Alzheimer's Disease and Treatment

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An Important Measure to Combat Alzheimer Through Phytomedicine - A Way Forward Towards Nature Cure

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Published Online: Dec 07, 2020

eBook: Alzheimer's Disease & Treatment

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

Key words: Alzheimer's disease; Neurodegenerative disorders; Phytomedicine; Dementia; Amyloid plaque; Neurofibrillary tangles; COVID-19; Antibiotic Resistance.

Abstract

There is an emerging interest in using music as a non-invasive non-pharmacological therapy for various mental disorders. The study of music and medicine is a rapidly growing field which had been largely focused on the use of music as a complementary therapy. Despite its evident universality and high social value, the ultimate biological role of music and its connection to brain disorders is poorly understood. This communication is an attempt to link known facts about the potential of music as a non-pharmacological therapy in treating neurological disorders with special emphasis on Alzheimer's disease.

AD has gained considerable amount of attention over these years. Various disease models have been identified and studied amongst which some of them have been discussed in the paper. Development of potent drugs for the treatment is essential and indispensable. Primeval traditions like aromatherapy and naturopathy have been used for the treatment of Alzheimers Disease.

Introduction

Alzheimer's Disease (AD) is a progressive furthermore an irreversible brain disorder which knocks down memory as well as thinking skills and in due course the ability to carry out simplest tasks. For all one knows, AD is one of the most important degenerative diseases today perhaps because of its recurrent occurrence and catastrophic nature. It is the sixth foremost cause of death in the United States. Dementia is generally seen in older people and biologically it was proved that Alzheimer's plays a huge role in causing this problem. When there happens loss of memory and other cognitive propensities serious enough to hinder with daily life, then we term this as dementia. There exhibits a wide variety of symptoms but the very first problem that most of the people notice and face is forgetfulness. This can become serious enough that it can start affecting the capability of a person to function at home, at work or even to enjoy their hobbies. The other visible symptoms are the patient may seem to look confused, can get lost in a very much familiar place, lose track of things or have difficulty with language. It is estimated that worldwide almost 50 million people are suffering from dementia and nearly more than half of them are dwelling in low or middle income countries. Nearly 10 million novel cases head up every year. It is reckoned that approximately 82 million people may suffer from dementia in 2030 and around 152 million by the time we reach 2050. Currently, there is no treatment available to change the progressive course. There are various new treatments which are investigated in numer-

Citation: Thomas SV, Shukla S (2020). An Important Measure to Combat Alzheimer Through Phytomedicine - A Way Forward Towards Nature Cure. Alzheimer's Disease & Treatment, MedDocs Publishers. Vol. 3, Chapter 1, pp. 1-12.

ous stages of clinical trials. Increasing age is the greatest known risk of Alzheimer's. As the age increases to 65 and older there is a huge risk for Alzheimer's. Not just the age, there are several other etiologies contributing to the pathogenesis of AD. They are primarily age, genes, family history, side effects of various drugs etc. The disease typically makes its way gradually in these three stages. They are-Early, Middle and late. It is generally observed that the symptoms worsens over time. Since the disease is dependent on the individual, its rate of progression differs. Thus, it also shows that it has a huge potential to be studied under the upcoming branch of personalized medicine. Personalized medicine which is also known as precision medicine is a medical representation that helps people separate into various categories with the help of medical practices, interventions, decisions or products. These are being tailored on to the individual convalescent according to their predicted risk and response of the disease. As mentioned above Alzheimer's are divided into four stages. In the initial stages of Alzheimer's a person generally functions independently. That person may still continue to work, drive and take part in social activities normally. In spite of this, the person may forget familiar words, everyday objects, locations etc. In this stage people may face memory lapses. Through the middle stage, the person may get confused with words, get frustrated or angry or even act in peculiar unexpected ways. It can be as unexpected as refusing to take a bath. The difficulty that happens to express thoughts and perform routine tasks mainly happens as a result of damage to the nerve cells. In the course of reaching the final stage, things often worsens to an extent that people lose their ability to respond to their environment. They may lose their ability to control their movement or carry on a conversation etc. Unfortunately there is no treatment available to cure dementia or improve the progressive course. At various stages of clinical trials numerous novel treatments are being investigated. In order to battle against the situation, there are various alternative and cutting edge approaches evolving for example phytotherapeutics which we will be discussing upon.

History of alzheimer's

In today's world neurodegenerative disorders are commonly found amongst the elderly population. With a dramatic rise in life expectancy from 49 years to 79 years, the 20th century has seen a rise in the population suffering from neurodegenerative disorders. Amongst which AD is the most prevalent late-life mental failure among humans. When a clinical psychiatrist and neuroanatomist-Alois alzheimer reported "A peculiar severe disease process of the cerebral cortex" at the 37th Meeting of South-West German Psychiatrists in Tubingen [1] on 3rd November in early 20th century. The early days of research on Alzheimer's disease did not invite the attention and interest of scientists. While the Tubigen press commented extensively on psychoanalytic lectures, the lecture on Alzheimer's had to fit in two lines. It was only after the work of Blessed, Tomlinson, and Roth in late 1960s, that AD was recognized as a common basis for senile dementia. The first patient of Alzheimer's, a woman named August. D., showed the cardinal symptoms of the disease, seen even today-progressive impairment in the memory; the cognitive function was disordered; the behavior was altered and exhibited paranoia, delusions etc. The patient's alertness is well preserved, and his/her motoric and sensory functions are essentially intact in the early and middles phases of the interminable process. As the patient loses ground, the slowing of motor functions often resemble extrapyramidal motor disorders such as Parkinsonism. However, this situation began to change in 1960s, after the advent of electron microscopy which allowed Michael Kidd in England and Robert Terry in the United States to describe the striking ultrastructural changes underlying the two classical lesions which Alzheimer had linked- neurofibrillary tangles and senile (neuritic) plaques. Death and disappearance of nerve cells mainly from the cerebral cortex is marked as a superlative pathological attribute. This ultimately led to a substantial atrophy in the temporal regions especially in the frontal, parietal and medial zones. The two kinds of microscopic lesions about which is being mentioned above are distinctive for the disease. The first is the neurofibrillary tangles which majorly consists of accumulations of intraneuronal and filamentous materials. This is strong neuropathological evidence since these fibrillar masses play an important role in mortalizing death of neurons. Both of these histopathological changes that is the formation of neurofibrillary tangles as well as the loss of synapses are linked to dementia. Another valid histopathological change is characterized by the occurrence of thickened neuronal processes which consists of both axons and dendrites is cumulatively referred to as neurites. They are present commonly in the form of rings which are in irregular shape surrounding the deposits of amyloid fibrils. The chromosome 21 lodges the amyloid peptide (β or A4 peptide) gene. This is exactly where the familial AD gene is also been localized in some families. The Key enzyme which is responsible for the Acetylcholine is Choline acetyltransferase. With the help of biochemical studies, it was revealed that in AD, there is a reduction in the production of this key enzyme in the cerebral cortex. Acetylcholine which was synthesized by neurons underwent severe degeneration even though it was variable. It was observed that in the limbic and cerebral cortices, there was a decrease in the enzymes choline acetyltransferase and acetylcholinesterase (synthetic and degradative enzymes). This observation made a way to an attempt in the research field in order to improve the functioning of acetylcholine levels in the synaptic cleft thereby inhibiting and preventing the degradative enzyme from functioning. Through various clinical trials, only two drugs were approved which were Donepezil and Tetrahydroaminoacridine. Subsequently, boundless neuropathological as well as substantial biochemical, genetic, transgenic, cell biology related models were studied. This contributed to the growth of the etiopathogenesis of AD. Even though the Food and Drug Administration has approved some drugs specifically for the treatment of AD, the results are often unsatisfactory. This certainly gives a space for various alternative medicines and majorly phytomedicine.

Genetics and epigenetics of alzheimer's disease

The ubiquity of AD elevates exponentially from around 2% during 60-65 years to more than 30% - 35% in patients older than 80 years [2]. The 2020 reports states that approximately 50 million people have Alzheimer's or correlated dementia globally and 1 in every 4 people have been successfully diagnosed. Around 70% of the forecasted increase in the implication of dementia by 2050 will take place in low and middle income countries. Alzheimer's is least common in the areas like Sub-Saharan Africa. Whereas in the US, it is the sixth prime cause of death [3]. Therefore, it is evident that dementia is a major health problem all over the world. Dementia leads to progressive stagnation of cognition and function. It is irreversible and hence results in a wide range of challenging behavioral disturbances and ultimately death. Extracellular amyloid lesions that are commonly observed in AD are the neuritic plaques. These depositions are often associated with axonal and dendritic injuries. They are primarily found in huge numbers in the associa-

tion and limbic cortices [4]. They contain extracellular deposits which principally occur in filamentous form and these deposits are called Amyloid β-protein (Aβ). Their recognition as amorphous plaques in the late 1980s and their detection region also contained many neuritic plaques led to a totally new concept [5]. They are referred to as diffused plaques. They are also called as pre- amyloid plaques. It became apparent when it was determined that the Aβ peptides settled in Alzheimer's brain mainly culminated either Aβ40 or Aβ42. These terminating at Aβ42 subunits and consisted of diffused plaques with little or on Aβ40 immunoreactivity compared to the one which stayed mixed (Aβ42 plus Aβ40) which were observed in the fibril-rich neuritic plaques [6]. Many neurons in regions of the brain like the hippocampus, amygdala, etc., have large non membrane bound bundles. These bundles were made with abnormal fibres and they occupied much of perinuclear cytoplasm. Studies were conducted with the help of electron microscopy and it was observed that these fibres consisted of pairs of filament of around 10nm which wound to the helices of 160 nm. Neurofibrillary tangles were composed of microtubule- based protein- Tau and they were observed through biochemical and immunocytochemical analysis in the beginning of 1985 [7]. The prevalence of extracellular Aβ plaques and intracellular neurofibrillary tangles along with the tau protein (hyperphosphorylated) which is a microtubule associated protein accelerates the process of neurodegeneration. Various biological processes are linked to neurodegeneration. These processes may include abnormal ubiquitination, oxidative stress or reduction in the synthesis of neurotransmitters. As mentioned above the two classical lesions of the disease which are neurofibrillary tangles and neuritic plaques and they can exist and occur independently of each other. Physiological, genetic, epigenetic, environmental factors play a very important role in the development of AD. There are multiple genetic factors which are linked to AD development which are either predictive or susceptibility. Predictive is mutational dependent and susceptibility is linked to the vulnerability towards different risks on a day to day basis. The phenomena where there is no typical change in the sequence of the genetic material or nucleotides but the phenotypic changes can pass from one generation to another, it is called Epigenetics. There are various epigenetic mechanisms through which this can happen. Some mechanisms are DNA methylation, DNA histone modifications, etc. There are the regulatory elements which control the metabolic pathways at the very molecular level.

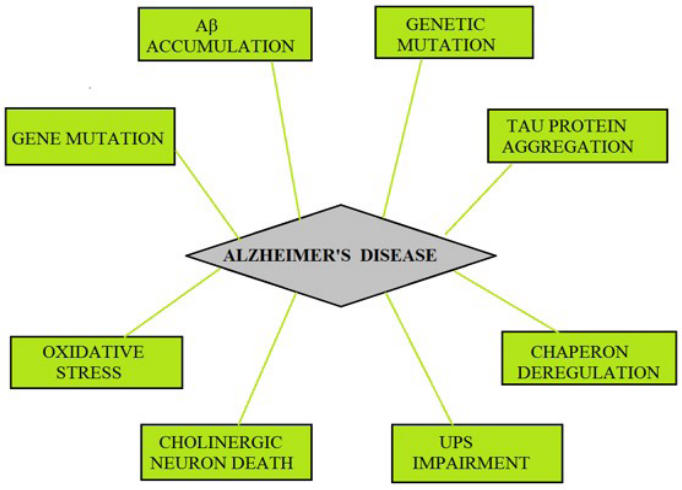


Figure 1: Histopathological determinants of Alzheimer's disease.

The involvement of epigenetic mechanisms in the development of memory formation has helped researchers and scholars to understand pathobiology as well as physiological conditions better. The role of epigenetic factors has gained importance and acceptance since different studies validated that cytosine methylation of genomic DNA in various tissues of mammals reduces with age [8]. Mutations can happen in predictive genes and they account for less than 10% for the early onset variant in Alzheimer's disease which is also referred to as EOAD [9]. In contrast to this the development of AD lately is dependent primarily on various environmental factors, genes which are susceptible and they are referred to as Apolipoprotein E or APOE gene. It is one of the rarest diseases where just one single gene gives rise to sporadic risk [10]. Recent studies have shown that mutations in the amyloid precursor proteins also give rise to inadequate production or processing of amyloid. But in maximum cases of Sporadic and familial AD, a clear cause hasn't been discovered till now. The onset of the disease and subsequently the course and influence of the therapeutic response to drugs which are conventional can be determined by the accumulation of defects in the genes in AD.

Phytotherapy and potent drugs for alzheimer's disease

In order for the various developments in the field of Alzheimer's Disease (AD), several landmark studies and numerous pathobiological mechanisms have been presumed [11]. The perturbations in the metabolism for the development in AD was done through various epidemiological clinical studies and it was seen that there was an association of AD with diseases like diabetes, obesity, etc. [12,13]. Certainly, plants have important agents for general well being of human [14]. In the western society, it's becoming common phenomena that people have started using botanical health products as dietary supplements. AD as well as other neurodegenerative disorders are a therapeutic problem and has huge socio-economic consequences on life expectancy. Treatments currently available for these disorders provide only symptomatic relief even though various pathological and clinical aspects are explored. These symptomatic relieve neither provide improvement to the diseased condition nor delay the progression of the disease. But medicinal plants on the other hand have shown a positive symptomatic relief not only in AD but also in various other neurodegenerative diseases. There are treatments available currently in the market as rivastigmine, donepezil. But they are symptomatic and do not lessen the progression of the condition. Numerous pharmacological activities and properties like antioxidant and anti-inflammatory properties are observed in compounds present in plants and they are utilized for phytotherapeutic purposes [15]. Vitamins C and E are used as a form of phytotherapy in AD patients and they are yielded from aged garlic extracts, Ginkgo biloba extract, green tea, Curcumin, etc [16]. Positive results were seen with the water insoluble active compounds of Curcuma longa too. Numerous studies have occurred and in one of the experiments, Curcumin was fed to the aged mice with β-amyloid plaque accumulation. It was observed that there was a reduction in the plaque deposition. This is primarily due to the reduction in the oxidative damage status in the brain. Another experiment revealed that a dose of 5-10 μM in range protected PC12 cells of the mice at odds with Aβ-induced neurotoxicity and this was possible by the ability of curcumin to inhibit oxidative damage and prevent hyperphosphorylation of tau. Curcumin has also shown positive results in lowering the concentrations of β-amyloid proteins in the plasma. Another similar phytochemical property was observed in Convolvulus pluricau-

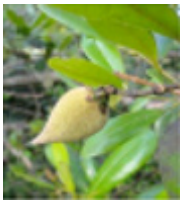
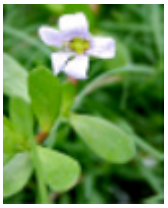
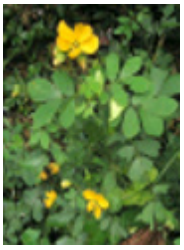
lis. They contain active compounds like terpenoids, flavonol and steroids that enhance memory. Another study revealed that the regulation of stress hormones like adrenaline and cortisol levels in the body could calm the nerves. Administration of C pluricaulis orally alleviated certain activities like neurotoxic effects by deteriorating the protein induction and mRNA levels if AβPP and Tau [17].

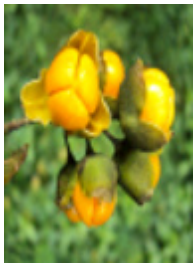
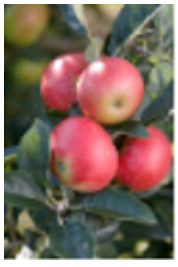
A chemical derived from a specific type of club moss called Huperzia serrata called Huperzine A had medicinal properties similar to caffeine and cocaine. These substances acts as a drug more than just a herb. In China it was once sold for memory loss and impairments as a dietary supplement [18] Mechanistic effects have been shown by phytochemicals towards pathological targets. Cannabinoids derived from Cannabis sativa, Resveratrol, Curcumin are emerging as potential therapeutic agents and through investigations, it was proved that they exhibited activities towards dementia [19]. Beneficial anti-cancer properties along with anti-inflammatory and anti-allergic activities are showcased by citrus-derived flavonoids. They manifest various cardio-protective as well as neuroprotective effects [20]. Citrus Flavonoids have manifested anticancer and chemopreventive effects on various vital organs of our body like lung, bladder, mammary, prostate gland [21]. Compound called Hesperidin takes action against Aβ-associated neurotoxicity and provides protection to cortical neurons. They also acted and prevented glutamate-induced excitotoxicity. Nobiletin is another important compound which works alongside other active compounds like Tangerine and Sinensetin to exhibit pharmacological activity. They are found in the outer parts of percarp on Citrus L. genus (Rutaceae). Around 61 types of Polymethoxy Flavonoids are reported in citrus species [23]. AD also deficit the significant functions of the body like it interrupts the olfactory functions of the body. Also impairments in learning and memory is a result of progressive degeneration of the cholinergic system in the brain [24]. One of the important steps in the pathogenesis of a patient with AD is the deposition of extracellular Aβ plaques. This elicits an inflammatory response which is significantly microglial mediated [25]. Aging process as well as various other pathobiological responses in this neurodegenerative disorder is enhanced by chronic oxidative stress. Here, Nobiletin plays a huge role by preventing aging with its antioxidant properties. Traditional as well as collateral remedies for AD have been examined with the help of modern as well as evidence based researches. The application of various animal based products which has an ability to inhibit cellular toxicity and inflammation and at the same time demonstrate viability for the development of pharmaceuticals is gaining tremendous importance in the field of science and research. Devastating neurodegeneration which is observed in the case of AD is seen to deteriorate with the use of numerous antioxidant, neuroprotective and anti-inflammatory phytochemicals.

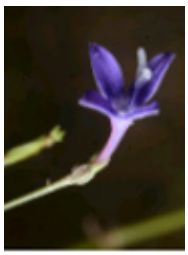
AD has gained a considerable amount of attention since the complete cure for the disease has not been identified till now. Thus various animal models have been designed to understand the molecular mechanisms that underlie pathology of AD. Various plant names, species with their mechanism of action in rat models have been listed below (Table 1).

Table 1: Medicinal Plants and their mode of action against Alzheimer's disease in rat models.

S.No	Plant name	Species	Picture	Mechanism of action	Reference
1	Zingiber officinalis	Zingiberaceae		Exerts Aβ aggregating antioxidant and AChE inhibitory activity.	[26]
2	Withania Somnifera	Solanaceae		Semi Purified extract of Withania Somnifera reverse Alzheimer's disease pathology. Nerving tonic, aphrodisiac, rejuvenative, antioxidant activity, calming effect, reverses behavioural deficit.	[27]
3	Vitis amurensis	Vitaceae		Inhibits neuronal apoptosis and exhibit antioxidant activity in cultures of rat cortical neurons. Improves learning and memory in mice models of AD	[28]

4	Valeriana amurensis	Valerianaceae		Inhibits the expression of β-APP, Aβ 1-40 and formation of senile plaques decreases. Reduces pro-inflammatory cytokines and cellular fate of cortical and hippocampal neurons in rat model of AD.	[29]
5	Uncaria rhynchophylla	Rubiaceae		Inhibits fibril formation of both Aβ1-40 and Aβ1-42 in vitro	[30]
6	Abies koreana	Pinaceae		Improves the memory in scopolamine model of AD in mice	[31]
7	Acorus gramineu	Acoraceae		Exerts AChE inhibitory and antioxidant activity. Increases the learning and memory ability in rat model of AD.	[32]
8	Avicennia officinalis	Acanthaceae		Exerts AChE inhibitory activity in vitro	[33]
9	Bacopa monnieri	Plantaginaceae		Improved cognitive function and reduced loss of neurons in animal model of AD. Enhances learning and memory in randomized double blind placebo controlled trial.	[34]
10	Berberis darwinii	Berberidaceae		Exerts AChE inhibitory activity in vitro	[35]
11	Cassia obtusifolia	Fabaceae		Attenuates oxidative stress and Ca+2 dysregulanon in primary hippocampal cultures	[36]

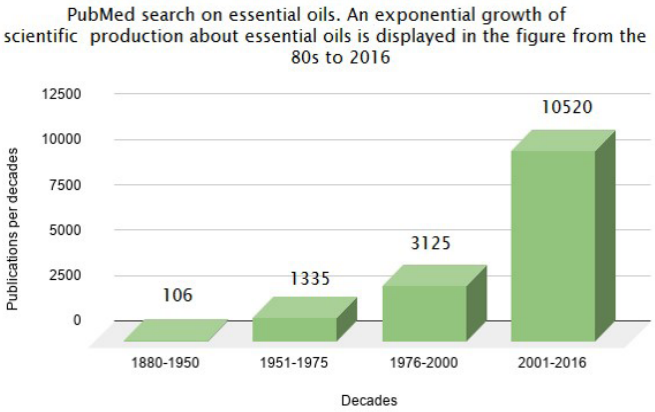
12	Caulis spatholobi	Fabaceae		Exerts AChE inhibitory activity	[37]
13	Celastrus paniculatus	Celastraceae		It sharpens memory and improves concentration as well as cognitive function	[38]
14	Centella asiatica	Apiaceae		Reduces apoptosis and hippocampal Aβ levels in vitro and in vivo. Enhances learning and memory function in mice models of AD. Potential use in the prevention and treatment of beta-amyloid toxicity and AD.	[39]
15	Cinnamomum Zeylancium	Lauraceae		Inhibits the formation of Aβ oligomers. Reduces Aβ toxicity in neuronal PCl2 cells. Reduces A β oligomer and improves cognition in mice model of AD.	[40]
16	Hupezia Serrata	Huperziaceae		National Institute of Aging has the clinical trial in Plane II of its extract particularly on AD	[41]
17	Lavendula angustifolia	Lamiaceae		Reduces aggression and improves neuropsychiatric behavior in a cross over randomized trial for treating agitated behaviors of demented people in Hong Kong	[42]
18	Malus domestica	Rosaceae		Improves learning and memory in and process organized synaptic signaling in open label trial. Exerts antioxidant activity in mice model of AD	[43]

19	Morus alba L	Moraceae		Augments the antioxidant defense system. Improves learning and memory in mice model of AD	[44]
20	Murraya koenigii	Rutaceae		Improves memory and learning in mice models of AD	[45]
21	Physostigma venenosa	Labiatae		Its Psysostigmine content has relevance to cholinergic therapy in AD	[46]
22	Salvia leriifolia	Lamiaceae		Exerts AChE inhibitory activity in Vitro	[47]
23	Oldenlandia affinis	Rubiaceae		Inhibits β-secretase activity and decreases Aβ production	[48]

In order for the fulfilment of a strategy focused at the treatment, various traditional medicines are now being rediscovered. [49] Bioavailability is a critical factor in order to synthesize therapeutic compounds for the treatment of AD and various other neurodegenerative disorders [50].

Pharmacotherapy and aromatic plants for the treatment of dementia in patients with alzheimer's disease

It was stated in a survey that more than 50% of all the cases of dementia are related to AD. In particular, the WHO describes dementia as a clinical syndrome due to disease of the brain, usually of a progressive nature, which leads to disturbances in multiple higher cortical functions, including memory, orientation, thinking, calculation, comprehension, learning capacity, language, and judgment. The cognitive deficits include memory impairment and aphasia [51]. The most fundamental goal is to maintain and manage Behavioral and Psychological Symptoms in Dementia (BPSD) [52]. Aromatherapy is a particularized segment of phytotherapy that uses essential oils, extracted from the different organs of aromatic plants, more often administered through inhalation or topical application and massage for several minor, clinical uses [53].



Graph 1: Statistical graph representing the number of searches on essential oils in PubMed.

The exceptional increase of the scientific production dealing with essential oils, occurring from the 80s to 2016, accounts for the intensity of the phenomenon "aromatherapy." Furthermore, aromatherapy has provided the best evidence, together with psychological treatment, for the management of agitation in dementia [52]. In particular, the essential oils of two spe-

cies of the Lamiaceae family, Melissa officinalis L. (lemon balm) and Lavandula officinalis L. (lavender), are the most practiced aromatherapeutic treatments for BPSDs in dementia [54]. A traditional medicinal plant from the Lamiaceae family known as Melissa officinalis L. (Lemon balm) is a native plant of west Asia primarily the Mediterranean region where it is popularly known as Badranjbooye [55]. Scientists evaluated eight samples of leaves which were dried in human cortex tissue during postmortem and observed the inhibition of receptor binding properties Acetylcholinesterase (AChE). We know that Lavender belongs to the family of Lamiaceae and lavender essential oils have been in use for a long time and they can be utilized after distillation. The main components of Lavender essential oil are camphor, linalyl acetate (35%), α-pinene, limonene etc [56]. According to the existing literature, lavender essential oil is able to inhibit glutamate and GABA receptor binding [57]. It is observed that lavender can lower cortisol levels in the plasma [58] and this can help to reduce the need for analgesic after a surgery [59]. Various hypotheses have been derived and one amongst them is the possible effect of lavender essential oil on tryptophan [60]. Different analgesic activities have also been observed after inhaling the oil [61]. The effectuality of aromatherapy could be partly due to the terpenes content of the used essential oils since these molecules undergo quick lung absorption and are able to cross the blood-brain barrier. Among the alternative treatments, aromatherapy has provided substantial evidence for agitation handling in AD [52]. The olfactory nerve system is responsible for the transmission of this stimulus to the hippocampus, limbic system, and amygdala and then to the hypothalamus with the consequent release of neuromediators [62]. It has been hypothesized that aromatherapy can promote neurogenesis in dentate gyrus of the hippocampus. Accordingly, systemic absorption (following direct inhalation or inhalation after topical application) and distribution of pharmacologically active components of the phytocomplex are requisite for aromatherapy to control BPSDs, and this may minimize the role of the psychological action. The mechanism of action of constituents of aromatic plants has yet to be discovered [63].

Efficacy of naturopathy in alzheimer's disease

A well defined type of primary care medicine amalgamated with primeval traditions with advances in the field of science and research is known as Naturopathy. Unique set of propositions that identify the healing capacity of our body guides the way of naturopathy. It majorly provides emphasis on disease prevention as well as it prevail the individual about his/her responsibilities to secure optimal health. The modalities of the naturopathic treatment include diet and clinical intake of nutrients and vitamins. Consecutively, behavior change hydrotherapy as well as homeotherapy are also practiced under naturopathy. As a supplementation, physical medicine, botanical medicine and minor surgeries are also given [64]. An illness is contemplated in naturopathic theory as a process of disturbance or misbalance to the health and subsequent recovery in the milieu of natural systems. Optimal health can be disturbed by many factors. The predominant causes are poor nutrition, toxic manifestation of stress for a long time or addictions etc. The ultimate goal is to identify as well as minimize these disturbances. Our health is a natural state and it is developed as a result of the interaction with the existing environment. Health of a person depends on many conditions and they all help create a healthy state. This state of health can be determined by various determinants [65]. These determinants can be internal (Figure 2) or external (Figure 3).

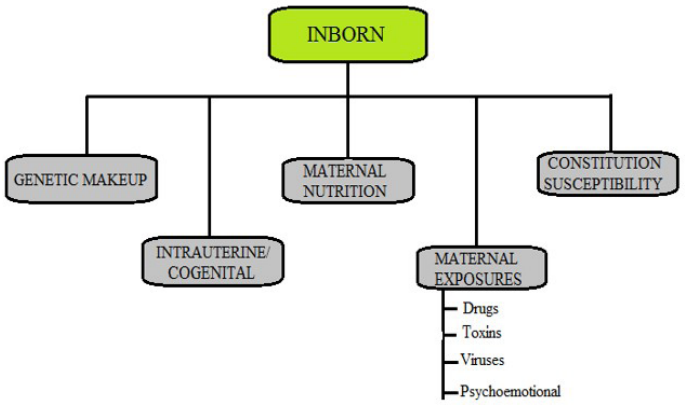


Figure 2: Internal factors responsible for creating disturbances in our natural system.

Figure 3: External factors responsible for causing disturbances in our natural systems.

This is certainly an upcoming field of medicine in this dynamic era. There are ample therapeutic options mainly in the sphere of botanical medicine, nutrition and in the modalities of traditional Asian medicine. Various case histories support the fact that naturopathic medicines not only support the cognitive function but they also increase the medication efficacy too in order to boost cognitive health. There are various groups of clinical activities which are prevalent now that were once outside the scope of allopathic medical practices. These types of non-conventional medical practices are now termed as Complementary and Alternative Medicine (CAM) [66]. Today naturopathy (whose roots are known to be from Germany) is considered as a whole medical system and is part of the above mentioned system CAM. This alternate form of medicine was founded towards the end of the 19th century by John Sheel and Benedict Lust. They wanted to practice one single therapy blending homeopathy, diet therapy, herbalism etc. Naturopathic medicine is regarded as a primary healthcare profession in countries like the USA and Canada. In regard to Alzheimer's health supportive use of nutritional supplements, homeopathy, physical medicine and herbalisms are included in the therapeutic regimen. By improving the functions of the body's health systems, one can seek to improve the neurologic disease directly or indirectly. Improvement in the gastrointestinal functions, detoxification, repairing and regenerating cellular as well as endocrine systems, balancing and strengthening the immune system has shown positive results [67]. Ameliorating emotional and spiritual factors with all this is duly important in order to observe physiological benefits. One such therapy in order to treat the AD is done by us-

ing omega-3-fatty acids. A component of omega-3-fatty acids called the Docosahexaenoic Acid (DHA) is known to be a crucial Polyunsaturated Fatty Acid (PUFA). Through experiments, it was found that they are known to be present in the phospholipid fractions of the brain. They maintain membrane fluidity and exerts a positive role in maintaining a long term potentiation which is an action necessary for memory [68]. DHA is present in cold water fishes since fish oil has high levels of omega-3-fatty acids. Epidemiological studies revealed that there is a decrease in the risk of AD with an increase in fish consumption [69]. There was a reduction observed in the levels of PUFA (in postmortem brains), DHA, and Cerebral Spinal Fluid (CSF) in the plasma of convalescents with AD [70]. All these studies make it evident that there is a relationship between Alzheimer's disease pathology and decrease in the levels of DHA and PUFA. Two clinical trials were conducted in order to evaluate the efficacy of Essential Fatty Acids (EFA) and DHA as a supplement for dementia. It was observed that in the first trial, a double- blind placebo controlled trial for patients (n=100) was conducted [71]. Omega 3/ omega 3 fatty acids were given to a treatment group in a ratio 4:1. They received the fatty acid mixture in a quantity of 0.5 g/ day for 4 weeks. For this study, cognitive measures were not recorded. Instead the rating of the subject were done on the basis of 12 behavioral variables. The results revealed that EFA enhanced short term memory, mood, sleep, appetite etc. Even though there was a positive benefit showcased but there was no standard testing conducted to study the cognitive function. Some standard tests to assess the cognitive functions are Alzheimer's disease Assessment Scale which is a cognitive subtest. Apart from that Mini-mental State Examination (MMSE) is also conducted for the same [72]. The second clinical trial conducted was a pilot study. The results were examined after administering 0.72 g of DHA/day on elderly patients for 1 year. These patients were suffering from moderately severe dementia which was a result of thrombotic cardiovascular disease [73]. A comparative study between the two groups at baseline (DHA=20.1, control= 19.7) was done using mean MMSE scores. There was a comparable increase in the MMSE scores after continuous supplementation of 6 months. It was observed that there was an increase in the DHA as well as eicosapentaenoic acid levels. Alzheimer's disease care teams forming and naturopathic doctors are giving a unique perspective of health and disease which gives the team a more clear and rounded view of the convalescent with AD as an individual [74]. But the critical issue still persists as naturopathy's survival since biomedicine dominates socially, economically and politically. A solidified foundation in the modalities of health as well as healing in a nonorthodox and traditional way needs to be emphasized for better apprehension.

Alzheimer drugs as a nexus to battle against antibiotic resistance

The World Health Organization reports that antibiotic-resistant pathogens represent an imminent global health disaster for the 21st century. Antimicrobial resistance has led to increased medical costs with the emergence of new antibiotic-resistant infections in the United States and other countries. Antibiotic resistance has led to the assessment of preventive strategies associated with newer drug development to assist clinicians in the treatment of diabetics, geriatrics, and Alzheimer's disease individual [75]. Gram-Positive superbugs pose a threat of breaching last-line antibiotic treatment, and the pharmaceutical industry antibiotic development pipeline is waning. Combating antibiotic resistance remains a critical global health priority [76]. It was found through research that dangerous antibiotic-resistant bacteria could soon be targeted with a drug initially developed to treat Alzheimer's disease. A potential treatment for Alzheimer's and Huntington's disease which was developed recently was the hydroxyquinoline PBT2. Bacterial pathogens encounter significant fluctuations in metal ion abundance during host colonization and have been shown to be highly susceptible to phagocytic cell induction of zinc toxicity [77]. As a preventive approach to improve antibiotic treatment in geriatric and aged individuals, antibiotic resistance and their genomic information become essential in genomic medicine. In aging and Alzheimer's disease, the amyloid-beta peptide has become of critical interest to antimicrobial drugs with its therapeutic role as a natural antibiotic [78]. We know that Bacteria establish stable communities, known as biofilms, that are resistant to antimicrobials. Biofilm robustness is due to the existence of an extracellular matrix, which for several species - among them Bacillus subtilis - includes amyloid-like protein fibers. Biofilm proteins and amyloids share similar characteristics and by repurposing anti-amyloid drugs, it was found that it could prevent the formation of biofilm in Salmonella bacteria. Amyloid proteins represent key components of the biofilm matrix of several microorganisms. These microbial amyloid fibers are structurally and biochemically similar to the pathogenic variants found in humans. Therefore, they are good candidates to be used as targets in screens for molecules that may serve two purposes: Anti-biofilm and anti-amyloid agent [79].

Conclusion

As the population ages globally, an immense amount of resources will be required to adequately care for the people afflicted with Alzheimer's disease. AD is evidently the most common reason for dementia primarily in elderly people suggests the way of torment for patients and families. Additionally, the costs intricate in a patient's long-term care totally disable the economy of the family. Research is in progress to develop interventions to delay both the disease onset as well as its slow progression. Effective interpositions may significantly reduce the prevalence and incidence of Alzheimer's disease. And this will ultimately improve the quality of life of both the patients and their caregivers. Alzheimer's disease is a progressive disease and people who have the disease often require a superior level of care for a long time. Genetic, pharmacological and cell biological studies continue to unravel the possibility of targeting the effector molecules, pathways of inflammation and oxidative stress in order to treat AD. An escalating number of herbal extracts, poly-herbal and herbo-mineral preparations, and phytochemicals obtained from herbs have been studied as their neuroprotective potential in AD is showing wonders for the past decade. As discussed earlier, its multifactorial etiology is responsible for the unsatisfactory efficacy of most of the drugs. However, multi-target directed ligand approach seems to be a possible effective way out and current growth of anti-AD agents amongst which the majority of them are acetylcholine inhibiters seems to extent the pharmacological contour. There are a number of potential implications for the convalescents of Alzheimer's Disease (AD) stemming from the global spread of SARS-CoV-2. Individuals with AD are at a high risk of contracting SARS/Cov2. Genetic and socioeconomic factors influencing the rates of (Type 2 Diabetes) T2D, (Alzheimer's disease) AD. Individuals with AD are at a high risk of contracting SARS/Cov2. Thus, it is necessary to recognize the people suffering from Alzheimer disease and protect them. There is certainly a need for the development of disease-modifying drugs not only for AD but also for various other degenerative comorbid diseases.

There is certainly a necessity of a drug or biomarkers that can identify, modify, stabilize and cure the diseased condition.

Acknowledgement

Authors are thankful to Amity University Uttar Pradesh (AUUP) for providing necessary platform, infrastructure and laboratory facilities to carry out the research work.

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