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Review Article

Treatment of Age Related Memory Impairment with Natural Products: A Review of Literature

Sarthak Bothra[1,2], Changda Liu[1], Xiaoke Chen[1,3] and Xiu-Min Li[1]*

[1]Icahn School of Medicine, Center for Integrative Medicine for Allergies and Wellness, pediatric Allergy and Immunology, China
[2]Affiliated with University of Connecticut, USA
[3]The Eighth Affiliated Hospital, Sun Yat-sen University, Shenzhen, China

***Corresponding Author:** Dr. Xiu-Min Li, Professor of Pediatrics, Division of Allergy and Immunology, Jaffe Food Allergy Institute; Director, Center for Integrative Medicine for Allergies and Wellness; Icahn School of Medicine at Mount Sinai, New York; Tel: 212-659-1493; E-mail:

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Abstract:

Background: Memory impairment is a natural occurrence that accompanies the aging process and is considered one of the most predominant outcomes of aging. However, it can lead to more serious impairments of cognitive function such as dementia. The aging of the global population has resulted in an increasing prevalence of dementia around the world. As a result, there has been an increase in interest to find novel approaches to alleviate cognitive impairment. Recently, there has been increased focus on the use of natural products for the treatment of memory impairment through the use of herbal medicine found in traditional medicines by slowing the aging related neurodegenerative process.

Methods: In this study, data was gathered from the following search engines: PubMed, ScienceDirect, Google and ClinicalTrials.gov. When searching these databases, the following keywords were used to select studies: "memory impairment", "cognitive'', "herbal medicine", "plant", "inflammation", and "oxidative stress". All references used in this review article were written in English and the interval of time since publication did not exceed 20 years. References used in this review contain clinical, preclinical, in vivo, ex vivo, and in vitro studies with subjects including humans and numerous species of rats and mice.

Results: After extensive research, 4 natural products Berberine, Ginseng, Ginkgo biloba, and BacopaMonnieri have shown significant success in studies to aging related cognitive impairment process. Treatment with these products appears to have desired effects on combating neurological disorders by interacting with the underlying mechanisms involved in the pathogenesis of many diseases.

Conclusion and future directions: Further studies are required to further confirm the efficacy of herbal medicine in aged human patients afflicted with these neurological conditions.

Keywords: Aging; Cell Death; Herbal Medicine; Neuroinflammation; Oxidative Stress; Synaptic Plasticity

Introduction: Aging of the global population has been accompanied by increasing cases of cognitive impairment, including mild cognitive impairment (MCI) and the diseases associated with dementia. Alzheimer's disease (AD), the most common form of dementia, affects over 47.5 million individuals worldwide, with millions more suffering from other causes of dementia. The number of aged adults suffering from AD is expected to increase and currently there are 7.7 million new cases each year. AD is marked by a progressive loss of cognitive function induced by the presence of plaques and tangles in the hippocampal region of the brain and is, along with other dementia inducing diseases, a growing problem around the world [1].

Currently, much of the efforts are being directed towards advancing the diagnosis, progression, and therapy for the diseases associated with dementia. While over the past 30 years knowledge about the pathophysiology of these disorders has increased greatly, there is still no satisfactory treatment to slow

or stop the underlying processes involved. Instead, there are a handful of approved drugs that exist, which provide only a modest slowing of cognitive decline. The current treatment available is unsatisfactory because it only helps with symptom management, and does not slow cognitive decline [2].

This is why natural products and traditional medicines are receiving a great deal of attention currently, as they offer novel treatments for memory decline that Western Medicine has not been able to achieve so far. Such forms of traditional medicine such as Traditional Chinese Medicine (TCM), Ayurveda, Kampo, Traditional Korean Medicine (TKM), and Unani have been practiced for centuries and as a result, have transitioned to highly regulated systems of medicine. Herbal Medicine offers many options to combat the progression and symptoms of AD. Recently a trend in the marketing of drugs based on medicinal plants has developed, allowing them to gain momentum and scientific significance in health-relevant areas [3].

Herbal medicine has been practiced in many areas of the world and has blossomed into regulated systems of medicine over time. When used for drug development, natural products provide some clear advantages, such as abundant clinical experiences and a large diversity of chemical compounds and wide array of therapeutic effects. This paper reviews the literature on the viability of herbal medicine for the treatment of memory impairment and dementia in the aged population [4].

How Memory Works: When referring to memory, the term generally refers to the ability to reproduce experiences or learned content. Memory can be classified as implicit or explicit, where implicit memory generalizes nonverbal habitual memory (riding a bicycle) and explicit memory stands for active or passive recall of facts (factual knowledge, speech, etc.). Another common distinction is between short term and long term memory, where short term memory pertains to a time span of seconds to minutes, and long term memory refers to recall over a long period of time. Another way memory has been classified is with regard to content: episodic memory, verbal memory, visual memory, and olfactory memory [5].

Hippocampus plays a critical role in learning and memory, in which functional and structural changes within the hippocampus are involved in learning and memory, which includes the acquisition, consolidation, and retrieval of information. Additionally, neurogenesis in the hippocampus, defined as the generation of new nerve cells, is involved in memory formation. Increased neurogenesis is improved spatial memory while impaired neurogenesis indicates poor cognitive function. The hippocampal network, including the parahippocampal gyrus, hippocampus, and neocortical areas, play a major role in the process of memory consolidation and retrieval. Although its function has not yet fully been understood, the hippocampus seems to be involved in binding features of an event into a mental representation, which is important to form episodic memory [2,5].

In addition, the cortical regions also play an important role in memory. The frontal lobe plays a crucial role in the coordination of information and is therefore important in working memory [6]. The temporal lobe is associated with autobiographical memory in particular as well as recognition memory. Damage to the temporal lobe has been found to impair long-term episodic memories [7]. The parietal lobe can be associated with being responsible for assisting with verbal short-term memory. Consequently, damage to this region could result in short-term memory loss [8].

Age Related Memory Impairment: In the aging process, pathophysiological changes occur in the brain that eventually lead to the diseases associated with memory impairment. Some of the most notable physical changes include a loss of volume in the brain that is caused by dendrites withering away, causing communication between cells to become less effective. Additionally, the myelin sheath becomes thinner with age, resulting in the brain receptors firing at a slower rate. As there are many possible causes of memory decline, each need to be considered in detail. One likely cause of mental decline is due to diminished blood flow in small vessels that can become clogged by cholesterol and fats or can rupture from high blood pressure. These changes are usually undetected, however can cause cumulative damage over time. Another common cause is due to a lifetime accumulation of oxidative free radicals, which are a result from energy metabolism. With age, inflammation becomes a greater risk factor as well, as when brain cells die or get damaged, healthy neurons are assaulted with inflammatory cytokines which have been shown to lead to memory impairment as well [9].

Normal Aging: Not all forms of aging have the same impact on the brain. The least severe effect of aging on memory can be seen in normal aging, otherwise

known as Age Associated Memory Impairment (AAMI). This is a form of decline predominantly in episodic memory that is not associated with any neuronal degeneration and is experienced by the majority of individuals over time [10]. According to the guidelines set by the Memory Disorders Project, an individual at least 50 years old is considered for AAMI if they meet the following criteria: patient has noticed a decline in memory performance, the patient scores below normal levels on a standard test of memory, and all other causes of memory decline have been ruled out [10,11].

Mild Cognitive Impairment: Mild cognitive impairment (MCI) is an intermediate stage between the expected cognitive decline associated with normal aging and the more aggressive decline of dementia, where an individual's memory declines below the level considered normal for their age group [11]. It can result in problems with thought, memory, and language that are greater than normal age related changes. This is a state where memory loss does occur, however not enough to influencenormal daily functioning. Currently the exact causes and mechanisms of MCI are unknown, however studies have shown that it can increase the risk of progressing to dementia caused by AD or other neurological diseases in the future [10].

Dementia: On the most severe end of the spectrum in terms of memory impairment is dementia, which describes a variety of symptoms that affect memory function, thought, and social abilities severe enough to interfere with daily functioning [10]. Some of the most common diseases associated with dementia include Alzheimer's disease, Vascular Dementia, Parkinson's disease, and Huntington's disease. Of these, Alzheimer's disease is the most prevalent form of dementia, accounting for 60-70% of all dementia cases. Over time, Alzheimer's disease results in nerve cell death and tissue loss throughout the brain, causing it to shrink dramatically over time. The pathogenesis of AD involves the formation of plaques and tangles, which interfere with normal neuronal function [12]. The formation of plaques occurs when abnormal clusters of beta-amyloid protein fragments build up between nerve cells and block cell-to-cell signaling. Tangles form inside the nerve cells and cause tau protein to collapse into twisted strands, preventing nutrients from moving through cells and eventually leading to cell death. Many mechanisms such as oxidative stress, inflammation, cholinergic dysfunction, and synaptic plasticity deficits are major contributors to the pathogenesis of AD, as well as many other diseases associated with dementia [12]. Currently, the leading theory for the progression of AD is known as the Amyloid Cascade Hypothesis (ACH). According to the ACH, the initial deposition of Aβ is the pathological trigger for Alzheimer's disease. This is subsequently followed by the formation of neurofibrillary tangles (NFTs), which results in neuronal death and dementia. Mutations of amyloid precursor proteins (APP) result in Aβ42 aggregation. The Aβ42 aggregates then form soluble forms of oligomeric Aβ as well as deposited Aβ peptides, both of which result in aggregate stress. Elevated stress then can lead to formation of NFTs, which consist primarily of the protein tau. Over time, elevated stress and presence of Aβ peptides lead to neuronal dysfunction and death, the cause of dementia [13].

Mechanisms of Memory Impairment: Oxidative Stress: One factor that has a crucial role in the pathogenesis of many diseases involving memory impairment is oxidative stress, which results from an imbalance between free radicals and antioxidant systems. Oxygen free radicals can attack proteins, nucleic acids, and lipid membranes, through which they can disrupt cellular function as a whole. The Brain tissue contains large amounts of polyunsaturated fatty acids that are extremely vulnerable to radical attack. Known as lipid peroxidation, this form of oxidative damage is thought to be one of the more damaging forms of oxidative degradation that damages the cell membrane and produces numerous secondary products that have neurotoxic effects [2]. Under normal conditions, damage by reactive oxidative species (ROS) is kept in balance by an effective multitude of antioxidant systems that are able to terminate the oxidation chain reactions that can damage cells [14]. However, over time through the aging process, the antioxidant defense system becomes weaker and as a result, there are fewer antioxidants to keep the oxidative species in check. The imbalance between free radicals and antioxidant systems allows the free radicals to attack proteins, nucleic acids, and lipid membrane, therefore negatively impacting cellular function and integrity. As brain tissue contains large amounts of polyunsaturated fatty acids, radical damage to the lipid membrane (lipid peroxidation) is known to be a very damaging form of oxidative degradation [2].

Neuroinflammation: Another mechanism that has been proven to result in memory impairment is neuroinflammation, which is often triggered by an external stressor. While studies have shown that age is a contributing factor to the extent of inflammatory

response in the brain, the mechanisms that facilitate the central inflammatory response are still unknown [15,16].

Glial cells have a critical role in the inflammatory response present in the central nervous system (CNS), which are generally activated during neuropathological conditions. Specifically the role of glial cells in the inflammation process involves the proliferation, migration, and induction of proinflammatory molecules (cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), etc.) to the target area. As a result, glial cells are a major cause of memory impairment caused by inflammation because activated glia result in neuronal and synaptic plasticity through the release of proinflammatory and cytotoxic factors such as iNOS-derived nitric oxide, tumor necrosis factor alpha (TNF- α), and Interlekin 1 beta(IL-1β). The production of these factors eventually leads to neuronal and synaptic damage, which is a major cause of memory impairment resulting from inflammation.

Arguably the most important pathway involved in neuroinflammation is the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) signaling pathway, as it is a master regulator of inflammation and plays a critical role in the control of many genes involved in inflammation. In addition the NF-kB pathway acts as an essential transcription factor for the induction of many inflammatory cytokines such as iNOS, COX-2, and TNF- α. As such, it is a key target for many anti-inflammatory drugs [17].

Cholinergic Dysfunction: The cholinergic system is considered one of the most important neurotransmitter systems involved in the regulation of cognitive functions throughout the CNS as it allows for communication between cells. There is a large body of evidence suggesting that cholinergic activity is involved in memory processes. It seems that cholinergic activity is essential to learn several tasks and recent works suggest that acetylcholine plays an important role during the early stages of memory formation. Damage to the cholinergic system, which is responsible for producing the neurotransmitter acetylcholine (Ach), has been shown to be associated with memory impairment most commonly associated with AD. In the hippocampus, Ach is a crucial neurotransmitter involved in both memory and learning, two components which are greatly impacted as AD progresses. In the cholinergic hypothesis of AD, it was proposed that reduced synthesis of acetylcholine was a possible cause of Alzheimer's disease, while increasing the levels of acetylcholine could reduce the severity memory impairment caused by AD [18].

Synaptic Plasticity Deficits: The human brain is comprised of over a trillion (10^{12}) neurons, and a quadrillion (10^{15}) synapses, which in combination allow for the entirety of human perception. While the nervous system is generally thought to be genetically hard-wired, the neural circuits undergo extensive rewiring based on given stimuli. This process of experience dependent changes in synaptic connectivity where synaptic connections are strengthened and weakened is known as synaptic plasticity and is what allows of memory and learning in the brain. With the aging process however, pathological manifestations of aging such as an increase in the presence of ROS or inflammatory cytokines can play a negative role in the modulation of neuronal processes, which then leads to memory impairment over time. While ROS are known to be necessary components of the signal transduction cascades underlying normal synaptic plasticity, research conducted by Hu et al. indicates that the presence of ROS shifts from a positive role to a negative role during the aging process, acting as a neurotoxic agent that likely contributes to brain dysfunction [16].

Mechanism Interactions: Figure 1 outlines a visual depiction of the main mechanisms involved in the progression of impairment. Studies show that generally there is more than onemechanism involved in aged memory impairment. Instead, many of the known neurodegenerative mechanisms contribute to the impairment of cognitive function simultaneously. This is of note because medicines that target multiple mechanisms will be far more effective than drugs that can only target a specific symptom or pathway. Oxidative stress is one mechanism that is widely known for inducing cognitive function due to an increase in ROS. As shown in the diagram, levels of oxidative stress markers, which cause an increase in ROS and lipid peroxidation, as well as levels of antioxidant defense markers, which reduce oxidative stress, can be used to measure the extent of oxidative stress in the brain. The compounds 8-Hydroxy-2′deoxyguanosine (8-OHdG), malondialdehyde (MDA), Superoxide dismutase (SOD), catalase (CAT), and Reduced glutathione (GSH) are some of the main components involved in oxidative stress. Neuroinflammation can damage tissue in the brain and is caused by an increase in the proinflammatory cytokines: interferon gamma (IFN-γ),

interleukin-1 (IL-1), interleukin-6(IL-6), iNOS, and TNF-α. The NF-κB inflammatory signaling pathway can be activated by proinflammatory cytokines such as IL-1 and TNF-α. It plays an important role in regulating the expression of the proinflammatory cytokines mentioned above, and as a result, is the target for many anti-inflammatory drugs. One significant problem that makes single mechanism drugs ineffective in treating oxidative stress and inflammation is that they form a positive feedback loop, where oxidative stress results in the production of proinflammatory cytokines TNF-α and IL-6, leading to an increase in inflammation. Elevated levels of proinflammatory cytokines result in an increase of ROS in the brain, resulting in more oxidative stress.

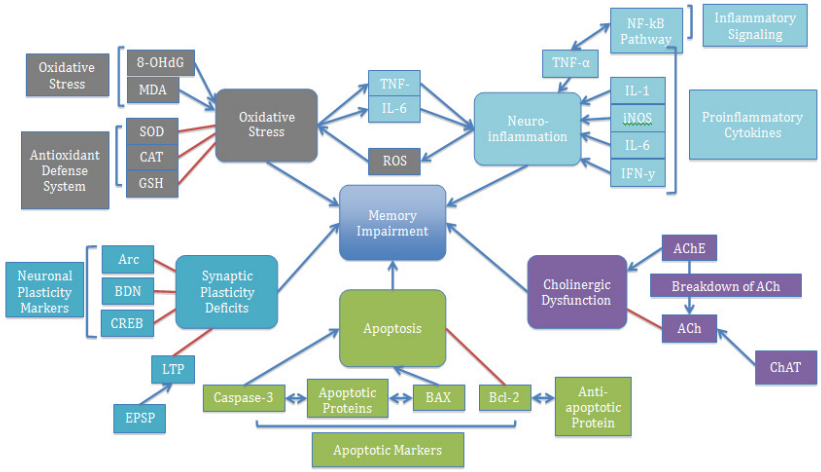


Figure 1: Visual depiction of major mechanisms underlying memory impairment, including oxidative stress, neuroinflammation, synaptic plasticity deficits, apoptosis, and cholinergic dysfunction. Also shown in this figure are key molecules that have shown promoting or suppressing properties in the laboratory setting. Blue arrows indicate promotion of the respective mechanism and red lines indicate suppression of the respective mechanism. 8-OHdG, 8-Hydroxy-2′deoxyguanosine; MDA, malondialdehyde; SOD, superoxide dismutase; CAT, catalase; GSH, reduced glutathione; TNF-α, tumor necrosis factor alpha; IL-6, interleukin-6; ROS, reactive oxidative species; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; IL-1, interleukin-1; iNOS, inducible nitric oxide synthase; IFN-γ, interferon gamma; BDNF, brain-derived neurotrophic factor; CREB, cAMP response element binding protein; EPSP, excitatory postsynaptic potential; LTP, long term potentiation; BAX, bcl-2-like protein 4; Bcl-2, B-cell lymphoma 2; AChE, acetylcholinesterase; Ach, acetylcholine; ChAT, choline acetyltransferase

Acetylcholine (ACh) is an important neurotransmitter in the cholinergic system. It gets synthesized by the enzyme choline acetyltransferase by catalyzing the transfer of an acetyl group from acetyl-CoA to choline, yielding acetylcholine. As correct cholinergic function is required for normal learning and memory formation, cognitive deficits arise when the enzyme acetylcholinesterase breaks down acetylcholine. This results in synaptic transmission being impaired, eventually leading to learning and memory deficits.

Apoptosis leads to impairment of learning and memory through neuron cell death. Three crucial molecules that regulate cell death are Caspase-3, Bax, and Bcl-2, which are also used as apoptotic markers, indicating apoptotic levels in the brain. Caspase-3 and Bax proteins promote neuronal apoptosis while Bcl-2 regulates apoptosis as an inhibitor.

Current Treatment for Memory Impairment: Current treatments for Alzheimer's disease and other forms of dementia don't offer a satisfactory remedy for these diseases as they only mask the symptoms of the disease, but do not treat the underlying disease or delay its progression. Commonly in the treatment of Alzheimer's disease, cholinesterase inhibitors such as donepezil, galantamine, and rivastigmine are used. These drugs prevent the enzyme acetylcholinesterase from breaking down the neurotransmitter acetylcholine, which is a crucial molecule in the cell signaling process. While these drugs were developed for thesymptomatic treatment of Alzheimer's disease, they have been tried in other dementias, particularly vascular dementia, with limited success. The most serious flaws of these drugs is that they do not remedy the underlying problems of Alzheimer's disease by reducing beta-amyloid deposits, and instead treat the symptoms of the disease through an alternate mechanism.

Additionally, the side effects of these drugs are extensive, ranging from mild to moderate effects that could potentially result in further complications. Some of the possible side effects resulting from administration of cholinesterase inhibitors such as donepezil include nausea, diarrhea, weight loss, stomach pain, changes in vision, among others [12].

Another drug used to treat memory impairment is memantine, which is an NMDA (N-methyl-D-aspartate) receptor antagonist, which regulates the activity of glutamate, another important neurotransmitter involved in learning and memory. Attachment of glutamate to NMDA receptors allows calcium to enter the cell, however in Alzheimer's disease, excess glutamate results in overexposure to calcium, eventually causing cell damage. Memantine combats this process by partially blocking NMDA receptors and preventing an influx of calcium. Similar to the cholinesterase inhibitors, memantine has significant side effects as well, which include blurred vision, rapid weight gain, altered heartbeat, stomach pain, among others [10].

Piracetam is a nootropic drug in the racetams group. Although it is not approved for use by the FDA, piracetam is commonly used by individuals in many European countries, Asia, and South America to enhance cognitive function and to slow the onset of age-related memory loss by elderly individuals. While the mechanisms of action utilized by piracetam are not fully understood, it has been shown to improve the function of acetylcholine and impact NMDA glutamate receptors, both of which are directly involved with learning and memory [19]. However, studies on piracetam have given conflicting evidence in terms of its effectiveness in treating memory impairment and its possible side effects. A 2002 and 2004 review concluded that there was not enough evidence to support piracetam for improving dementia or cognitive problems [19,20]. A 2005 review, however stated that piracetam had some positive effects in older patients with those problems [21]. Based on the research conducted, piracetam is not a reliable treatment for aged memory impairment due to the conflicting reviews.

Brain Reserve Capacity as a Confounding Factor: In recent years, the concept of 'brain reserve capacity' has emerged. It is a term that can be used to describe an inherent difference between individuals in their 'baseline adaptive neuroplasticity', where there is a greater potential for remodeling of cortical circuits in response to stressors [22]. This reserve potential in individuals is hypothesized to have neuroprotective effects in late life disorders ranging from cognitive impairment, to depression. This may serve as a confounding factor in studies that examine cognitive impact of aging, as drugs will have varying mechanistic interactions with inter-individual differences in the recruitment of networks and cognitive processes. In addition, brain reserve capacity might prove to be problematic when determining efficacy of a treatment of interest, as both may have potential to mitigate cognitive impairments.

Herbal Medicine Used for the Treatment of Memory Impairment: Currently there is a great deal of interest in the use of herbal medicines for the treatment of memory impairment. As a result, there is a great deal of research being conducted on a variety of active compounds and extracts that have been found in traditional medicine around the world. As shown in Table 1, there are a large number of herbal medicines being studied currently that are known to ameliorate cognitive and memory impairment in aged individuals [2,23-29]. As an examination of all of the most well known herbal medicines is beyond the scope of this review article, it will instead focus on four of the most promising medicinal herbsthat are currently under investigation: *Berberis spp.*, *Panax ginseng*, *Ginkgo Biloba,* and *Bacopamonnieri.* These herbal medicines show a great deal of potential due to the fact that they have been shown to impact multiple major mechanisms that can result in memory impairment [19,24,25]. As a result, these medicinal herbs have a higher therapeutic potential, as they can reduce memory impairment through the use of multiple mechanisms instead of just one. Additionally, there is more knowledge on the clinical impacts of the herbal medicines discussed in this article than those listed in Table 1, therefore their risks and side effects are well known in comparison [2].

	Popular herbal treatments currently in study for the treatment aged memory impairment	Author and Publication Date
1	Bacopa monnieri [27]	Aguiar and Borowski (2013)
2	Berberis spp. [24]	Kumar et al. (2015)
3	Celastrus paniculatus [2]	Jivad and Rabiei (2014)
4	Cyperus rotundus [2]	Jivad and Rabiei (2014)
5	Epimedium spp. [23]	Yuan et al. (2016)
6	Galantamine [28]	Jivad and Rabiei (2014)
7	Ganoderma spp. [29]	May et al. (2013)
8	Ginkgo Biloba [26]	Belviranli and Okudan (2015)
9	Huperzine A [2]	Jivad and Rabiei (2014)
10	Hypericum perforatum [2]	Jivad and Rabiei (2014)
11	Lavandula officinalis [28]	Jivad and Rabiei (2014)
12	Lepidum meyenii [2]	Jivad and Rabiei (2014)
13	Lycopodium serratum [2]	Jivad and Rabiei (2014)
14	Melissa officinalis [2]	Jivad and Rabiei (2014)
15	Morinda citrifolia [2]	Jivad and Rabiei (2014)
16	Panax ginseng [30]	Lu et al. (2009)
17	Polygala tenuifolia [2]	Jivad and Rabiei (2014)
18	Prunella vulgaris [2]	Jivad and Rabiei (2014)
19	Saliva officinalis [28]	Ghasemian et al. (2016)
20	Zizyphus jujube [2]	Jivad and Rabiei (2014)

Table 1: A table highlighting 20 of the most popular herbal medicines found in traditional medicine that have shown therapeutic potential for the treatment of memory impairment in aged patients.

As there is no effective treatment to stop the decline in cognitive function with illnesses such as Alzheimer's disease, other treatments are being considered as alternatives to the drugs used presently for the treatment of memory impairment [2]. As Table 2 shows, the medicinal herbs discussed in this review (*Berberis spp.*, *Panax ginseng*, *Ginkgo Biloba,* and *Bacopamonnieri*) exhibit an array of therapeutic effects that combat the underlying mechanisms of aged memory impairment. Herbal medicine has the possibility to be a very effective treatment for memory impairment for a few reasons. As forms of traditional medicine such as Traditional Chinese Medicine (TCM) and Ayurveda have existed for thousands of years, there are a great deal of clinical observations that demonstrated the effects of the medicinal herbs in humans. Additionally, herbal medicines have a variety of chemical compounds, which can result in diverse therapeutic benefits. Studies have shown that the relative amount of side effects presented by administration of herbal medicines is lower than those presented by drugs in contemporary medicine [2,3].

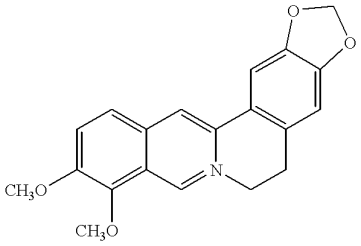
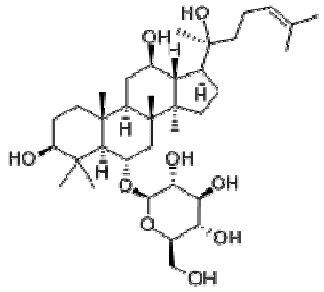
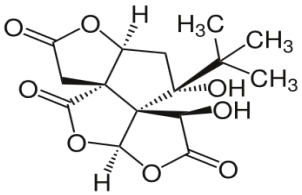
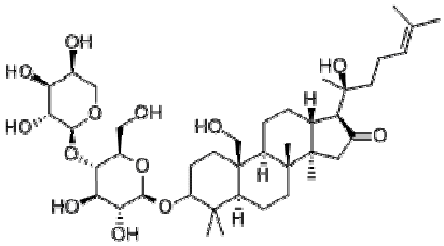
Compound of Interest	Herbal Medicine of Origin	Chemical Structure	Mechanisms
Berberine	*Berberis spp.*		• Antioxidant [18,21] • Anti-inflammatory [17] • Acetylcholinesterase Inhibitor [21]
Ginsenoside Rh1	*Panax ginseng*		• Antioxidant [22,24] • Anti-inflammatory [22] • Amyloid plaque inhibitor [25]
Bilobalide	*Ginkgo biloba*		• Antioxidant [2,27] • Anti-inflammatory [2] • Amyloid plaque inhibitor [2] • Anti-apoptotic [2] • Synaptic plasticity protector [28]
Bacoside A	*Bacopa monnieri*		• Antioxidant [30] • Anti-inflammatory [30] • Synaptic plasticity protector [29] • Acetylcholinesterase Inhibitor [50]

Table 2: Plant of origin, chemical structure, and mechanisms utilized by the compounds of interest: Berberine, Ginseng, Ginkgo biloba extract, and Bacosides.

Berberine: Berberine, a benzylisoquinoline alkaloid, is an active component found in many plants such as the genus *Berberis*, *Hydrastiscanadensis, Xanthorhizasimplicissima,* and *Phellodendronamurense,* among others and is usually extracted from the roots, rhizomes, stems, and bark of these plants [24]. In traditional Chinese medicine (TCM), berberine has been used to treat a wide variety of medical ailments, ranging from treatment for inflammation to diabetes and constipation [30]. Given the extent of its use in traditional medicines, berberine has a beneficial role in the treatment of human diseases. A search on https://clinicaltrials.gov of "berberine" showed that currently there have been 29 clinical trials conducted on the efficacy of berberine for many diseases, including Colorectal Adenoma, Hyperglycemia, Gastritis, Type 2 Diabetes Mellitus, Atherosclerosis, and coronary artery disease. However, currently there have been no clinical trials conducted on the efficacy of berberine

in treating neurological disorders [24,30]. The search on https://clinicaltrials.gov indicates that there has been little change since 2015 in the number of clinical trials addressing the use of berberine as a treatment for age induced memory impairment, as there are currently no clinical trials in progress in regards to the efficacy of berberine in this regard.

Berberine has extensively been studied in the laboratory setting for its therapeutic potential against neurodegeneration and has shown promise to be a potential candidate for the treatment of various neurological disorders. As shown in Table 2, berberine combats a variety of mechanisms that are potentially responsible for memory impairment. Berberine decreased the degree of oxidative stress in the hippocampus of male Sprague Dawley rats after a pilocarpine injection, shown by a significant decrease in MDAlevels and an increase in a rise in the levels of antioxidative agents CAT, SOD, and GSH [31]. The decrease in MDA levels indicate that berberine can prevent the rise in lipid peroxidation in the brain, while the increase in antioxidative agent levels indicate an increase in antioxidant defense after supplementation of berberine. Morris water maze results show a dose dependent decrease in escape latencies in pilocarpine injected rats treated with berberine, indicating that administration of berberine could ameliorate memory deficits induced by pilocarpine. A separate review study conducted presented similar results, summarizing a decrease in MDA levels and an increase in GSH and SOD levels after administration of berberine [32].

Lee et al. studied the anti-inflammatory effect of berberine and its impact on scopolamine induced memory impairment in rats. The study found that treatment with berberineintraperitoneally at a dose of 20 mg/kg significantly reduced the levels of IL-1B and IL-6 proteins in the plasma [25]. Berberine also increased levels of brain-derived neurotrophic factor (BDNF) and cAMP response element binding protein (CREB) while lowering levels of IL-1B, TNF- α, and COX-2 in the hippocampus. Results from the water maze test showed a reduction in escape latency for rats treated with berberine, an indicator that berberine can ameliorate scopolamine induced deficits to spatial memory and learning [9,25].

Bhutada et al. evaluated the effect of berberine administration on streptozotocin (STZ) induced cognitive impairment through the amelioration of cholinergic function [33]. The results showed that chronic treatment with berberine significantly and dose dependently reduced cognitive impairments, cholinergic dysfunction, and oxidative stress markers in STZ-induced diabetic rats. As mentioned earlier, cholinergic neurotransmission is a crucial process that underlies memory and cognitive function. Cholinergic basal forebrain neurons innervate the cerebral cortex and hippocampus and are essential for learning and memory formation. The study found that cholinesterase (ChE) activity was significantly increased in the cortex of the STZ injected rats. Treatment with berberine significantly decreased the ChE activity in the hippocampus. Morris water maze tests show a decrease in escape latency of STZ injected rats treated with berberine, in a dose-dependent manner [33].

Currently, there is very limited evidence that reports adverse effect of treatment with berberine, however some important studies regarding side effects of berberine administration are discussed here. Berberine treatment at a dose of 5-15 mg/kg decreased the number of dopamine releasing neurotransmitters in the substantia nigra region in the midbrain region [18,34]. In addition, berberine has shown to inhibit dopamine synthesis in cell culture medium. It was found to be neurotoxic at a dose of 10-30 μM by increasing the neurotoxicity of 6 – hydroxydopamine [35]. Future studies should be conducted to determine toxic doses of berberine as well as its interactions with other chemicals.

Ginseng: Ginseng is a highly valued plant in the east and only recently has gained widespread in the west over the past decade. Its roots and especially its main root have been used in traditional medicine for thousands of years and are used to treat various diseases [36,37]. Ginseng is known to have a wide range of pharmacological uses due to the large number of ginsenosides present in ginseng. Approximately 40 ginsenoside compoundshave been identified so far, and appear to be responsible for the majority of the properties of ginseng, two of which include antioxidation and anti-inflammation [36]. A search on https://clinicaltrials.gov shows that 107 clinical trials are being conducted on the effects of ginseng in the treatment of conditions including Alzheimer's disease, autoimmune disease, depression, diabetes mellitus, rhinitis, among many others. Clinical trials conducted on memory decline indicate that ginseng has potential to be used for the treatment of many memory disorders like Alzheimer's disease [2].

Although there are a large number of identified ginsenosides that all share a four-ring, steroid-like structure, they can be separated into two groups

based on the number and position of their sugar groups, namely the 20(S)-protopanaxadiol(Rg3) and 20(S)-protopanaxatriol(Rg1) saponins. Rg1 is normally metabolized into the ginsenosides Rh1, the main metabolite with one moiety, and Ppt, the end metabolite with no sugar moiety. On the other hand, the Rg3 ginsenoside is hydrolyzed into Rh2 which contains two sugar moieties, and Ppd, which has no sugar moieties. The various metabolites formed are likely responsible for the diverse bioactivity of ginsenosides observed *in vivo* [38]. Ginsenoside Rh1, for example, has memory-improving effects in normal mice and scopolamine-induced amnesic mice [39]. Ginsenoside Rh1 (20 μmol/kg; 40 μmol/kg) administered to the mice intraperitoneally for 23 day, prevents cognitive impairment induced by sleep deprivation, and its ability to reduce oxidative stress in cortex and hippocampus may contribute to the mechanism of action [40].

Lee and Oh studied the effects of red ginseng on memory decline in aged C57BL/6 mice to determine if ginseng could be used as a potential nutraceutical for memory impairment [41]. Levels of proinflammatory cytokines iNOS, COX-2, TNF- α, and IL-1B were measured in the hippocampus of mice after administration of red ginseng (20 mg/kg/day) for 3 months. When compared to the control group of aged mice, the mice treated with ginseng pellets showed a significant decrease in the levels of proinflammatory cytokines, indicating that red ginseng has anti-inflammatory capabilities. Levels of the antioxidant agent GSH were also measured, and results indicate that treatment with red ginseng raised GSH to normal levels in aged mice. This indicates that red ginseng improved free radical scavenging ability in aged mice, evidence of its antioxidant properties. In this study, three memory tests were performed, the Y-maze task, novel object task, and the Morris water maze test, used to measure willingness to explore new environments, long-term memory index, and learning and spatial memory respectively. Data from each test indicated a decrease in memory impairment in aged mice, as spontaneous alternation (%) and total entries were increased to normal levels after treatment with red ginseng in the Y-maze task, and there was a significant decrease in escape latency for aged mice treated with red ginseng in the water maze test [41].

Kim et al. evaluated the efficacy of fermented ginseng on memory impairment and β-amyloid reduction in a scopolamine-induced amnesia model in male ICR mice [42]. Aβ42, a toxic form of Aβ that increases in AD, was measured in the mouse brain to determine the effect of fermented ginseng on the progression of AD. In mice treated with fermented ginseng, there was a significant reduction in the levels of Aβ42 by over 44.95±5.08% when compared to the control group. This study concluded that ginsenosides Rg3, Rg5, and Rk1 were responsible for the Aβ42 reducing property of fermented ginseng [42].

There are a high number of studies that examine the pharmacological properties of products containing *P. ginseng*, both in the laboratory and clinical setting. The UK Medicines Control Agency has received reports of adverse effects of *P. ginseng* in 17 patients with no fatal outcomes. Reports of headache, nausea, acute hypotension, arrhythmia, gastrointestinal disorders, and rashes were shown after consumption of ginseng monopreparations. Overall however, ginseng is well tolerated by most users with the most common side effects being mild and reversible [43].

Ginkgo Biloba: Ginkgo biloba is an herbal medicine native to China, and is now cultivated in many western regions including Europe and America [2,44]. In China, it has been used to treat a variety of ailments for thousands of years ranging from blood circulation problems to depression in the elderly populations. The extract of Ginkgo biloba (EGb 761) is used for treatment and is reported to contain about 24% Flavonoids and 6% Terpene lactones [2,45]. Reliable evidence shows that Ginkgo biloba has potential to combat memory impairment through its neuroprotective mechanisms, including reducing apoptosis, inhibition of membrane lipid peroxidation, anti-inflammatory effects, and inhibition of beta-amyloid aggregation. Currently there have been extensive clinical studies conducted on the role of Ginkgo biloba in cognitive disorders. 57 studies have been conducted so far, which establish it as an effective treatment for stopping the progression of neurodegeneration [2].

Bilobalide is a sesquiterpenetrilactone isolated from the leaves of *Ginkgo biloba*. Structurally, the presence of a side chain of Bilobalide close to an oxygen atom results in a polar environment of the molecule. Its polar nature as well as other structural features influence how Bilobalide interacts with $\alpha_1\beta_2\gamma_{2L}\gamma$-aminobutyric acid ($GABA_A$)receptors, thus resulting in the effects *Ginkgo biloba* has on cognition [46].

A study of Ginkgo biloba extract (GBE) on cognitive functions and oxidative stress levels in aged female rats was conducted by Belviranli and Oxudan

and found that Ginkgo biloba supplementation lowered MDA and 8-OHdG levels in brain tissue and increased BDNF levels in plasma, which regulate neuronal development [26]. It was concluded that GBE supplementation improved cognitive functions by decreasing oxidative damage and increasing BDNF levels. Results from the Morris water maze test supported this conclusion, with administration of GBE resulted in a decrease in escape latency as well as an increase in number of platform crossings in the aged mice.

A different study conducted by Williams et al. examined the effect of standardized Ginkgo biloba extract (EGb 761) on synaptic plasticity and excitability [35]. It concluded that chronic administration of EGb 761 significantly increased long-term potentiation (LTP) in aged C57BL/6 mice. The population spike (PS) threshold was also increased with EGb 761 administration, indicative of a reduction in basal neuronal excitability. The authors of this study propose that a reduction of neuronal excitability could be advantageous in an aged system, acting as a protective mechanism against hyper excitability.

Das et al. studied the efficacy of Ginkgo biloba in inhibiting AChE activity in the brain of scopolamine injected male Swiss mice [47]. A specific focus was placed on the ability of Ginkgo biloba to combat dementia resulting from disruption of the central cholinergic system and cholinergic neuronal loss in the hippocampus. The study demonstrated that Ginkgo biloba was effective in reducing AChE activity and scopolamine-induced dementia at a dose of 30 and 60 mg/kg, however was not viable at a dose of 15 mg/kg. The authors concluded that Ginkgo biloba has potent cognitive enhancing properties through its mechanism of improvement of disrupted cholinergic function [47].

A study conducted by Moulton et al examined the effect of *Ginkgo Biloba* in healthy males on memory and cognition. Among one of the factors monitored were the adverse effects of *Ginkgo biloba* supplementation. The study reported that 86.7% of participants did not report any side effects. Of the remaining participants who did report adverse effects, they included minor headaches, heartburn, and indigestion [48].

BacopaMonnieri: Bacopamonnieri is a medicinal herb native to India and Australia and has been used in Ayurvedic medicine for over 1400 years [27]. The entire plant is used medicinally, and has been used as a brain tonic, memory enhancer, cardio-tonic, and anticonvulsant agent [49]. Results from studies indicate that it has an important role in therapies for the treatment of cognitive disorders of aging, due to its antioxidant, anti-inflammatory, and analgesic properties. The nootropic activity of Bacopamonnieri extract can be attributed to the presence of two major saponins: bacoside A and B. Although clinical research on Bacopamonnieri is far from complete, at least six detailed, randomized, double-blind, placebo-controlled human trials have been conducted on the efficacy of Bacopa monnieri [27]. A systematic review of the clinical studies was conducted by Pase et al. and concluded that Bacopamonnieri could potentially be clinically prescribed as a memory enhancer, even for patients not afflicted with dementia [50].

Bacoside A is a mixture of the four triglycosidicsaponinsbacoside A3, bacopaside II, bacopasaponin C and bacopaside X. These bacosides are all types of triterpenoid saponins with jujubogenin or pseudojujubogenin moieties as the aglycone units [51]. Saponins are susceptible to glycosidic cleavage at varying sites, which result in the formation of secondary metabolites. Recent studies have shown thatthese metabolites show better biological activity and pharmacokinetic characteristics when transformed *in vivo*. This suggests that the chemical constituents of Bacopamonnieri may be converted to its subgroups that have the capacity to inhibit AChE activity in the brain.

Dhanasekaran et al. assessed the neuroprotective mechanisms of Bacopamonnieri extract and their effects on oxidative stress cascades, scavenging of reactive speciesand hydrogen peroxide-induced lipid peroxidation in the brain [52]. The study concluded that treatment with Bacopamonnieri extract could reduce beta-amyloid levels in the brain, dose-dependently reduce levels of ROS, and decrease the formation of lipid peroxides.

Chronic treatment with Bacopamonnieri also ameliorates age associated neuroinflammation in aged female Wistar rats [28,53]. The rats were treated with bacosides at a dose of 200 mg/kg over a period of 3 months, extracted from Bacopamonnieri extract resulting in approximately a 30-40% yield of saponins. Levels of iNOS and proinflammatory cytokines such as IL-1B, TNF- α, and IFN-y were found to be significantly higher in brain homogenate of aged rats when compared to young rats. After bacoside treatment, there was a significant decrease

in iNOS and proinflammatory cytokine levels, indicating that Bacopamonnieri has potential as an anti-inflammatory medicine.

A study conducted by Das et al. explored the therapeutic potential of a bacoside A enriched alcoholic extract (CDRI-08) in a scopolamine induced amnesic Swiss mice to see the effects of molecular markers of brain plasticity [47]. Results of the study indicate that CDRI-08 extract significantly enhanced the expression of plasticity markers in the cerebrum of the amnesic mice in addition to up regulating both BDNF mRNA and protein levels. The authors concluded that CDRI-08 extract might activate cholinergic signaling and eventually transcription of memory linked neuronal and glial plasticity markers.

A randomized, double blind, placebo-controlled study on the cognitive effects of a standardized *Bacopamonnieri* extract reported that a total of 41 adverse effects were reported by the patients, twenty three from the placebo group and eighteen from the standardized *Bacopamonnieri* group. Of the effects reported by the treatment group, "flu-like symptoms" and digestive problems were the most commonly stated, however the study concluded that there was no statistical difference in the adverse effects between the placebo and treatment groups [54].

Conclusion: Currently there is no treatment available to slow or stop the progression of dementias such as Alzheimer's disease [2]. There are only a limited number of FDA drugs that can be used to temporarily improve symptoms. The effectiveness of these treatments can vary greatly across the population and none treat the underlying mechanisms of the diseases. Herbal medicine shows a great deal of promise in the treatment of cognitive diseases because of their array of cognitive benefits and more importantly, their mechanisms of action which target the fundamental pathophysiology of the disease [28]. One of the greatest advantages of traditional medicine therapeutics is the principle of "synergism" that is present in many herbal medicines. In other words, herbal medicines often have multiple active components and compounds that in conjunction can result in an effect that is greater than that of an individual compound [4].

The herbal medicines discussed in this paper all showed potent neuroprotective properties shown through both laboratory and clinical trials, although for some herbs, further clinical testing was needed. The herbal compounds mentioned in this review all showed evidence of targeting multiple underlying mechanisms of memory impairment, including oxidative stress, inflammation, acetylcholine reduction, cholinergic dysfunction, and beta-amyloid aggregation. The neuroprotective properties of the herbal medicines on these mechanisms mentioned indicate a significant potential for their use in ameliorating aged memory impairment through cognitive diseases.

Future Directions: The aim of this review was to provide an overview of the protective role of widely used herbal medicines that are common in traditional medicines around the world specifically on neurodegenerative diseases. There is a large amount of literature supporting claims of herbal medicine as a potential effective treatment for memory impairments, however there is much work yet to be done. As traditional medicine has been around for many centuries, there is valuable information on natural products where documents and data are unfortunately mixed in with speculation without scientific basis and useless rumors [4]. Therefore, further clinical studies on the neuroprotective role of the herbal medicines Berberine, Ginseng, Ginkgo biloba, and Bacopamonnieri are needed on patients affected by neurodegenerative diseases to provide documented evidence of their efficacy. Additionally, there is little known about the constituent molecules present in many herbal medicines nor is much known about their underlying mechanisms of action [2]. Research focus should be placed on identifying the many molecules present in herbal medicines, including the large number of ginsenosides present in ginseng, flavonoids present in Ginkgo biloba, and bacosides in Bacopamonnieri, as well as understanding their mechanisms of treatment. Finally, as mentioned above, the reason herbal medicine has shown such promise in the treatment of a variety of medical conditions can be attributed to the biological chemodiversity found in herbal medicine. Currently not much is understood on the effects of interaction between chemical molecules on the treatment of neurological disorders. Current drugs utilize a "one disease, one target, one drug" approach to cognitive diseases. A synergistic approach to the treatment of complicated disorders, such as dementia, cardiovascular diseases, and diabetes, should be examined in extensively and in depth.

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