Neurological Disorders

Juma, J Neurol Disord 2015, 3:4
http://dx.doi.org/10.4172/2329-6895.1000244

Review Article Open Access

A Current Understanding of Alzheimer's Disease and the Prospects of Phytopharmacological Intervention as a Management Strategy

Juma KK*

Department of Biochemistry and Biotechnology, Kenyatta University, Nairobi, P.O. Box 43844-00100, Kenya

Abstract

Alzheimer's disease is a mental disorder that accounts for 60-70% of dementia. Its specific causes have not been determined to date. It is understood as neurodegenerative diseases which progressively gets worse over time. It is characterized by short term memory loss, language disorientation, mood disorders, lack of motivation and self-care, and as well as behavioral challenges. Management's strategies of AD are limited and are not effective. Common therapeutic mechanisms target the inhibition of acetyl cholinesterase and N-methyl D aspartate (NMDA). Post mortem evaluation and Magnetic resonance imaging techniques have demonstrated similarities between Multiple Sclerosis and Alzheimer's disease in pathogenesis of the disease through neurodegeneration and inflammation. Similarly, findings using Echo-Color Doppler technique and MRI along other techniques have demonstrated a strong association of development of Chronic CerebroSpinal Venous Insufficiency (CCSVI) with MS resulting from vascular damage of jugular veins leading to changes in the hemodynamics in the brain. Due to the similarity in mechanism of pathogenesis promoting neurodegeneration; it is possible that Alzheimer's disease is also associated with chronic cerebrospinal venous insufficiency. Little is known on alternative management of Alzheimer's disease using plant herbal extracts. Using these new findings in MS and its relation to AD; it is possible that it can serve as a new therapeutic target to management of MS and therefore AD. This study is therefore a review of the current understanding of Alzheimer's diseases, diagnosis, management strategies and the prospects of phytopharmacological studies in offering alternative solution to management of Alzheimer's disease.

Keywords: Alzheimer disease; Mental disease; Ginkgo biloba; Curcuma; Phytopharmacological studies; Chronic cerebrospinal venous insufficiency; Alternative management of Alzheimer's disease.

Introduction

Alzheimer was first defined and described by Alois Alzheimer; a German psychiatrist and pathologies. Alzheimer's Disease (AD) has been shown to account for 60-70% of the cases of dementia [1]. AD starts and grows as a neurodegenerative diseases that progressively leads to brain damage. The main causes of Alzheimer's disease is not well understood [1]. However, more than 70% of the causes is attributed to genetic as a result of the disorders with many genes [2]. Many other causes includes injuries to the head, long sessions of depressions, hypertensions [1]. It is also believed that the disease is caused by the formation of plaques, tangles and other things in the brain. These are known to promote hypertension since they may lead to occlusion of the blood flowing to the brain leading to death. The current diagnostic procedures involve a series of imaging, determination of biomarkers for loss of neural functions in blood so that possible causes can be ruled out [3]. Early symptoms are associated with aging. In order to make proper diagnosis, the examination of the brain is required to make conclusive diagnosis. Increased involvement in mental, physical exercise and avoiding obesity may lower the propensity to Alzheimer's disease. Currently, no new medication has been developed for management of AD [2]. Nutritional supplements do not have any specific effect in prevention of AD [4]. Therefore, no medication is available that can reverse the progression of neuro degeneration process. However, some drugs have been shown to improve the symptoms. Most subjects with AD are dependents and rely on other people for assistance and support and more especially the caregivers. Some of the pressures that promote stress to people with AD includes social, psychological, physical and economics factors [5]. Exercise is also known to increase their daily activities and boost the health outcomes for better living [6]. Management of behavioral problems in dementia is managed with antipsychotics. However, use of antipsychotics is not recommended since it is not beneficial and may even cause death of the victims [7,8]. AD has common clinical and pathological symptoms to Parkinson's disease and Multiple Sclerosis.

Prevalence of Alzheimer's Disease

According to statistics collected in 2010, about 35 million people suffer from AD [9,10]. It occurs mainly among the elderly people in the society. However, 4- 5% of the cases may have an early onset while 6% and even more represents people with 65 years of age and above. Similarly, about 490,000 deaths may also occur annually. Above all, it has serious financial impacts to the national governments; it is very expensive for the government [11].

Characteristics of Alzheimer's Disease

The disease is characterized into four main stages which are associated with cognitive and functional destructions: Pre-dementia, early, moderate and advanced stage of disease progression. Pre-dementia is associated with the early stages where one is likely to be attributed to aging as a result of stress [12]. At this stage, the tests for neuropsychological testing suggest very mild cognitive challenges to the period not later than 8 years before they can be able to be diagnosed with AD [13]. It also significantly affects an individual's daily engagement with the activities [14]. However, short term loss of memory is observed

***Corresponding author:** Kelvin Kisaka Juma, Department of Biochemistry and Biotechnology, Kenyatta University, Nairobi, Kenya, P.O. Box 43844-00100, Tel: 254728898233; E-mail: juma.kelvin85@gmail.com

Received July 04, 2015; **Accepted** July 28, 2015; **Published** July 31, 2015

Citation: Juma KK (2015) A Current Understanding of Alzheimer's Disease and the Prospects of Phytopharmacological Intervention as a Management Strategy. J Neurol Disord 3: 244. doi:10.4172/2329-6895.1000244

characterized by the inability to remember recent facts and even getting new information [13,15]. They may also have problems with paying attention, planning, flexibility, simple processes of thinking associated with memory of meanings and close relationships [13]. Apathy develops and becomes more persistent leading to neuropsychiatric symptoms [16]. Depressions, irritability, and reduced memory are common. The early phase increases the destruction with impairment of learning and memory eventually may promote the diagnosis. During this stages, difficulty with the language, executive functions, perception, movements (apraxia) are more prominent and more than the memory problems. However, at this stage, older memories, facts learned, implicit memory may not be affected to a lesser extent. Language challenges are characterized by shrinking the vocabulary, less fluency, and loss of oral and written language. They are also capable of communicating basic ideas adequately [13-16]. At the moderate phase, deterioration hinders independence, through the deterioration of the speech difficulties, inability to recall vocabulary, reading and writing skills are also lost [17,18]. The complex motor sequences also become less coordinated and progresses at this stage. Memory problems increases and the risk of falling increases [17]. In this phase, memory problems becomes worse, and may even lead to failure to recognize even close people [17]. Eventually, ling term memory is also become impaired. Behavioral and neuropsychiatric changes are more prevalent with manifestations of wandering, getting irritated and labile effects, crying, outbursts of aggressions, resistance to caregivers and many others. Finally, at the advanced stage of the disease, the subjects are dependent on caregivers [17]. They can only be able to use simple phrases and simple words leading to total loss of speech. They also respond to issues emotionally, with frequent aggressions and irritations. There is also extreme apathy and exhaustion. The body muscle mass also disappears and are often bed ridden. Consequently, they may not be able to feed themselves. Death occurs at this time usually from an external disease or infection such as pressure ulcers, pneumonia and never AD [18].

According to the evaluation of the age related degenerative factors in the development of neurodegeneration in the brain; disease state in neurodegeneration varies with age in morphological and functional cerebral veins evaluated using echo-color Doppler (ECD) method. The younger patients aged 30 years and lower, show cerebral veins stenosis and blocked flow of blood in internal jugular veins and vertebral veins compared to the older patients aged 30 years and above. It was established that only the duration of the disease can be able to explain the disease differences [19].

Causes of Alzheimer's Disease

A review of family studies have shown the about 49-79% of the patients with AD are genetic [20,21]. About 0.1% of the cases are as a result of the familial autosomal disorders inheritance occurring before 65 years of age [22]. Hence, it is referred to as early onset familial AD. The genetic autosomal and familial AD is associated with three gene mutations associated with formation of Amyloid Precursor Proteins (APP) and presenilins 1 and 2 [23]. Mutations in proteins promote the production of small proteins Aβ42 known to be a component of senile plagues [24]. A variant of Aβ42 (Aβ40) have also been found [25,26]. Presenilins cause mutations even in low concentrations. AD is common in places on which both environment and genetics factors may be risk factors. Some genetic factors include ε4 allele derived from Apo lipoprotein E (APOE) [27,28]. About 40-80% of the people with AD have APOE ε4 [28]. In addition, mutations in TREM2 genes are linked to between 3 and 5 times more risk in development of Alzheimer's diseases [29]. Research has shown that when TREM2 is mutated, the WBC in brain becomes unable to control the amount of beta amyloid present [29].

Previously, several hyponthesis have been postulated to explain the onset of the disease and how it progresses. First, the cholinergic hypothesis is one of the oldest and most useful hypothesis on which current drug therapies are based for the management of AD [30]. It links cholinergic effects to aggregation of amyloids and inflammation of the neurons [31-34]. Secondly, amyloid hyponthesis suggest that AD develops and exhibit the symptoms at 40 years of age [35,36]. Apo lipoproteins E 4 (APOE4) are a major genetic risk factor for AD by promotion of beta amyloid breakdown and consequently build up in the brain [37]. Vaccines developed for AD have shown promising results but failed to clear dementia [38]. Improvement in the theory in 2009 has suggested a close relation between beta amyloid breakdown and deposition in the brain to development of AD. It has also been associated to the aging process in life [38]. Moreover, Tau hypothesis proposes that the disease cascade may be initiated by the tau protein [34]. In this case, the hyper phosphorylated tau pairs with other tau which form neurofibrillary tangles inside the nerve cell bodies [39]. This result in disintegration of microtubules leading to destruction of cells cytoskeletons which promote the collapse of the neuron transport systems [40]. This interferes with the biochemical communications between neurons later in life in cells of the body [41].

Multiple Sclerosis (MS) like AD is a neurodegenerative disease. There is a possibility of a strong similarly in the mechanism of pathogenesis of AD to MS supported by the pathogenetic theory. This theory holds that increased venous pressure could be the main reason for the formation of colloids, lymphocyte and erythrocyte extravasation, promoting an inflammatory reaction in the brain and spine in cases of MS [42]. Evidence of pathogenesis shows a close association between chronic cerebrospinal venous inhibitions (CCSVI) to MS supporting the pathogenetic theory (Table 1) [42-49]. It is possible that this is also the cause of neurodegeneration in AD. A recent finding on evaluation of MS which is similar to AD suggests that age may be a significant contribution to the disease development of MS [19,20,22]. Moreover, it is demonstrated that the longer the duration of the disease, the higher the damage of the vascular tissues and hence the greater the degree of disability [19]. This may also be shared by AD. The extent of the damage in MS is associated to an intricate of complex venous hemodynamics alterations induced by the damage in the vascular walls. This has been suggested to cause occlusion or blocking of blood flow leading to stenosis that may be responsible for the increase in blood pressure in the skull. This has been expressed as a possible mechanism of action for the damage of the cerebral cells causing more serious morphological abnormalities. In addition, it is possible that the change

Authors	Method of Assessment applied	Link between CCSVI and MS	Reference No
Zamboni et al.	ECD + TCCS	Yes	[42]
Zamboni et al.	ECD + MRI	Yes	[43]
Al-Omari and Rousan	CDUS	Yes	[44]
Zivadinov et al.	ECD	Yes	[45]
Ciccone et al.	ECD	Yes	[46]
Floris et al.	CDV	Yes	[47]
Zaniewski et al.	CDUS	Yes	[48]
Lianzillo et al.	CDS	CCSVI is age related	[49]

Note: 1) CCSVI: chronic cerebrospinal venous insufficiency; CDUS: Color-Doppler ultra-sound; ECD: Echo Color Doppler; CDS: Color Doppler Sonography; MRI: magnetic resonance imaging; MS: Multiple Sclerosis; TCCS: Transcranial Color-coded Sonography.
2) Yes indicates there is association between CCSVI and MS.

Table 1: Evidence of involvement of CCSVI in MS in pathogenicity theory.

in the hemodynamic profiles of the venous system interferes with the endothelial functions of the veins. This has also been implicated in the destruction of the cerebral vein return affecting the control of the function of the cerebral vascular blood outflow [19].

Diagnosis of Alzheimer's Disease

The diagnosis is made on individual basis on the person's medical history from the relatives and other behavioral observations. They also check for the presence of the neurological and neuropsychological features through the determination of the absence of other conditions. Advanced medical imaging's can also be done using Computer Tomography (CT), magnetic resonance imaging (MRI), and Single Photon Emission Computed Tomography (SPECT) and sometimes, Positron Emission Tomography (PET) can be used in the determination of the precise medical conditions and excluding other extreme forms of cerebral pathology. CCSVI has been evaluated using ECD, UDC, UDS, TCCS, and even MRI [19]. Intellectual functions may also be assessed by memory testing which is the main characteristic of AD [20]. Post mortem can also be done when the brain materials are availed for histopathological assessment [50].

New method for assessment of development and evaluation of changes in the hemodynamics has been developed. Many studies have applied the use of Echo-color-Doppler technique in measuring the degree of venous vascular degeneration of loss of endothelial capacity associated with the development of CCSVI [19,46]. While CCSVI syndrome is related to MS [46], there is significant potential that this may also be responsible for the change of clinical symptoms in patients with AD since they all develop neurodegeneration as a common clinical condition. However, replicate studies will be required to justify these findings in cases of AD. But there is potential for positive findings since they share most of the clinical symptoms.

Management Strategies for Alzheimer's disease

There is no precise form of AD prevention [51]. Research findings for drugs have been inconsistent. Epidemiology has led to association of AD with factors such as diet, cardiovascular diseases, and involvement in intellectual activities. Further clinical trials are required for better research findings. Current medications targets secondary risk factors such as hypercholesterolemia, hypertension, diabetes and smoking in the development of AD. However, drugs have shown little success in the progression of the diseases [52,53]. Long term use of NSAIDs has potential in reducing inflammations and formation of amyloid plagues [54]. Hormone replacement therapy has also been used but findings suggested that it increases dementia. Change of lifestyle has also been recommended as a possible management strategy for AD. People are encouraged to participate in reading, participating in sports, solving puzzles, music and involvement in many other social activities. Good diet is also recommended for people with AD because it is known to improve the outcome in the disease [55]. Caffeine, tea and red wine is also protective. Flavonoids in cocoa are also known to lower the risks of AD. Vitamins A, C, folic acid and E, together with minerals selenium and Zinc are highly recommended [55].

Conventional management of Alzheimer's disease

So far, there is no effective treatment for AD. Most of the common drugs only reduce the symptoms of this disease. Studies have shown a close relationship between the levels of Acetyl Cholinesterase (ACh) present in the synapses and improvement in the cognitive function [56]. The main goals of the current therapies are to promote increased cholinergic activity in the brain. Consequently, uses of acetyl cholinesterase inhibitors have shown improvement in clinical symptoms of the diseases. However, this therapeutic target as an intervention is limited [56]. Intensive research on new interventions using latest monitoring and evaluation tools for AD and other associated diseases such as Parkinson's disease and MS are required that focus on the mechanisms of disease progression. Example of conventional ACh inhibitors include: Galantamine, rivastigmine, tacrine and donepezil.

Similarly, N-methyl-D-aspartate (NMDA) receptor antagonists have also been applied in the management of AD: Memantine has also been used. NMDA serves as a glutamate receptor and is also linked to an ion channel protein which is located in the nerve cells. The activation of the NMDA receptors by the binding of glycine and glutamate allows the transmission of positive ions through the cell membrane. Using the NMDA receptors antagonists are also limited in management of AD. New findings of significant association between MS and CCSVI offers new green light to management of CCSVI [19,46]. The same is strongly expected to be replicated in AD. There is potential in reversing vascular degeneration of the tissues in CCSVI using the active phytopharmacological interventions.

Potential Phytopharmacological management of Alzheimer's disease

Gingko biloba has been evaluated for management of AD. Previously, it was shown to contain active compounds that promoted blood flow in the cerebral system and was established to have effects on the functioning of the neurotransmitters, cellular redox reactions, regulated nitric oxide levels and was postulated to have antagonistic effects on the Platelet Activating Factors (PAF) [57,58]. It has also been suggested to possess activity in amyloid aggregation and in tissue pathology [59-61]. When prepared as a supplement, it is shown to be rich in flavones, glycosides and terpenoids. Findings from a randomized placebo controlled trial using 120 mg daily of Gingko biloba extract showed a statistically significant benefit of Gingko biloba on the Alzheimer's disease assessment scale cognitive and the geriatric evaluation by relative rating instrument. However, this has been demonstrated not to have any clinical bearing to improvement of the condition of AD [62]. Similar findings have also been established in a meta- analysis performed in 1998 [63] and 2002 [64]. This therefore suggests little clinical benefits of Gingko biloba in the management of AD. Current application of Gingko biloba in combination with approved cholinesterase inhibitors has also been demonstrated. Despite challenges of bleeding problems in the use of Gingko biloba, it is still applied as a current strategy due to its wider safety property [64].

Huperzine serrate is another herb dominant in china and commonly used by the Chinese in the management of AD. It has been shown to contain an extract Huperzine A (HupA). It is known to be a selective inhibitor of acetylcholine esterase with significant pharmacodynamics and kinetic properties in the brain demonstrated in animal studies [65]. It has long half-life and tolerance with few cholinergic side effects [65]. It also reduces toxicity induced by glutamate in the neurons [66]. It has been suggested that this may be as a result of the probable effect of HupA on the modulation of glutamate-NMDA receptors interaction. The other mechanism suggested has been the promotion passage of calcium ions through the ion channels [66]. Besides the toxic effects on the neurons, it has been suggested to possess great potential in neuroprotection and antioxidant activities [67]. Uniquely, all existing studies have been done in China involving a double blind placebo controlled studies [68,69]. Findings showed improvement in memory, thinking and behavior change in 58% of the persons that received HupA against 36% that received the placebo treatment. HupA has no

toxic effects [70]. Gastro intestinal tract disturbances has however been recorded in some patients that use HupA [70].

Curcuma Longa is also a herb in the ginger family of plants. It is dominant in Asia. Turmeric is a commercial extract form the rhizome of the Curcuma longa. Curcumin is also an extract from the plant, initially identified in 1815. Extracts of the plant are known to possess medicinal values for management of liver diseases, urinary tract infections, flatulence and also works as a blood purifier. It has been suggested that turmeric is anti-inflammatory, anticancer, antiviral (HIV). Trials on the possibility of their activity in management of AD are ongoing. Findings from in vitrio and in vivo studies have demonstrated its potential in the management of AD as a result of their anti-oxidation, anti-inflammatory and its possible direct effect in the beta amyloid aggregation [71-73]. Other studies have shown possible permeability ability on the blood brain barrier [73]. Moreover, it also lowers cholesterol in the body [73]. It also reduces oxidative damage and retains the pathology of the amyloid in cases of AD [74,75]. Besides, curcumin is considered safe. However, curcumin has been shown to promote thyroid follicle cells hyperplasia, and hepatotoxicity when administered in very high doses.

Periwinkle is a herb also referred to as Vince minor. The main pharmacological extract from the plant is referred to as vinpocetine. It is a dominant herb in Europe and India for management of wasp stings, bleeding problems, antidiuretic and expectorants. Extracts from flowers was used in Europe for treating eye irritations. Research has demonstrated that the plant extracts promotes cerebral metabolism, boosts consumption of glucose and oxygen and protects the brain from hypoxia [76]. It has also demonstrated abilities in the management of cerebral vascular resistance [77]. Moreover, it inhibits platelet aggregation and causes deformation of red blood cells [78]. It has been shown to block the voltage gated sodium ion channels, controlling the releases of neurotransmitters as a mechanism of action [79]. Findings from a clinical trial with increasing doses of vinpocetine in a pilot study failed to show any positive clinical impact of the extract [80,81]. Not many herbal plants have been explored on their potential in the management of AD and hence, there is very little knowledge on the use of herbal phytochemical extracts in the management of AD (Table 2).

Potential of phytopharmacological intervention in management of AD

Special findings have been suggested the potential for use of phytopharmacological intervention in the management of AD. In addition, ECD has also been found to be relevant in the determination of CCSVI in cases of MS. The similarity in the symptoms between AD and MS demonstrate the possibility of CCSVI being involved in the clinical symptoms of AD. However, no research has been done using ECD and other techniques on MS to suggest the phytopharmacological benefits in management of CCSVl. The same has also not been demonstrated in case of AD. The use of ECD will allow the monitoring of the effect of the phytopharmacological extracts in reversing the vascular degeneration alterations on the jugular vein in the brain as demonstrated in CCSVI. The same effect may also be replicated in the regeneration of damaged neuron tissues in the brain helping to manage AD. The potential of the anti-oxidation, anti-inflammatory effects [71-73], protection of vascular damage [77], and ability to modulate the activity of Ach [65], and regulating the NMDA receptors in the brain [66] suggest the possibility of phytopharmacological intervention of AD.

Pathological similarity in MS and AD for potential common management strategies

Evaluation of MS using studies from postmortem [82-84] and quantitative studies done using MRI as a diagnostic technique [85-87] suggests that MS is not only a product of inflammatory demyelination, but also neurodegeneration [84]. It has been demonstrated that neurodegeneration occurs early in the disease [85] while inflammatory demyelination and loss of function of neuronal axons are associated with the damage in MS [85]. These two mechanisms have a significant role in the pathogenesis of MS in patients and eventual disability with the disease [88]. AD also results from a combined effect of neurodegeneration and inflammation. Positron Emission Tomography (PET) and other studies on the pathology in AD show activation of microglial [89,90]. It is suggested that reactions to deposition of amyloid promotes the loss of cerebral tissues [91], while inflammation may be a significant therapeutic target to management of both AD and MS [85,92]. Limited information is available on whether using inflammation as a therapeutic target may be harmful or beneficial in AD, more especially with regard to clearance of amyloid [91]. Currently, there is a growing body of knowledge supporting the involvement of CCSVI in MS. Little information has been determined for AD. It is a possibility that CCSVI is also a mechanism of action in AD. Use of ECD, TCCS, UDC, UDS MRI and PET techniques can be adopted in the evaluation of involvement of CCSVI in AD. This will provide more information on the sensitivity of these techniques and probably provide more information on the role of CCSVI in AD. This will allow for evaluation of the potential of phytopharmacological intervention as a strategy in the management of AD.

Herbal Plant	Active Compounds	Effects	Benefits	Limitation	Sources
Gingko Biloba	Flavonoids, glycosides. terpenoids	**Promotes activity of neurotransmitters; Regulate Nitric oxide formation; antagonist to PAF; regulates amyloid aggregation.**	Non toxic, Safe	Causes bleeding	[57-61]
Huperzine Serrate	Huperzine A (HupA)	Inhibits Ach Reduce toxic effects induced by glutamate targeting NMDA	Non toxic, Has long half life, High tolerance, Has cholinergic effects, Improves memory and thinking behavior	Cause gastro intestinal disturbances	[65-70]
Curcuma longa	Turmeric, Flavonoids, polyphenols	Anti-oxidation; Anti-inflammatory Beta-amyloid aggregation; protects the damage of vascular tissues in the brain	Safe, Non toxic	None reported	[71-75]
Periwinkle herbs (Vincor minor)	Vincocetine	Boosts cerebral metabolism; Improves glucose consumption; Protects brain from hypoxia; Inhibits platelet aggregation; Control sodium ion channels; Regulate release of neurotransmitters	Safe, Non toxic	None reported	[76-80]

Note: NMDA: N-Methyl D-Aspartate; PAF: Platelet Activating Factors.

Table 2: Phytopharmacological activity of a few selected herbs in AD.

Conclusion

The numbers of people with AD are increasing over time. This has been associated with the presence of ineffective drugs targeting acetyl cholinesterase and N- methyl D- Aspartate receptors. However, the finding of chronic cerebrospinal venous insufficiency association with MS may offer a new green light which may also be evaluated in AD. The similarities between neurodegeneration and inflammatory mechanisms between MS and AD have also been demonstrated. There is a great potential of phytopharmacological intervention in reversing vascular damage to tissue which promote CCSVI and offers a new therapeutic target for management of MS and therefore also AD. Already, phytopharmacological intervention in management of inflammatory reaction has been widely been researched. Hence, phytopharmacological intervention for management of AD offers great potential for management of AD. However, bioprospecting for potential herbal phytochemical extracts as possible drugs through rigorous research and clinical trials processes for bioscreening of prospective future drugs for management of Alzheimer's disease targeting the inflammatory and in reversing vascular damage responsible for CCSVI. This will possibly offer a non-invasive, effective and low cost intervention in treatment and also reduce the ever rising cases of Alzheimer's diseases.

References

1. Burns A, Iliffe S (2009) Alzheimer's disease. BMJ 338: b158.
2. Ballard C, Gauthier S, Corbett A, Brayne C, Aersland D, et al. (2011) Alzheimer's disease. Lancet 377: 1019-1031
3. http://pathways.nice.org.uk/pathways/dementia/dementia-diagnosis-and-assessment.pdf
4. http://www.nia.nih.gov/Alzheimer's/announcements/2010/06/more-research-needed-ways-prevent-Alzheimer's-panel-finds
5. Thompson CA, Spilsbury K, Hall J, Birks Y, Barnes C, et al. (2007) Systematic Review of Information and Support Interventions for Caregivers of People with Dementia. BMC Geriatrics 7: 18.
6. Forbes D, Thiessen EJ, Blake CM, Forbes SC, Forbes S (2013) Exercise programs for people with dementia. Cochr Satabase of Syst Rev 12: CD006489.
7. https://www.nice.org.uk/advice/ktt7/resources/non-guidance-lowdose-antipsychotics-in-people-with-dementia-pdf. Accessed 1st July 2015
8. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124830.htm
9. http://www.who.int/mediacentre/factsheets/fs362/en/
10. Querfurth HW, LaFerla FM (2010) Alzheimer's disease. New Engl J Med 362: 329-444.
11. Mendez MF (2012) Early-onset Alzheimer's disease: nonamnestic subtypes and type 2 AD. Arch Med Res 43: 677-685.
12. Waldemar G, Dubois B, Emre M, Georges J, McKeith IG, et al. (2007) Recommendations for the Diagnosis and Management of Alzheimer's Disease and Other Disorders Associated with Dementia: EFNS Guideline. Eur J Neurol 14: e1-26.
13. Bäckman L, Jones S, Berger AK, Laukka EJ, Small BJ (2004) Multiple cognitive deficits during the transition to Alzheimer's disease. J Inter Med 256: 195-204.
14. Nygård L (2003) Instrumental Activities of Daily Living: A Stepping-stone towards Alzheimer's disease diagnosis in subjects with mild cognitive impairment? Acta Neurologica Scandinavica 179: 42-46.
15. Arnáiz E, Almkvist O (2003) Neuropsychological features of mild cognitive impairment and preclinical Alzheimer's disease. Acta Neurologica Scandinavica 179: 34-41.
16. Landes AM, Sperry SD, Strauss ME, Geldmacher DS (2001) Apathy in Alzheimer's disease. J Amer Geriatr Soc 49: 1700-1707.
17. Förstl H, Kurz A (1999) Clinical features of Alzheimer's disease. Euro Arch Psych Clin Neurosci 249: 288-290.
18. Frank EM (1994) Effect of Alzheimer's disease on Communication Function. J South Carol Med Assoc 90: 417-23.
19. CiciarelloF, Mandolesi S, Galeandro AI, Marceca A, Rossi M, et al. (2014) Age-related vascular differences among patients suffering from multiple sclerosis. Curr Neurovasc Res 11: 23-30.
20. Wilson RS, Barral S, Lee JH (2011) Heritability of different forms of memory in the Late Onset Alzheimer's Disease Family Study. J Alzheimer's Dis 23: 249-255.
21. http://www.alz.org/research/science/Alzheimer's_disease_causes.asp
22. Gatz M, Reynolds CA, Fratiglioni L, Johansson B, Mortimer JA, et al. (2006) Role of genes and environments for explaining Alzheimer disease. Arch Gen Psychiatry 63: 168-174.
23. Waring SC, Rosenberg RN (2008) Genome-wide association studies in Alzheimer disease. Archives of Neurology 65: 329-34.
24. Selkoe DJ (1999) Translating cell biology into therapeutic advances in Alzheimer's disease. Nature 399: A23-31.
25. Borchelt DR, Thinakaran G, Eckman CB, Lee MK, Davenport F, et al. (1996) Familial Alzheimer's disease-linked presenilin 1 variants elevate βA1-42/1-40 ratio in vitro and in vivo. Neuron 17: 1005-1013.
26. Furukawa Y, Nukina N (2013) Functional diversity of protein fibrillar aggregates from physiology to RNA granules to neurodegenerative diseases. Biochim Biophys Acta 1832: 1271-1278.
27. Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance M, Enghild J, et al. (1993) Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. Proceed Nat Acad Sci USA 90: 1977-1981.
28. Mahley RW, Weisgraber KH, Huang Y (2006) Apolipoprotein E4: a causative factor and therapeutic target in neuropathology, including Alzheimer's disease. Proceed Nat Acad Sci USA 103: 5644-5651.
29. Jonsson T, Stefansson H, Steinberg S, Jonsdottir I, Jonsson PV, et al. (2012) Variant of TREM2 associated with the risk of Alzheimer's disease. New Engl J Med 368: 107-16.
30. Francis PT, Palmer AM, Snape M, Wilcock GK (1999) The Cholinergic Hypothesis of Alzheimer's Disease: a Review of Progress. J Neurol Neurosurg and Psych 66: 137-147.
31. Shen ZX (2004) Brain Cholinesterases: II. The Molecular and Cellular Basis of Alzheimer's Disease. Med Hypo 63: 308-321.
32. Wenk GL (2003) Neuropathologic Changes in Alzheimer's Disease. J Clin Psych 64 Suppl 9: 7-10.
33. Hardy J, Allsop D (1991) Amyloid Deposition as the Central Event in the Aetiology of Alzheimer's Disease. Trends in Pharm Sci 12: 383-388.
34. Mudher A, Lovestone S (2002) Alzheimer's disease-do tauists and baptists finally shake hands? Trends in Neurosci 25: 22-26.
35. Nistor M, Don M, Parekh M, Sarsoza F, Goodus M, et al. (2007) Alpha- and Beta-secretase Activity as a Function of Age and Beta-amyloid in Down Syndrome and Normal Brain. Neurobiol Aging 28: 1493-1506.
36. Lott IT, Head E (2005) Alzheimer Disease and Down Syndrome: Factors in Pathogenesis. Neurobiol Aging 26: 383-389.
37. Birks J, Grimley EV, Van Dongen M (2002) Ginkgo biloba for cognitive impairment and dementia. Cochrane Database Syst Rev: CD003120.
38. Holmes C, Boche D, Wilkinson D, Yadegarfar G, Hopkins V, et al. (2008) Long-term Effects of Abeta42 Immunisation in Alzheimer's Disease: Follow-up of a Randomised, Placebo-controlled Phase I Trial. Lancet 372: 216-223.
39. Goedert M, Spillantini MG, Crowther RA (1991) Tau Proteins and Neurofibrillary Degeneration. Brain Patholy 1: 279-286.
40. Iqbal K, Alonso Adel C, Chen S, Chohan MO, El-Akkad E, et al. (2005) Tau Pathology in Alzheimer Disease and Other Tauopathies. Biochemica Et Biophysica Acta 1739: 198-210.
41. Chun W, Johnson GV (2007) The role of Tau phosphorylation and cleavage in neuronal cell death. Front in Biosci: A J and Virt Lib 12: 733-756.
42. Zamboni P, Galeotti R, Menegatti E, Managoni AM, Tacconi G, et al (2009) Chronic cerebrospinal venous insufficiency in patients with multiple sclerosis. J

Neurol Neurosurg Psychiatr 80: 392-399.

43. Zamboni P, Menegatti E, Weinstock-Guttman B, Schirda C, Cox JL, et al. (2009) The severity of chronic cerebrospinal venous insufficiency in patients with multiple sclerosis is related to altered cerebrospinal fluid dynamics. Funct Neurol 24: 133-138.

44. Al-Omari MH, Rousan LA (2010) Internal jugular vein morphology and hemodynamics in patients with multiple sclerosis. Int Angiol 29: 115-120.

45. Zivadinov R, Marr K, Cutter G, Ramanathan M, Benedict RH, et al. (2011) Prevalence, sensitivity, and specificity of chronic cerebrospinal venous insufficiency in MS. Neurology 77: 138-144.

46. Ciccone MM, Galeandro AI, Scicchitano P, Zito A, Gesualdo M. et al. (2012) Multigate quality Doppler profiles and morphological/hemodynamic alterations in multiple sclerosis patients. Curr Neurovasc Res 9: 120-127.

47. Floris R, Centonze D, Fabiano S, Stefanini M, Marziali S, et al. (2012) Prevalence study of chronic cerebrospinal venous insufficiency in patients with multiple sclerosis: Preliminary data. Radiol Med 117: 855-864.

48. Zaniewski M, Kostecki J, Kuczmik W, Ziaja D, Opala G, et al. (2013) Neck duplex Doppler ultrasound evaluation for assessing chronic cerebrospinal venous insufficiency in multiple sclerosis patients. Phlebology 28: 24-31.

49. Lanzillo R, Mancini M, Liuzzi R, Di Donato O, Salvatore E, et al. (2013) Chronic cerebrospinal venous insufficiency in multiple sclerosis: A highly prevalent age-dependent phenomenon. BMC Neurol 13: 20.

50. McKhann G, Drachman D, Folstein M, Katzman R, Prince D, et al. (1984) Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the Auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology 34: 939-944.

51. Kawas CH (2006) Medications and Diet: Protective Factors for AD? Alzheim Dis Assoc Dis 20: S89-S96.

52. Reiss AB, Wirkowski E (2007) Role of HMG-CoA Reductase Inhibitors in Neurological Disorders: Progress to Date. Drugs 67: 2111-2120.

53. Kuller LH (2007) Statins and Dementia. Curr Ather Rep 9: 154-161.

54. Szekely CA, Town T, Zandi PP (2007) NSAIDs for the Chemoprevention of Alzheimer's Disease. Sub-Cellular Biochem 42: 229-248.

55. Solfrizzi V, Panza F, Frisardi V, Seripa D, Logroscino G, et al. (2011) Diet and Alzheimer's disease risk factors or prevention: the current evidence. Exp Rev of Neurotherap 11: 677-708.

56. McGleenon BM, Dynam KB, Passmore AP (1999) Acetylcholinesterase inhibitors in Alzheimer's disease. Br J Clin Pharmacol 48: 471-480.

57. Smith JV, Luo Y (2004) Studies on molecular mechanisms of Ginkgo biloba extract. Appl Microbiol Biotechnol 64: 465-472.

58. Ahlemeyer B, Krieglstein J (2003) Neuroprotective effects of Ginkgo biloba extract. Cell Mol Life Sci 60: 1779-1792.

59. Yao ZX, Han Z, Drieu K, Papadopoulos V (2004) Ginkgo biloba extract (Egb 761) inhibits beta-amyloid production by lowering free cholesterol levels. J Nutr Biochem 15: 749-756.

60. Longpre F, Garneau P, Christen Y, Ramassamy C (2006) Protection by EGb 761 against beta-amyloid-induced neurotoxicity: involvement of NF-kappaB, SIRT1, and MAPKs pathways and inhibition of amyloid fibril formation. Free Radic Biol Med 41: 1781-1794.

61. Wu Y, Wu Z, Butko P, Christen Y, Lambert MP, et al. (2006) Amyloid-beta-induced pathological behaviors are suppressed by Ginkgo biloba extract EGb 761 and ginkgolides in transgenic Caenorhabditis elegans. J Neurosci 26: 13102-13113.

62. Le Bars PL, Katz MM, Berman N, Itil TM, Freedman AM, et al. (1996) A placebo-controlled, double-blind, randomized trial of an extract of Ginkgo biloba for dementia. North American EGb Study Group. JAMA 278: 1327-1332.

63. Oken BS, Kishiyama SS, Kaye JA, Jones DE (1999) Age-related differences in global-local processing: stability of laterality differences but disproportionate impairment in global processing. J Geriatr Psychiatry Neurol 12: 76-81.

64. Birks J, Grimley EV, Van Dongen M (2002) Ginkgo biloba for cognitive impairment and dementia. Cochrane Database Syst Rev CD003120.

65. Bai DL, Tang XC, He XC (2000) Huperzine A, a potential therapeutic agent for treatment of Alzheimer's disease. Curr Med Chem 7: 355-374.

66. Ved HS, Koenig ML, Dave JR, Doctor BP (1997) Huperzine A, a potential therapeutic agent for dementia, reduces neuronal cell death caused by glutamate. Neuroreport 8: 963-968.

67. Wang R, Tang XC (2005) Neuroprotective effects of huperzine A. A natural cholinesterase inhibitor for the treatment of Alzheimer's disease. NeuroSignals 14: 71-82.

68. Xu SS, Gao ZX, Weng Z, Du ZM, Xu WA, et al. (1995) Efficacy of tablet huperzine-A on memory, cognition, and behavior in Alzheimer's disease. Zhongguo Yao Li Xue Bao/Acta Pharmacologica Sinica 16: 391-395.

69. Xu SS, Cai ZY, Qu ZW, Yang RM, Cai YL, et al. (1999) Huperzine-A in capsules and tablets for treating patients with Alzheimer disease. Zhongguo Yao Li Xue Bao/Acta Pharmacologica Sinica 20: 486-490.

70. Wang R, Yan H, Tang XC (2006) Progress in studies of huperzine A, a natural cholinesterase inhibitor from Chinese herbal medicine. Acta Pharmacologica Sinica 27: 1-26.

71. Yang F, Lim GP, Begum AN, Ubeda OJ, Simmons MR, et al. (2005) Curcumin inhibits formation of amyloid beta oligomers and fibrils, binds plaques, and reduces amyloid in vivo. J Biol Chem 280: 5892-5901.

72. Lim GP, Chu T, Yang F, Beech W, Frautschy SA, et al. (2001) The curry spice curcumin reduces oxidative damage and amyloid pathology in an Alzheimer transgenic mouse. J Neurosci 21: 8370-8377.

73. Ringman JM, Frautschy SA, Cole GM, Masterman DL, Cummings JL (2005) A potential role of the curry spice curcumin in Alzheimer's disease. Curr Alzheimer Res 2: 131-136.

74. Zhang L, Fiala M, Cashman J, Sayre J, Espinosa A, et al. (2006) Curcuminoids enhance amyloid-beta uptake by macrophages of Alzheimer's disease patients. J Alzheimer's Dis 10: 1-7.

75. Cole GM, Morihara T, Lim GP, Yang F, Begum A, et al. (2004) NSAID and antioxidant prevention of Alzheimer's disease: lessons from in vitro and animal models. Ann N Y Acad Sci 1035: 68-84.

76. Erdo SL, Cai NS, Wolff JR, Kiss B (1990) Vinpocetin protects against excitotoxic cell death in primary cultures of rat cerebral cortex. Eur J Pharmacol 187: 551-553.

77. Kemeny V, Molnar S, Andrejkovics M, Makai A, Csiba L (2005) Acute and chronic effects of vinpocetine on cerebral hemodynamics and neuropsychological performance in multi-infarct patients. J Clin Pharmacol 45: 1048-1054.

78. Hayakawa M (1992) Effect of vinpocetine on red blood cell deformability in vivo measured by a new centrifugation method. Arzneimittel-Forschung 42: 281-283.

79. Bonoczk P, Gulyas B, Adam-Vizi V, Nemes A, Karpati E, et al. (2000) Role of sodium channel inhibition in neuroprotection: effect of vinpocetine. Brain Research Bulletin 53: 244-254.

80. Thal LJ, Salmon DP, Lasker B, Bowe D, Klauber MR (1989) The safety and lack of efficacy of vinpocetine in Alzheimer's disease. J Am Geriatr Soc 37: 515-520.

81. Szatmari SZ, Whitehouse PJ (2003) Vinpocetine for cognitive impairment and dementia. Cochrane Database Syst Rev 2003:CD003119.

82. van Waesberghe JH, Kamphorst W, De Groot CJ, van Walderveen MA, Castelijns JA, et al. (1999) Axonal loss in multiple sclerosis lesions: magnetic resonance imaging insights into substrates of disability. Ann Neurol 46: 747-754.

83. Peterson JW, Bo L, Mork S, Chang A, Trapp BD (2001) Transected neurites, apoptotic neurons, and reduced inflammation in cortical multiple sclerosis lesions. Ann Neurol 50: 389-400.

84. Trapp BD, Ransohoff R, Rudick R (1999) Axonal pathology in multiple sclerosis: relationship to neurologic disability. Curr Opin Neurol 12: 295-302.

85. Filippi M, Rovaris M, Inglese M, Barkhof F, De Stefano N, et al. (2004) Interferon -1a in patients at presentation with syndromes suggestive of multiple sclerosis. A randomized, double blind, placebo-controlled trial. Lancet 364: 1489-1496.

86. Filippi M, Bozzali M, Rovaris M, Gonen O, Kesavadas C, et al. (2003) Evidence for widespread axonal damage at the earliest clinical stage of multiple sclerosis. Brain 126: 433-437.

87. Inglese M, Ge Y, Filippi M, Falini A, Grossman RI, et al. (2004) Indirect evidence for early widespread gray matter involvement in relapsing remitting multiple sclerosis. NeuroImage 21: 1825-1829.

88. Coles AJ, Wing MG, Molyneux P, Paolillo A, Davie CM, et al. (1999) Monoclonal antibody treatment exposes three mechanisms underlying the clinical course of multiple sclerosis. Ann Neurol 46: 296-304.

89. Itagaki S, McGeer PL, Akiyama H, Zhu S, Selkoe D (1989) Relationship of microglia and astrocytes to amyloid deposits of Alzheimer disease. J Neuroimmunol 24: 173-182.

90. Cagnin A, Brooks DJ, Kennedy AM, Gunn RN, Myers R, et al. (2001) In-vivo measurement of activated microglia in dementia. Lancet 358: 461-467.

91. Golde TE (2002) Inflammation takes on Alzheimer disease. Nat Med 8: 936-938.

92. Aisen PS (2002) The potential of anti-inflammatory drugs for the treatment of Alzheimer's disease. Lancet Neurol 1: 279-284.

Citation: Juma KK (2015) A Current Understanding of Alzheimer's Disease and the Prospects of Phytopharmacological Intervention as a Management Strategy. J Neurol Disord 3: 244. doi:10.4172/2329-6895.1000244