Chapter 2

Natural Products for Treatment of Alzheimer's Disease

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1. Alzheimer Disease (AD)

Aging is a complex process accompanied by several changes, including shrinkage in human brain, in addition to changes in brain white matter. Loss of neurons and myelinated axons are supposed to be the cause of decrease in weight and volume of the aged brain. The common human age-related neurodegenerative disorders such as Alzheimer's disease (AD) andParkinson's diseases (PD) are characterized by the progressive loss of brain function and memory decline. It is well known that the risk to develop dementia causing diseases increases with chronological aging. Several studies indicated that the age-dependent changes at gene and protein expression level, are multifactorial as human brain aging could result from the combination of the normal decline of biological functions with environmental factors that contribute to defining disease risk of late-life brain disorders. The initiation and progression of age-related neurodegenerative disorders is a complex process not yet fully understood [1].

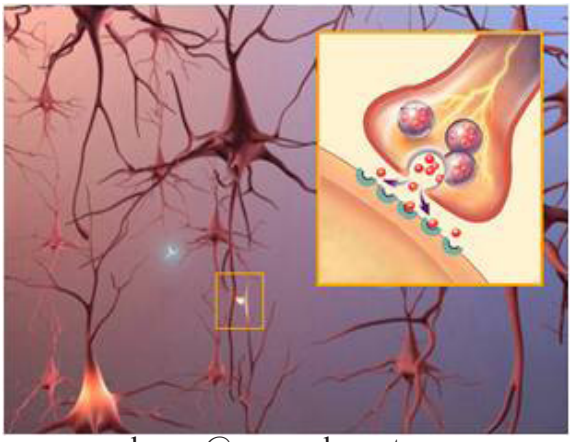
Dementia privilegeis predicted to increase at an alarming rate in the least developed and developing regions of the world despite mortality resulting from malnutrition, poverty, war, and infectious diseases. WHO suggest that by 2025, about three-quarters of the estimated 1.2 billion people aged 65 years and older will reside in developing countries [2]. Currently; dementia is diagnosed based on clinical symptoms, but significant brain damage have already occurred by the time a clinical diagnosis of dementia is made which may be too late for any effective intervention. Thus, defining a panel for biomarkers of Alzheimer's disease (AD) would be of great public health and preventive value; that precedes the clinical manifestation of dementia and could permit early detection of persons at a higher risk for developing dementia,

specifically Alzheimer's disease dementia. Nevertheless, for the purpose of large-scale screening, circulating peripheral blood-based biomarkers are more appropriate and practical as being less invasive than lumbar puncture, simple, reliable, reproducible, , and less costly than brain amyloid imaging, and can be easily accessed and non-time-consuming [1].

2. Alzheimer's and the Brain

The brain has 100 billion nerve cells (neurons). Each nerve cell connects with many others to form communication networks. Groups of nerve cells have special jobs. Some are involved in thinking, learning and remembering. Others help us see, hear and smell.

The picture below depicts nerve cells, or *neurons,* in the brain. Neurons are the chief cells destroyed by Alzheimer's disease.



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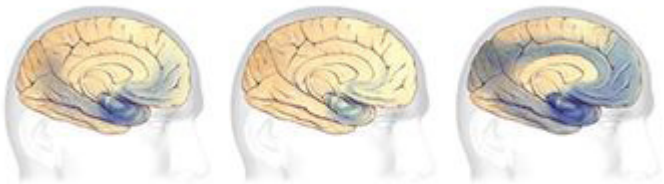
To do their work, brain cells operate like tiny factories. They receive supplies, generate energy, construct equipment and get rid of waste. Cells also process and store information and communicate with other cells. Keeping everything running requires coordination as well as large amounts of fuel and oxygen.

Scientists believe Alzheimer's disease prevents parts of a cell's factory from running well. They are not sure where the trouble starts. But just like a real factory, backups and breakdowns in one system cause problems in other areas. As damage spreads, cells lose their ability to do their jobs and, eventually die, causing irreversible changes in the brain [3].

3. The Role of Plaques and Tangles



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Plaques and tangles tend to spread through the cortex as Alzheimer's progresses.Two abnormal structures called plaques and tangles are prime suspects in damaging and killing

nerve cells. **Plaques** are deposits of a protein fragment called beta-amyloid that builds up in the spaces between nerve cells.

Tangles are twisted fibers of another protein called tau that builds up inside cells. Though autopsy studies show that most people develop some plaques and tangles as they age, those with Alzheimer's tend to develop far more and in a predictable pattern, beginning in the areas important for memory before spreading to other regions.

Scientists do not know exactly what role plaques and tangles play in Alzheimer's disease. Most experts believe they somehow play a critical role in blocking communication among nerve cells and disrupting processes that cells need to survive. It's the destruction and death of nerve cells that causes memory failure, personality changes, problems carrying out daily activities and other symptoms of Alzheimer's disease [2,3].

4. Treatment of Alzheimer

FDA-approved drugs[3]

The U.S. Food and Drug Administration (FDA) have approved five medications (listed below) to treat the symptoms of Alzheimer's disease.

Drug name	Brand name	Approved For	FDA Approved
1. donepezil	Aricept	All stages	1996
2. galantamine	Razadyne	Mild to moderate	2001
3. memantine	Namenda	Moderate to severe	2003
4. rivastigmine	Exelon	All stages	2000
5. donepezil and memantine	Namzaric	Moderate to severe	2014

5. How Alzheimer's Drugs Work

In the brain, neurons connect and communicate at synapses, where tiny bursts of chemicals called neurotransmitters carry information from one cell to another. Alzheimer's disrupts this process, and eventually destroys synapses and kills neurons, damaging the brain's communication network. Current FDA-approved Alzheimer's drugs support this communication process through two different mechanisms:

1. *Cholinesterase inhibitors* work by slowing down the process that breaks down a key neurotransmitter. *Donepezil, galantamine and rivastigmine* are cholinesterase inhibitors.

2. *Memantine*, the fifth Alzheimer's drug, is an *NMDA (N-methyl-D-aspartate) receptor antagonist,* which works by regulating the activity of glutamate, an important neurotransmitter in the brain involved in learning and memory. Attachment of glutamate to cell surface "docking sites" called NMDA receptors permits calcium to enter the cell. This process is important

for cell signaling, as well as learning and memory. In Alzheimer's disease, however, excess glutamate can be released from damaged cells, leading to chronic overexposure to calcium, which can speed up cell damage. *Memantine* helps prevent this destructive chain of events by partially blocking the NMDA receptors.The effectiveness of cholinesterase inhibitors and memantine varies across the population [3].

6. Alzheimer Treatment with Natural Products

Despite modern medicine's incredible innovation and resulting accumulation of valuable knowledge, many of the world's most problematic diseases such as Alzheimer Disease (AD) still lack effective cures and treatments. Western medicine has revealed many genetic, cellular, and molecular processes that characterize AD such as protein aggregation and inflammation. As the need for novel and effective treatments increases, researchers have turned towards traditional medicine as a resource. Modern, evidence based research examining traditional and complementary remedies for AD has generated promising results within the last decade [4].

Dementia pathologies such as Alzheimer's disease (AD) are reaching epidemic proportions, yet they are not successfully managed by effective symptomatic treatments. Only five drugs have been developed to alleviate cognitive symptoms, and more effective and safe treatments are needed for both the cognitive symptoms and behavioural and psychological symptoms of dementia (BPSD). As two of these licensed drugs (cholinesterase inhibitors (ChEIs) are naturally derived (galantamine and rivastigmine), the potential for plants to yield new therapeutic agents has stimulated extensive research to discover new ChEIs together with plant extracts, phytochemicals and their derivatives with other mechanistic effects relevant to dementia treatment [5].

The current therapeutic drugs for Alzheimer's disease are predominantly derived from the alkaloid class of plant phytochemicals. These drugs, such as galantamine and rivastigmine, attenuate the decline in the cholinergic system but, as the alkaloids occupy the most dangerous end of the phytochemical spectrum (indeed they function as feeding deterrents and poisons to other organisms within the plant itself), they are often associated with unpleasant side effects. In addition, these cholinesterase inhibiting alkaloids target only one system in a disorder, which is typified by multifactorial deficits. The present paper will look at the more benign terpene (such as *Ginkgo biloba*, Ginseng, *Melissa officinalis* (lemon balm) and *Salvia lavandulaefolia* (sage)) and phenolic (such as resveratrol) phytochemicals; arguing that they offer a safer alternative and that, as well as demonstrating efficacy in cholinesterase inhibition, these phytochemicals are able to target other salient systems such as cerebral blood flow, free radical scavenging, anti-inflammation, inhibition of amyloid-β neurotoxicity, glucoregulation and interaction with other neurotransmitters (such as γ-aminobutyric acid) and signalling pathways (e.g. via kinase enzymes) [6].

Guzior et al. [7] review current development of multifunctional potential of anti-AD agents, most of which are acetylcholinesterase inhibitors that extend the pharmacological profile. Thus compounds that offer hope are symptomatic and suggest causal treatment of AD.

Advantageous properties include the amyloid-β antiaggregation activity, inhibition of β-secretase and monoamine oxidase, an antioxidant and metal chelating activity, NO releasing ability and interaction with cannabinoid, NMDA or histamine H3 receptors. These unusual molecules possess heterodimeric structures that interact with multiple targets which in turn might combine different pharmacophores, original or derived from natural products or existing therapeutics (tacrine, donepezil, galantamine, memantine). There is minimal reaction to these findings since several described compounds may be promising drug candidates. Others may be valuable inspirations as we continue to search for new effective AD therapies [7].

7. Treatment of AD with Different Natural Sources

Various natural animal and plant based products have enormous potential. We can therefore expect improved treatment and creation of drugs for certain diseases: cancer, diabetes, and heart disease, and expect that AD will be added. Natural products from invertebrates have already begun to be integrated into modern biomedicine, e.g. leeches are employed for plastic surgery or snail venom is used as an alternative to opioids for humans [8]. For example, alterations in uptake and release of glutamate, predominant excitatory neurotransmitter in the central nervous system, have been observed in various neurodegenerative diseases, including AD. Bee venom, which has been used in Traditional Korean Medicine, exerts anti-inflammatory effects, and has been assessed for its inhibition of glutamate as related to neurotoxicity. Protecting against cell death and inhibiting cellular toxicity, bee venom is a promising compound that may be helpful as a treatment against glutamatergic neurotoxicity for neurodegenerative diseases [9]. Moreover, compounds isolated from marine invertebrates have shown equally promising leads. Acetylcholinesterase (AChE) inhibition seems relevant for treating AD.

Moreover, compounds isolated from marine invertebrates have shown equally promising leads. Acetylcholinesterase (AChE) inhibition seems relevant for treating AD. Marine natural products may be effective as AChE inhibitors with curative potential [10].

Neurodegeneration is the term for the progressive loss of structure or function of neurons, including death of neurons. Many neurodegenerative diseases including Alzheimer's disease, Parkinson's disease,and Huntington's disease occur as a result of neurodegenerative processes [11]. Current interventions for Alzheimer's disease (AD) include acetylcholinesterase inhibitors (AchI), which are indicated for patients with mild to moderate symptoms. A spectrum of alternative treatments for AD has also been proposed and must be examined judiciously in preclinical, clinical, and evidence-based research (EBR) studies [12]. Therefore,

search for acetylcholinesterase inhibitors is useful for the treatment of Alzheimer's disease. Pharmacological studies with marine compounds affecting the nervous system involved three areas of neuropharmacology: the stimulation of neurogenesis, the targeting of receptors, and other miscellaneous activities on the nervous system. A new stigmastane type steroidal alkaloid 4-acetoxy-plakinamine B isolated from a Thai marine sponge Corticium sp. significantly inhibited acetylcholinesterase (IC50 = 3.75 μM). This compound is reported to be the "first marine derived acetyl cholinesteraseinhibiting steroidal alkaloid" [13]. The inflammatory component to the pathology of neurodegeneration was most notably in Alzheimer's disease but also in Parkinson's disease and motor neuron disease [14]. Hymenialdisine is an alkaloid isolated from marine sponges, such as Acanthellaaurantianca and Stylissamassa [15]. Hymenialdisine inhibits phosphorylation of the protein tau (which is hyperphosphorylated in Alzheimer's disease) with promising potential against human neurodegenerative diseases [16]. 11-Dehydrosinulariolide was obtained from formosan soft coral, S. flexibilis, promoting neuroprotective properties as a promising candidate for the treatment of Parkinson's disease [17].

8. Application of Phytochemicals and Nutraceuticals

Synthetic drugs are useful for managing AD and many other chronic illnesses; still there are side effects. Consequently, attention of researchers has inclined toward phytochemicals as promising therapeutic agents. Many are anti-inflammatory, antioxidative and possess anticholinesterase activities with minimal side effects [18]. Approaches to Traditional Chinese Medicine (TCM) remedies reveal first that traditional herbs and phytochemicals may delay AD onset and slow its progression but also allow recovery by targeting multiple pathological causes that possess antioxidative, anti-inflammatory, and antiamyloidogenicproperties [19]. Furthermore herbs regulate mitochondrial stress, apoptotic factors, free radical scavenging systems, and neurotrophic factors. Neurotrophins such as BDNF, NGF, NT3, and NT4/5 may also participate in neuronal and nonneuronal responses to AD.

Neurotrophin depletion accelerates progression of AD and therefore, replacing such neurotrophins could serve as a potential treatment for certain neurodegenerative diseases. Emphasis concerning mechanisms rests on phytochemicals that mediate signaling pathways involved in neuroprotection specifically neurotrophin-mediated activation of Trk receptors and members of the p75(NTR) superfamily. Research conducted by Venkatesan et al. [19] focused on representative phenolic derivatives, iridoid glycosides, terpenoids, alkaloids, and steroidal saponins as regulators of neurotrophin-mediated neuroprotection. There is evidence derived from encouraging advances, since these phytochemicals have attracted attention due to their in vitro neurotrophin potentiating activity, yet there is still a need for in vivo and clinical efficacy trials. Currently, proof of neuroprotective effects in certain preclinical models and in humans is unclear [19].

Here is where we are with respect to therapeutic approaches. According to Frautschy and Cole [20], AD involves a complex pathological cascade perhaps triggered initially by accumulation of beta-amyloid peptide aggregates or aberrant amyloid precursor protein processing. Moreover, there is credible information concerning factors initiating AD process significantly before onset of cognitive deficits. However, there is an unclear understanding of any events that immediately precede and precipitate cognitive decline. Without these events defined or at least clarified more adequately we are left with a major limiting factor that hinders rapid development of adequate prevention and treatment strategies. If we agree with the hypothesis of inhibiting certain pathways, clearly efforts have focused on pleiotropic activities of omega-3 fatty acids and anti-inflammatory, antioxidant, and anti-amyloid activity of curcumin in multiple models that consider many steps in the AD pathogenic cascade [20]. AD reveals that inflammation contributes to neurodegenerative disease. Knowing this it is therefore suggested that early prevention and management of inflammation might conceivably delay onset or reduce symptoms of AD, but what is a likely target? With aging, normal physiological changes in the brain include depletion of long chain omega-3 fatty acids. Analyses have shown that brains of AD patients possess lower levels of docosahexaenoic acid (DHA). In agreement, Thomas et al. [20] report that DHA supplementation reduces markers of inflammation. Research devoted to epidemiological, dietary intervention, and supplementation support roles of long chain omega-3 fatty acids in preventing or delaying cognitive decline in AD during its early stages. These results support further investigation of long chain omega-3 supplementation in early stage AD, and maintains the importance of overall quality and composition of diet to protect against AD and dementia [21].

Complementary and alternative medicine reveals nutraceuticals whose properties are both anti-inflammatory and anti-cancer. For example, mangosteen, the fruit from a tropical evergreen tree native to Southeast Asia, has nutraceuticals which possess multiple beneficial properties, especially neuroprotective, anti-oxidative, and anti-inflammatory effects. Treatment with mangosteen based nutraceuticals decreased cell death and increased brain-derived levels of neurotrophic factor. Moreover, mice fed a mangosteen supplemented diet showed improved inflammation related cognitive function, demonstrating its promise in treating AD [22]. Another nutraceutical that has garnered interest as an antioxidant is quercetin. Oxidative stress plays a role in the progression of various diseases and conditions including AD. Thus quercetin has received attention as a food derived antioxidant for its promising biological effects and ability to prevent oxidative damage [23].

9. Traditional Medicine and AD

Traditional Chinese Medicine has accumulated many experiences in the treatment of dementia during thousands of years of practice; modern pharmacological studies have confirmed the therapeutic effects of many active components derived from Chinese herbal medicines

(CHM). *Ginsenoside Rg1*, extracted from Radix Ginseng can inhibit the apoptosis of neuron cells. Tanshinone IIA, extracted from Radix *Salviaemiltiorrhizae*, and baicalin, extracted from Radix Scutellariae can inhibit the oxidative stress injury in neuronal cells. Icariin, extracted from *Epimediumbrevicornum*, can decrease the hyperphosphorylation of tau protein, and can also inhibit oxidative stress and apoptosis. Huperzine A, extracted from *Huperziaserrata*, exerts a cholinesterase inhibitor effect. Evodiamine, extracted from FructusEvodiae, and curcumin, extracted from Rhizoma*Curcumaelongae*, exert anti-inflammatory actions. Due to the advantages of multi-target effects and fewer side effects, Chinese medicine is more appropriate for long-term use [4].

Despite increasing prevalence of AD worldwide, in addition to extensive research efforts to find a cure, we still have no long term solution. Effective therapeutic and preventative treatments are urgently needed to combat the devastating cognitive decline observed in patients with AD. This is especially pertinent as many potential remedies and medications for neurodegenerative diseases have been derived from traditional medicine [4].

According to Liu et al. [24] Traditional Chinese Medicine (TCM) has been in use for more than 2,000 years. Recently herbal medicines employed to treat AD in China are based on TCM or modern pharmacological theories; this approach has resonated with respect to etiology and pathogenesis of AD, TCM therapy, and herbal extracts useful in treating AD. Evidence suggests that TCM therapy may offer certain complementary cognitive benefits for treating AD. Moreover, Chinese herbs may be advantageous if we consider multiple target regulation especially compared with single-target antagonist [24].

10. Polyphenols and AD

Despite modern medicine's incredible innovation and resulting accumulation of valuable knowledge, many of the world's most problematic diseases such as Alzheimer Disease (AD) still lack effective cures and treatments. Western medicine has revealed many genetic, cellular, and molecular processes that characterize AD such as protein aggregation and inflammation. As the need for novel and effective treatments increases, researchers have turned towards traditional medicine as a resource. Modern, evidence based research examining traditional and complementary remedies for AD has generated promising results within the last decade. Animal based products inhibiting cellular toxicity, anti-inflammatory nutraceuticals such as omega-3 fatty acids, and plant based compounds derived from herbal medicine demonstrate viability as neuroprotective treatments and possible application in developing pharmaceuticals. Analysis of antioxidant, anti-inflammatory, and neuroprotective phytochemicals used in various traditional medicines around the world reveal potential to ameliorate and prevent the devastating neurodegeneration observed in AD [4].

A large number of polyphenolic compounds showing promising results against AD

pathologies have been identified and described in the past decade. Many efforts have been made to unravel the molecular mechanisms and the specific interactions of polyphenols with their targets in the pathway. The diet related chronic diseases of modern society are now the single largest cause of death encompassing diabetes, cardiovascular disease, hypertension, obesity and cognitive decline. To sustain healthy aging requires dietary restraint, a reduction of the consumption of processed foods and fatty diets, with negative nutritional attributes such as high energy refined sugars, saturated fats, high sodium content and an increasing affinity and tendency to consume those with positive health attributes including nutraceuticals, phytochemicals and micronutrient rich foods. Carbohydrates, lipids and proteins are the primary dietary fuels that yield metabolic energy providing body function and performance, whereas dietary phytochemicals and herbal medicines rich in polyphenols [25] are associated with a decreased risk of several human chronic diseases, sustain the cellular molecular machinery, preventing the development of disorders, gain of toxic function and disease conditions. For example, by stimulating lipid metabolism in rats, the green tea flavanolepigallocatechingallate (EGCG) reversed the high-fat diet induced hypercholesterolemic levels in rats and provided protection for the cardiovascular system. The enzymatic and non-enzymatic antioxidant levels were improved, activated sirtuin 1, endothelial nitric oxide synthase and adenosine monophosphate-activated protein kinase α, are all indicators that the protective effect of EGCG and other catechins in green tea act as strong activating agents through stimulation of the metabolism of high-level fats that may lead to a lower risk of developing heart disease [26].

Natural products utilized in folk medicine have demonstrated safety profiles since they have already been utilized for decades for the treatment of disease in humans and animals, we use them as templates for the generation of analogues for the development of therapeutic compounds, and probing molecular mechanisms underlying cellular dysfunction. The major liabilities of herbal medicinal products have poor biocompatibility, pharmacokinetic profiles and BBB permeability [26].

Alkaloids, terpenes, polyphenolic compounds represent the most prevalent classes of herbal constituents with anti-dementia benefit. It is unclear to what extent many of these bioactive phytochemicals, utilized in single or herbal formulae doses can reach the brain in sufficient concentrations and in a biologically active form to exert their neuroprotective effects [27]. For AD therapy, herbal products offer a wider range of brain-targets, nutritional benefits, safer dosage, long-term applications and efficacious treatment of AD pathology. For *in vivo* and large epidemiological studies, the quality assurance of herbal bioactives and production of mass quantities is another challenge for the translation of natural products into therapeutic agents. The majority of herbs are consumed as aqueous extracts so their formulation has to provide increased bioavailability and blood brain barrier permeability. Strategies for enhancing polyphenol bioavailability include encapsulation as phospholipid nanoparticles;

incorporation with biodegradable polymers; use of bioactive analogues; modifications to improve pharmacokinetics, use of adjuvants as absorption enhancers.

Dementia is a multifactorial disease, linked to aging, environmental impacts and is different in each patient. Herbs and food supplements are readily available so it is imperative that the molecular mechanisms of their significant health benefits are determined so herbs or formulations are able to complement approved drugs and provide the best therapeutic treatment against Aβ toxicity [28].

Polyphenols are found in a wide variety of foodstuffs and beverages and the high intake of fruits, vegetables, herbs and many plant foods is inversely related to the incidence of several degenerative diseases, highlighting the increased consumer attention to the importance of a balanced diet in relation to human health. It has been estimated that a balanced diet may provide around 1 g of polyphenols daily. Polyphenols are able to (a) react with free radicals blocking their activity, (b) modulate the expression of genes (epigenetics) involved in metabolism, act as signaling molecules increasing antioxidant defense, and (c) protect and repair DNA damage. Our research efforts focus on the molecular mechanisms that correlate the health benefits of polyphenols against the most common diseases related to oxidative stress driven pathologies, including neurodegenerative, cancer, cardiovascular diseases, inflammation, type II diabetes and metabolic syndrome diseases [26].

Another characteristic feature of polyphenols is their interactions with peptides and proteins. Animal and human studies have demonstrated that dietary flavonoids from chocolate, including (-)epicatechin, promote cardiovascular health, the result of antioxidant and antithrombotic mechanisms. The consumption of dark chocolate increases blood plasma (-)epicatechin, these effects are diminished when consumed with milk/milk chocolate. This indicates not only milk proteins, but also other dietary foods may interact/impair/reduce bioavailability and the absorption of flavonoids from chocolate *in vivo* negating the potential health benefits from dark chocolate. A high cocoa flavanol intervention enhances dentate gyrus function, improving cognition in older adults, most likely by the improved vascular function of (-)-epicatechin. Fortunately the ubiquitous polyphenol-protein interactions also have beneficial effects. The propensity of certain natural polyphenols to interact with $A\beta_{42}$ monomers, blocks their rapid self-association to form low molecular weight oligomers, enables polyphenols to function as $A\beta_{42}$ inhibitors. One of our challenges in designing $A\beta_{42}$ inhibitors is to find the chemical 'Polyphenol Lipinskinisation' changes necessary, that is, to modify polyphenol structures to improve their pharmacokinetics and efficacy. $A\beta_{42}$ peptides misfold into soluble oligomers and protofibrils associated with AD. The mechanism of Aβ inhibition is driven by hydrophobic interactions that involve π-π bonding between the planar faces of the polyphenol structure and the aromatic residues of $A\beta_{42}$. Additionally, hydrogen bonding occurs between the peptide and the phenolic hydroxyl groups. The polyphenols intercede/impose between two

β_{42}-amyloid aromatic residues prevents their stacking, blocking the amyloid self-assembly-β-oligomer-sheet-fibril formation and gain of toxic function. Herbal polyphenols are known to also modulate Aβ production by stimulating the α-secretase and inhibiting the β-site amyloid precursor protein cleaving enzyme-1 (BACE1), γ-protease pathways. (−)-Epicatechin, epigallocatechin are potent inhibitors of amyloid precursor protein processing (APP). Some phenolics show both, a strong inhibition of APP-Aβ generation and anti-amyloidogenic binding [28]. The flavonoids quercetin and myricetin inhibit BACE1 activity, dose-dependently inhibit amyloid fibril formation with myricetin>quercetin>catechin = epicatechin. Similarly, EGCG, resveratrol, curcumin, oleuropein, pentagalloylglucose inhibit β-amyloid misfolding and aggregation by forming nontoxic complexes with the peptide, they also have other benefits against the onset of neurodegeneration. EGCG directly interacts with β-sheet structures in amyloid fibrils leading to an decrease in the binding of Aβ to the fluorescent dye thioflavin T and promotes the assembly of large, spherical oligomersintosafe species, unable to seed fibrillogenesis; remodels Aβ mature fibrils into smaller, amorphous protein aggregates by direct binding to the β-sheet-rich aggregates and mediating a conformational change without generating potentially toxic oligomers [28]. Curcumin is the main constituent of the spice turmeric, whose extensive use apparently accounts for the lower prevalence of AD in the Indian population. *In vitro*curcumin inhibits fibril formation and also destabilizes preformed fibrils, binds to plaques and reduces amyloid levels *in vivo*. Curcumin and resveratrol bind to the N-terminus (residues 5−20) of $A\beta_{42}$monomers. Many *in vitro* studies have demonstrated the multiple potential therapeutic effects of resveratrol, found in herbs, red wine, but it'sin *vivo* efficacy is controversial. The beneficial effects of resveratrol may contribute to its protective effects on cognitive function; however the volume of red wine to be consumed for resveratrol therapy is not practicable. Danshen constituents, salvianolic acid B, rosmarinic acid, tanshinones inhibit $A\beta_{42}$, disaggregate fibrils, and protect cultured cells. Oleuropein in olive oilpreventsformation of β-amyloid oligomers, and dietary oleuropeinaglycone improves the cognitive performance of young/middle-aged mice [26].

One neuroprotective plant that is widely used in Traditional China Medicine (TCM) as herbal medicine is *Evodiarutaecarpa* Bentham. Evodiamine (Evo), an extract of *E. rutaecarpa* Bentham, presents an extensive array of beneficial properties. First, Evo exhibits anti-AD and anti-inflammatory functions. Second, a surfeit exists. There are anticancer, antiobesity, antinomic, antinociceptive, and antimetastatic functions. These results are enormously positive for treating neurodegenerative disorders [29]. Moreover, TCM has also given us compounds that require improvement or alternative substitutes for existing AD. Retinoid X Receptor (RXR) agonist, Targetin, is an effective treatment for AD in mouse models. The TCM compounds β -lipoic acid and sulfanilic acid are also strong candidates as RXR agonists. Forming viable bonds with the RXR protein receptors, these TCM compounds exhibit potential to be developed into anti-dementia drugs [30].

Research on the promising compound Nobiletin employed in Traditional Japanese Medicine (Kampo) has yielded promising results. Nobiletin, a citrus flavonoid, exhibited memory improving functions when tested in several animal models. Demonstrating beneficial effects against oxidative stress, cholinergic neurodegeneration, dysfunction of synaptic plasticity-related signaling, and formation of plaques, nobiletin shows potential as a natural anti-dementia compound. In addition, nobiletin exerts certain possible novel pharmaceutical and preventative applications. When tested in mice, Nobiletin enhanced learning and memory, reversing the impairment inflicted on short-term memory and recognition memory [31,32]. Further investigation of Kampo treatments has revealed another herbal medicine *ninjin'yoeito* (NYT). NYT has been analyzed in clinical trials for its long term effects on cognitive function and mood. Twenty-three patients at varying stages of disease progression who had all shown insufficient responses to treatment with donzepil alone were tested. Eleven patients were treated with donzepil alone, whereas twelve received a combined combination of donzepil supplemented with NYT for two years. After this period, patients receiving donzepil and NYT showed both cognitive improvement and a reduction of AD related depression [33].

Ayurveda, Traditional Indian Medicine, has also contributed to the growing list of valuable compounds. Results have validated ancient remedies for nervous system disorders, including memory related conditions such as dementia. Efforts have been made to analyze Ayurvedic medicine experimentally and to understand its effects on geriatric diseases such as AlzhiemerDisease [34]. Traditionally used as Ayurvedic brain tonic medicine, the plant *Centellaasiatica* (L.) Urban, native to Southeast Asia, exerts various neuroprotective effects. Reducing oxidative stress, inhibiting enzymes, and preventing the formation of amyloid plaques in AD, *C. asiatica* exhibits comprehensive neuroprotection, a potential phytopharmaceutical [35].

11. Application of Integrative Approaches

Modern biomedicine mostly utilizes a Western approach towards solving current medical problems, and has revealed many of the genetic, cellular, and molecular processes that characterize AD such as protein aggregation and inflammation. The unmistakable influence and value of primitive animal models in advancing our understanding of neurodegenerative disease is evident in studies that continue to analyze Drosophila and *C. elegans*. Animal models serve as cost-effective genetic sources for evaluating treatments, enhancing our understanding of conserved biochemical pathways. However, in spite recent insights into mechanisms that underlie AD pathology, current treatments lack efficacy and adequacy, and a significant cure is yet to be found-still, we persevere [4].

As the need for novel and effective treatments increases, researchers have turned towards ancient knowledge and alternative practices. Using a rigorous, evidence based approach to

analyze compounds attributed in CAM and various traditional medicines, researchers revealed viable alternate treatments that show promising anti-inflammatory, memory improving, and neuroprotective effects. They utilize similar animal models to evaluate their potency and value, a confirmation of their still largely untapped utility. Most products are animal or plant based, and their compounds have possible applications whose development into pharmaceuticals reveals promising cures and potential prevention. Acceptance and practice of theory based medicines in Western biomedicine may require significant time to first become integrated or even totally accepted. However, utilizing Western methodology and approaches to medicine to investigate Traditional Medicine and CAM is a more pragmatic approach to integration. Evidence based research and successful application of alternative and traditional compounds have shed light on potential methods and cures for preventing AD, yielding encouraging results that point towards progress and even beyond [4].

12. Future Treatment Breakthroughs

Researchers are looking for new ways to treat Alzheimer's. Current drugs help mask the symptoms of Alzheimer's, but do not treat the underlying disease or delay its progression. A breakthrough Alzheimer's drug would treat the underlying disease and stop or delay the cell damage that eventually leads to the worsening of symptoms. There are several promising drugs in development and testing, but we need more volunteers to complete clinical trials of those drugs and increased federal funding of research to ensure that fresh ideas continue to fill the pipeline.

13. Special Remarks

• The global population is growing, therefore also aging and dementia increases in almost all parts of the world.

• Studies related to autosomal dominant AD indicate that the disease process begins around 20 years prior to onset of dementia [36].

• Recent research provides evidence that life style factors and environmental stresses that increase blood pressure may also increase the risk of AD through Angiotensin II-angiotensin type1a pathway [37].

• There is a need to generate more healthy consumer food products, and with public passion, encourage early adoption of healthy lifestyle-better diets and regular exercise as preventive strategies to reduce cognitive impairment.

• To explain the extended AD pathogenic process over 2 decades, amyloidosis, the incremental neuronal damage caused by non-sequestered β-oligomers is the early pathological event and accumulates over time eventually resulting in neurodegeneration (hypometabolism)

and then widespread cognitive impairment [38, 39].

• (−)Epicatechin and other flavonoid inhibitors of BACE1 proteolysis/cleavage of APP could be protective against early amyloidosis events of AD provided they are included in the diet. Studies suggest the efficacy of orally delivered (−)-epicatechin in a transgenic model of AD in reducing $A\beta_{42}$ production and pathology *via* modulation of BACE1 as a risk reduction strategy, supporting the positive effects of flavonoid rich diets against the development of cognitive impairment [40,41].

• The increase intake of flavonoids and polyphenols is a dietary preventative strategy to (a) reduce β-amyloid formation and (b) competitively prevent β-amyloid misfolding and toxicity against development of AD. A key question is: can these findings translate into preventative benefit for healthy humans?

• The protective effects of flavonoid rich diets against the development of dementia needs to be translated into clinical trials to directly test their efficacy in at risk individuals or those with mild cognitive impairment.

14. Conclusion

Despite extensive knowledge about how diet and nutrition has advanced beyond understanding cellular energy status, diet related chronic diseases of modern society are now the single largest cause of death. Epidemiological investigations indicate that nutrition and dietary patterns are modifiable risk factors that can help limit and prevent chronic diseases, enabling the achievement of the overall objective in slowing human aging diseases such as AD and thereby improving the quality of healthspan of everyone.

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