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The Use of Herbal Supplements on Minimizing the Clinical Manifestations of Alzheimer's Disease

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THE USE OF HERBAL SUPPLEMENTS ON MINIMIZING THE CLINICAL MANIFESTATIONS OF ALZHEIMER'S DISEASE: A LITERATURE REVIEW

by

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Abstract

Alzheimer's disease (AD) affects over 5 million individuals in the United States annually. By the year 2050, the number of individuals living with AD is projected to triple (Latest Alzheimer's Facts and Figures, 2016). Although there is no cure for AD, there are many prescriptive pharmacologic agents used to help manage the clinical manifestations of the disease. Complementary and alternative medicines (CAM) and herbal supplements are also used in the treatment of AD, however indications for their use and effectiveness during the progression of AD have not been examined. The purpose of this study was to examine the use of herbal supplements in managing the clinical manifestations of AD. The secondary purpose was to compare a variety of herbal supplements used to treat the clinical manifestations of AD and to evaluate the most widely used and most beneficial for clinical practice. A literature review examining herbal supplements and their risks, benefits, and uses in AD was conducted from multiple online databases. Peer reviewed articles published in the English language from 1998-2016 that focused on herbal supplements used to control the clinical manifestations of mild to severe AD were included for synthesis. Results from 14 studies that used herbal supplements as a treatment for the clinical manifestations of AD were compared for effectiveness in the management of symptoms. The findings suggest Ginkgo Biloba is the most effective and widely used herbal supplement in the treatment for cognitive decline in AD. Other supplements including Saffron, Curcumin, Cistanches Herba, and Sage were found to improve memory function and activities of daily living in individuals with AD. Herbal supplements can be cost effective and easier to retrieve for many individuals in comparison with prescriptive drug therapy. Although the research demonstrated beneficial results with the use of herbal

supplements, the limitations of these studies make the application of the results problematic. Therefore, further research in this area is required.

Dedications

To my loving family and friends for the constant support and love throughout this journey.

To my grandfather James Donohue for giving me the inspiration and drive to build such an interest in this topic.

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Introduction

Alzheimer's disease (AD) affects over 5 million individuals in the United States annually. Due to the older generation population growing, by the year 2050, the number of individuals living with AD is projected to triple. (Latest Alzheimer's Facts and Figures, 2016). Although there is no cure for AD, there are many prescriptive pharmacologic agents used to help manage the clinical manifestations of the disease. Agents used to treat AD include cholinesterase inhibitors, antidepressants, antipsychotics, tricyclic antidepressants, and benzodiazepines. These pharmacologic agents lessen memory loss and confusion, and treat mood and sleep changes. Complementary and alternative medicines (CAM) and supplements are also used in the treatment of AD, however indications for their use and effectiveness during the progression of AD have not been examined.

Although prescriptive pharmacologic therapy is widely used by individuals for the treatment and management of AD, the use of herbal supplements in relation to AD is not widely studied. Over–the-counter, herbal supplements are used daily for a variety of different ailments including; improving memory function, lowering cholesterol, preventing colds, preventing nausea and vomiting, and lessening joint pain. Although there are herbal supplements recommended for patients with AD, their effectiveness in regards to symptom management and disease progression has not been established. Most studies conducted on the use of herbal supplements and their effectiveness at managing the clinical manifestation of AD have been based on testimonials and small sample sizes, indicating the need for further research.

Problem

Clinical manifestations of AD are often debilitating and difficult to control. Although pharmacological therapy is the most widely prescribed and used treatment plan for controlling the signs and symptoms of AD, some individuals prefer complementary and alternative therapies for a variety of reasons. There is a lack of evidence to support the use of herbal supplements on managing the clinical manifestations of AD as a solo therapy or in concurrence with prescribed agents. Herbal supplements must be further evaluated to better understand the risks and benefits as agents used for relief of the clinical manifestations of AD.

Purpose

The purpose of this literature review is to examine the use and effectiveness of herbal supplements and their benefits on minimizing clinical manifestations of AD. There is insufficient research to show herbal supplements have a positive and significant effect on the clinical manifestations of AD. There is also a lack of evidence on when herbal supplements should be included as part of an individual's therapy and how early herbal supplements should be started in treating the manifestations of the disease as it progresses in symptom severity. Most of the research has been based on small sample sizes and inconsistently designed research methods, yielding mixed or insignificant results.

Understanding the benefits of herbal supplement use for controlling the clinical manifestations of AD can provide options for an individual's course of treatment, either as solo therapy or as an adjuvant to prescriptive therapy. Research is needed to educate individuals with AD about different herbal and drug therapy options they can use to help control certain clinical manifestations of the condition, including memory loss and sleep disturbances. Individuals may prefer CAM treatments over pharmacologic treatments, so healthcare providers must obtain the knowledge on herbal supplements and their safety and effectiveness to help aid individuals in the right direction of treatment.

Method

A literature review was performed using research articles available from 1995 to 2016 regarding the use of herbal supplements and their relationship in managing clinical manifestations of Alzheimer's disease. The focus was mainly related to the use of herbal supplements as drug therapy for Alzheimer's disease. Databases that were used to search for articles included Cumulative Index to Nursing and Allied Health Literature (CINAHL), Educational Resources Information Center (ERIC), Elton B. Stephens Co. Host (Ebsco Host), Medical Literature On-line (Medline), and Psychological Information Database (PsychINFO). Searches used a combination of the following terms: Alzheimer's, dementia*, herbal supplement*, clinical manifestation*, symptom*, benefit*, and risk*. Inclusion criteria consisted of 1) published research in English, 2) herbal supplements used at all stages of AD and as adjuvant therapy to prescriptive agents, and 3) herbal supplements used in AD to control clinical manifestation of the condition. Articles that were excluded focused on AD therapy with only prescriptive agents and AD treatments that did not include the use of herbal supplements.

Each article was evaluated and individually critiqued for relevance to the topic and application to the use of herbal supplements in people with dementia. In the appendices, Table 1 summarizes the findings for each article that was reviewed for this thesis. Studies in this review include both quantitative and qualitative studies, and systematic literature reviews that were published between 1998-2016. None of the single articles included in this research were included in the systemic literature reviews. The studies were published in a range of different countries, including the United States, London, the Netherlands, China, Korea, and the United

Arab Emirates. The data was extracted to synthesize the relationship between the benefits of herbal supplements in controlling the clinical manifestations of AD. Subsequently, all the critiqued articles were synthesized by the researcher, and key findings were extracted along with consistent and inconsistent findings and gaps in the literature. Limitations of the study and recommendations for future research also were noted.

Background

AD, the leading cause of dementia, is a progressive, neurological disorder that destroys brain cells, causing memory loss and dysfunction. The underlying pathophysiologic cause of AD is not completely understood, however, research has highlighted the clinical manifestations and expected progression of the disease. AD is thought to be caused by the buildup and degradation of amyloid beta peptides in the brain. An increase of amyloid beta peptides causes neurologic inflammation in the central nervous system, both in the blood brain barrier and the brain parenchyma, resulting in neurofibrillary tangles and neuron remodeling. In addition, peripheral immune cells also have the ability to assist in the neuro-inflammatory process in the blood brain barrier and brain parenchyma. Research in brain injury related to AD suggest the neuro-inflammatory response may lead to neurodegeneration, causing brain damage (Dá Mesquita et al., 2016).

There is an abundance of known risk factors leading to AD. Genetics and environmental factors can influence a diagnosis of AD in individuals that exhibit the symptoms. A leading risk factor for AD is the expression of the ApoE ε4 allele. This allele is found in the majority of persons with AD, and has a direct connection to the development of AD and the course of the disease process. ApoE ε4 may also increase the severity of vascular risk factors associated with AD. Other risk factors include high cholesterol, smoking, cognitive impairment issues, low education levels, female gender, elevated homocysteine levels, and elevated human placental lactogen (Panpalli Ates, Karaman, Guntekin, & Ergun, 2016). These risk factors should be closely monitored in individuals, so the disease can be caught at an early stage. In the future,

individuals with risk factors may be tested for the ApoE ε4 allele to help make the diagnosis. With continuous research on the ApoE ε4 allele, researchers may be able to find better therapies for the management of AD and for therapy that can lead to improved quality of life in individuals suffering from the clinical manifestations of AD. In addition, further research on benefits of herbal supplements that may affect the ApoE ε4 allele is needed to determine when this therapy should be started in the course of AD.

AD progresses through four stages: predementia, moderate, mild, and severe. Predementia levels can be measured by arterial spin-labelling cerebral blood flow (ASL-CBF). Stage 1 predementia is defined as a decrease in ASL-CBF, with abnormal amyloid-β (Aβ) in both the temporal and parietal regions in the brain. Stage 2 predementia has both abnormal Aβ and total-tau with decreased ASL-CBF in the temporal regions of the brain (Binnewijzend et al., 2016). As the CBF decreases, AD advances into more severe stages. After the predementia stages, an individual will progress through multiple phases of AD. In the mild stage of AD, individuals begin to have trouble remembering recent events, misplace items, and have a tough time planning events. These individuals are still able to function independently, but start to withdraw themselves from certain events and daily tasks. The moderate or middle stage of AD begins when an individual can't recall what day it is, or mistake people in their family for the wrong person. The confusion and forgetfulness manifests and progressively worsens. The individual will need assistance with certain activities of daily living. In the final stage, the severe or late stage of AD the individual requires total care. The individual is unable to converse, and physical abilities, including walking become a challenge. The disability will progress and result in complications and comorbidities that will eventually lead to death. The leading cause of death

in AD is usually infection or respiratory failure (Alzheimer's stages, 2015). Medications or alternative therapies can be used at any stage in an effort to control symptoms or delay progression, but they are not curative.

The predominant clinical manifestations of AD are progressive memory loss and changes in mental status. These often manifest as apathy, delusions, hallucinations, anxiety, agitation, and irritability (Tokuchi et al., 2016). Some individuals will become extremely violent, while others prefer isolation. Due to the progressive memory loss associated with AD, recognition of people, places, and objects becomes increasingly difficult to distinguish. For example, individuals with later stages of AD often fail to recognize family members, or accuse loved ones of stealing. Often times, an individual with AD has realistic delusions that their significant other is having an affair, which leads to anger, mistrust, and frustration. AD is difficult to manage because of the differentiating manifestations of each individual. Likewise, individual's that are taking prescription drug therapy or herbal supplements will often present with varying response to these agents and the majority will show some form of AD clinical manifestations despite therapy.

Pharmacological therapies are most often used to manage the clinical manifestations of AD. Some of the most common drugs used for AD are Acetylcholinesterase Inhibitors (AChEI), N-Methyl-D-asparate Receptor Antagonists (NMDA), and Amyloid Binders. AChEI's are used to increase the brain's cholinergic functions, and are usually well tolerated. NMDA's work to block the overstimulation of nitric oxide. Overstimulation of nitric oxide leads to cell death, so NMDA's are a common treatment individuals receive. Amyloid Binders help to prevent the formation of Aβ senile plaques. (Mendiola-Precoma, Berumen, Padilla, & Garcia-Alcocer, 2016). Some individuals will be prescribed a combination of medications used to treat AD as

well as a variety of other medications to manage manifestations, including mood changes, and sleep disturbances.

Nonpharmacological therapies, or CAM, are not as widely used to treat the clinical manifestations of AD. However, CAM such as exercise, mental challenges, folic acid supplements, and the Mediterranean diet have been shown to improve cognitive function in individuals with AD (Mendiola-Precoma et al., 2016). Herbal supplements are not commonly known for the management of AD, however certain herbal supplements may have the ability to help prevent the start of AD, or help to manage the cognitive decline of the brain once the disease is already diagnosed. Herbal supplements are used by many people with AD, but only limited studies have found any statistical evidence to support their use.

The use of herbal supplements in AD and their effectiveness in controlling the clinical manifestations of the condition is not fully understood. Although research suggests herbal supplements can have a positive impact on the clinical manifestations of AD, much of the research was based on small sample sizes and may not be applicable to the larger population. There is no significant evidence to support the therapeutic benefits of herbal supplements for the treatment of clinical manifestations of AD, such as memory loss and irritability. Although current research provides us with mostly inconclusive results, several studies showed promising results with certain herbal supplements, supporting the need for further research on the topic.

Herbal supplements are regulated differently than prescription pharmacologic agents, causing many individuals to misunderstand the safety and use of herbal-based products. Herbal supplements are often misused by individuals because they choose to self-treat instead of consulting their provider. Individuals that use herbal supplements for their intended purpose

agree they are an effective and a safe means of treatment (Gray & Rutledge, 2013). Individuals often appreciate that herbal supplements cost less than prescriptive drug therapies, and many would prefer herbal supplements if health insurance covered the costs (Gray & Rutledge, 2013).

Individuals with AD often use herbal supplements as part of their treatment and begin taking herbal supplements in the early stages of the disease. By beginning the herbal supplement use in the early stages of AD, individuals hope to preserve their memory function and delay other clinical manifestations of the disease as much as possible. In most cases, individuals that have AD are willing to try herbal supplements in conjunction with prescriptive agents to help control the manifestations of the disease.

Herbal supplements commonly used to treat AD include flavonoids, resveratrol, and gingko biloba. After several small clinical trials, Flavonoids have been considered effective in the treatment of AD and aid in protecting neurologic functions (Mendiola-Precoma et al., 2016). Resveratrol has been shown to assist in protecting neurons from cell death and oxidation. It is an anti-inflammatory substance, and has also been shown to promote the normal function of neural mitochondria (Mendiola-Precoma et al., 2016). Ginkgo biloba is the most researched herbal supplement in relation to AD. Ginkgo biloba used in combination with cholinesterase inhibitors show a significant improvement on a mini mental state examination (MMSE) in individuals with AD, however both gingko biloba and the cholinesterase inhibitor used alone did not show a substantial improvement on MMSE scores (Canevelli et al., 2014). Gingko biloba is known to have minimal side effects, and other herbs such as sage and balm have been found to have memory improving effects as well (Perry, Pickering, Wang, Houghton, & Perry, 1998). There are a variety of herbal supplements which may have beneficial effects for an individual with AD,

but the lack of substantial research and knowledge related to their effectiveness and ability to improve the quality of life in individuals with AD makes their use questionable.

Nonetheless, studies have suggested fewer sleep disturbances and improved memory function when individuals with AD include certain herbal supplements in their treatment. One study showed the therapeutic effect of Ginkgo Biloba had similar effects as Donepezil, which is a pharmacologic drug that treats impairment of memory. Individuals preferred the use of Ginkgo Biloba compared to Donepezil because it had minimal side effects compared to Donepezil (Perry et al., 1998).

Results

Fourteen studies related to herbal supplement effectiveness on the clinical manifestations of AD were included in this literature review. Of the fourteen studies reviewed, five studies solely focused on the effectiveness of herbal supplements compared to a placebo group. These studies indicated that herbal supplements can show an improvement in individual's cognitive function through better scores on the short cognitive performance test (SKT), the Neuropsychiatric inventory (NPI), Alzheimer's Disease assessment scale-cog (ADAS-Cog), and the Clinical-Dementia Rating scale (CDR). These citations also concluded no harm was found by using an herbal supplement as treatment. One citation compared a sole pharmacologic treatment, which is most often used in managing the clinical manifestations of AD, to an herbal supplement combined with a pharmacologic treatment. This study found the group receiving the combination treatment had a much higher Mini-mental status exam (MMSE) score compared to the solo pharmacologic therapy. Another citation compared solo pharmacologic treatment with solo herbal supplement treatment and both displayed similar benefits. The remaining seven citations were based on qualitative studies and literature reviews. These studies suggested decreased production of Aβ plaques, improvement in behavioral and cognitive decline, neuroprotective effects, anti-oxidant effects, and improving both quality of life and activities of daily living.

Table 1 discusses the findings of the articles, which were analyzed to determine the benefits of herbal supplements in treating the clinical manifestations of AD. The researched examined within this thesis provides a framework of herbal supplement use in managing the clinical manifestations of AD. Although many herbal supplements were studied, Ginkgo Biloba,

Resveratrol, and Curcumin were the most widely researched. Ginkgo Biloba had the most significant and reliable results for controlling the clinical manifestations of AD.

Ginkgo Biloba

Ginkgo Biloba is the most widely studied herb in relation to treating manifestations of AD, however, mixed results regarding the effectiveness have been found. Spatial memory, one of the deficits frequently affected in early AD, includes recognizing your hometown or the layout of a house. Gingko biloba was found to have protective effects against spatial cognitive impairment in early AD (Anekonda & Reddy, 2005). In another study Ginkgo Biloba was combined with AChEI's and was compared to solo AChEI treatment. Although the sample size was 828, only 29 participants received the combined treatment. The combined treatment showed a significantly higher mini-mental status examination (MMSE) score than solo drug therapy with an AChEI, however it did not show a significant improvement in the ADAS-Cog score or activities of daily living (ADL's) (Canevelli et al., 2014). Furthermore, a Ginkgo Biloba supplement of EGb 761 was studied in a trial against a placebo treatment group. The Egb 761 group showed an SKT score improvement of -1.4 and a total NPI increase of -3.2, while the placebo group showed minimal change (Ihl et al., 2011). In two qualitative studies both showed Ginkgo biloba to improve cognitive function in patients with AD (Mendiola-Precoma et al., 2016) (Perry et al., 1998). A literature review examined 6 articles on Ginkgo Biloba and 5 of these articles showed Ginkgo Biloba having a positive impact on improved cognitive functions and activities of daily living in individuals with AD (Yang et al., 2014). Although the majority of the studies have shown beneficial effects with the use of Ginkgo Biloba, further research is needed to confirm these effects due to small sample studies and animal testing. Likewise, the

studies examining the use of Gingko biloba were limited to early onset of AD manifestations, such as forgetfulness and spatial recognition, and did not address issues related to advanced disease or progression of symptoms.

Curcumin

Aβ plaque accumulation noted on advanced scanning techniques, such as magnetic resonance imaging (MRI) of the brain, is one of the main signs of AD. In a research study involving the effects of curcumin intake in people with AD, curcumin blocked the aggregation of Aβ1–40 and the formation of Aβ1–42 fibrils and oligomers. These substances accumulate in the brain as individual's age and are associated with the onset of AD. In the same research, the accumulation of Aβ plaques was found to be reduced in aging mice (Anekonda & Reddy, 2005). A study evaluating the effects of curcumin on mice found that the mice receiving curcumin were able to perform better in memory task related activities, and showed improvement in spontaneous behavior, compared to mice in the control group not receiving curcumin (Mi Hye, Sung-Hoon, & Woong Mo, 2014). Further research in human participants could possibly provide insight into the beneficial effects of curcumin in slowing the progression of plaque formation in the brain.

Saffron

Saffron was shown to be safe and effective in treating certain clinical manifestations of mild-moderate AD including fatigue, depression, and memory loss. Saffron used as the sole treatment for AD showed significant improvement on the ADAS-Cog and CDR tests compared to the placebo group. On both the ADAS-Cog and CDR tests, the higher the score, the higher

level of cognitive dysfunction is present in the individual. By week 16 of the trial, the group receiving saffron improved by -3·69 on the ADAS-Cog and -0·67 on the CDR test. No significant difference was found in adverse effects including dizziness, dry mouth, and nausea between the saffron and placebo groups. These results concluded that although saffron was found effective, it was only for short term use and needs to be further evaluated. (Akhondzadeh et al., 2010)

Resveratrol

Resveratrol has been studied for use in a variety of conditions, including AD. Resveratrol has been tested in both humans and rats and was found to have multiple benefits. In rats, resveratrol prevented oxidative stress and both intracerbroventrical and straptozotocin induced cognitive impairments. Oxidative stress is an imbalance between reactive oxygen species (ROS) and the body's ability to detoxify and repair the resulting damage (Anekonda & Reddy, 2005). Oxidative stress arises early on in the process of AD, preceding the events of plaque and neurofibrillary tangles. In human cells, resveratrol protected from ROS which keeps the body's normal balance preventing oxidative stress, and also prohibited DNA fragmentation (Anekonda & Reddy, 2005). It also showed an increased life span in relation to resveratrol, however this trial was performed on mice (Giulietti et al., 2016). Lastly, in a qualitative study resveratrol as a supplement showed neuroprotective effects in AD. Resveratrol activates SIRT1 which is a sirtuin that protects neurons from apoptotic process (cell death) and oxidative stress. SIRT1 also displayed reduction of the pathway of glial cells that are unprotected from Aβ. These neuroprotective effects help promote cell survival and the correct functioning of mitochondria. (Mendiola-Precoma et al., 2016).

N-3 FA

One study that was reviewed in this literature dealt with omega-3 fatty acids and its effect on cerebrospinal fluid in individuals with AD. This study had a small sample size (n=33) and showed minimal cognitive benefits on individuals with mild AD. The trial on individuals with moderate-severe AD was unsuccessful and showed no benefit (Freund Levi et al., 2014).

Cistanches Herba

Cistanches Herba is a desert plant that is said to have a positive impact on memory function. The effects of Cistanches Herba on the clinical manifestation of AD were compared to Donepezil (Aricept®) an AChEI commonly prescribed for AD, and no treatment for individuals with mild-moderate AD. Cistanches Herba and Donepezil both showed close to the same improvement in cognitive function and slowing down hippocampus atrophy. Hippocampus atrophy is a common sign of AD and with MRI can be tracked in moderate-severe stages of AD. At week 0, all three groups had a score of about 20 on the MMSE. The higher the score on the MMSE, the better cognitive function the individual is displaying. By the 48th week of the study, the herbal and pharmacologic group improved to a score of 24 while the group receiving no treatment dropped to an 18. Moreover, the ADAS-cog scores showed less significant scores, but still displayed improvement in the two treatment groups and a degradation of score for the group receiving no treatment. It was also noted that Cistanches Herba is much cheaper and easier to retrieve, so some individuals may prefer this treatment over Donepezil (Li et al., 2015).

Others

Flavonoids were discussed in a few studies and were found to be safe, portray neuroprotective effects, improve memory, and inhibit the production of acetylcholinesterase (Mendiola-Precoma et al., 2016). In one study green tea extract was discovered to reverse memory deficits by inhibiting AChEI activity (Anekonda & Reddy, 2005). Fig, which is under the class of a polyphenol, demonstrated improvements in behavioral and cognitive function in AD, and reduced the accumulation of Aβ (Giulietti et al., 2016). Lastly, crocus, sage, lemon balm, and Fuzhisan were compared to either a placebo or orthodox medication and showed an improvement in individuals with AD on the ADAS-Cog test (Yang et al., 2014). Herbs have been used for a variety of reasons for centuries, but further studies can assist in proving their benefits and effectiveness in the use for treating clinical manifestations of AD.

Discussion

The studies examined for this thesis can offer insight into a complementary and alternative treatment for individuals with AD. Research findings showed the benefits of using herbal supplements as part of treatment for managing the clinical manifestations of AD. Although the literature review presented mixed results, the majority of studies revealed several positive effects that herbal supplements demonstrated in minimizing early, debilitating clinical manifestations of AD.

Using herbal supplements as part of treatment for AD may be beneficial and cost effective to many individuals, since herbal agents often do not cost as much as prescriptive drug therapy. In addition, when compared to pharmacologic agents, Ginkgo Biloba was found to have minimal side effects compared to Donepezil which has various side effects including dizziness, nausea, vomiting, and diarrhea (Perry et al., 1998). Some individuals prefer natural and herbal therapies compared to pharmacologic treatments, so providing information about herbal supplements that have been effective in reducing clinical manifestations of AD is useful. With millions of individuals being diagnosed with AD each year, and the number of individuals continuing to rise, exploring treatment options is essential. Because AD is an incurable disorder, pharmacologic treatment is aimed at slowing down the progression of the disease and lessening the symptoms. Likewise, there are many nonpharmacological treatments that can also be used to slow the progression of AD and its clinical manifestations, which include herbal supplements, probiotics, and dietary and lifestyle changes, however theses therapies are much less studied

(Mendiola-Precoma et al., 2016). Producing further research on nonpharmacological therapies can help lessen the symptoms of AD.

The studies portrayed a variety of different herbal supplements with many different benefits. Most of the herbal supplements showed benefits in improving cognitive function and neuroprotective effects in individuals with mild-severe AD that was in the early stages of the disease. Several studies compared solo pharmacological treatment with pharmacological and nonpharmacological treatments combined, yielding mixed results. One study showed a significant benefit in the individuals who took both the AChEI and Gingko Biloba (Canevelli et al., 2014), although the synergistic effect of the agents combined was vague and not fully explained. Although many of the articles portrayed the same type of benefits with herbal supplements, many had small sample sizes or were tested on animals, which limits the applicability of the research, warranting the need for further studies.

Despite the limitations of small sample sizes and animal testing, the current study provides information on a variety of herbal supplements that have been shown to have some sort of positive effect on individuals with AD. It shows that herbal supplements have the ability to successfully treat certain clinical manifestations of this disease process. Additional research on herbal supplements effectiveness in managing clinical manifestations of AD would be beneficial to help better validate their uses.

In further studies, the stage of AD and the comparison to pharmacological should be put into more consideration. In many of the studies, the herbal supplements were compared to a placebo group. These studies help to show the benefits of herbal supplements, but did not show

how effective they were in comparison to pharmacological treatment. Comparing herbal supplement treatment findings to pharmacological treatment findings can demonstrate the effectiveness of herbal supplements. Comparing the herbal supplements and pharmacologic treatments can also provide the price differences, dosage sizes, and availability of the agents, which can be extremely beneficial to individuals with AD. Several of the studies specified the stage of AD, whereas some of the studies did not. Each stage of AD may respond differently to herbal supplements, so knowing the stage may be helpful in portraying more accurate and reliable results. Curcumin blocked the formation of AB plaque in the brain, therefore this herbal supplement may be beneficial in predementia stages and may be used as a preventative measure for AD in the future (Anekonda & Reddy, 2005). Finally, combining herbal supplements with pharmacological treatment may be superior to either treatment alone (Canevelli et al., 2014). Studies on combining the two treatments may assist in finding the best treatment for AD overall.

When analyzing the studies reviewed, despite limitations, there was a consistency in findings with certain herbal supplements researched in a multitude of the studies. The herbal supplements can slow cognitive decline, produce neuroprotective effects, improve ADL's, and improve memory function. Studies should be conducted on comparing herbal supplement effectiveness with pharmacological effectiveness to establish a better understanding of how beneficial herbal supplements are.

Complementary and alternative therapies are growing in use and can be used in a variety of disease processes. In specific, herbal supplements provide benefits including anti-psychotic, anti-inflammatory, anti-depressant, and anti-oxidant properties (Anekonda & Reddy, 2005). Furthermore, in a specific study comparing an herbal supplement to a pharmacological agent in

management of AD, the herbal supplement was found to be less expensive, and easier to come by (Li et al., 2015). Some individuals are holistic and would prefer to use CAM instead of pharmacologic therapy, so having it as an option is essential.

In conclusion, there should be further studies on herbal supplement use in controlling clinical manifestations of AD. Further studies can help to clarify the benefits of herbal supplements in comparison to pharmacological treatments. However, with the evidence presented herbal supplements can be safe and effective in treating clinical manifestations of AD and therefore, should be offered as a treatment option to individuals with AD. In addition, although a few herbal supplements showed no effect, none of the herbal supplements had a negative effect on managing the clinical manifestations of AD, suggesting that individuals should use herbal supplements to better manage their symptoms of AD.

Limitations

This literature review contained several limitations. The initial search examined many different treatments for AD, and therefore did not solely focus on the purpose of this study. Once a more narrow search was executed, and keywords Alzheimer's, herbal supplement*, and benefit* were used, more relevant research was discovered. After excluding AD therapy focused only with prescriptive agents or others not including herbals, minimal studies were found. These findings indicate the need for further research in comparing herbal supplement benefits with pharmacologic treatments on treating the clinical manifestations of AD.

Several of the studies had small sample sizes, were tested on animals, were compared to a placebo rather than a pharmacological agent, and did not specify what stage of AD the individuals were in. Animal testing trials have discovered benefits from herbal supplements, but because mice and rats do not have the same brain capacity and function as a human, human trials with well-designed clinical trials are needed to determine human benefits. The majority of the studies focused on elder individuals who had mild-severe AD and used herbal supplements as the sole treatment for the clinical manifestations of AD. However, for some of the studies it was only listed that individuals had mild-severe AD. Because every stage of AD is different, it's important to know the specific stage the individual is in, so that the research is more reliable. Knowing what stage of AD and how efficient the herbal supplements worked in that stage will give individuals a better understanding of when they can use the herbal supplements as a treatment.

The sample sizes ranged from *n=26* to *n=828.* The smallest sample size group was one of the most important studies which compared Cistanches Herba, Donepezil, and no treatment.

This study found that Cistanches Herba (herbal supplement) and Donepezil (pharmacologic agent) showed close to the same improvement in cognitive abilities (Li et al., 2015). This study provided a significant finding, so it is imperative that future studies involving larger sample sizes occur. The study with an adequate sample size of n=828 compared alone AChEI treatment to an AChEI combined with gingko biloba. The combined treatment did show a higher MMSE scored compared to the alone treatment, however only 29 participants chose to use the combined treatment, indicating the need of further clarification to understand the effectiveness of combining therapies (Canevelli et al., 2014). Furthermore, the other studies researched all showed a positive impact of herbal supplements on controlling the clinical manifestations of AD aside from one, but due to the small sample sizes further research is required.

Three of the studies in this research were performed on mice or rats. Although cognitive decline was found to be decreased and many of the herbals studied were found to have neuroprotective effects and reduce Aβ-induced oxidative stress, the studies were not performed on a human, making the results inconclusive. Further clinical trials need to be performed on humans to better understand the benefits of these herbal supplements.

Lastly, many of the clinical trials of herbal supplements were compared to a placebo group rather than a pharmacological agent. This gives the opportunity to understand the effectiveness of herbal supplements in managing the clinical manifestations of AD, but without comparing it to a pharmacological agent, understanding if herbals are as effective as these agents is difficult. Providing further research in comparing and/or combining the two therapies can be extremely beneficial to individuals with AD.

Implications for Nursing

Due to the slow, progressive symptomology of AD, exploring herbal treatment options for controlling the clinical manifestations of the disease is significant. Herbal supplements can slow cognitive decline and portray neuroprotective effects, so knowing that AD continuously gets worse over time, individuals may want to know about this treatment option. Continuing research on this topic is imperative, so that individuals can receive the most beneficial treatment for controlling the clinical manifestations of AD.

Individuals with AD and their caregivers should be educated on the various herbal supplements available as treatment options for the clinical manifestations of AD. Some individuals prefer complementary and alternative therapies as opposed to pharmacological treatments, so offering these supplements is essential. Health care facilities should implement herbal supplements as a complementary or alternative therapy for managing the clinical manifestations of AD, as there is no research that shows harm from these supplements. Educating health care providers on this option is important to create adequate patient satisfaction.

Due to numerous limitations throughout the study, further research is needed to determine how effective herbal supplements are in managing the clinical manifestations of AD. However with the research presented, herbal supplements can have a positive impact on managing the clinical manifestations of AD, and combining herbal supplements and pharmacological therapies can be superior to the use of either solo therapy.

APPENDIX A: TABLE OF EVIDENCE

Author(s) Year Location	Study Design & Purpose	Sample Size & Screening Measures	Results	Herbal supplement effectiveness 1=useful 2=inconclusive 3=not useful
Akhondzadeh et al. (2010) Massachusetts	Randomized, placebo controlled trial Assess the efficacy of saffron in the treatment of mild-moderate AD	N= 42 Saffron capsule (n=22) Placebo capsule (n=20) Protocol was approved by the Instituional Review Board of Tehran University of Medical Sciences. Inclusion criteria: Age 55 and older, and a baseline MMSE score of 15-26.	Saffron produced a significantly higher outcome for the cognitive function on the ADAS-cog and CDR tests and was found safe and effective. ADAS-cog: F = 4·12, d.f. = 1, P = 0·04 CDR: F = 4·12, d.f. = 1, P = 0·04 No difference in the adverse effects was observed between the two groups.	1 In this trial, 30 mg/day saffron was being used on its own to treat manifestations of mild-moderate AD This study showed that saffron is safe and effective in short term use, but needs further trials to validate this remedy.
Anekonda & Reddy (2005) Netherlands	Systemic literature review Examined herbal medicines as a form of treatment for AD	This review was based off of a survey of PubMed literature and included information from 168 articles It reviews the current strategies for treating the clinical manifestations of AD with herbal medicines.	Curcumin was found to reduce the accumulation of Aβ plaques in the brain. Ginkgo biloba was found to protect spatial cognition decline. Dispacus asper improved cognitive dysfunction in a passive avoidance task. Ginkgo biloba, ascorbyl, vitamin E, pycnogenol, and palmitate increased the life span in the mice.	2 The studies reviewed in this article showed significant benefits with the use of herbal supplements including decreased production of Aβ plaques, less cognitive decline, anti-oxidant effects, and a longer life span; however these studies were performed on mice and rats. Herbal drugs have been found to easily cross the blood brain barrier, and

			Resveratrol and centella asitica improved cognitive function and decreased oxidative stress. Huperzine A combined with an AChEI was found to increase the concentration of the acetylcholine. Green tea extract worked to reverse memory deficits by inhibiting AChEI activity.	are less toxic with less adverse effects than pharmacological treatments, but need to be further studied on humans to determine the greatest benefits and risks.
Canevelli et al. (2014) London	Prospective multicenter cohort study Evaluates course, treatment outcomes, and socioeconomic status impact on AD in Europe	N=828 Combined treatment (n=29) (Only 29 participants chose to try out the combined therapy) Alone AChEI treatment (n=799) Involved 29 centers from 12 European countries all a part of the European Alzheimer Disease Consortium Inclusion criteria: Diagnosis of probable AD, MMSE score ranging from 10-26, living in a community with a well-identified informal caregiver,	Combined treatment group showed a significantly higher score on the MMSE compared to the alone AChEI treatment group MMSE mean differences (follow-up-baseline) AChEIs only -1.44±0.12 AChEIs & Gb +0.42±0.66 The ADAS-Cog score also showed an increase for the combined treatment group, however it was not statistically significant No differences in ADL's were observed	1 In this study ginkgo biloba was combined with AChEI's as treatment. It was compared to a group only taking AChEI's for the treatment of the clinical manifestations of mild-moderate AD. The group receiving combined treatment showed and confirmed a much higher MMSE score, however because there was not a significant difference in the ADAS-Cog score and it was a low number of participants, the effectiveness of

		absence of known conditions reducing to less than 2 years the patient's life expectancy, and signed informed consent		ginkgo biloba needs further clarification.
Freund et al. (2014) Massachusetts	Randomized placebo controlled study Evaluates oral supplementation of omega-3 FA's and its effects on the FA in cerebrospinal fluid	N=33 n-3 FA supplement (n=18) Placebo (n=15) Ethical committee at Karolinska University Hospital approved the study protocol. Inclusion criteria: Diagnosis of mild-moderate AD, MMSE score between 15-30, and treatment with a stable dose of AChEI for at least 3 months before the study.	n-3 FA supplement group displayed significant increase in CSF EPA, DHA, and n-3 FA levels, whereas no increase was observed in the placebo group. An increase in DHA in the CSF causes a greater change in AD and inflammatory biomarkers.	2 Participants received a dietary supplement of n-3 FA to improve the cognitive decline caused by mild-moderate AD. Results show there may be some form of preservation of memory in individuals with extremely mild AD, however the n-3 FA supplement in individuals with moderate-severe AD has been unsuccessful.
Giulietti et al. (2016) United Arab Emirates	Systemic literature review Examines the effects of nutritional supplements on the clinical manifestations of AD.	Systemic review of the most recent literature (129 articles) on the effects of nutrition on progression of AD. Keywords used in searches included: Acetylcholinesterase inhibitors, Alzheimer, antioxidant, metals, nutritional supplements, PUFAs	Vitamin E showed a neuroprotective role in mice, but there was little evidence of this role in humans. Fig a polyphenol was shown to reduce Aβ and improve behavioral and cognitive defects in AD. Resveratrol was tested in mice and not only helped to control the cognitive decline of AD, but these mice also had an increase in life expectancy.	2 Although the mice trials showed beneficial effects on some of the clinical manifestations of AD from these herbal supplements, not all have been tested on humans. More clinical trials are needed to define the benefits of these herbal supplements.

			Ginkgo biloba was found to be ineffective in preventing AD, but was found to have an anti-amyloid aggregation effect.	
Ihl et al. (2011) New Jersey	Randomized controlled trial Tests the efficacy and safety of a once a day formulation of ginkgo biloba in patients with dementia with neuropsychiatric features	N=404 EGb 761 treatment (n=202) Placebo (n=202) Protocol was approved by the Ethics Committee of the State Pharmacology Centre at the Ukraine Ministry of Health. Patients were recruited at 20 outpatient clinics in Ukraine Inclusion criteria: At least 50 years of age, and had one of the following diagnoses: probable AD in accordance with the NINCDS-ADRDA, possible AD with cerebrovascular disease, or probable VaD according to NINDS-AIREN.	Patients treated with EGb 761 treatment improved in cognitive test performance and neuropsychiatric symptoms. EGb 761 treatment SKT score improved by -1.4 NPI total score improved by -3.2 The placebo group showed minimal or no change. Placebo treatment SKT score deteriorated by +0.3 NPI total score did not change There was consistent and statistically significant outcome measures for the EGb 761 treatment group.	1 This trial included patients with AD, vascular dementia or a mixed form of dementia. Participants were given either 240 mg of EGb 761, or placebo both once a day for 24 weeks. Primary outcome measures were the SKT score and the 12 item NPI score. Secondary outcome measures included the NPI caregiver stress score, the ADCS-CGIC score, the ADL-IS score, the DEMQOL-Proxy scale, and the Verbal Fluency test. Participants receiving the EGb 761 showed improvement in both primary measures whereas the placebo group showed minimal to no change in the primary measures. Secondary outcome measures also showed superiority in the EGb 761 treatment group compared to the placebo group.

Li et al. (2015) China	Randomized placebo controlled study Investigates the potential of Cistanches Herbal to have neuroprotective effects for moderate AD	N=26 Cistanches Herbal capsule (n=11) Donepezil (n=9) No treatment (n=6) 26 participants were chosen from the second and fifth affiliated hospital of Zhengzhou University from 2013-2014. Inclusion criteria: MMSE and ADAS-scores from 10-20 and 29-40	Cistanches Herba can improve cognitive abilities in AD and slow down hippocampus atrophy, suppress T-tau, TNF-a, and IL1B in CSF in AD	1 In this trial there were 3 different groups being compared. Participants had AD and were either given the supplement Cistanches Herbal, donepezil, which is an AChEI, or no treatment at all. At 24 weeks there was no significant difference between the 3 groups cognitive abilities, however by the 48th week there were changes. Both the Cistanches Herbal group and the Donepezil group showed improvement, however they showed about the same improvement as each other. Cistanches Herbal was shown to be much cheaper and easier to retrieve than donepezil, so because they showed about the same outcomes, some individuals may prefer this herb over donepezil.
Mendiola-Precoma et al. (2016) New York	Qualitative ethnographic study Evaluates both pharmacological and nonpharmacological treatments and their effects on treating	Combines own research and other research articles. Studies throughout the article were based on observation of either human or mice.	Pharmacological treatment: AChEI's were shown to improve memory loss and are well tolerated. NMDA's are approved in mild-moderate AD for cognition.	1 This study suggests combining pharmacological treatments with 2 or more nonpharmacological treatments,

	clinical manifestations of AD		Muscarinic and Nicotinic Ach receptors along with histamine receptors have the potential to be beneficial in treatment of clinical manifestations of AD, but need further research. Nonpharmacological treatments: Exercise and mental challenges have preventive benefits for AD. Herbal supplements studied included flavonoids, alkaloids, terpenoids, ginkgo biloba, and polyphenols. Resveratrol is a polyphenol and was found to have neuroprotective effects on AD. Flavonoids are considered safe and have also been found to have neuroprotective effects on AD. Ginkgo biloba is shown to help memory function in AD.	including herbal supplements such as ginkgo biloba, resveratrol, and flavonoids can be most beneficial in controlling the clinical manifestations of AD.
Mi Hye (2014) Korea	Qualitative ethnographic study This research article was designed to investigate the effectiveness of certain herbs on cognitive impairment in AD.	Combines own research and other research articles. Studies throughout the article were based on observation of either human or mice.	Berberine is an herb that may improve cognitive impairment and decrease Aβ production. Curcumin was shown to improve spontaneous behavior and better recognize memory tasks.	2 The majority of these herbs benefits were shown through studies on mice or rats, making it an inconclusive conclusion for the benefits for humans.

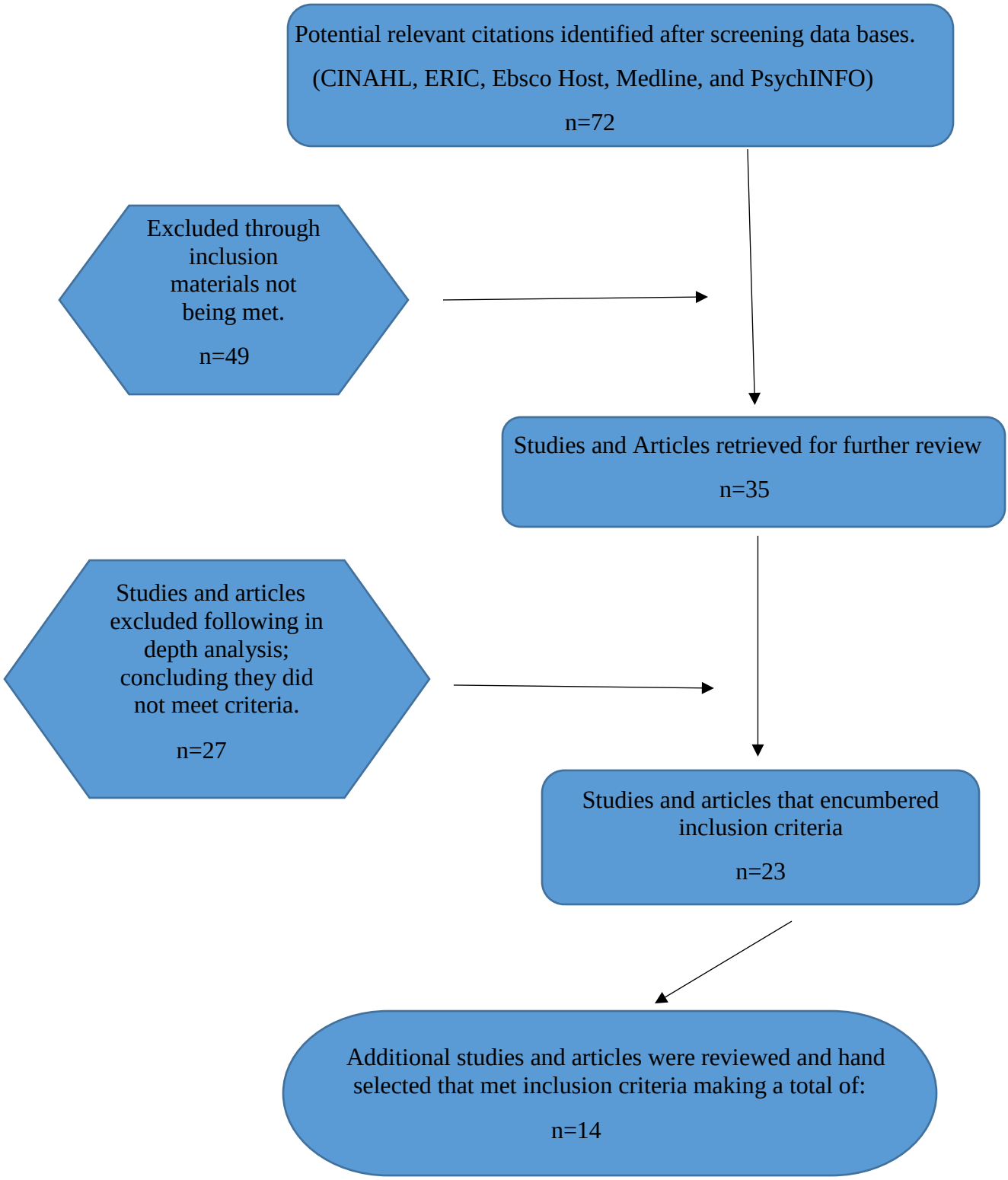
			Ginsenoside Rg1 was shown to block Aβ induced neuronal injury and demonstrated neuroprotective effects. Puerarin was shown to decrease Aβ-induced cell death. Silibinin is thought to improve recognition memory and protect against Aβ-induced oxidative stress.	
Perry et al. (1998) New York	Qualitative ethnographic study This study examines different methods and herbal supplements used in different countries to treat the clinical manifestations of AD.	Combines own research and other research articles. Studies throughout the article were based on observation and statistics from humans.	Ginkgo biloba was proven to improve cognitive function in mild-moderate AD. Balm essential oil combined with lavender showed a slight increase in general functioning in a small number of patients with dementia. For centuries, sage is shown to have memory enhancement and promote calmness. A Chinese medicine known as Salvia was reported to be effective in memory function in 40% of patients with AD. Ancient Greeks used rosemary to stimulate memory.	1 This article examines many different traditions from around the world. Although some of these treatments weren't on patients with AD, these herbs were still shown to improve memory which is one of the main clinical manifestations of AD. These herbs have been around for ages, and should be further researched to clarify exactly what they are capable of.
Posadzki et al. (2012) Massachusetts	Literature review Evaluates the literature on complementary and	225 articles were considered, however a systemic review of 6 articles on 4 data bases from their	Only 6 articles met the inclusion criteria. Based on these articles, the evidence to support	2 Some of the herbal supplements reviewed in this

	alternative medicine for AD	inception until May 2011 were used. MEDLINE, EMBASE, AMED and the Cochrane Library were searched Inclusion criteria: reporting and comprehensiveness of searches, repeatable eligibility criteria, avoidance of selection bias, presence of a validity assessment tool, robustness of data analysis and supportiveness of conclusions.	CAM for the treatment of AD is unclear. As some herbal medicines show a promise in managing AD, future research is defensible.	literature review included lemon balm, sage, ginkgo biloba, lycopodium serratum, and panaz ginseng. Out of these herbal supplements ginkgo biloba and ginseng were shown to improve cognitive function and quality of life, however were only compared to placebo and not current drug therapy for AD.
Wang et al. (2015) United States	Randomized controlled study Investigates the effects of a combination of nutrients in APP-PSN in mouse model of AD	N=96 Double transgenic mice (n=72) Wild-type littermates (n=24) Study protocol was approved by the Medical Ethics Committee of Harbin Medical University Inclusion criteria: Mice purchased from the Model Animal Resource Platform of Nanjing University, acclimatized for 1 week	Mice given the nutrient combination had significantly lower B-amyloid peptide accumulation and a greater antioxidant capacity. The nutrient combination mice also had higher behavioral test scores.	2 This study included one group of mice receiving their normal feeding and another group of mice receiving added dietary supplements in their food. The group receiving extra dietary supplements showed improvement concluding that these supplements could be considered as a strategy to slow cognitive decline in AD. This study was done in mice therefore, more research needs to be done to prove the effectiveness of the dietary

				supplements in this study.
Yang et al. (2014) New Jersey	Systemic review in randomized controlled trials Evaluate the efficacy of natural medicines for the treatment of AD	Systemic review of literature published from 1950 through July 2013. MEDLINE, EMBASE, the Cochrane Library, and PSYCHINFO were searched. Inclusion criteria: Published, double blind randomized, placebo-controlled studies, diagnostic criteria of AD from either DSM or NINCDS-ADRDA, and comparisons of natural medicines to placebo or orthodox medications.	21 clinical reports fit the inclusion criteria. Many natural medicines had minimal benefits, but ginkgo biloba showed to have better outcomes compared to the placebo for both cognitive being and activities of daily living.	1 This review discussed herbal supplements including sage, lemon balm, crocus, curcumin, huperzine Fuzhisan, and ginkgo biloba. Crocus, sage, lemon balm, and Fuzhisan were found to improve cognitive function through the ADAS-Cog test. These were all compared to a placebo group and were not compared to AD drug therapy. Huperzine and curcumin showed no significant improvement in cognitive function in individuals with AD. Ginkgo biloba was shown to have a positive effect on cognitive function and activities of daily living in 5 out of the 6 articles that

				focused on this herb.
Zeng et al. (2015) Pennsylvania	Systemic review in randomized controlled trials Evaluate the effectiveness and safety of Chinese herbal medicine for kidney nourishment (CHMK) in patients with AD	7 medical databases were searched from their inception to July 19, 2014. Inclusion criteria: Citations reviewed, risk of bias assessed, and data extracted independently	20 studies were included in the meta-analysis and none were able to show the safety or effectiveness of CHMK. Bias and low quality trials prove the need for further studies to define the role of CHMK in AD.	1 This article compared the oral administration of CHMK plus normal pharmacotherapy with pharmacotherapy used by itself. The safety effectiveness of CHMK is not able to be determined by this study because of small sizes and poorly designed studies.

APPENDIX B: FIGURE 1



Key Search Terms: Alzheimer's, dementia*, herbal supplement*, clinical manifestation*, symptom*, benefit*, and risk*

Limiters: English language, peer reviewed, published 1995-2016

REFERENCES

Alzheimer's stages: How the disease progresses - Mayo Clinic. (2015, November 24). Retrieved October 23, 2016, from http://www.mayoclinic.org/diseases-conditions/alzheimers-disease/in-depth/alzheimers-stages/ART-20048448

Latest Alzheimer's facts and figures. (2016). Retrieved September 21, 2016, from http://www.alz.org/facts/

Akhondzadeh, S., Shafiee-Sabet, M., Harirchian, M. H., Togha, M., Cheraghmakani, H., Razeghi, S., . . . Moradi, A. (2010). Saffron in the treatment of patients with mild to moderate Alzheimer's disease: a 16-week, randomized and placebo-controlled trial. *Journal of Clinical Pharmacy & Therapeutics, 35*(5), 581-588. doi:10.1111/j.1365-2710.2009.01133.x

Anekonda, T. S., & Reddy, P. H. (2005). Can herbs provide a new generation of drugs for treating Alzheimer's disease? *Brain Research. Brain Research Reviews, 50*(2), 361-376.

Binnewijzend, M., Benedictus, M., Kuijer, J., Flier, W., Teunissen, C., Prins, N., . . . van Berckel, B. N. M. (2016). Cerebral perfusion in the predementia stages of Alzheimer's disease. *European Radiology, 26*(2), 506-514. doi:10.1007/s00330-015-3834-9

Canevelli, M., Adali, N., Kelaiditi, E., Cantet, C., Ousset, P.-J., & Cesari, M. (2014). Effects of Gingko biloba supplementation in Alzheimer's disease patients receiving cholinesterase inhibitors: Data from the ICTUS study. *Phytomedicine, 21*(6), 888-892. doi:10.1016/j.phymed.2014.01.003

Dá Mesquita, S., Ferreira, A. C., Sousa, J. C., Correia-Neves, M., Sousa, N., & Marques, F. (2016). Insights on the pathophysiology of Alzheimer's disease: The crosstalk between

amyloid pathology, neuroinflammation and the peripheral immune system. *Neuroscience And Biobehavioral Reviews, 68,* 547-562. doi:10.1016/j.neubiorev.2016.06.014

Freund Levi, Y., Vedin, I., Cederholm, T., Basun, H., Faxén Irving, G., Eriksdotter, M., . . . Palmblad, J. (2014). Transfer of omega-3 fatty acids across the blood-brain barrier after dietary supplementation with a docosahexaenoic acid-rich omega-3 fatty acid preparation in patients with Alzheimer's disease: the OmegAD study. *Journal of Internal Medicine, 275*(4), 428-436. doi:10.1111/joim.12166

Giulietti, A., Vignini, A., Nanetti, L., Mazzanti, L., Di Primio, R., & Salvolini, E. (2016). Alzheimer's Disease Risk and Progression: The Role of Nutritional Supplements and their Effect on Drug Therapy Outcome. *Current Neuropharmacology, 14*(2), 177-190. doi:10.1093/ijnp/pyu115.

Gray, D. C., & Rutledge, C. M. (2013). Herbal supplements in primary care: patient perceptions, motivations, and effects on use. *Holistic Nursing Practice, 27*(1), 6-12. doi:10.1097/HNP.0b013e318276fb32

Ihl, R., Bachinskaya, N., Korczyn, A. D., Vakhapova, V., Tribanek, M., Hoerr, R., & Napryeyenko, O. (2011). Efficacy and safety of a once-daily formulation of Ginkgo biloba extract EGb 761 in dementia with neuropsychiatric features: a randomized controlled trial. *International Journal of Geriatric Psychiatry, 26*(11), 1186-1194. doi:10.1002/gps.2662

Li, N., Wang, J., Ma, J., Gu, Z., Jiang, C., Yu, L., & Fu, X. (2015). Neuroprotective Effects of Cistanches Herba Therapy on Patients with Moderate Alzheimer's Disease. *Evidence-*

Based Complementary And Alternative Medicine: Ecam, 2015, 103985-103985. doi:10.1155/2015/103985

Mendiola-Precoma, J., Berumen, L. C., Padilla, K., & Garcia-Alcocer, G. (2016). Therapies for Prevention and Treatment of Alzheimer's Disease. *BioMed Research International, 2016,* 1-17. doi:10.1155/2016/2589276

Mi Hye, K., Sung-Hoon, K., & Woong Mo, Y. (2014). Mechanisms of Action of Phytochemicals from Medicinal Herbs in the Treatment of Alzheimer's Disease. *Planta Medica, 80*(15), 1249-1258. doi:10.1055/s-0034-1383038

Panpalli Ates, M., Karaman, Y., Guntekin, S., & Ergun, M. A. (2016). Analysis of genetics and risk factors of Alzheimer's Disease. *Neuroscience, 325*, 124-131. doi:10.1016/j.neuroscience.2016.03.051

Perry, E. K., Pickering, A. T., Wang, W. W., Houghton, P., & Perry, N. S. L. (1998). Medicinal plants and Alzheimer's disease: integrating ethnobotanical and contemporary scientific evidence. *Journal of Alternative & Complementary Medicine, 4*(4), 419-428. doi:10.1089/acm.1998.4.419

Tokuchi, R., Hishikawa, N., Sato, K., Hatanaka, N., Fukui, Y., Takemoto, M., . . . Abe, K. (2016). Differences between the behavioral and psychological symptoms of Alzheimer's disease and Parkinson's disease. *Journal Of The Neurological Sciences, 369*, 278-282. doi:10.1016/j.jns.2016.08.053

Yang, M., Xu, D. D., Zhang, Y., Liu, X., Hoeven, R., & Cho, W. C. S. (2014). A Systematic Review on Natural Medicines for the Prevention and Treatment of Alzheimer's Disease

with Meta-Analyses of Intervention Effect of Ginkgo. *American Journal of Chinese Medicine, 42*(3), 505-521. doi:10.1142/S0192415X14500335