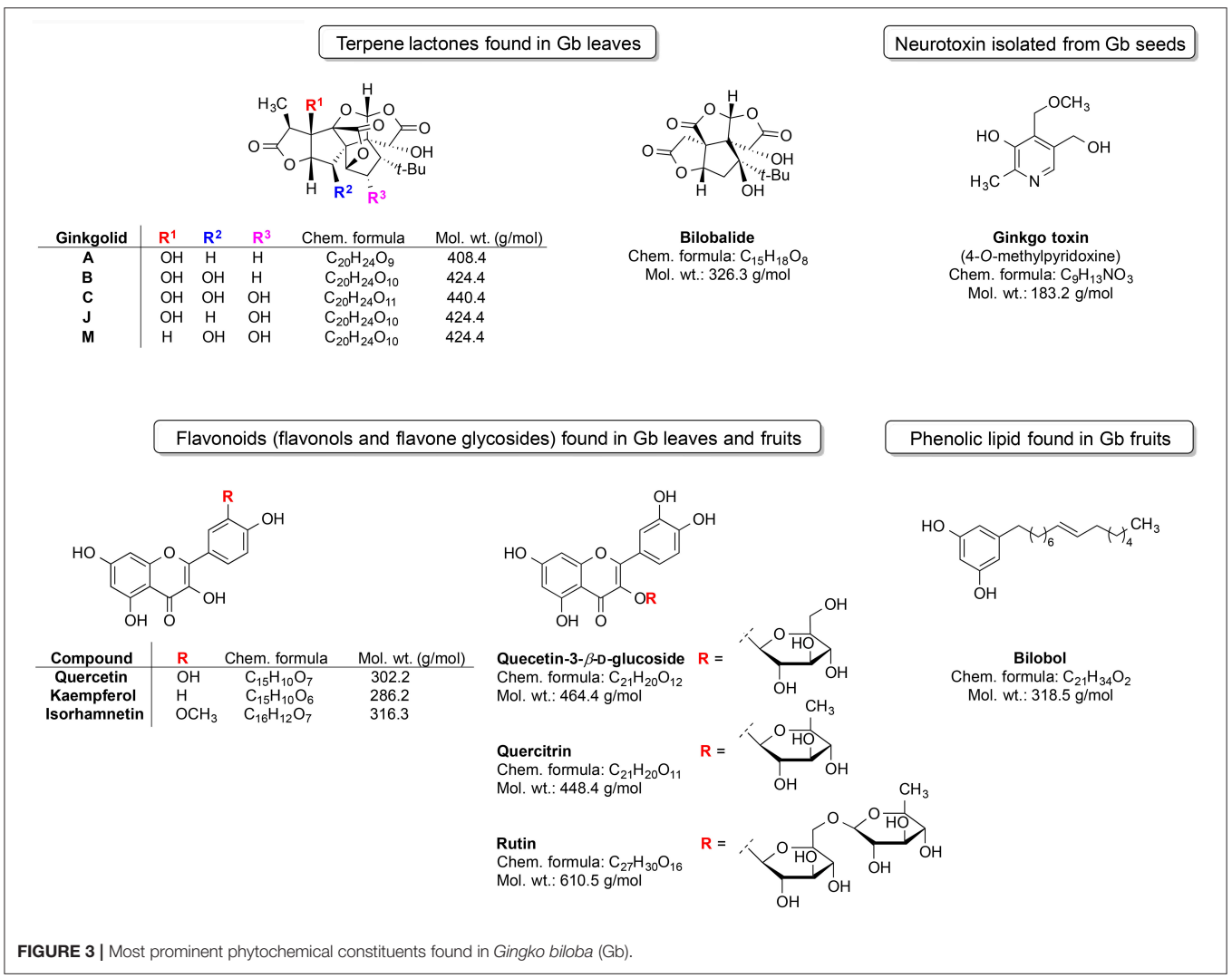


FIGURE 3 | Most prominent phytochemical constituents found in *Gingko biloba* (Gb).

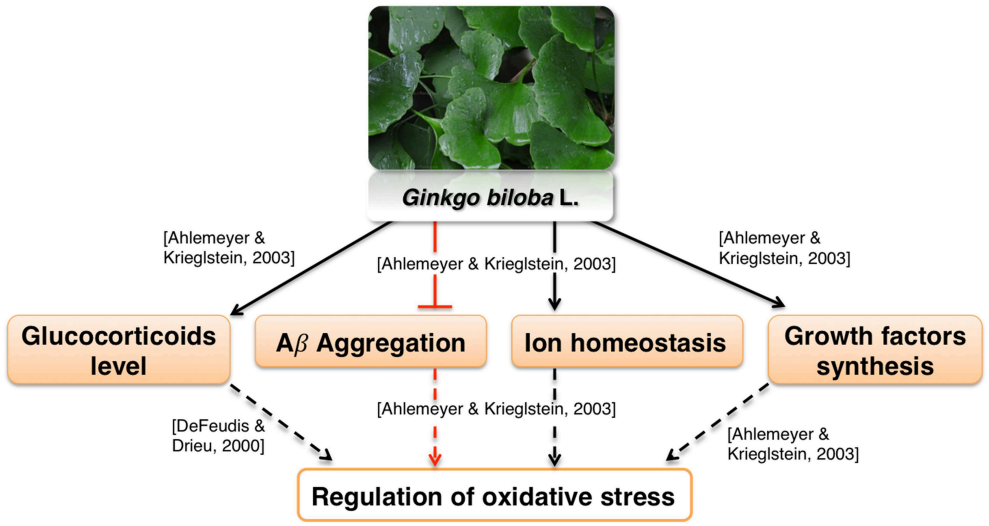


FIGURE 4 | Neuroprotective effects of *Gingko biloba* L.

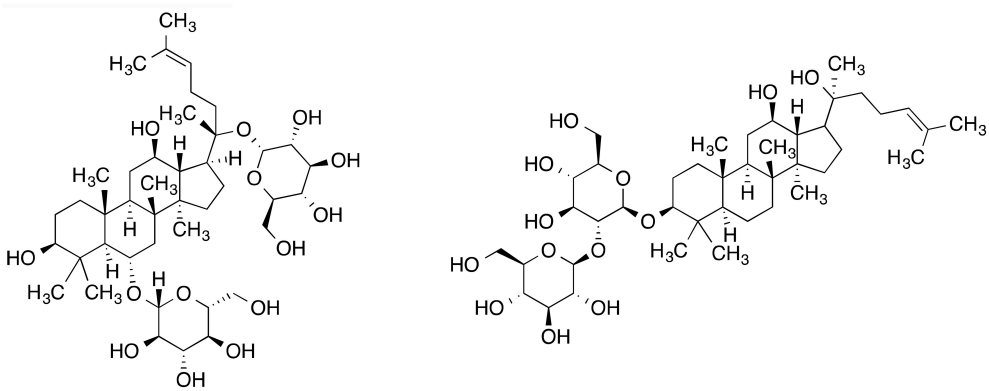


FIGURE 5 | Phytochemical constituents of ginseng.

Panax ginseng C.A. Meyer (Ginseng)

Ginseng is broadly used as an additive for dietary supplements or medicines. It serves as an adaptogen, which is a substance promoting homeostasis and protecting against various biological stressors. The dried root of this plant was used in the traditional medicine mainly in China and Korea (Yun, 2001).There are several species of *Panax* including *P. ginseng* (Oriental ginseng), *P. japonicus* (Japanese ginseng), *P. quinquefolius* (American ginseng), *P. trifolius*, *P. notoginseng* (Burkill), and *P. major* (Ngan et al., 1999). *Panax ginseng* CA Meyer is the most frequently used and extensively researched species of ginseng (Lee et al., 2005). The species is widely distributed in the northeastern part of China. The plant has been used in traditional Chinese medicine for a more than 2000 years as a tonic for fatigue, weakness and aging (Wang et al., 2010). Some constituents of this plant, such as ginsenosides Rg1 and Rg3 (**Figure 5**) and ginseng polysaccharides, have been investigated for their therapeutic potential (Yin et al., 2013; Song et al., 2017; Sun et al., 2017). The neuroprotective effect of ginseng is mainly attributed to the 20(*S*)-ginsenoside Rg3 (**Figure 5**), which has a steroidal backbone structure with carbohydrate part and aliphatic side chain (Yang et al., 2009). Rg3 is generated by heating the roots at high temperature (Popovich and Kitts, 2004; Sun et al., 2010).

A significant reduction of the amyloid-β40 and amyloid-β42 levels was reported after the ginsenoside Rg3 treatment in the brains of transgenic mice (Tg2576 line), as well as in

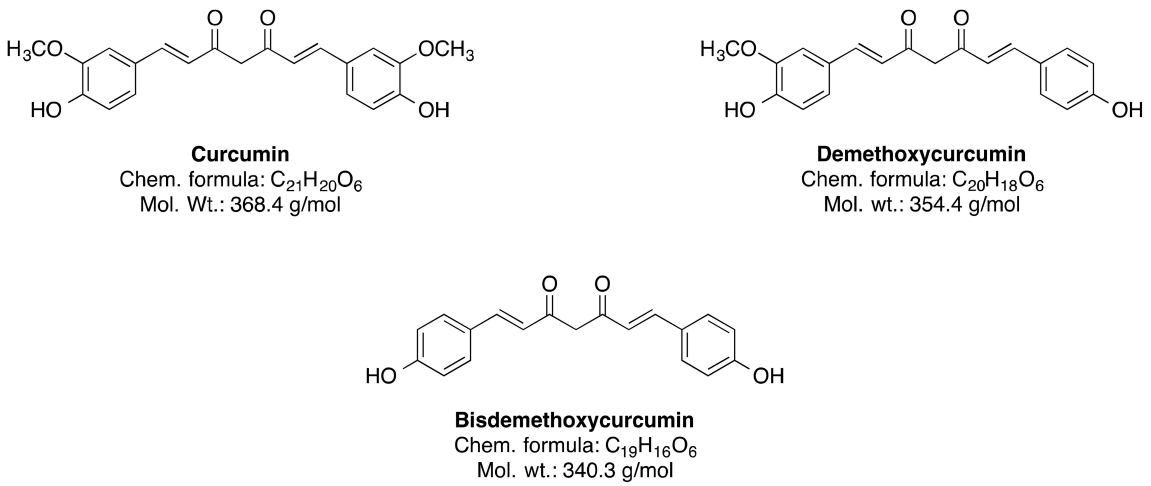


FIGURE 6 | Chemical structures of curcuminoids.

cultured cells (Chen et al., 2006). Ginsenoside Rg3 also protects against glutamate-induced neurotoxicity in cultured cortical neurons (Kim et al., 1998). Similarly, another ginseng constituent ginsenoside Rg1 (GRg1) suppressed Aβ-induced neurotoxicity, likely through p38 pathway activation in neuroblastoma cells (Li et al., 2012). Ginsenosides also regulate nicotinic acetylcholine receptor channel activity (Nah, 2014). As acetylcholine signaling mediates learning and memory, modulation of acetylcholine receptor activity may be involved in the compound effectiveness against dementia (Bartus et al., 1982; Giacobini, 2004). The ginseng extract specifically enriched with ginsenoside Rg3 rescues scopolamine-induced memory impairment possibly through modulation of the AChE activity and the NF-κB signaling pathway in the hippocampus of mice (Kim et al., 2016). NF-κB is a protein complex, which regulates neuroinflammation and is activated by ROS (Kaur et al., 2015). On a similar note, GRg1 reduces the Aβ-associated generation of ROS and cell death (Wang and Du, 2009). Correspondingly, many publications show protective effect of ginseng constituents on brain mitochondrial activity under multiple toxic conditions, including ischemia (Ye et al., 2011), calcium treatment (Tian et al., 2009; Zhou et al., 2014), hydrogen peroxide treatment (Tian et al., 2009), and even incubation of cells with Aβ *in vitro* (Ma et al., 2014).

A recent meta-analysis of randomized clinical trials showed inconsistent effect of ginseng on AD (Wang et al., 2016). Generally, the trials suffered from small sample size and poor design, including lack of placebo groups (Wang et al., 2016). Thus, there is a need of larger trials to determine the efficacy of ginseng in AD.

In summary, ginseng constituents are suggested to modulate a number of dementia-related mechanisms, such as amyloid-β metabolism, oxidative stress, neuroinflammation, and acetylcholine signaling. Unfortunately, the effect of gingseng on dementia patients remains poorly understood despite some efforts.

Curcuminoids from Genus Curcuma

The genus Curcuma (commonly termed as Turmeric) comprises around 80 species and is considered as one of the biggest genera of the *Zingiberaceae* family (Sirirugsa et al., 2007). Curcumin and its curcuminoid analogs, demethoxycurcumin and bisdemethoxycurcumin, are responsible for the typically yellow color of turmeric (Chin et al., 2013). However, the main bioactive phytoconstituent of Curcuma genus is curcumin (**Figure 6**).

It is an approved natural food colorant (E100) and can be easily obtained from turmeric through solvent extraction and crystallization (Chin et al., 2013). Furthermore, curcumin is widely used in traditional Indian medicine for the treatment of anorexia, hepatic diseases, cold, cough, and other disorders (Chin et al., 2013; Huminiecki et al., 2017). Nowadays, *in vivo* studies suggest that curcumin has potential neuroprotective properties including antioxidant, anti-neuroinflammatory, antiproliferative, anti-amyloidogenic, and neuro-regulative effects (Chin et al., 2013). A large epidemiological Indo-US Cross National Dementia study showed that the peasant Indian population has a low prevalence of AD and AD-associated dementia compared to the US population, and that may be linked to the high curcumin consumption in the Indian population (Chin et al., 2013), although such correlation does not necessarily imply causative connection.

Curcumin is comprised of two feruloyl moieties with 3-methoxy-4-hydroxy substituents (**Figure 7A**; Sahne et al., 2017). Both side units are linked together by an unsaturated seven-carbon spacer that includes a β-diketo function so that the molecule of curcumin is almost symmetric. Depending on pH of the environment, curcumin can exist in two possible tautomeric forms: enol and diketo (Sahne et al., 2017). The keto form is predominant in acidic and neutral media (pH $\leq$ 7.4) as well as in solid state, while in non-polar and basic milieu (pH $\geq$ 8.0) the enol form is occurring (Sahne et al., 2017). Moreover, the enol form co-exists in two equivalent tautomers that undergo

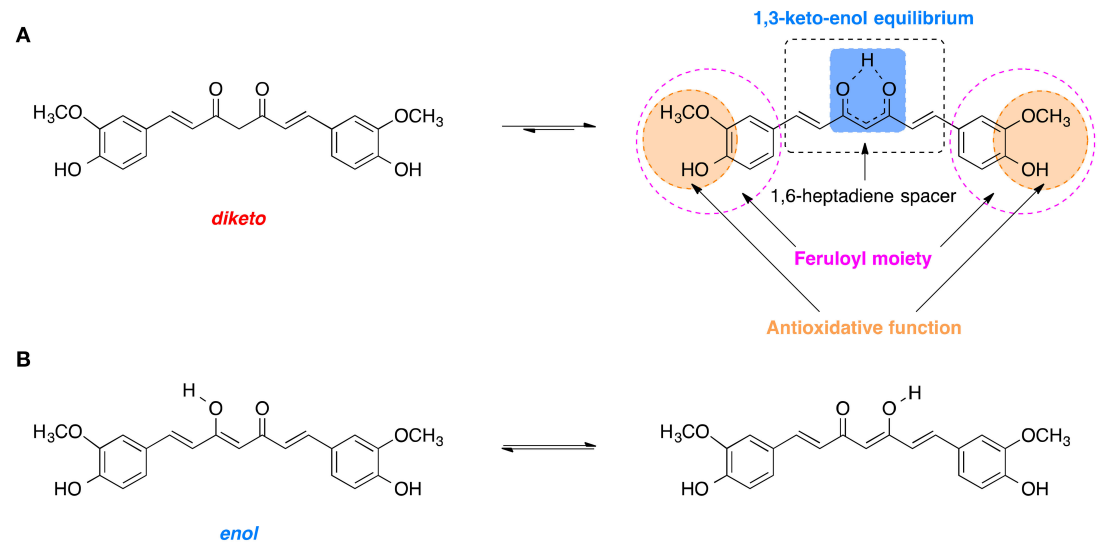


FIGURE 7 | Tautomerism of curcumin: **(A)** Diketo and 1,3-keto-enol equilibrium form of curcumin with its biologically relevant structural units. **(B)** Hydrogen transfer in the most stable enol form.

intramolecular hydrogen transfer (**Figure 7B**; Anjomshoa et al., 2016). Under physiological conditions (pH ∼7.4) curcumin can reach its 1,3-keto-enol equilibrium state. Some of the most important antioxidant properties of curcumin and its ability to scavenge ROS are associated with the stability and the antioxidative capability of the methoxy phenolic type groups that are present. The structural features of curcumin including its tautomeric forms and pharmacophores are present in **Figure 7**.

Curcumin suppresses tumor necrosis factor (TNF) activity, formation of Aβ plaques and protects brain cells from noxious agents (Belkacemi et al., 2011). In recent years, the natural polyphenols are being implemented in the treatment of different neurological disorders (Pathak et al., 2013; Hügel and Jackson, 2015).

Curcumin-enriched diet enhances memory and hippocampal neurogenesis in aged rats (Dong et al., 2012). This effect may be mediated by curcumin-induced modulation of expression of genes involved in cell growth and synaptic plasticity (Dong et al., 2012). Neuroprotective properties of curcumin are often attributed to its anti-inflammatory, antioxidant and lipophilic potential (Mishra and Palanivelu, 2008). For example, enhanced hippocampal expression of pro-inflammatory proteins TNF-α and IL-1 beta, which was caused by intracerebroventricular infusion of Aβ42 peptide solution, was at least partially normalized by infusion with curcumin-loaded lipid-core nanocapsules (but not free curcumin) (Hoppe et al., 2013a). Similarly, in neuroblastoma cells, curcumin suppressed the radiation-induced increase in activity of the pro-neuroinflammatory complex NF-κB (Aravindan et al., 2008). Activity of the neuroinflammation- and oxidative damage-related proteins NF-κB, Nrf2, and Sirt1 was also regulated in presence of curcumin in human neuroblastoma cells (Doggui et al., 2013). Curcumin treatment reduces ROS level in neuroblastoma cell lines treated with the noxious agent acrolein and in rat primary neurons with induced Ab42 hyper-expression (Ye and Zhang, 2012; Doggui et al., 2013). Curcumin protects mitochondria from noxious factors such as oxidative stress and rotenone (inhibitor of electron transport chain) *in vitro* (Daverey and Agrawal, 2016; Ramkumar et al., 2017). It also alleviates the age-associated loss of mitochondrial and oxidative activity in rodent brains (Dkhar and Sharma, 2010; Eckert et al., 2013; Rastogi et al., 2014). Curcumin also was shown to stimulate Sirt1 and Bcl-2 expression and to decrease brain cell death in experimental stroke (Miao et al., 2016). Reports also show that curcumin increases cell viability at low dosages (Ye and Zhang, 2012) and binds Aβ peptides, thus preventing them from aggregation into Aβ plaques (Yanagisawa et al., 2011). Due to its lipophillic properties, the curcumin can cross the BBB, bind to the plaques and decrease the β-amyloid plaques in AD by inducing phagocytosis of Aβ (Mishra and Palanivelu, 2008). Some of the curcumin derived pyrazoles and isoxazoles also bind to Aβ42 (**Figure 8**; Narlawar et al., 2008).

Curcumin treatment decreases Aβ40/42 and PSEN1 protein and mRNA levels in APP-overexpressing neuroblastoma cells (Xiong et al., 2011). Curcumin derivatives also increased the uptake of Aβ by macrophages, which were isolated from blood of AD patients and cultivated *in vitro* (Zhang et al., 2006). This is a relevant information, because peripheral macrophages are known to infiltrate brains of AD patients and participate in clearance of amyloid plaques (Gate et al., 2010). Moreover, in human neuroblastoma cells curcumin inhibits Aβ-induced tau phosphorylation likely via PTEN/Akt/GSK-3β pathway (Huang et al., 2014). Other researchers report, that Akt/GSK-3β and ERK pathways mediate the protective effect of curcumin on Aβ induced memory impairments (Hoppe et al., 2013b; Zhang et al., 2015). Curcumin treatment also improved hippocampal-dependent memory of Aβ-infused rats (Hoppe et al., 2013b).

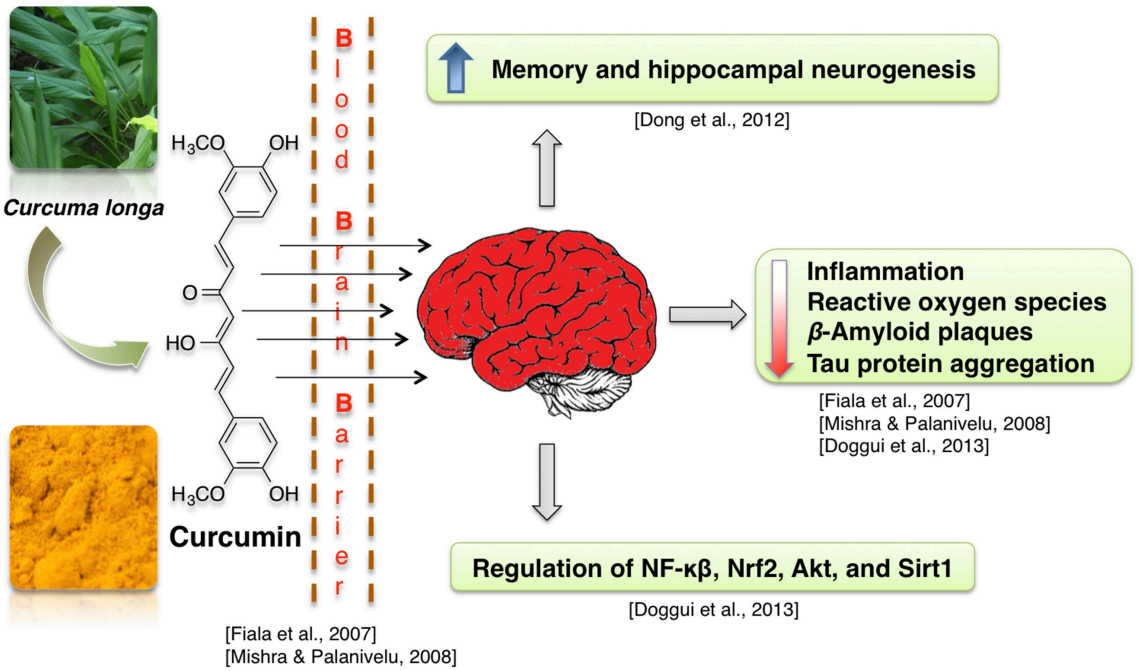


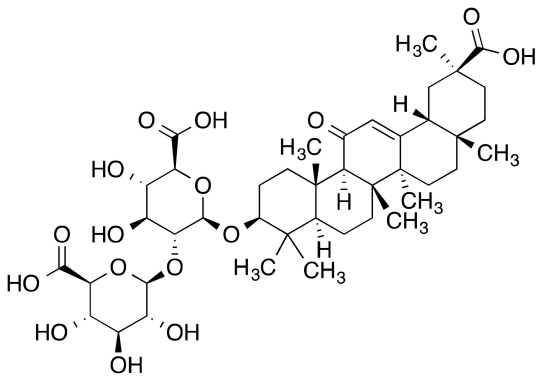
FIGURE 8 | Neuroprotective effects of curcumin.

A systematic review by Brondino et al. showed, that the few clinical trials studying the effect of curcumin on AD yielded inconclusive results (Brondino et al., 2014). Although curcumin was found to be safe during short-term use, future clinical studies need to determine its long-term safety and efficacy on human subjects (Brondino et al., 2014). Since the systematic review arrival, another clinical study was published on the topic, showing improvement of working memory and mood after curcumin treatment in a fairly small group of elderly participants (Cox et al., 2015). There is also a study showing correlation between consumption of curcumin-containing spice—curry—with cognitive performance in elderly (Ng et al., 2006). This finding should be taken with a grain of salt in context of curcumin-dementia research, as curcumin concentration in curry is fairly low (Tayyem et al., 2006) and the extent of biologically available curcumin ingested with curry is disputed. Co-administration of curcumin and donepezil (reversible cholinesterase inhibitor) had synergistic effect on cognition and oxidative stress (Akinyemi et al., 2017). Combined donepezil/curcumin therapeutic also showed good BBB permeability (Yan et al., 2017). Concluding, curcumin protects brain cells against damage induced by oxidative stress and Aβ pathology. These properties may underlie beneficial effects of curcumin for treatment of dementia symptoms, as seen in animal model studies. The data suggest, that curcumin may be a promising candidate for novel dementia medication, but conclusive clinical research that could verify this hypothesis is still lacking. Moreover, to date, researchers analyzed the efficacy of curcumin exclusively against AD-associated dementia, leaving out other dementias.

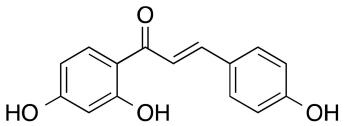
Glycyrrhiza Genus

Genus *Glycyrrhiza*, also known as licorice (liquorice), is a member of Fabaceae family and consists of about 30 species. Most of the plants of this genus are perennial herbs native to Mediterranean region, Asia, Southern Russia, and Iran (Asl and Hosseinzadeh, 2008). The *Glycyrrhiza* species are cultivated all throughout Europe and Asia (Blumenthal et al., 2000; Asl and Hosseinzadeh, 2008). The licorice roots and rhizomes are used worldwide as natural sweetener and a herbal medicine mainly for the therapy of autoimmune hepatitis C, jaundice, peptic ulcer, and skin diseases such as atopic dermatitis and inflammation-induced hyperpigmentation (Asl and Hosseinzadeh, 2008; Callender et al., 2011; Tewari et al., 2017); further studies suggest that licorice roots may also have pharmacologically useful properties such as anticancer, antioxidative, anti-inflammatory, antiviral, antimicrobial, hepato- and cardioprotectitve effects (Asl and Hosseinzadeh, 2008; Waltenberger et al., 2016). The main bioactive phytoconstituents of *Glycyrrhiza glabra* (liquorice) root are the sweet-tasting triterpene saponin glycyrrhizin (glycyrrhizic acid) and the phenolic type compound isoliquiritigenin (**Figure 9**). Other important constituents also include several isoflavonoid derivatives such as shinpterocarpin, glabrone, glabridin, galbrene, lico-isoflavones A and B (Asl and Hosseinzadeh, 2008).

Due to their antioxidative properties, several species of *Glycyrrhiza* were investigated for possible therapeutic effects as neuroprotectants against neurodegenerative disorders such as PD, AD, and dementia. For example, extract from *Glycyrrhiza inflata* prevents tau misfolding *in vitro* (Chang et al., 2016). Thus, the extract of this plant may be effective against various



Glycyrrhizin (Epigen™, Glycyron™)
(glycyrrhizic acid or glycyrrhizinic acid)
Chem. formula: $C_{42}H_{62}O_{16}$
Mol. wt.: 822.9 g/mol



Isoliquiritigenin
Chem. formula: $C_{15}H_{12}O_4$
Mol. wt.: 256.3

FIGURE 9 | Chemical structures of the major phytoconstituents of *Glycyrrhiza glabra*.

taupathies and AD. *G. inflata* extract decreased oxidative stress in cell models of spinocerebellar ataxia type 3 (SCA3), also known as Machado-Joseph disease (MJD), by upregulating the activity of PPARGC1A and the NFE2L2-ARE pathway (Chen et al., 2014). Glycyrrhizin prevents cytotoxicity, ROS generation and downregulation of glutathione (GSH), which are elicited by 1-methyl-4-phenylpyridinium (MPP^+) (Yim et al., 2007). MPP+ is a neurotoxic substance acting via interference with the mitochondrial oxidative phosphorylation (Yim et al., 2007). The GSH downregulation is noteworthy, because it is a crucial element of the antioxidative system of the brain (Dringen, 2000). Increased oxidative stress in dementia is attributed to dwindled levels of GSH (Yim et al., 2007; Saharan and Mandal, 2014). Similarly, *G. inflata* extract was shown to inhibit oxidative stress *in vitro* (Chang et al., 2016). The brain cells are susceptible to the oxidative stress. The effect of licorice extract on the oxidative stress may be connected to the beneficial effect of isoliquiritigenin on mitochondrial function (Yang et al., 2012). Licorice may reduce the damage to the brain cells, improve the neuronal function and prevent the memory impairment by diminishing oxidative stress associated with several dementia types (Ju et al., 1989; Dhingra et al., 2004).

Figure 10 summarizes the valuable effects of licorice root extract that may be useful for the treatment of dementia and/or AD-related dementia. Some authors suggest that memory-enhancing activity of the licorice root extract may be connected to its anti-inflammatory effect (Yokota et al., 1998; Dhingra et al., 2004). This data is in agreement with the known tight relationship between inflammation and oxidative stress (Dandekar et al., 2015). *Glycyrrhiza* is used in various polyherbal formulations. One of such formulations used in traditional Japanese Kampo medicine is yokukansan, which is composed of seven different plants including *Glycyrrhiza uralensis* Fisher. *Glycyrrhiza* extract antagonizes α2A adrenoceptors (Ikarashi and Mizoguchi, 2016). Several phytoconstituents of *Glycyrrhiza*: glycyrrhizin, glycycoumarin, liquiritin and isoliquiritigenin show neuroprotective effects when applied as a component of the yokukansan (Ikarashi and Mizoguchi, 2016). Isoliquiritigenin inhibited the activity of the NMDA receptors (Ikarashi and Mizoguchi, 2016). Noteworthy, memantine, an important synthetic drug against dementia, also shows antagonism for NMDA receptors (Danysz and Parsons, 2003). Moreover, the neuroprotective effect of glycycoumarin may be due to its ability to suppress the pro-apoptotic activity of caspase-3 (Kanno et al., 2015; Ikarashi and Mizoguchi, 2016).

Extract from another *Glycyrrhiza* species—*Glycyrrhiza glabra*—improved the learning ability of mice after 7 days of oral administration (Parle et al., 2004). However, another study reported the paradoxical sedative properties of the extract (Hikino, 1985). This shows that the *G. glabra* extract is useful for the improvement of the learning ability but its dose should be established carefully to prevent the sedative effects. A glycyrrhizin salt, diammonium-glycyrrhizinate, prevented the mitochondrial and cognitive dysfunctions induced by Aβ42 in mice (Zhu et al., 2012). Although not yet proven in context of brain function, licorice constituents have a potential to interact with other drugs because of its modulating activity of P450 proteins, which belong to the main regulators of xenobiotic metabolism (Qiao et al., 2014). In summary, glycyrrhiza extracts show anti-inflammatory and antioxidative properties and modulate glutamate signaling and apoptosis. Similarly to above described herbal medicines curcumin and ginseng, despite animal model-based evidence for glycyrrhiza effectiveness in regulating cognitive deficits, there are currently no studies on effectiveness of this plant for dementia therapy in patients.

Camellia sinensis Kuntze

Camellia sinensis Kuntze (green tea) brew is one of the most extensively consumed beverages in the world (Goenka et al., 2013). Several beneficial effects of green tea consumption

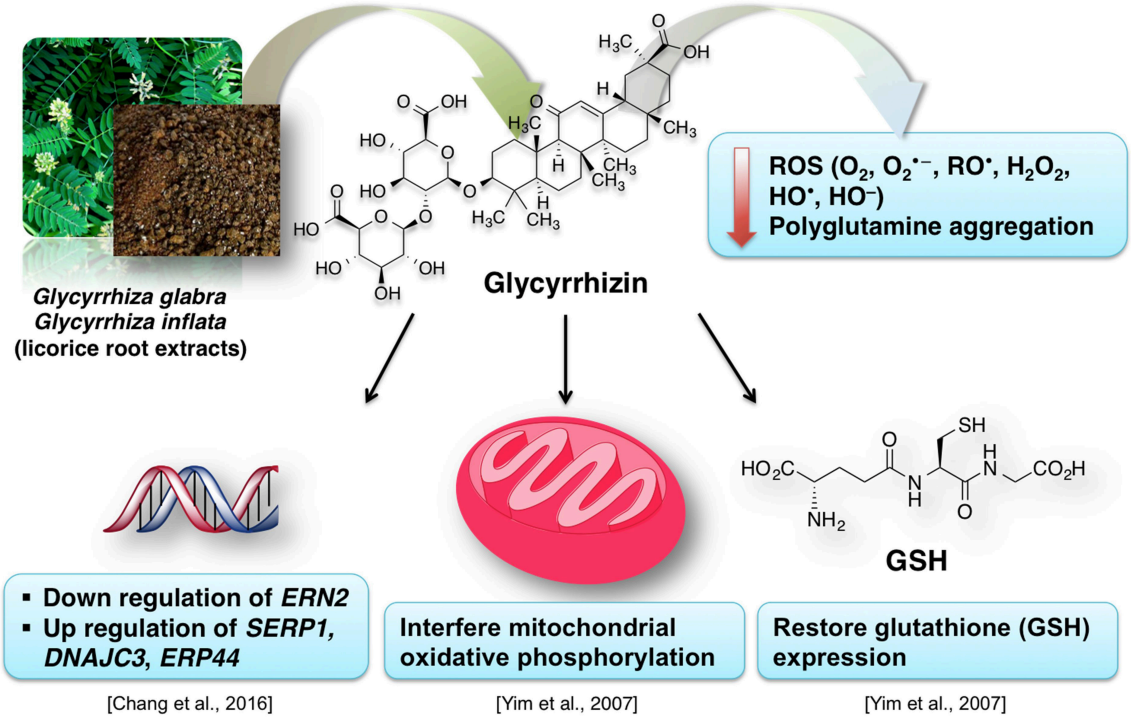


FIGURE 10 | A simplified representation of the neuroprotective effects of licorice for dementia treatment.

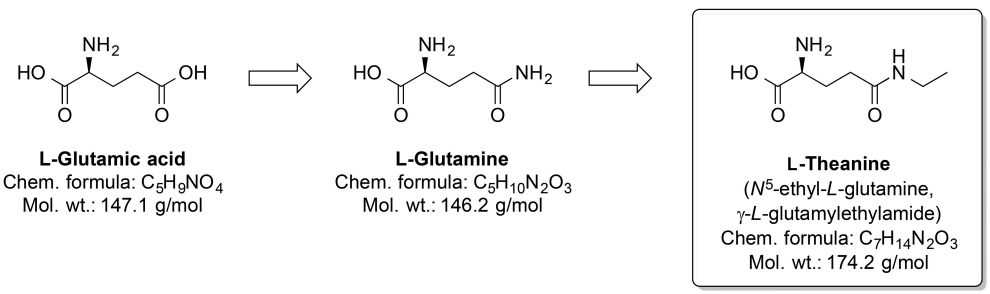


FIGURE 11 | Chemical structures of the nootropic drug L-Theanine and its proteinogenic amino acid analogs.

are reported for various conditions like obesity, diabetes, inflammation, coronary artery disease, stroke and some malignancies (de Mejia et al., 2009; Chacko et al., 2010). Consumption of green tea-related compounds [e.g., (-)-epigallocatechin-3-gallate] improves cognitive functions and prevents memory impairment in animals and humans (Rezai-Zadeh et al., 2008; de Mejia et al., 2009; Mandel et al., 2011).

Around one-third out of 4,000 bioactive compounds of *C. sinensis* are polyphenols (Mahmood et al., 2010). The gene expression and activity of the membrane metalloendopeptidase (MME) were enhanced by green tea extract. Several MME are capable of degrading Aβ peptides (Wang et al., 2006). Pretreatment by infusion with extract of green tea leaves into the left hippocampus of a rat prevented cognitive impairments and superoxide dismutase activity changes, and corrected deregulated activity of pro-inflammatory enzyme COX and AChE, which were induced by injecting $AlCl_3$ into the same brain area (Jelenkovic et al., 2014). When injected i.p. L-theanine, one of the amino acid components of *C. sinensis*, protects against memory impairment and cell death caused by ischemia (Egashira et al., 2007, 2008). Interestingly, chronic ingestion of L-theanine in rats also caused improvement in cognitive functions (Yamada et al., 2008) and decreased oxidation levels in the brain of the rats (Nishida et al., 2008). Similarly, in transgenic mouse AD model, the green tea constituent epigallocatechin-3-gallate normalized the dysregulated ROS production, as well as mitochondrial respiration and MMP (Dragicevic et al., 2011). Generally,

L-theanine is an *N*-amino-ethylated analog of the proteinogenic neurotransmitter L-glutamic acid and its precursor L-glutamine (**Figure 11**). L-theanine protects against Aβ42-induced memory deficits and death of cortical and hippocampal cells, possibly by suppressing the ERK/p38 and NF-κB signaling pathways and reducing the oxidative damage (Kim et al., 2009).

Daily consumption of green tea is hypothesized to reduce the risk of AD and age-related dementia (Ayoub and Melzig, 2006). In some clinical studies, L-theanine improved the cognitive functions and mood in combination with caffeine in healthy human subjects (Haskell et al., 2008; Owen et al., 2008). On the other hand, the results of studies on the effects of L-theanine alone on mood are inconclusive (Kimura et al., 2007; Haskell et al., 2008). Green tea catechins can regulate activity of P-glycoprotein (Zhou et al., 2004), which may influence brain availability of co-administered substances. Summarizing, green tea extract shows antiapoptotic and antioxidative activities and may even directly inhibit Aβ plaque formation. Moreover, several human studies provide credibility to the hypothesis that green tea constituents may be effective for modulation of human cognition and perhaps in dementia treatment.

CONCLUSIONS

In this work, we discuss that a large number of plants have been used for dementia treatment worldwide. The mechanisms of action of the reviewed five prominent representative plants generally involve anti-inflammatory, antioxidative, and antiapoptotic activity that are mainly associated with the neuroprotective effects of these plants or their bioactive constituents. Some of such naturally occurring compounds exhibit promising potential as alternative therapeutic strategies. For example, curcumin showed remarkable synergetic effects on cognition and oxidative stress, as well as good BBB permeability, when co-administrated with the approved reversible ChE inhibitor donepezil. Moreover, such combined donepezil/curcumin application may be useful for treatment of dementia symptoms, as seen in animal model studies. Furthermore, combined supplement treatment with some mitochondrial antioxidants, such as α-lipoic acid and acetyl-L-carnitine has been shown to reduce both physical and mental weariness or even to restore memory function in age-related diseases, including AD and different types of dementia, as provided in transgenic mouse model of AD. However, there are still many unknowns in this research area that need to be clarified by planning future studies. The scientific community needs more comprehensive research focused on identifying active ingredients of plants and investigating their mechanism of action. Such research will facilitate clinical studies evaluating the potential of the featured herbal products in dementia treatment. We conclude that further research on plants used in different ethnomedicinal practices and the traditional medicine could lead to the development of novel therapeutics for dementia and, therefore, is of a very high interest.

AUTHOR CONTRIBUTIONS

DT, AMS, and AA have written the first draft of the manuscript. AM, ANS, LH, JH, and NT revised and improved the first draft. All authors have seen and agreed on the finally submitted version of the manuscript.

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