A Review on Current Therapies and Challenges in Alzheimer's Disease and Role of Indian Spices in its Treatment as a Futuristic Approach

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Abstract

Background: Spices play major role in adding taste to the Indian food by imparting various flavours. In addition to the various flavours of food, spices also possess certain medicinal properties that provide sound health to the human body and can cure the diseases in the form of traditional medicine which is known as Ayurveda in India. Cholinesterase inhibition based therapy is a significant method for the treatment of neurodegenerative diseases. Various cholinesterase inhibitors are used for the treatment of memory loss and dementia, but these compounds have been reported to have side effects, including gastrointestinal disturbances. Hence, the present review focussed at understanding the epidemiology of the disease and its mechanism; also the current treatment methods and their side effects are mentioned. Finally, the herbal spices which are traditionally used in India and many parts of the world to enhance memory were studied and their therapeutic evidences were collected.

Conclusions: The studied Indian spices can be a rich source for development of new and promising agents which can be significant for the treatment of memory loss and dementia. Further studies are needed to isolate, identify and characterize the active compounds from the spices which are responsible for cholinesterase inhibition activities.

Keywords: Alzheimer's diseases; Spices; Therapeutic potential

Introduction

Dementia and Alzheimer's disease

Dementia is an acquired impairment of intellectual and memory functioning caused by impairment of the brain. The diagnosis of dementia begins with the clinical recognition of a progressive decline in memory as well as defects in other mental abilities such as abstract thinking, judgement, personality, language, praxis, and visual perception skills. The most common type of dementia is Alzheimer's diseases (AD), which makes up 50% to 70% of cases. Other common types include vascular dementia, lewy body dementia and fronto-temporal dementia.

AD is a progressive neurodegenerative disorder that affects major spots of the cerebral cortex and hippocampus. The symptoms are first observed in the frontal and temporal lobes of the brain tissue, which then progresses to the other areas of the neocortex. AD is generally seen in person above the age of 60 but many cases has been seen at a very young age as well. Different phases and patho-physiological characteristics of Alzheimer's disease are mentioned in Table 1.

Epidemiology and mechanism

The duration of the disease is around 10 years but the some symptoms may stay till the death of the patient. The dementia in AD is associated with neurodegeneration synaptic injury [1-3], also by neuronal loss [4]. Astrogliosis can also be a reason for dementia in AD [5], along with microglial cell proliferation [6,7]. Hyperphosphorylated tau and neurofibrillary tangles with dystrophic neurites are the other aspects [1,8,9]. Progressive accumulation of amyloid-β (Aβ) oligomers also causes severe damage to the signalling activity of the nerve cell, hence causing the disease. Proteolytic cleavage of amyloid precursor protein (APP) by the action of γ-secretase causes the formation of Aβ oligomer, this reaction also included presenilin 1 (PS1,) and PS2 (PSEN2) (Figure 1) [10-12].

Degeneration of nerve cell in others terms can also be called as deficiency in the concentration of acetyl choline (ACh) and butyryl choline (BuCh). These are the organic molecules liberated at the nerve endings as a neurotransmitter. It is produced by the synthetic enzyme choline acetyltransferase which uses acetyl coenzyme-A and choline as substrates for the formation of ACh and BuCh respectively, in specific cells known as cholinergic neurons. The synaptic transmission gets terminated by the cleavage action of cholinesterase enzyme, whose primary mechanism is to maintain the level of ACh and BuCh at the synaptic junction. Hence, due to over-expression of this enzyme there is a significant level of reduction in the concentration of these cholinergic transmitters which hampers the neurotransmission, hence causing memory loss or dementia (Figure 2).

Currently available drugs for such conditions are either AChE inhibitors like tacrine, physostigmine etc., or BuChE inhibitors as tetrahydro furobenzofuran cymserine (THFBFC), which have been proved to improve the situation of AD patients to some extent. So far, the Food and Drug Administration (FDA) have approved four drugs for AD which are tacrine, rivastigmine, donepezil, and galanthamine. They have shown some success in slowing down neuro-degeneration in patients with AD. The limitations of these drugs are their side effects such as aggression, depression, gastrointestinal disturbances and hepatotoxicity. Furthermore, these drugs are expensive and require weekly blood monitoring (Table 2).

Plants and their pharmaceutical importance

Plants are a significant group among all living organisms, which acts as support system for human beings as well as other living organisms. They have been supporting human civilization through the biologically active compounds which they contain. India is among the majorly

Stage	Characteristics
Stage 1	No impairments are identified (the person doesn't experience any memory related issues).
Stage 2	Appearance of very mild cognitive decline.
Stage 3	Mild cognitive decline (duration - 2 to 7 years). Early-stage of AD is diagnosed at this stage. The patient has faces little difficulties with word recall, organization, planning and failing to remember recently learned data.
Stage 4	Moderate cognitive decline (duration - about 2 years). Hardly identifies familiar people and is aware of self. Experiences reduced memory of personal history and hence with these symptoms diagnosis is easy.
Stage 5	Moderately severe cognitive decline (duration - about 18 months). Serious reduction in cognition level and the patient will not be able to survive independently and also may require some assistance in daily acticities.
Stage 6	Severe cognitive decline (duration - about 2½ years). Memory continues to fall and there is a significant change in personality where the patient definitely requires complete assistance in day to day activities.
Stage 7	Very severe cognitive decline (duration - 1 to 2½ years). Last stage of AD. Patients don't have the ability to respond or speak and eventually cannot control movement, the duration of this stage depend on the level of care that the patient is provided with.

Table 1: Stages and characteristics of Alzheimer's disease.
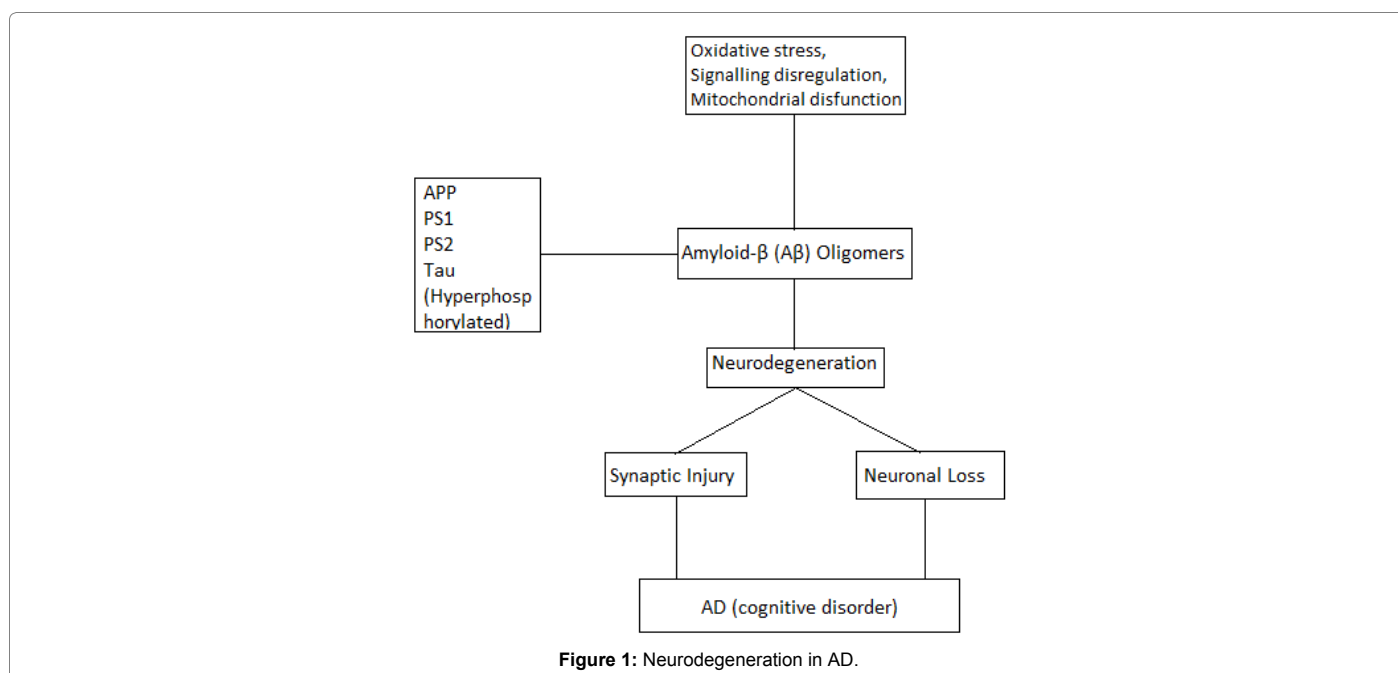

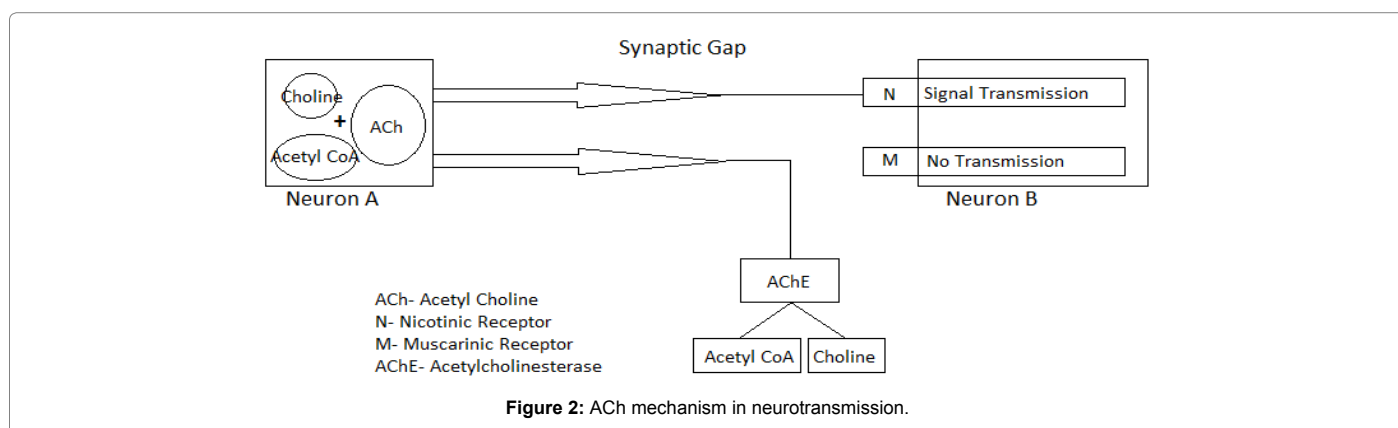**Figure 1:** Neurodegeneration in AD.

Figure 2: ACh mechanism in neurotransmission.

diversified countries of the world, having rich biodiversity. They harbour a total of 47,513 plant species and represents about 11.4% of total world flora. It also represents 12.5% of world's phytogeography [13].

Plants being a source of medicine has been identified and used from ancient times. They are a major resource used in therapy of many diseases in India and all over the world. In west the plants and herbs are used as a source of medicine which is approximately 40% of the population are who are reported to use it for the treatment of many ailments. There are around 45,000 plant species in India that are reported to have medicinal properties, which are distributed throughout the geographical area of the country. The officially recognised medicinal plants and herbs are few but traditionally people are using more than 6000 plants. India is the one of largest contributor

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Generic	Brand	Stage of AD	Side effects
Donepezil	Aricept	All stages	Nausea, loss of appetite and vomiting
Memantine	Namenda	Moderate to severe	Dizziness, constipation and confusion.
Galantamine	Razadyne	Mild to moderate	Increased frequency of bowel movement, vomiting and headache.
Rivastigmine	Exelon	Mild to moderate	Vomiting, nausea, loss of appetite and increased frequency of bowel movement.
Memantine + Donepezil	Namzaric	Moderate to severe	Constipation, headache, vomiting and dizziness.

Table 2: FDA approved drugs for AD treatment and their side effects.

of medicinal plants and herbs and is recognised as the botanical garden of the world. In rural India, over 70 per cent of the total population depend on the traditional medicine which is popularly known as the Ayurveda.

Approximately around 80,000 species of plants are utilized by different structures of Indian medicine. The information about plants and their products are detailed, sophisticated, and has evolved into a separate shastra itself, called Dravya Guna Shastra. Plants have been studied on the basis of many biological parameters like rasa (taste), vipaka (metabolic property), guna (quality), prabhava (biological effect) and virya (potency). The systemize traditions have introduced about 25,000 plant drug formulations that have emerged from detailed studies. In addition to this, over 50,000 formulations are believed to be existing in the folk and tribal traditions. All these information and exhaustive knowledge about medicinal plants have existed in this land from time immemorial [14].

Spices

The spices are obtained from distinct parts of a plant like flowers, fruits, leaves, seeds, rhizomes, roots, buds, secretory products (such as gums, resins, volatile oils), and also from the bark. Spices can be generally defined as tropical herbal plant or a distinct part of it that is cherished for providing colour and aromatic flavouring with stimulating odour for use in cooking and in condiments, as well as in candies, cosmetics, fragrances, and medications. Herbal products have been used since ancient times to flavour foods and for preparing incenses and perfumes because they are aromatically scented. Spices can add taste, flavour, aroma and colour to the food. They can also be used in form of preservatives, appetizers and digestives. A major part of spice production in the world is contributed by India, because of its varying climate and diverse soil conditions. According to the Indian Spice board, India produces 3.2 million tons of spices valued at approximately 4 billion US dollars every year. India supply around half of the share of the world trade in spices. Many spices have been reported globally to have medicinal properties. Spices plays major role in adding taste to Indian food by imparting various flavours such as sweet, chilly, sour, and bitter. In addition to the various flavours of food, spices can also possess some medicinal properties, which provide the human body with sound health and can cure the diseases in the form of traditional Indian system of medicine called Ayurveda. The spices can be administered orally in the form of powder or as decoctions (extract). Based upon its potency and mechanism of action on a specific organ or system like digestive system, respiratory system, etc., the medicinal value of any particular spice can be carried out. Therefore, usage of specific plant parts has been recommended in Ayurveda in case of particular ailments [15].

Spices and their role in Alzheimer's disease

Since over 4000 years, ayurvedic medicines in India has been exploiting various plant species, shrubs, herbs and spices for the cure of many cognitive or central nervous system disorders as well as in improving the learning and memory capabilities [16-18]. Hence it will be appropriate to screen these spices in detail in search of new AChE and BuChE inhibitors, as the ayurvedic drug combinations from these spices are well tolerated with fewer side effects and possess a definite effect on the CNS. The current review was done to identify and compare the therapeutic effects of spices in cholinesterase inhibition by enhancing the memory. In this review 5 common Indian spices were selected based on their traditional evidences in Ayurveda for the improvement of learning, memory and other cognitive functions.

Coriandrum sativum: *C. sativum* has been studied for the effect on CNS disorders and they are found useful in the treatment of neurodegenerative diseases, such as AD, because they have various potencies, like, memory-improving property, cholesterol-lowering property and anti-cholinesterase activity [19]. *C. sativum* has been used in form of tonics and also for the treatment for memory loss. Their paste has been reported to be effective against swellings and boils and causes relief when applied over forehead and temples during headache [20]. This spice has shown reduction in brain AChE activity in young and aged mice. In young mice, the percentage of inhibition of AChE activity was found to be 10.3% and in the aged mice, it was 8.7% [21]. The effects of coriander volatile oil (1% and 3%, daily, for 21 days) when inhaled directly were assessed in an Aβ (1-42) rat model of AD. It was found that *C. sativum* reverts Aβ (1-42)-induced spatial memory impairment by attenuation of the oxidative stress in the rat hippocampus [22].

Trachyspermum ammi: The anticholinergic activity of thymol has been reported [23] and other studies have suggested that the potency of thymol and its derivatives, like thymoquinone and thymohydroquinone as inhibitors of AChE could be related or linked to its additional antioxidant potential [24]. In another study the treatment of Ajwain has been resulted in effective fall in brain AChE and with rise in brain GSH level, thereby decreased oxidative damage [25].

Foeniculum vulgare: *F. vulgare* extract in stress reduction and memory enhancement in rats showed that this herb has several functions such as anti-stress proceeding, increase in memory and antioxidant effects which may reduce stress and stress-related disorders [26]. Reports have shown that there are number of plants, whose utilisation is considered to effectively improve the memory and intelligence. *F. vulgare* is an ayurvedic drug or material that has many neuro-pharmacological activities. The spice is reported to have antidepressant activity of that has been well documented in ethno medicine and is considered as the most significant spice against depression [27].

Myristica fragrans: In a study the application of *M. fragrans* on memory and learning in mice was carried out. The spice was found to be effective in reversing scopolamine and diazepam-induced impairment in learning and memory of young mice and also enhanced learning and memory capacities of both young and aged mice [28]. *M. fragrans* (5 mg/kg for 3 days), have reportedly significantly decreased AChE activity as compared with their respective vehicle-treated groups [29]. The results

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of a study, carried out *in vitro* and *in vivo* experiment, conclude that *M. fragrans* can be used effectively in the treatment of AD [30].

Nigella sativum: Various experiments have the evidence where administration of *N. sativa* capsule (500 mg) by elderly individuals twice daily for nine weeks, have shown positive regulatory effects on memory and learning [31]. The hydro-alcoholic extract of *N. sativa* (200 or 400 mg/kg) has shown previously to prevent the scopolamine-induced spatial memory deficits in rats, which was carried out by inhibition of AChE activity as well as protection against oxidative damage in brain tissues [32]. Memory improving effect of *N. sativa* is thought to be due to its antioxidant and anti-inflammatory activities. In another study, the hydro-alcoholic extract has shown to facilitate and positively regulate the learning and memory impairments as well as oxidative damage in brain tissues after pentylenetetrazol-induced repeated seizure in rats [33]. Reports on the effects of this spice and its seeds on the CNS with neurodegenerative disorder are few but various studies have also shown to improve spatial memory. Spatial memory stores information in the brain which functions in recognizing, codifying, storing, and recovering information about objects or incidents. Spatial memory has both working memory as well as reference memory components and this is normally associated with exploratory behaviour and curiosity [34].

Conclusion

The current scenario in use of medicine in the world has been replaced by non-toxic plant products with traditional medicinal uses. And traditionally studies have shown that spices have much medicinal or therapeutic impact hence, modern drug can be developed from these after extensive investigation through research. The present review explains the epidemiology and mechanism of Alzheimer's disease and the current medications available along with their side effects. In this study it has been identified that spices play major role memory enhancement and hence extensive research needs to be performed. Spices have been proved to have many therapeutic properties due to their high phytochemical content, essential oils and antioxidant properties. *In vitro* cholinesterase inhibition assay of these spices may have a potent memory enhancing property by modulating the flow of choline for signal transmission in the nervous system. Moreover, these *in vitro* assays may demonstrate their potential activity as inhibitor of cholinesterase enzyme and also may be considered as preventive agents against oxidative stress. Further study needs be carried out to determine the exact source of antioxidant and anticholinesterase properties by isolating and investigating the active components from them. Hence *in vivo* study should to be performed and further the pharmacovalidation of these spices and their active compounds needs to be proved.

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