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A REVIEW ON POTENTIAL CLINICAL VALUE OF CURCUMIN IN THE TREATMENT OF ALZHEIMER'S DISEASE

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ABSTRACT

Background: Alzheimer's disease is a progressive disorder characterised by progressive cognitive deterioration along with declining activities of daily leaving and behavioural changes. It is the most common cause of dementia in older adult. In its early stages, memory loss is mild but with last stage of AD, individual loss the ability to carry on a conversation and response to their environment. Curcumin is an ayurvedic medicine. They are hydrophobic polyphenol obtained from the rhizome of the herb *curcuma longa.* They are also used treat many diseases like acute dermatitis, hepatitis, cancer, cardiovascular, respiratory infection and neuro-degenerative diseases.

Methods: Previously published articles regarding the therapeutic application of curcumin in AD have been collected and reviewed. **Observations:** The hallmark of AD is the accumulation of β-amyloid (Aβ peptide) outside neurons that interferes with neuron to neuron communication at synapsis and possibly contributing to cell death. Curcumin play a crucial inhibitory role in pathophysiology of AD. Oral administration of curcumin or its metabolite helps in the inhibition of Aβ deposition, Aβ oligomerization and tau phosphorylation in the brain of AD. Further clinical trials are thus warranted for efficient use of curcumin in the treatment of curcumin.

KEYWORDS: Curcumin, beta-amyloid, Alzheimer's disease.

INTRODUCTION

Alzheimer's disease is an age dependent and progressive neuro-degenerative disease, characterized by the loss of memory, cognitive function and change in behavioural and personality. It is associated with multiple cellular changes including mitochondrial damage, loss of synapses, amyloid beta(Aβ) formation and accumulation, activation of microglia and astrocyte, phosporylation of tau and neurofibrillary tangles formation and loss of neurons.[1] Curcumin have the ability on reducing beta amyloid aggregation,[2] and thus is a promising candidate for treating human AD. This plant also known as turmeric, is a member of the zingiberaceae, or ginger family. Component of turmeric are currently undergoing scientific evaluation for their anti-inflammatory agent for the treatment of HIV, cancer, cystic fibrosis.[3]

The two hypothesis considered to cause AD are- 'cholinergic hypothesis' and 'amyloid hypothesis'. The cholinergic hypothesis suggest that AD is caused by a deficiency in the brain level of the cerebral neurotransmitter acetylcholine (ACh), which is hydrolysed by acetylcholine-esterase (AChE). Butyryl choline-esterase (BChE) activity is increased by 40%-90% during the progression of AD, and BChE inhibition is considered as an important aspect of treating AD. Prevention of Aβ accumulation is considered as an important part of preventing AD.[4]

According to WHO report 35.6 billion people worldwide suffer from this disease and as the lifespan of elderly population increases and it is estimated that frequency will be doubled by 2030[5] Physical exercise and healthy diet help to delay the disease progression of AD in elderly individual and improved cognitive function in person with mild cognitive impairment.[6]

Curcumin is more potent than its metabolite when curcumin is taken orally it sis conjugated with glutathione, glucuronate to give water soluble compound in liver and intestine or alternatively reduced to hexahydrocurcumin(HHC) and tetrahydrocurcumin (THC) when taken through intraperitoneal injection. In this review, recent studies about the effect of curcumin on the pathophysiology of AD are summarized and reviewed their potential in AD prevention and therapy.

Chemistry of curcumin

Curcumin is a natural polyphenol, also known as diferuloylmethane($C_{21}H_{20}0_6$). There are two aryl rings containing ortho-methoxy phenolic OH-groups, that are symmetrically linked to β-diketone moiety.[7] Curcumin is hydrophobic in nature, thus it has poor water solubility. They have greater solubility in organic solvent such ethanol, methanol, acetone.[8] Curucmin is biosynthesised in two ways. Phenyl-alanine is the precursor molecule and cinnamic acid is the 1st by-product of curcumin biosynthesis.

Cinnamic acid+5-melonyl CoA ⟶ bis-dehydroxybisdesmethoxy-cur

This compound can be converted to bisdemethoxycur and demethoxycur which can be transformed into curcumin. the second pathway invole n curcumin synthesis is the production of cinnamic acid, which is then converted to p-coumaric acid, and ferulic acid. The ferulic acid reacts with 5-malonyl to form curcumin.[9] Curcumn has two tautomeric form, the bis-keto form found in neutral and acidic condition and in a solid phase and enolate form is found in alkalate condition. Half life of curcumin is crucial in biosystem for elimination or clearance point of view. The main biliary metabolites of curcumin are glucuronide conjugates of tetrahydrocurcumin(THC) and hexahydrocurcumin.

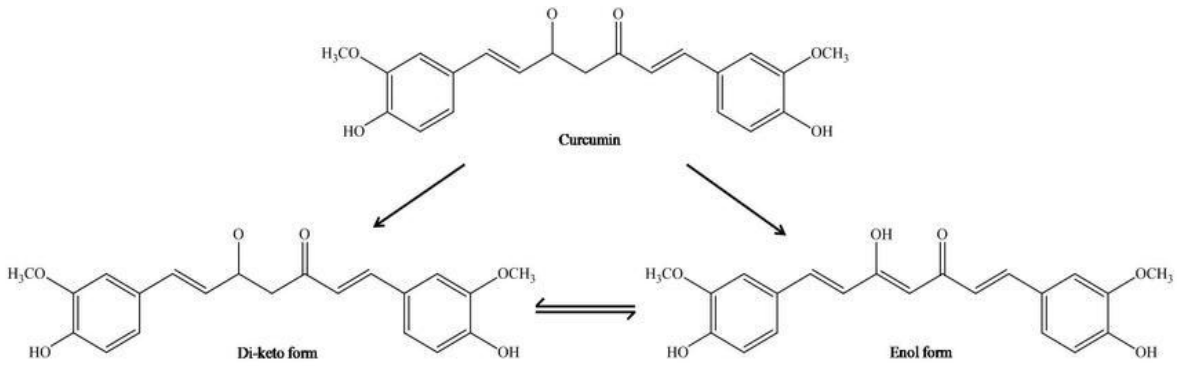

Figure 1: 1keto and enol form of curcumin.

Role of curcumin in reduction of aβ in ad pathogenesis

Amyloid beta is usually treated as one of the hallmark 0of AD pathogenesis. Alzheimer's disease patient possess abnormalities in brain (neurofibrillary tangles, senile plaques and extensive neuronal loss in brain) depends on two key protein- amyloid beta protein and tau protein. Amyloid beta protein mainly responsible for senile plaque formation and tau protein responsible for neurofibrillary tangles. Defective phagocytosis of Aβ may be related to the down regulation of β-1,4-mannosyl-glycoprotein 4-β-N-acetyl glucosaminyltransferase (MGAT-3). Transcription of toll like receptor (TLR)-3, ditTLR4, TLR5, bditTLT7, TLR8,

TLR9, TLR10 is severely depressed in mononuclear cell of AD patients on Aβ stimulation in comparison with those of controlled subjects. Bis-demethoxy curcumin, a curcuminoid compound can enhance the defective phagocytosis Aβ and also the transcription of MGAT-3 and TLRs and the translation of TLR2-4 and thus bis-demethoxy curcumin helps in the correction immune defect in AD.[10]

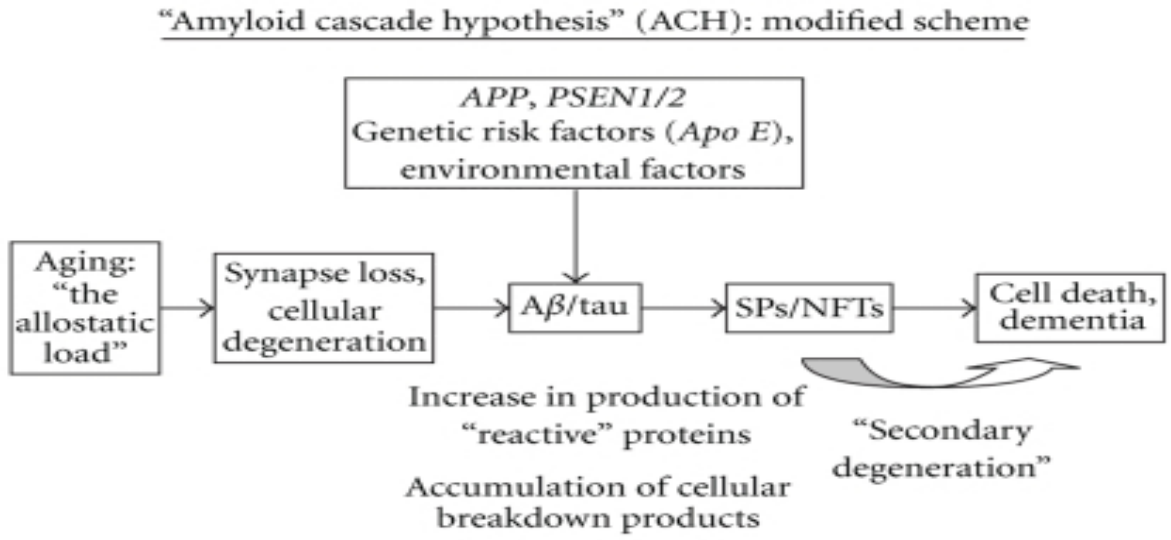

Figure 2: Amyloid cascade hypothesis.

Anti-infmammaory and anti-oxidant effect of curcumin in alzheimer's

Curcumin, inhibits Aβ-induced expression of Egr-1 PROTEIN AND Egr-1 DNA binding activity in THP-1 monocytic cells. Cytochemokine gene expression in monocyte is induced by Egr-1. Curcumin lays a major role in the inhibition of Egr-1 DNA binding activity, thus reduces the inflammation. Also, chemotaxis of monocytes which occurs in response to chemochine from activated microglia and astrocytes in brain can be decreased by curcumin.[11,12] The reduction of release of ROS by stimulated neutrophils, inhibition of AP-1and NF inhibit activation of pro-inflammatory cytokines TNF alpha and IL1 beta.[13] Thus, curcumin decreases he main chemical for inflammation and transcription of inflammatory cytokines.

Curcumin inhibit the activity of AP-1(transcription factor involved in the expression of amyloid). It also decreases LDL oxidation and free radicals that cause deterioration of neurons in AD. It protects brain mithochondria against various oxidative stress. When curcumin given as pre-treatment it protects brain mithochondria aganinst prroxinitrite (potent

oxidant) which attach wide range of cells by direct detoxification and by elevation of total cellular glutathione levels.[14]

Scope of review

The study aims in reviewing the potential biological effect of curcumin in the treatment of AD thereby they can be used as anti-alzheimer's disease agent in a better way.

CONCLUSION

Curcumin has various biological properties like antioxidant, anti-inflammatory, anti-tumour activity and anti-Aβ aggregation. Recent studies on curcumin revealed that it boosts cognitive function in human by reducing Aβ deposition, oligomerizaton, and tau phosphorylation in AD brain. All these findings suggest that curcumin may be one of the most promising compound for the development of AD therapy.

Clinical trial on curcumin for AD has been reported not enough to judge the effect of curcumin for AD. Thus, further studies are required for better molecular level understanding of potential of curcumin in the treatment of AD.

Conflict of interest

The author(s) declared no conflict of interest with respect to the authorship, research or publication of the article.

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