A REVIEW – PROBABLE MECHANISM OF ACTION OF CURCUMIN FOR THE TREATMENT OF ALZHEIMER DISEASE (AD)

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ABSTRACT: Many drugs are tried for delaying the process of Alzheimer diseases. The drugs are synthetic in view of the function and synthesis of the neurotransmitters. However Researchers observe the slowing process of the Alzheimer disease and improve the cognitive function of the diseased patient with Herb extract-Curcumin. But the possible role or mechanism of action is needed to explore.

KEY WORD: Curcumin longa, Alzheimer disease, Cognitive enhancer

INTRODUCTION: Curcumin longa, a perennial herb and a source of spice turmeric, is used in Chinese and Ayurvedic system of medicine as an anti-inflammatory, for the treatment of flatulence, jaundice, menstrual irregularities, hematuria, haemorrhage and colic. Now a day-current research has focused on curcumin as antioxidants, hepatoprotective, anti-inflammatory, anticarcinogenic and antimicrobial properties and its use in cardiovascular diseases and gastrointestinal diseases. The active compounds are the flavonoid curcumin and various volatile oils—termerone, atlantone, zingiberone. 40-85% of oral dose is passed through GIT and metabolised in the intestinal mucosa and liver.

AD which is resulted from neuronal loss and atrophy particularly in temporo parietal and frontal cortex with an inflammation response to the deposition of amyloid plaque and abnormal cluster of protein fragments and tangled bundles of fibres (neurofibrillary Tangles-NFT) and also increased presence of monocytes or macrophages in cerebral vessel wall and reactive or reactivated microglial cell in the parenchyma^{1,2} along with decrease level of neurotransmitter (NT)-Acetylcholine

The present mainstay treatments for AD are:-

- 1) Replacement of NT by increasing ACH (Acetylcholine) synthesis
- 2) Augmentation of the action of muscarinic and nicotinic receptor.
- 3) Reduction of synaptic ACH degradation with cholinesterase inhibitors (tacrine, donepezil, rivastigmine and galantamine)
- 4) Removal of amyloid plaque, NFT with anti-oxidant and anti-inflammatory agent (NSAIDs).
- 5) Prevention of metal toxicity

Out of the above five mainstays, the feasibility of removing of amyloid plaque and the delaying effect on NFT formation may result in slowing of cognitive decline in the elderly.

The promising drug-Curcumin (Turmeric), a Herb, taken as a food additive which is used extensively in the treatment of many medical condition is studied & evaluated for the treatment of Dementia and brain injuries including AD. Curcumin which is approved as an anti-oxidant, anti-inflammatory and antilipophilic agent improves the cognitive function of the patient suffering from AD.

MECHANISM OF ACTION: The three cholinesterase inhibitors- Rivastigmine, galantamine, donepezil which are approved by FDA, are used in US & Europe. They have the requisite affinity and hydrophobicity to cross the blood brain barrier and exhibit a prolonged duration of action, along with an excitatory amino acid transmitter mimic, memantine, constitute current modes of therapy; these are not disease modifying and have no well-documented actions on the pathology of Alzheimer's disease, however the bulk of the evidence indicates that they show the decline in cognitive function and behavioural manifestation for limited interval of time. Current clinical research efforts are directed to synergistic actions of arresting inflammatory process or neurodegeneration and combining cholinesterase inhibitor with selective cholinergic receptor modulation.¹⁹

The probable mechanism of action of curcumin as an anti-oxidant, anti-inflammatory, also for delaying the degradation of neurons, metal chelation, and decreasing microglia transition is discussed in considering the findings and observations of the researchers and investigators.

It can act as a free radical scavenger and an anti-oxidant inhibiting lipid peroxidation and oxidative DNA damage. Curcumin as a potent inhibitor of cytochrome P450 can induce glutathione-S-transferase & protect spatial memory impairment due to amyloid β protein⁴. It can diminish plaque burden and overall inflammation⁵ thereby reducing the size of plaque and neurotrophic dystrophy in AD⁶. It has possible effect on neurogenesis in hippocampus & increase level of brain derived neurotrophic factors^{7,8,9}

Curcumin inhibits the suppression of oxidative damage, inflammation, cognitive disease amyloid accumulation¹⁰ thereby decreasing progress of AD. Zhang¹¹ stated that Curcumin helps the macrophages to clear amyloid plaque indirectly through immune system. Further this agent when used for longer duration produces chronic activation of microglia cell which secretes cytokines and some reactive substances that exacerbate A β -beta pathology. It has antiproliferative action on microglia by differentiating into a mature cell or undergoes apoptosis. It involves decreased astrocytes proliferation, improved myelogenesis and increased activity and differentiation of oligodendrocytes.

The inflammatory changes such as microgliosis, astrocytosis, & deposition of amyloid X2 β peptide are decreased by curcumin^{3, 12}. It inhibits Cox², phospholipases, transcription factor and enzyme involved in metabolising the membrane phospholipid into prostaglandins. It decreases the main chemical for inflammation and transcription of inflammatory cytokines and also a potent inhibitor of proinflammatory cytokine production which are differ according to nature of target cells. It decreases lipid peroxidation and lipofuscin accumulation that is normally increased with age¹⁵ and increases the activity of superoxide dismutase and Na-K ATPase which is normally decrease with age. This agent protects cells from Beta A insult through antioxidant pathway⁶ and elevation of total cellular glutathione level⁶.

Curcumin is a potent inducer of hemoxygenase, a protein that provides sufficient cytoprotection by promoting the S-S inactivation of Nrf2. Keap1 complex and increased binding to Nrf2 thereby significant elevation of oxidised glutathione content^{3,17,18} The level of β

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amyloid in AD is decreased with curcumin which is more effective in low dose of longer duration than large dose of short duration⁵ but at high dose it binds to β amyloid and block itself. It increases phagocytosis of β amyloid which effectively clearing them from brain of patients with AD.⁸

DISCUSSION: As on 2008 numerous clinical trials³ for various diseases like multiple myeloma, pancreatic and colon cancer, psoriasis etc are carried out by using Curcumin. Investigators like Shukala¹ and StixG² observed the anti-oxidant, anti-amyloid and anti-inflammatory properties of curcumin.

Curcumin as an antioxidant inhibits LDLP (low density lipoprotein) oxidation and also free radical that deteriorate neurons associated with AD, Huntington chorea, (HC), Parkinson disease¹³. It improves neurological deficits, decreases mortality and reduces water content in brain¹⁴ and also helps to ease symptoms of AD.

Curcumin by interaction with heavy metals- cadmium, lead, prevent neurotoxicity caused by these metals through suppressing inflammatory damages by preventing metal induction of NF-Kappa. Amyloid plaque formation is increased by intracellular accumulation of cholesteryl esters. Curcumin might exert beneficial effects on AD¹² by inhibiting cholesterol formation and decreasing serum peroxides as the formation of amyloid plaque due to intracellular accumulation of cholesteryl ester is decreased

Further many UCLA Researchers observed that AD patients who stay indoor all the time and having Vit D deficiency, is having beneficial effect when treated with curcumin along with Vit D₃ as curcumin stimulate macrophages of immune system that clear the amyloid β plaque. Curcumin enhances binding of β amyloid macrophages and Vit D could strongly stimulate the uptake & absorption of β amyloid in macrophages in most of the patients.¹⁷

Macrophage type (I) and Vit D₃; and macrophage type (ii) and Curcumin though they perform different function independently, must allow to work together for removal of amyloid protein effectively in the brain. Most people need to supplement with 5000-7000 units of Vit D₃ per day or rely on sun exposure to obtain the ideal level. Adding of curcumin to the diet 300-500 mg per day will provide a synergistic effect to clear brain tangles and prevent Alzheimer's dementia.¹⁸

Any person with significant cognitive decline due to inefficient Trash removal will have to use Vit D which actually turns on the genes within macrophages to rejuvenate the Trash removal ability. It certainly would not hurt to add some curcumin to the brain rejuvenation program. Vit D₃ and curcuminoid activate the opening of chloride channel which supports the uptake of amyloid beta in macrophages type one.¹⁸

Conclusion:

Diet supplements—vegetables /foods containing antioxidants like vitamin C and E when taken/given together with curcumin improve the cognitive capability/memory of the elderly as the activity of curcumin for removal of amyloid beta plaque may be potentiated or slowing down the function of NFT or delayed the accumulation of Trash in the brain.

Thus, from the above probable mode of action of Curcumin extract, if purified may be very essential for delaying the progress of AD as well as for use as cognitive enhancer. But, further investigation and detailed studies will reap a great dividend in future for the treatment of Alzheimer disease associated with cognitive defects particularly for the geriatric patient.

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