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The role of phytochemicals in the prevention and treatment of alzheimer's disease

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Abstract
Alzheimer's disease is a degenerative neurologic condition for which there is no known cure. Between 2002 and 2019, 99.6% of all drug candidates tried failed in achieving the goal of preventing or treating the development of Alzheimer's disease. In view of the fact that many of the current FDA approved pharmacologic agents utilized in the treatment of Alzheimer's disease are directly derived from plants, a resurgence in research is underway to find phytochemicals capable of preventing and treating this devastating disease. Phytochemicals such as curcumin, saffron and lemon balm have efficacy in preventing and mitigating disease progression in Alzheimer's dementia.

Keywords: dementia, Alzheimer's, phytochemicals, curcumin, lemon balm, saffron

Introduction

Alzheimer's disease is a degenerative neurologic condition for which there is no known cure. Between 2002 and 2019, 99.6% of all drug candidates tried failed in achieving the goal of preventing or treating the development of Alzheimer's disease. Neuro- scientists involved in the research of Alzheimer's disease have been unable to understand the specific epigenetic processes that would reveal the mysteries of this disease. Our nation is currently in the midst of an epidemic from dementia, mostly related to Alzheimer's disease. According to the CDC, in 2020 there were 5.5 million Americans living with Alzheimer's dementia. Of these approximately 5.3 million are 65 years of age and older, and around 200,000 individuals are under the age of 65 (CDC, 2021). It is estimated that approximately 20% of the population aged 65 or older will develop Alzheimer's disease by the year 2050 (CDC, 2017). These numbers are startling, and present a massive healthcare and economic challenge for the United States Healthcare System.

Although much research is being conducted on newer treatment modalities to prevent the development of Alzheimer's disease, a similar amount of research is being conducted in the field of understanding the neurologic and biologic components of this memory-robbing disease. As neurologists and researchers achieve a greater understanding of the precise mechanisms involved in the development of Alzheimer's disease, a greater emphasis can be placed on the targeted information needed to interrupt the progression of this disease.

Materials and Methods

We conducted a literature review of scholarly articles indicating shortcomings in Pharmacotherapeutic innovation in the management of Alzheimer's disease, and also conducted a scholarly literature search on peer-reviewed scientific articles from 1999 through 2021 looking for quality research on proven and effective phytochemical interventions in the prevention and treatment of Alzheimer's disease. A total of 31 articles in peer-reviewed scholarly journals were analyzed for applicability to this review. Of these 9 articles were found to have statistically significant positive effects in either the prevention or treatment of Alzheimer's disease and dementia in general. We report our synthesis of the literature on not only current pharmacologic products but also current phytochemical products with efficacy in the prevention and treatment of Alzheimer's disease. Furthermore, we discuss the underlying pathophysiology of Alzheimer's disease in this context.

Discussion

In a review article by Sabbagh (2009) [2], the author talks about the limitations of current FDA approved medications in the treatment of Alzheimer's disease and how these medications have failed to make a significant impact on the burden of morbidity and mortality associated with Alzheimer's disease in patients over 65 years of age.

In view of the fact that many of the current FDA approved pharmacologic agents utilized in the treatment of Alzheimer's disease are directly derived from plants, a resurgence in research is underway to find phytochemicals capable of preventing and treating this devastating disease.

The etiology of Alzheimer's disease is poorly understood. Many researchers believe that there is a significant genetic component in the development of Alzheimer's disease. Additional research has proposed factors such as closed head injury, major depressive disorder, and hypertension as causal factors in the development of Alzheimer's disease. The primary pathologic lesion associated with Alzheimer's disease is the development of plaques and tangles in the

brain. The tangles are defined as neurofibrillary tangles and cause demyelination of neuronal tracts in the hippocampus of the brain. This pathology causes a reduction in recent memory, which is the hallmark of the disease.

Although, every patient with Alzheimer's disease will present differently, they all follow a similar course with a well- defined trajectory. According to the Global Deterioration Scale for the Assessment of Primary Degenerative Dementia (GDSAPDD, 2009) there are 7 distinct stages of Alzheimer's disease.

Stage 1: There is no cognitive decline, no memory loss, and the patient appears normal one and physical examination.

Stage 2: Very mild cognitive decline with the patient complaining of some memory deficits related to names of people and location of objects. On a clinical interview there's no concrete evidence of memory decline in typically the patient continues to perform well on well- designed psychological assessment tests.

Stage 3: Mild cognitive decline with objective evidence of memory loss on clinical examination. Typically, the patient may get lost when driving, may misplace import and objects such as keys, driver's license, wallet, and passport. At this stage the patient also experienced a significant anxiety related to the memory loss and also utilizes a coping mechanism of denial about the memory loss when questioned by family members or call workers.

Stage 4: In this stage there is clear-cut moderate cognitive decline. The patient has difficulty concentrating and has significant problems in travelling in handling personal finances. Typically, the patient will exhibit decreased recollection of recent events and also will have difficulty remembering components of important family history. There may also be difficulties with the orientation to time and place.

Stage 5: This stage is characterized by early dementia. The patient has moderately severe cognitive impairment and is clearly unable to function without some assistance. At this stage days of the week time of the day, and the calendar month are frequently confused. A patient in stage 5 may have difficulty selecting appropriate clothing to wear outside of the house.

Stage 6: This stage is known as middle dementia. It is characterized by severe cognitive decline. The patient will invariably forget the name of their own spouse or caregiver. There is significant loss of memory for nearly all recent events including what the patient had the bad they as well as weather conditions and important appointments. Cognitive impairment at this stage results in difficulties with the activities of daily living, and the patient is frequently incontinent to urine.

Stage 7: This stage is known as late dementia and is characterized by very severe cognitive decline. Most patients in this state are unable to speak and cannot form intelligible sounds. Additionally, many patients in this state are unable to swallow and have difficulty maintaining body temperature. They are completely incontinent to urine and stool. Death from cardiopulmonary arrest due to central mechanisms is common.

Currently, Alzheimer's disease can be diagnosed utilizing a combination of screening tools that assess cognitive function and memory, and brain imaging technologies such as MRI, and Single Photon Emission Computed Tomography (SPECT). On brain imaging characteristic signs indicative of Alzheimer's disease include volume loss in the pre-frontal cortex and in the area of the hippocampus. Additionally, pathologic lesions such as neurofibrillary tangles and amyloid plaques can be seen in both the pre-frontal cortex and in the hippocampus. Unfortunately, brain imaging is useful only in diagnosing Alzheimer's disease in stage 4 and later. Thus, there are no radiologic or biochemical screening tests that can help identify dementia in the early stages. By the time Alzheimer's disease lesions are visible on brain imaging the disease is usually well established and treatment options are very limited. Research into identifying biochemical markers that can detect Alzheimer's dementia at an early stage are currently underway.

An elegant article by Muth and associates (2009) looks at neuroimaging of Alzheimer's. Perhaps the first step in the prevention of Alzheimer's disease is this screening process which allows neurologists to determine if the diseases active or not. This article discuss describes volume loss in the basal forebrain region of the cerebral cortex as an indicator of the development of dementia. The use of Single Photon Emission Cerebral Tomography (SPECT) and f-MRI imaging has been pivotal in the early detection of Alzheimer's disease which is crucial in the timing of initiating treatment to protect the individual from the progression of this devastating disease (Muth, 2009).

Although pharmacotherapy for Alzheimer's disease has been largely unsuccessful, current pharmacological agents utilized in the treatment of Alzheimer's disease attempt to target the acetylcholine receptors in the pre-frontal cortex and the hippocampus of the brain. The pre-frontal cortex and the hippocampus, in conjunction with the amygdala are responsible for transitioning short term memory into long-term memory components. This process known as long-term memory potentiation is mediated by brain derived neurotrophic factor (BDNF). Signal impulses arising from the hippocampus cause the release of acetylcholine and norepinephrine in targeted areas in the pre-frontal cortex which have been postulated to potentiate long-term memory. Therefore, pharmacological agents which increase post synaptic acetylcholine levels, or inhibit pre- synaptic acetylcholine reuptake through catechol-O- methyl transferase (COMT) have been the target for most interventions. There have been no pharmacologic agents that attempt to reduce the deposition of Tau proteins or amyloid in the myelin sheath of cerebral white matter. Currently, there are five FDA approved pharmaco-therapeutic agents for use in the treatment and prevention of Alzheimer's disease. These include Donezepil, Galantamine, Rivastigmine, Memantine, and Cyanocobalamin (Vitamin B-12).

Donezepil is a pharmacological agent marketed under the trade name Aricept ®. Although it does not have an impact upon the progression of the disease, it tends to treat symptoms of cognitive impairment by blocking cholinesterase at cholinergic synapses. It is FDA approved for the treatment of mild, moderate, and severe dementia although clinical trials evaluating patients at six, 12, and 18 months have been disappointing. In view of the fact that this

is a cholinergic drug common side effects include diarrhea and vomiting muscle cramps and anorexia. Thus, it is important to continue to monitor the patient's weight and nutritional intake throughout the therapeutic window.

Galantamine is a pharmacological agent derived from a plant known as the Caucasian Snowdrop. It was first extracted an isolated in the former Soviet Union in 1959. That principle mechanism of action of Galantamine is by blocking the hydrolysis of acetylcholine at the post synaptic membrane. By blocking acetylcholine at the post- synaptic membrane, it is postulated that intrasynaptic levels of acetylcholine will be enhanced, and it is through this mechanism that it appears to have a role in enhancing and improving cognition in patients with Alzheimer's disease. Clinical trials utilizing this agent have been disappointing, however, it was FDA approved for use in mild to moderate Alzheimer's disease and vascular dementia in the United States in 2006. Side effects of this medication include nausea, vomiting, diarrhea and the potential for severe dehydration. For this reason it is prudent for providers to encourage increased fluid intake while on this medication.

Rivastigmine is a medication which has a significant cholinergic effect at the post synaptic membrane. Similar to other analogues it has the potential to increase levels of acetylcholine and thereby, potentially enhance cognition and memory. One of the advantages of this medication is that it can be administered as both an oral formulation and as a transdermal patch. The advantages of the transdermal patch are significant in that it reduces nausea, vomiting, and diarrhea which are common in other medications of this class. It is FDA approved in the United States for the treatment of moderate to severe Alzheimer's disease, however, clinical trials showing some mild benefit in improvement of cognition and memory do not show any long-term effect upon the progression of this disease.

Memantine is marketed under the tradename Namenda ®. This is a novel drug that has no effect on the cholinergic receptors, but is a purely glutamatergic antagonist, blocking the NMDA reuptake in the post-synaptic cleft. One of the mechanisms involved in cognition signaling in animal studies has been the reduction of NMDA levels through the glutamatergic system. It has been postulated based upon this research that compounds that increase cortical NMDA levels may improve cognition and memory (Williams, 2011) [3].

Cyanocobalamin is FDA approved for the prevention of Alzheimer's disease. One of the mechanisms for oxidative stress in the development of Alzheimer's disease is due to hyperhomocysteinemia. There is a strong correlation between serum levels of Homocysteine and vitamin B12. This is an inversely proportional relationship, in that elevated levels of Homocysteine are associated with reduced serum vitamin B12 levels (Ryan-Harshman, Aldoori, 2008). From this it follows that increasing serum levels of vitamin B-12 can reduce serum Homocysteine levels. In view of the fact that elevated Homocysteine levels can cause oxidative stress in cerebral pre-frontal cortical areas and in the hippocampus, any compound that can reduce Homocysteine levels inside the central nervous system has the potential to reduce oxidative stress and, thereby, enhance cognition and prevent further demyelination. Thus, Vitamin B-12 has an FDA approved indication in the prevention of Alzheimer's disease.

The primary pathophysiology involved in the development of Alzheimer's disease is an oxidative stress, with the production of free radicals, which are capable of damaging components of the brain which are rich in lipids and have high oxygen consumption (Huang, *et al*., 2016). Under normal circumstances a meticulous balance exists between oxidants and anti- oxidants. This balance can be altered most commonly due to an increase in free radicals. The presence of one or more unpaired electrons in the outer shell of a chemical species is the hallmark of a free radical. Once molecular oxygen contained in a water molecule is reduced it yields a super- oxide molecule. This super-oxide molecule, through the addition of an electron, can then form hydrogen peroxide. The further reduction of this hydrogen peroxide yields potent hydroxyl radicals which are called reactive oxygen species (ROS). The reactive oxygen species have the capability of reacting with numerous body tissues by attacking proteins, lipids and nucleic acids. This attack destroys the structure and function of the underlying tissue. The reactive oxygen species have the capability of inducing chemical change in the underlying tissue that may manifest in one of two ways. First, the reactive oxygen species have the capability of destroying the lipid matrix of certain cell walls which causes a breach in the integrity of the cell wall leading to a reversible damage in the underlying tissue. The second mechanism through which reactive oxygen species can cause significant similar damage is through the induction of nucleic acids to form novel protein compounds that can cause damage through deposition in key areas of the cell.

In the case of Alzheimer's disease, the brain being composed of mostly lipids, and having high blood flow and resultant high oxygen extraction rates, is highly vulnerable to oxidative stress by free radicals. Histopathology of brain sections of patients with Alzheimer's disease shows free radical induced degradation and degeneration of the lipid matrix of cell walls resulting in a breach in the integrity of the cell. Additionally, histopathology of brain sections of patients with Alzheimer's disease shows a deposition of Tau proteins and amyloid compounds in both the gray and white matter (Hyman, Bradley, *et al*., 1984). The deposition of Tau proteins and amyloid compounds can cause further cellular damage due to the release of large amounts of intracellular free calcium.

A further mechanism that has been postulated to cause cellular damage in the cerebral white and gray matter is the formation of oxidative stress mediators such as reactive nitrogen species (RNS) and nitric oxide (Huang, *et al*., 2016). Under normal circumstances, the cytochrome P450 transport system in the mitochondria buffers reactive nitrogen species and nitric oxide through anti- oxidants obtained through dietary sources and produced indigenously by the mitochondria. In the case of Alzheimer's disease available anti- oxidant compounds are insufficient to buffer the free radical assault leading to overwhelming oxidant stress and irreversible tissue damage. This mechanism has been the area of focus for potential new pharmacological agents that can be utilized to prevent or reverse the effects of reactive oxidative stress in patients with Alzheimer's disease.

Another component of the pathophysiology of Alzheimer's disease is the role of zinc in neurodegeneration. Oxidative stress causes the release of large amounts of intracellular zinc which has a high affinity for the areas of the brain involving cognition and memory. Histopathology of the

brains of patients with Alzheimer's disease show significant staining for zinc in the areas of the hippocampus and the pre-frontal cortex. Knowledge of this role of zinc in causing oxidative stress and irreversible damage in specific brain areas has also been the focus of new research in an attempt to develop pharmacologic compounds that can potentially prevent the long-term effects of Alzheimer's disease.

Insight into the primary pathophysiology involved in the development of Alzheimer's disease, including the role of oxidative stress mediated through free radicals, coupled with heavy metal deposition such as zinc, leading to neurologic dysfunction and degeneration at the acetylcholine synaptic receptors has led to an increased interest in the role of phytochemicals as potential preventive and pharmaco- therapeutic agents for Alzheimer's disease. In view of the fact that many phyto- chemicals have the intrinsic ability to reduce inflammation and oxidative stress mediated through free radicals, and have the capability of optimizing heavy metal deposition, it has been postulated that these agents may have a potential role in the prevention and treatment of Alzheimer's disease. Knowledge of this disease mechanism has opened the door for clinical trials for many phyto chemicals that have been around for centuries as potential chemotherapeutic agents for Alzheimer's disease. Much of the current research involves phyto chemical compounds that are known to have strong anti-oxidant properties, and are known to reduce oxidative stress mediated through free radicals. Similarly, compounds that have the ability to reduce homocysteine levels and reduce deposition of zinc and calcium currently exist in the phyto chemical arsenal of compounds.

In an article by Panza and associates (2009) [1] the authors discuss the primary neurologic dysfunction in Alzheimer's disease and how phytochemicals are being developed to target the causative agent in the formation of plaques in the memory pathway.

In an article by Orhan and associates (2009) [8] the authors conduct a review of physostigmine derived phytochemicals of natural origin which can help with cognitive dysfunction in the later stages of Alzheimer's disease. They discuss how many of the new anti-cholinesterase drugs work and how phytochemicals may simulate the action of anti-cholinesterase drugs in the treatment of Alzheimer's disease.

One of the phytochemicals that has shown the most promise in the treatment and prevention of Alzheimer's disease is curcumin. Curcumin, also known as turmeric is an herb that has been utilized in South Asia for several 1000 years. It is utilized in cooking and has been one of the central ingredients utilized in Ayurvedic medicine. People in South Asia first utilized curcumin as a food and later understood its medicinal properties. As an Ayurvedic medicine, it has been extensively utilized for arthritis, cystitis, gout and as a pain reliever. Curcumin is a member of the ginger family. It is a plant that grows 3 to 5 feet tall and produces yellow flowers. The root system known as the rhizome, grows underground in an extensive tangled web of roots. The roots of the curcumin plant are the source of the phyto chemical. The roots are boiled, allowed to dry, and are ground up producing a bright yellow compound which is the classic color of curcumin. Curcumin can be utilized as a powder, as a poultice, as a dissolved drink and in pressed pill form.

An elegant study examining turmeric use in curry form and the problems of Alzheimer's disease in adults aged 60-93 years of age, found that the prevalence of Alzheimer's disease was 4.4 times less than in a non- turmeric utilizing cohort in the United States. This study involved 1010 patients (Shimyo, 2008). Additionally, an epidemiological study performed on 922 adult Males found that cognitive performance on a standardized test (MMSE), was higher in the test cohort that consumed curcumin at least once a month compared to the cohort which never ingested curcumin. (Shimyo, 2008).

Histological studies have demonstrated that curcumin has the capability of enhancing macrophage function to target and reduce beta amyloid deposition in the white matter the brain (Mishra, Palanivelu, 2008). Additionally, neurofibrillary tangles associated with the pathologic lesions of Alzheimer's disease are caused by astrocyte and microglial proliferation. Clinical trials at the University of California in Los Angeles division of Integrative Medicine have demonstrated a reduction in astrocyte and microglial proliferation due to reduced signal induction in patients given curcumin extracts for six months (Williams, 2011) [3].

Additionally, curcumin has been found to inhibit cyclo-oxygenase 2 (COX-2), an important anti- inflammatory mediator. Traditional COX-2 inhibitors are only capable of acting in the periphery and cannot enter the brain due to the integrity of the blood brain barrier. Conversely, curcumin being strongly lipophilic has the capability to enter the blood brain barrier and exert cyclo-oxygenase 2 inhibition activity in the central nervous system. This is an important mechanism in offsetting the oxidative stress mediated through free radicals in the cholinergic receptors of the hippocampus and pre-frontal cortex (Strong, Anderson, *et al*., 1995) [5].

Curcumin has a well -defined role in increasing cerebral perfusion. A study by researchers at the University of Nanjing in China demonstrated the effect of a single injection of 2 mg of curcumin intravenously in reducing the size of cerebral infarcts and improving cognitive function in post stroke patients (Shimmyo, 2008) [4].

Thus, it is clear that curcumin has well established properties that have been studied, and it is a proven and effective phyto chemical with the potential for prevention and treatment of Alzheimer's disease. Current research is underway to establish safety and efficacy, optimal dosage, enhancing Bio- availability, and understanding of optimal duration of treatment for curcumin in the management of Alzheimer's disease and other dementias.

Lemon Balm, (Melissa officinalis) is another important phytochemical that is being explored as an effective agent in treating Alzheimer's disease (Williams, 2011) [3]. In a placebo controlled study the efficacy of lemon balm was assessed utilizing 60 drops per day in patients with mild to moderate Alzheimer's disease. In this study which involved Alzheimer's patients between the ages of 65 and 80, a total of 42 patients were studied using the Alzheimer's disease Assessment Scale. Patients were randomized to receive either 16 drops per day of lemon balm, or a placebo. At the end of four months outcomes for cognitive function or improvement in the subset of patients receiving a lemon balm extract compared to placebo ($p < 0.00001$) were measured utilizing the Alzheimer's disease assessment scale. This study was replicated in three large tertiary treatment centers all with the same or similar results. PET scanning performed on a subset of patients in this study demonstrated a reduction in beta amyloid plaque formation

in the hippocampus and in the pre-frontal cortex of study patients (Muth, 2010) [7].

The lemon balm plant is a perennial herb found in South Central Europe and regions of the Middle East. It is a flowering plant that grows to a height of 28 inches and produces white flowers in the spring. The phyto- chemical that is utilized is derived as an extract from the leaves of the lemon balm plant. Traditionally, it has been utilized as a neuro stimulant and for weakness since at least the 4th century AD.

As a phyto- chemical, lemon balm has the capability of passing through the blood brain barrier and entering the cerebral cortex due to its high lipid content and fat solubility. In the pre-frontal cortex and the hippocampus lemon balm has the capability of inactivating glial cell over-growth and astrocyte proliferation. Both of these components are involved in the deposition of beta amyloid in the pre-frontal cortex and in the hippocampus (Park, Jang, 2009) [6]. As a result of these effects lemon balm can be utilized as a neuro protective agent in both Alzheimer's disease and in vascular dementia. Currently clinical trials are underway to determine the safety and efficacy of lemon balm in the treatment of early, stage three Alzheimer's disease (Park, Jang, 2009) [6].

Another phyto- chemical which has been studied extensively as a neuro- protective agent with general anti-oxidant properties and the ability to reduce oxidative stress from free radicals is saffron. Saffron is derived from a flowering plant called Crocus sativus. The plant has crimson colored flowers which are collected and dried. The crocus sativus plant grows in temperate climates of southwest Asia and Greece. It is one of the most expensive cultivated plants and has a distinct hay-like fragrance. Iran cultivates 90% of the world's crocus sativus plants.

A clinical study involving 16 weeks of a capsule of saffron 30 mg per day in one cohort of patients, and a similar number of patients involved in receiving a placebo were evaluated at the end of a 16 week period. Utilizing the Alzheimer's disease assessment score at the end of the six weeks. Patients demonstrated an improvement in cognitive function and short term memory in the arm receiving 30 mg of saffron compared to placebo (Williams, 2011) [3]. MRI scans in a select group of patients receiving 30 mg of saffron in two divided doses per day for 16 weeks showed an increase in hippocampal white matter and a reduction of beta amyloid plaque formation in the same area (Strong, 1995) [5].

Saffron is a known anti- oxidant and contains a compound, gallic acid, which also has the capability of suppressing beta amyloid plaque formation through a macrophage enhancing property. In view of the fact that saffron as lipophilic it is capable of crossing the blood brain barrier and exerting anti-oxidant effects in targeted areas of the hippocampus, amygdala, and the pre-frontal cortex. Gallic acid, a component of saffron also potentiates increased cerebral blood flow through a vasodilator action independent of the anti- oxidant effect (Williams, 2011) [3]. Currently, clinical trials are underway to determine the safety and efficacy of saffron extract administered intravenously in patients with stage 4 through stage 7 Alzheimer's dementia. Additionally, saffron is being studied for a novel mechanism through which it can reduce serum Homocysteine levels.

In summary, Alzheimer's dementia is a devastating worldwide disease for which there is no known cure. The use of phytochemicals in the prevention and disease progression mitigation of Alzheimer's disease is promising and requires more empirical research to implement as frontline Pharmacotherapeutic interventions.

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