Effect of medicinal plant extracts on alzheimer's disease

Alzheimer’s disease (AD) is a neurodegenerative disease which causes a lethal twist in the structural integrity, and a roadblock in the function of brain, this eventually channel the situation to degeneration and shrinkage of brain, and override the control of brain over other parts of the body, and comes to the final closing remark of the disease- death. Studies done on the topic have corroborated that the disease is not reversible, and the only patch of hope is slowing down its progress. But as the disease advances through mid stage and evolves into severe AD, the condition of patient becomes pathetic and care giving becomes more painful. Studies have reported that notable symptoms of AD are seen only after 60 years of age, even though the disease has started before that. Initial symptoms are loss of short term memory- being forgetful about the recent events, and gradually over a period of time patient seems more absent –minded about the environment, things which are chemically etched in the long term memory begins to be erased, and the final stage starts pushing the patient into severe AD which is tremendously pathetic.

Studies have proved that loss of function of neurons is the cause of AD. A closer look into the aspect revealed a complex set of events that precede the neuronal degeneration- oxidative stress and imbalance in homeostasis, formation of roadblocks in communication, falling apart of integrity and death of neurons. This enabled to go beyond the findings of superficial studies done and hypothesis developed, and helped to delve much deeper into the inner workings and mechanism of the disease. Hypotheses developed to explain mechanism of AD are: amyloid cascade hypothesis, cholinergic hypothesis and tau hypothesis. Amyloid cascade hypothesis says,

APP- Amyloid Precursor Protein, a transmembrane protein involved in main roles of growth, survival and repair of nerve cells- is snipped at wrong places by an enzyme called secretase, leading to the formation of amyloid β peptides which accumulates to form plaques- amyloid plaques- and bind to synapses blocking the communication channel, eventually causes memory loss. According to cholinergic hypothesis, downward drift in the levels of acetylcholine in brain is the cause for Alzheimer's disease. Loss of function of cholinergic neurons was found in Alzheimer's disease patients. Shift in the level of acetylcholine happens due to the lack of two enzymes involved in synthesis and breaking down of acetylcholine. This will lead to loss of function of neurons; brain's functionality falls apart, and eventually leads to symptoms of Alzheimer's disease. Tau hypothesis approaches the problem in another perspective, tau protein- a protein associated with microtubules in nerve cells- gets hyperphosphorylated, this enables cross linking among tau protein units, and they back off from being attached to the microtubules. This causes loss of structural integrity of nerve cells, and they collapse and clump to form tangles- neurofibrillary tangles. Studies conducted focusing on the inner workings of these hypothesis have found that oxidative stress is the reason that enhances plaque and tangle formation, repair mechanisms in cells are unable to solve the situation as the oligomer formation and cross linking are predominantly made by non peptide bonds. In another study, amyloid β peptides have shown close relation with some causes of mad cow disease. Studies related to genetics of AD have found the link between APOE gene on chromosome 21 and the disease. APOE gene codes for apolipoprotein, and one among its functions is breaking down of APP. APOE has variants, APOEε4 is the one which codes for less active protein whose

capacity to break down APP is sluggish. People with this variant gene are more tend to develop AD in later stages of life, and any abnormality related to chromosome 21 also results in AD over a period of time.

To know more about the mechanism of disease and its attachment to oxidative stress, further studies have done from different angles, and all the studies have come to a common point, the findings from all the studies stitched together gave a complex and elaborate picture about the mechanism of the disease. Free radical damage leads to oxidation of products in cell. Oxidation leads to new end products of glycation, nitration, lipid peroxidation, and oxidation of nucleic acids. These new end products chemically modify other proteins and compartments inside the cell. Oxidized derivatives impede with the channel of trace elements, and imbalances their homeostasis, and enables proteins like tau to form non peptide cross linking. In response to changes cell up the levels of heme oxygenase-1 (HO-1)- an antioxidant enzyme to mitigate the bad effects from free radical damage- but rapid heaping up of neurotoxic substances goes beyond control leading to severe imbalances, blockage of communication channels, and eventually death of neuron. Since mitochondria is the main source of free radicals and oxidative precursors. Certain deletions in mtDNA resulted in change in normal levels and rates of metabolism and production of free radicals. Free radicals formed in mitochondria are short lived and they do not have the ability to cross membrane and reach cytoplasm to cause damage, this led studies in a new direction and found free radicals- OH^- from cytoplasm- can attack guanidine in RNAs in cytoplasm and this both can cross the membrane and reach into mitochondria, and cause imbalance and

production of more stable $H_2O_2^-$ radicals which can come to cytoplasm and react with the channel of trace elements, and starts the primary events for the major causes for AD to come into being. AD starts at neocortex area of brain, and as the neurons die and rupture, the neurotoxic substances- plaques, free radicals, tangles, etc. – pervade the nearby nerve cells, and the cycle goes on and gradually covers the brain and makes it slip out of its normal being.

Oxidative stress in brain leads to degeneration of neurons, which eventually leads to dementia, and Alzheimer’s disease (AD). This oxidative stress in brain can be slowed down or reversed- to a small extent- using drugs to treat AD or using antioxidant capacity of some medicinal plants. In this study rats were arranged into seven groups, and different groups were treated with different plant extracts and rivastigmine. AD was induced using aluminum chloride- rats were given aluminum chloride for one month, and the dosage was 17mg/kg of body weight. One group was kept as control- healthy control and another group as AD-induced. Rivastigmine was given to group 3. Group 4 and 5 were treated with extracts of a medicinal plant- Salvia triloba; and group 6 and 7 were treated with extract made from Piper nigrum. The rats were given drug and extracts for three months. At the end of three months duration biochemical assays and histopathology was done to examine the changes happened to the brains. The following things were checked for in serum: malondialdehyde, total antioxidant capacity and nitric oxide, and level of superoxide dismutase were checked in erythrocytes. Acetylcholine and acetylcholine esterase levels were checked in brain samples and another group of brain samples were given for histopathology. From the results, the

rats which were treated with Piper nigrum extract and rivastigmine showed increase in brain Ach, and serum TAC and SOD; and a significant decrease in brain AchE, and serum MDA and NO. The rats which were treated with extract of Salvia triloba showed even better result in subduing the oxidative stress to a certain limit.

Antioxidant capacity of plants was used to bring down the effects of oxidative stress in brain. Here, the effect of the extract made from Boswellia serrata is compared with rivastigmine on rats with AD- induced by oral administration of aluminum chloride. Ninety male rats were used in the study. They were made into nine groups. Group 1 was kept as healthy control, group 2 was given with aluminum chloride for four weeks, and group 3 was treated with rivastigmine, group 4 and 5 were treated with two different concentrations of plant extract made from Boswellia serrata. Groups 3 to 5 were treated with a combination of aluminum chloride and other things to check the ability of extract and drugs to protect the brain from the stress. Group 6 was given with water after inducing AD. Group 7 was given with rivastigmine, and group 8 and 9 were given with two different concentrations of plant extract- this was done for twelve weeks. Cognitive tests were done at the beginning of each new stage of the study. At the end of the duration of the study, the brain samples were subjected to biochemical assays and histopathology. From the results, B. serrata has significant ability to reduce the oxidative stress in brain, and higher dose if the extract showed better effect- bringing down the severity of oxidative stress damage.

Bacopa monnieri is another plant used to trim the effects of AD. This plant is used since ancient times for improving intelligence, and in this study its ability to protect against AD is checked. Alcoholic extracts of the plant was made for the study. AD was induced using ethylcholine aziridinium ion (AF64A)- administered intracerebroventricular way bilaterally. Plant extract was given to the rats two weeks before and one week after the administration of AF64A. rats were subjected to cognitive tests. Rats treated with the plant extract cleared the tests in less time. Histopathology results showed, low dose of the plant extract brought down the degree of damage in brain- reduction of neurons density. Low dose showed better result compared to the medium and high dose. The study has not revealed the mechanism of action of the plant extract, but it showed the scope for a further study on the same.

Targeted drug delivery to brain in case of Alzheimer’s disease is more complex process due to many factors like blood brain barrier and actions of plasma proteins. But nanoparticles are used for targeted drug delivery, and this is again affected by physiochemical properties of Nanoparticles in different surfactants, stability of nanoparticles and organic coating or capping agent on nanoparticles. Blood brain barrier is a homeostatic defense mechanism used by brain to screen out pathogens and unwanted materials from entering brain. The barrier screens the solutes biochemically, physicochemically and structurally at the periphery. There are times when blood brain barrier breaks down due to certain infections or due to any physical reason, and this makes it skew from its usual nature- highly selectively permeable. Studies have been conducted to find how

nanoparticles are treated at blood brain barrier. In a study, nanoparticles were made by warm microemulsion precursors, and the nanoparticles were radiolabelled by entrapment. Then an in situ study was conducted to check how nanoparticles cross the blood brain barrier. From the study it was concluded that endocytosis or transcytosis as possible mechanism for the transport across the barrier- more studies are yet to be conducted. Studies have shown that clioquinol- a quinoline derivative- can solubilize amyloid β plaques in vitro and this could prevent accumulation of amyloid β plaques in Alzheimer's disease transgenic mice- an in vivo study. Clioquinol has shown its ability to dissolve plaques which are induced by Zn and Cu ions- NMR studies have shown that clioquinol can remove bound Cu ions from amyloid β plaques. The study conducted has overlooked the toxicity part of clioquinol- though clioquinol has many side effects attached to it at high doses. It has shown in the later part of the study that clioquinol coupled with nanoparticles could easily cross the blood brain barrier- higher degree of uptake by brain. So, clioquinol-nanoparticle delivery system is suggested to be considered as one among the models for treating Alzheimer's disease by targeted drug delivery. Even though using nanoparticles are considered for drug delivery, there are studies showing the side effects, and doses. In a study- toxicity of silver nanoparticles- it was found that exposure to more than 125mg/kg of silver nanoparticles will lead to liver damage due to toxicity.

In a study curcumin nanoparticle formulation was used to test its effect on Alzheimer's disease in mice. Nanocurcumin was synthesized and orally given to the mice for twelve days. Memory tests were done before starting every

new stage of the experiment. Results have shown that mice treated with nanocurcumin could clear the cognitive tests- significant improvements were observed.