ALZHEIMER’S DISEASE AND HERBAL APPROACHES IN THE TREATMENT - AN OVERVIEW

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Abstract

Alzheimer’s disease is a neurodegenerative disease among aged population. The incident rate of the disease is found to be increasing in a rapid manner. The disease have complex etiopathology. Current therapies of Alzheimer’s Disease only aim at managing the symptoms rather than stopping the progression of disease and have several side effects. So there is a need of plant based medicines as an alternative therapy. This article outlines what all plant based approaches have done towards the procurement and prevention of Alzheimer’s disease which will be useful to understand the contribution of different systems of medicines in different part of world to the treatment of this particular disease.

Keywords: Alzheimer’s Disease, Phytoconstituents, Systems of medicine, Amyloid-beta, tau protein, Herbal medicine

Introduction

Neurodegenerative diseases are disorders characterized by the progressive loss of neurons, typically affecting groups of neurons with functional relationships even if they are not immediately adjacent. Alzheimer’s Disease is a progressive neurodegenerative disease and is the most common type of dementia in elderly population. The etiology is multifactorial and the pathophysiology of the disease is complex, with a new case occurring in every 7 s; globally, the disease itself is becoming a slowly pandemic.

Alzheimer’s disease and other forms of dementia are a growing public health problem among the elderly in developing countries, where aging population is increasing rapidly. The reported incident rates for Alzheimer’s Disease is found to be lower in Asian countries than in the industrialized world. The incident rates of Alzheimer’s Disease in South India appear
to be much higher than that reported from rural north India comparable with that reported from China and marginally lower than that reported from the Western world.

ETIOLOGY PATHOGENESIS AND PHARMACOTHERAPY

Two characteristic features are seen in the brain of patients with Alzheimer’s Disease.

1. Senile plaques contain extracellular deposits of amyloid-beta (Aβ), a peptide synthesized by breakage of Aβ precursors. Abnormal deposits of Aβ are also found in blood vessels.

2. Neurofibrillary tangles, dense bundles of abnormal fibers in the cytoplasm of neurons which consist of an altered form of the microtubular-associated protein are found in patients with Alzheimer’s Disease.

Several hypotheses have been put forward for explaining the reasons of Alzheimer’s disease, though the exact cause of developing the disease are uncertain. They include cholinergic hypothesis, amyloid hypothesis, tau protein hypothesis, calcium hypothesis, isoprenoid change, inflammatory hypothesis, cholesterol hypothesis, vascular hypothesis, oxidative stress hypothesis etc.

The currently available drugs for Alzheimer’s disease 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 Alzheimer’s Disease patients to some extent. The Food and Drug Administration (FDA) have approved four drugs for Alzheimer’s Disease which are tacrine, rivastigmine, donepezil, and galanthamine. They have shown some success in slowing down neuro-degeneration in patients with Alzheimer’s Disease. 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. So alternative medicine are necessary which have less toxicity greater efficacy and less cost.

Herbal medicines are being used by about 80% of the world population primarily in the developing countries for primary health care. They have much importance from time to time because of their safety, efficacy, cultural acceptability and lesser side effects. Ancient literatures also mentions herbal medicines for age-related diseases like memory loss, osteoporosis, etc. for which no modern medicine or only palliative therapy is available. The chemical constituents present in them are a part of the physiological functions of living flora and hence they are believed to have better compatibility with the human body.
ALZHEIMER’S DISEASE IN TRADITIONAL MEDICINE SYSTEMS.

Medicinal plants have been reported for their possible anti-Alzheimer’s Disease activity in a number of preclinical and human trials. Ethnobotany, the study people-plant relation, is popular in China and in the Far East and possibly less emphasized in Europe, plays a crucial role in the discovery of anti-Alzheimer’s Disease agents from plants. The Chinese Material Medica (CMM) comprise Chinese medicinal plants which has been used traditionally for the treatment of Alzheimer’s Disease in China. Ayurveda, the ancient traditional treatment system of India, has already provided numerous lead compounds in drug discovery and many of these are undergoing clinical investigations.

In a number of preclinical and clinical trials, various traditional herbal formulations have also been reported as neuroprotective and psychoactive agents, which lights the way for the discovery of new drugs for the management of Alzheimer’s Disease.

AYURVEDA

Ayurveda is the first record of scientific medicine in the world, which was originated in India 6000 years ago and over 600 plants have been recorded in the original Ayurvedic literatures. Though there is no robust explanation for the exact molecular mechanisms of the action of Ayurvedic medicines, especially in case of cognitive disorders like Alzheimer’s Disease, the system of medicine is found to be very much effective in this area of treatment. In Ayurveda, the treatment approach to any disease is a holistic one. Here the individual is considered as a single unit towards the disease diagnosis and treatment. According to Tridosh Theory, Vata, Pitta and Kapha, are the tridoshas of our body at the physical level, and Satwa, Raja and Tama are the prime three factors acting at the mental level. Imbalance in these factors is manifested by disease development. According to Charak Samhita, mental disorders increase Vata leading to accumulation of Ama in the nervous tissue and inflammatory reactions and degeneration of the nerve cells. Geriatrics or Rasayanatantra was included as one of the eight medical divisions in Ayurveda and in Sanskrit. Intelligence and dementia are known as Buddhi (intellect) and Cittanasa respectively. Medhya rasayana mentioned in Ayurveda is known to enhance Buddhi and to reduce the Rajas and Tamas Doshas for better functionality of Manas. However, in Ayurvedic literatures there is no direct mention of Alzheimer’s Disease or any clinical condition which can be equated to Alzheimer’s Disease. But interestingly two specific terms were used in relation with each other; one is Smritinasha (memory loss) and another is Jara (aging). In classical Ayurveda it
has been mentioned that Smritinasha may occur due to Jara, which is quite literally a description of Alzheimer’s Disease itself. Another disorder related with memory has been described in Ayurveda as Smritibramsha (disturbance of memory), which is described as the spoilage of memory (Smriti) by passion (Raja) and obscurity (Tamas). This disorder is more or less similar to senile dementia which is more accurately described in Ayurveda as Jarajanya Smritibramsha.

TRADITIONAL CHINESE MEDICINES AGAINST ALZHEIMER’S DISEASE

Traditional Chinese Medicinal herbs have been centre of attraction for their wide range of pharmacological activities and better protective effects for patients. Some of the commonly used preparation for the treatment of Alzheimer’s Disease include Huanglian jiedu tang (HJDT), Jangwonhwang, LMK03, Naoerkang (NEK), Naoyikang (NYK), SuHeXiang Wan (SHXW), Tong Luo Jiu Nao (TLJN) etc. Some Traditional Chinese medicinal herbs in the treatment of Alzheimer’s Disease play crucial role in the discovery of new anti-Alzheimer’s Disease agents. They include Icariin and derivatives, Berberine and derivatives, Curcumin and derivatives, Green tea and their extract, Ganoderma extract and derivatives, ginsenosides and derivatives etc. These are found to be act as AChEs.

HOMEOPATHY

Some studies have found evidence for efficacy of homeopathic treatment for some conditions, but any mechanism of action of ultra molecular dilutions is not comprehensible in terms of current scientific concepts. The safety and effectiveness of homeopathy in treating dementia has not yet been the subject of a systematic review.

UNANI

Although the etiology is not very clear, the Unani scholars have mentioned that Alzheimer’s Disease is due to viscid phlegm (Balghame Ghaleez) and excess moistness (rutubat) in the brain or in other words due to sue mizaj barid ratab or sue mizaj barid yabis. In Alzheimer’s disease there is a decline in production of neurotransmitter acetylcholine which cause depression and depression stimulate the production of excess quantity of abnormal phlegm in the brain. The Hippocrates (460-370BC) believe that the body of the individual is composed of four biological fluids. Health is primarily a state in which these constituent substances are in the correct proportion to each other, both in strength and quantity, and are well mixed so that health and illness conditions are the result of balance or
imbalance of these four bodily liquids. He believed certain human moods, emotions and behaviours were caused by imbalance in body fluids (called “humors”): blood, phlegm, yellow bile, and black bile. The ancient Unani scholars were familiar with the basic concept of this disease, and known to treat the disease condition on the principle of Tanqia Dimagh with the help of Munzij and Mushil drugs. After tanqia they emphasis use of Muqqawwiyat-e-dimag.

AROMATHERAPY

Aromatherapy and use of essential oils, as complementary therapies, are effective non-pharmacological therapy against neurodegenerative disorders including dementia. Rosemary and lemon essential oils and lavender and orange oil mediated aromatherapy are reported to improve symptoms and cognition in clinical trials. Efficacy is also reported for lavender oil in a clinical trial among patients with agitated behavior associated with severe dementia. Moreover, lavender aromatherapy and massage therapy are being suggested in case of aggressive behaviour in aged people with dementia of Alzheimer’s Disease type. However some other study shows that aromatherapy did not decrease combative and resistive behaviors in dementia patients. Large sample size and well designed clinical trials as well as different types of aromatherapy and various types of dementia cases are needed to be considered to test the efficacy of such treatment against dementia.

SCOPE OF HERBAL DRUGS IN MODERN MEDICINE AND RECENT ADVANCES IN PLANT BASED DRUG DEVELOPMENT

Natural products play highly significant roles in drug discovery and development process. Many of the plant constituents have been recognized as potent and selective acetylcholine esterase inhibitors and are used clinically for the treatment of Alzheimer’s Disease in different part of the world. After the discovery of first neurotransmitter defect of Cholinergic neurons, clinical trials in Alzheimer’s Diseased patients were focused on drugs that can enhance ACh levels in brain. The presently existing NMDA receptor antagonist memantine, does not stop the worsening of dementia and moreover the outcomes are often satisfactory and still there is a vacant position for the place for alternative medicine, in particularly herbal medicine. Several reports clearly describes about the prevailing and existing therapeutic strategies for dementia across the world. They have shown promising results in terms of their cognitive benefits, though the basic mechanisms behind their action still remains unknown and many time they have been linked with reducing Aβ load and tau.
There are several plant based bioactive compounds under preclinical and clinical study from time to time and there emerges many perspectives for treating the disease. Some of spices and neutraceuticals are reported to have potent memory enhancing property and several of them are reported to be effective when used along with the normal treatment strategies.

Molecular hybridization is one of most valuable structural modification tool used for the discovery of ligands. There are also increasing efforts to discover hybrid drugs resulting from combination of pharmacophoric moieties of different known lead compounds have brought hope for various multifactorial disease treatment.

There are many recent techniques for the improvement of plants producing secondary metabolites against Alzheimer’s Disease. Some of them are;

1. **Cell, tissue and organ culture, elicitation and precursor feeding**

   Plant cell, tissue and organ culture have been used to produce a number of high value bioactive phytochemicals. The efforts made to upscale the production of various anti-Alzheimer’s Disease plant metabolites via in vitro culture techniques includes : Liquid culture (Eg. Scutellaria baicalensis root-derived cells has produced the flavonoids baicalein, baicalin and wogonin in a significantly high quantity), Callus culture (Eg.In cell suspension culture of Cistanche deserticola, 1.4-1.5-fold increase in acteoside production was found following single putrescine treatment and single Ag+ treatment respectively ) etc.

2. **Agrobacterium-mediated secondary metabolite production**

   Agrobacterium Ti/Ri plasmids are used to genetically engineer a number of medicinally important plants in order to produce valuable biopharmaceuticals. Eg. Optimization of catalpol production in Rehmannia glutinosa hairy roots transformed with Agrobacterium rhizogenes ATCC15834.

3. **Metabolic engineering**

   This involves engineering plant secondary metabolism via manipulating a number of biosynthetic genes or enzymes that has enabled the production of desired metabolites with biopharmaceutical applications. As a novel metabolic engineering technique for the production of biopharmaceuticals, artificial gene cluster in Escherichia coli was introduced to produce plant flavonones containing genes of heterologous origin. Similar technology was also achieved in Saccharomyces cerevisiae via engineering phenylpropanoid pathway.
4. Genetic and genomic resources

Comprehensive transcriptome analysis and genome and proteome analyses in plants have explained the biotic and abiotic stress tolerance, elucidated the development and also exploration of genes involved in secondary metabolic pathways in plants. This has led to the development of new biotechnological and metabolic engineering strategies. The transcriptome of the rhizome of the 3 varieties of Curcuma longa was analyzed via de novo transcriptome assembly from NGS emphasizing on secondary metabolite pathways and terpenoid biosynthesis pathways related to the synthesis of several bioactive molecule of pharmacological significance.

5. Mathematical and statistical techniques for empirical model building

Response surface methodology (RSM) and artificial neural network (ANN) are commonly used mathematical and statistical techniques for empirical modeling and prediction, popularly used to analyze nonlinear behavior and outputs of the systems. An anti-Alzheimer’s Disease and health promoting compound found in aged garlic (Allium sativum), RSM was applied to achieve 1.64-fold increase by addition of a freezing and thawing technique.

PROBLEMS ASSOCIATED WITH PLANT BASED MEDICINE PRODUCTION.

Medicinal plants continue to provide valuable therapeutic agents, both in modern medicine and in traditional systems of medicine. Attention is being focused on the investigation of efficacy of plant based drugs used in the traditional medicine because they are economic, have a little side effects and according to W.H.O, about 80% of the world population rely mainly on herbal remedies. The uses of traditional medicines are widely spread and plants represent a large source of natural chemicals that might serve as leads for the development of the novel drugs. Scientists have devised different ways of alienating the problem and one of the easy and cheapest options is herbal medicines.

About 25% of drugs prescribed worldwide are derived from plants. Still, herbs, rather than drugs, are often used in health care. For some, herbal medicine is their preferred method of treatment. Consumers should also be given science-based information on dosage, contraindications, and efficacy. To achieve this, global harmonization of legislation is needed to guide the responsible production and marketing of herbal medicines. If sufficient scientific
evidence of benefit is available for an herb, then such legislation should allow for this to be used appropriately to promote the use of that herb so that these benefits can be realized for the promotion of public health and the treatment of disease. However, if herbal medicines are to assume a respected place in the contemporary health care, the quality of the data and the quality of the herbal products themselves as well as regulatory control of herbal medicines must improve greatly. Herbal manufacturers and Prescribers together could bring a new sphere incredible revolution by reforming reshaping the herbal medicines to challenges of the 21st century by an equivalent effective, economical and safe treatment by utilizing mostly our own resources.

CONCLUSION

Since there is no effective treatment strategies for Alzheimer’s disease prevention in modern medicine by drug therapy, there is a need for production and implementation of plant based medicine for the same. Different traditional systems of medicines in different part of the world are found to be extensively using medicinal plants for memory enhancing activities. Plant based researches have shown positive results towards Alzheimer’s Disease prevention. There are also well developed biotechnologic strategies aiming at the increased production of biomolecules having memory enhancing activity and thereby development of anti Alzheimer’s Disease molecules. Regulations regarding the use of medicinal plants and technological inappropriateness towards finding and developing the desired compounds having activity from plants is still a limiting factor. A revolutionary change in the herbal drug development as well as research is necessary in developing the plant based therapeutic agents.

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