Therapeutic Effects of Curcumin Extracts on Tau Protein in Alzheimer's Disease: An Overview

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Abstract:
The degeneration of cholinergic neurons leads to Alzheimer's disease (AD), a neurodegenerative disorder that gradually impairs memory and cognitive processes. For the treatment of AD, research on herbal medications has recently been underway and has been shown to provide the condition with improved symptom relief. Studies demonstrate that using curcumin in treating AD decreases the degradation of cholinergic neurons because it is widely available and has fewer adverse effects than other drugs, such as allopathic ones.

Keywords: Alzheimer's disease, Curcumin, Hyper-phosphorylation, Tau Protein

Introduction:

AD is a progressive neurodegenerative disease characterized by beta-amyloid and tau protein. Although the pathogenesis of AD is unclear, it is thought to be brought on by beta-amyloid protein deposition and tau protein hyper phosphorylation [1]. Treatment options are available for AD, such as Anticholinesterase agents, NMDA receptor antagonists, and miscellaneous cerebroactive drugs, which show improvement in AD symptoms. Since the therapy is related to amyloid beta protein are less efficient in treating AD, researchers' primary focus is now on tau protein. Intraneuronal neurofibrillary tangles made by the microtubule-associated tau protein is a common manifestation in AD. Studies demonstrate that the use of curcumin in AD slows the degeneration of cholinergic neurons and is easily accessible, with less adverse effects when compared to other treatments, such as allopathic.

Methodology:

This review tries to highlight the possible role of curcumin in the pathogenesis of AD. Therefore, a comprehensive search was conducted on databases like PubMed, Scopus, and google scholar to obtain all the relevant articles from inception to October 2022. The keywords used were "Alzheimer's disease," "Tau protein," and "curcumin". The articles were included if they studied the effect of curcumin on AD. Studies on the effect of curcumin on other diseases and on the effect of other herbs or medicines on AD were excluded.

Tau protein

Tau protein, a microtubule-related protein, aids in the assemblage and stability of microtubules. Tau is a hydrophilic protein that has undergone extensive investigation of circular dichroism spectra in solutions. In the average human adult, tau contains two to three moles of phosphate per mole of tau protein. There are two isoforms of tau protein; one has three binding domains, and the other has four. The isoform with four binding domains has a higher affinity than the three binding domains. It can displace it from the microtubule [2]. Alpha and beta tubulin dimers are polymerized by components from the tau protein family, which also stabilizes microtubules. Tau is predominantly expressed in the neurons, is confined to the axon, and is crucial for the network and neuronal plasticity. Tau protein's precise function in the neurogenerative process is still up for dispute. Understanding the biological role of tau and the context that cause tau to become toxic is crucial [3]. According to a pathogenic hypothesis, the tau protein may undergo alteration, primarily by phosphorylation. This might lead to the generation of aberrant aggregates that are neurotoxic [4]. Hyperphosphorylation of tau depresses its biological activity. Tau oligomers are pathogenic forms, emerged during the initial phases of tau aggregation and are critical in causing the loss of neurons and behavioral disabilities. These neurodegenerative disorders are collectively termed as taupathies [1,3,5].

Biochemistry of Tau protein

The human brain has six distinct Tau protein isoforms, which may be distinguished by the number of binding domains they contain. Three binding domains are present in half of them, whereas four are present in the other half. The binding domain is located on carboxy terminals of the proteins and is positively charged, responsible for binding to negatively charged microtubules. The number of amino acids in Tau protein ranges from 352-441 depending on its isoforms. Tau protein is hydrophilic in nature due to the number of amino acids [6,7].

Regulations of Tau protein

Tau protein elimination involves the glymphatic system. Glymphatic system clearance is a novel regulatory mechanism that is responsible for Tau aggregation and neurodegeneration. Aquaporin 4 is a water channel encoded by AQP 4 gen which is a driver of the glymphatic system, which regulates tau protein level inside the brain. Aquaporin 4 deficiency/inhibition results in the accumulation of Tau oligomers inside the brain [8,9].

Curcumin

Curcumin is the yellow-coloured hydrophobic polyphenolic chemical constituent seen in Turmeric (*Curcuma longa*) belonging to the Family *Zingiberaceae* that targets the Tau protein in AD [10]. Curcuminoids, which make up between 3 and 6 percent of turmeric, include curcumin, demethoxycurcumin, and bisdemethoxycurcumin [11]. Curcumin is chemically referred to as diferuloylmethane (C-21 H- 20 O- 6) and has a molecular mass of 368.37 g/mol. The chemical structure consists of two aryl rings containing two ortho methoxy phenolic OH groups and are symmetrically connected to a beta diketone moiety [12]. These interactions affect curcumin's physiochemical characteristics, biological processes, and antioxidant activities. Additionally, it exhibits promise as a therapeutic choice for treating AD and cognitive impairment [13]. The chemical

structure of curcumin is demonstrated in figure 1.

Figure 1.

Mechanism of action of curcumin

As opposed to the anti-amyloid effects, curcumin's potential mpact on tau protein has not received as much attention. Numerous enzymes have been implicated in the phosphorylation of tau, including cyclin-dependent kinase (CDK)5, mitogen-activated protein kinase (MAPK), glycogen synthase kinase (GSK) 3 beta, and c-Jun N-terminal kinase (JNK) [6, 20]. Among them, curcumin is a potent inhibitor of GSK and JNK. With an IC 50 value of 66.3 nm, curcumin was found to be a dominant inhibitor of GSK3 beta in an in vitro test employing tau protein as the substrate [12,14].

Proline-directed kinase GSK3 has two isomers, GSK3 alpha and GSK3 beta, which are encoded by chromosomes 19 and 3, respectively. Of them, GSK3 beta, generally found in axons of CNS, is the primary kinase involved in the phosphorylation of tau. Axonal transport is altered, and hippocampal neurodegeneration results from tau disassembling from microtubules due to GSK3 beta overactivity [15]. Also GSK activity correlates with neurofibrillary tangle (NFT) in the brain [16]. In AD, the cytoplasm accumulates hyperphosphorylated tau, which causes microtubule disintegration, loss of neuronal integrity, and, finally the production of NFTs [17]. The phosphate-kinase imbalance in the brain was investigated by tau hyperphosphorylation, which identified GSK3 beta as a significant tau kinase that may be involved in AD pathology. Tau protein contains a substantial number of amino acid residues that GSK phosphorylates [18,19,20]. Microtubule disassembly and the promotion of tau oligomers and NFTs, which contribute to neuronal dysfunction, are produced by the hyperphosphorylation of tau protein, which is generated by the addition of a phosphate group on a specific Threonine 231 residue of tau protein. By interfering with signaling molecules at the same level as or immediately upstream of the MAPK level, curcumin may impact the JNK pathway. The suppression of the JNK pathway provides a potential mechanism by which curcumin may suppress NF-kB signaling. Hence we have to inhibit hyperphosphorylation of tau protein through inhibition of Glycogen Synthase kinase3 beta and JNK pathway [21], as shown in figure 2.

Therapeutic uses

The various therapeutic uses of curcumin are shown in figure 3.

a. Antioxidant effect:

Under normal physiological conditions, a neuronal cell requires energy for metabolic processes and homeostasis. The energy needed for the cell is provided by aerobic metabolism; during this process, reactive oxygen species (ROS) accumulate inside the neuronal cell [22]. Due to the imbalance between produce ROS and intracellular antioxidant defense mechanisms, oxidative stress inside neurons increases. This ROS damages the membrane of neuronal cells and causes neuroinflammation. Curcumin is a potent antioxidant that protects neuronal cell by scavenging free radicals [23, 24]. It also removes NO-based free radicals, as demonstrated in figure 4.

Figure 4.

b. Anti-inflammatory effect:

Astrocytes and microglial cells play a role in inflammation inside the brain. Microglial cells are a source of TNF alpha, IL -1, IL-6

and other proinflammatory citokines. On the accumulation of amyloid beta protein and hyperphosphorylated tau protein, these cells get activated and are unable to phagocytose these proteins and produce proinflammatory cytokines, which are responsible for inflammation. Curcumin also inhibits the cyclooxygenase and transcription factor involved in converting phospholipids to prostaglandin. Prostaglandins are lipid molecules with a multitude of applications, namely modulating inflammatory reactions. As a result, prostaglandin inhibition decreases neutrophil activity and prevents ROS release. The master regulator includes NF kappa, beta transcription factor, TNF alpha, IL- 1, and IL-6 invoke the inflammatory responses. Curcumin shows inactivation of the master regulator and inhibits neuroinflammation in AD [23, 24] (The effect of Turmeric on AD) shown in figure 5.

Figure 5.

c. Potent immunomodulatory effect:

The activation of B & T cells, macrophages, neutrophils, natural killer cells, and dendritic cells is modulated by curcumin. Dendritic cells treated with curcumin stimulate the growth of regulatory T cells and prevent the release of IL-10 and inflammation. In rats fed on a curcumin diet, Neutrophils, lymphocytes and NK cells are shown to eliminate infected cells and tumors. Also, the antibody response increased in those rats. It was discovered that curcumin inhibits TNF alpha, which in turn inhibits the intracellular adhesion molecule 1, the endothelial adhesion molecule 1, and the vascular cell adhesion molecule 1. Moreover, curcumin lowered beta cell proliferation, IgM secretion, and CpG (cytosine phosphate guanine dinucleotide) levels in the beta cells. Particularly, curcumin inhibits the phosphorylation of Extracellular signal-regulated kinase (ERK) and MAPK [23,24].

d. Cholesterol-lowering effect:

Researchers observed that curcumin induced a reduction in cholesterol levels. Curcumin is theorized to liberate cholesterol from cells, specifically adipocytes, through the Peroxisome proliferated activated receptor (PPAR) -gamma- Liver x receptor (LXR) - ATP- binding cassette transporter A1 (ABCA1) pathway. In this pathway, LXR is an essential regulator of cholesterol, which acts as a target for PPAR-gamma, and these receptors regulate ABCA1 expression. Both cholesterol and phospholipid homeostasis is accomplished by the ABCA1 transporter. This cholesterol-lowering effect of curcumin can contribute to its protective effect on the onset and progression of AD [23,24].

Discussion:

Dawn Chin et al., Yasser Bhuttanji et al. and Mala Thakur et al. discussed the various mechanisms involved in reducing Tau protein by the curcumin. It includes inhibition of the GSK (Glycogen Synthase Kinase) pathway, the antioxidant, anti-inflammatory and immunomodulatory effects of curcumin. [12,20,23]

Mengxi Tang et al. compare allopathic medicine with herbal medicine (curcumin) used in treating AD. It was observed that allopathic treatment has other detriments, such as cost and side effects, and it requires prescriptions and a lack of acccessability [25].

Nazomi Hishikawa et al. performed case studies on humans using turmeric extract. They completed three case studies on AD patients in which it was found that AD symptoms improved by using turmeric extract in the form of a capsule. During this study, they checked the improvement of

symptoms by mini-mental examination score and the Japanese version of the neuropsychiatric-a brief questionnaire (NPI-Q). In this case study, they gave 764mg/day of turmeric extract, equivalent to 100mg/day of (curcumin). After one year of treatment, patients could recognize their family members and other symptoms of AD were cured. They have a peaceful life without symptoms of dementia.[26]

Curcumin has difficulties when employed as a medicinal agent to treat Alzheimer's disease, including poor absorption, low serum concentration, limited tissue distribution, a short half-life, and fast metabolism via glucuronidation at different tissue sites, according to Preetha Anand et al. [27].

According to Lim et al. 2001, Consuming 160 parts per million (ppm) of curcumin over six months resulted in lowered levels of oxidized proteins, IL-1b, soluble and insoluble Amyloid beta protein, glial fibrillary acidic protein (GFAD), as well as plaque load [28]. Frautschy et al. and Belviranli et al ,also assessed the effectiveness of curcumin in Amyloid beta 40 (Ab40) and Amyloid beta 42 (Ab42)-treated Sprague Dawley rats displaying neurodegenerative symptoms. It was observed that oxidative damage and cognitive impairment is suppressed when the rats were given with 2000 ppm (5.43 mmol/ gm). Also, when measured with Morris water maze test (MWM), elderly female rats administered with curcumin for 12 days demonstrated improved memory with a reduction in cerebral oxidative damage [29, 30]. Feng.et al reported that curcumin, through suppression of Niemann pick c1 like, 1protein, lowers the cholesterol level. This protein is responsible for the uptake of cholesterol through vesicular endocytosis within the intestine [31]. Studies on rats on a high-fat diet indicated another potential mechanism of hypocholesterolemia, with curcumin being found to drastically lower cholesterol in blood. It was found to increase the conversion of cholesterol to bile acid by increasing the mRNA levels of cholesterol 7-alpha-hydroxylase (CYP7A1) [32, 33, 34]. More recently, it was discovered that curcumin combined with piperidine produced substantial alterations in the lipid profiles of rats on high-fat diet. Hypercholesterolemia is still thought to be a likely factor in the risk of developing AD [35,36,37]. If curcumin is proven to reduce cholesterol, using it could be another approach to treating AD. Ringman et al, performed a 24-week, double-blind, randomized, placebo-controlled trial with a 48-week open-label extension on two dosages of curcumin—2g/d and 4g/d—in individuals with mild to moderate AD. Being the first study to incorporate cerebrospinal fluid (CSF) biomarkers, there were no discernible variations in cognitive function, plasma or CSF amyloid -40/ Amyloid beta-42 or tau, between the intervention and placebo groups, according to the preliminary findings. Still, bioavailability was once again limited [38]

Serafini et al. stated that although certain initial clinical trials (NCT01297218 and NCT01696591) found no evidence of the neuroprotective effects of mesenchymal stem cell intracranial injection (MSCs) in humans, other trials are still enrolling participants [39].

Han-Chang et al, in a rat model for AD, reported a reduction oxidative stress and enhanced active avoidance and locomotory activity, following the consumption of curcumin [40]. According to McClure et al., the iv injectable formulation is unsafe for humans and can only be used in animal models. A distinct approach adopted the use

of aerosol to establish secured brain delivery of a curcumin derivative, F-methyl curcumin 1 (FMeC1) using 5XFAD (familial Alzheimer disease) mouse [41]. The study suggested that exposure to aerosolized FMeC1 ensured the delivery of compound to the nervous system [42]. Immunohistochemistry results have supported the aerosol delivery theory. Hippocampal regions and the cortex both have amyloid plaques that FMeC1 binds to amyloid plaque of those regions [43, 44]. Animal studies support the use of aerosolized form among humans as a non-invasive and practical approach to boost cognition, although this has not yet been put to the test [45, 46].

Because of its limited bioavailability and quick metabolism in the liver and intestinal wall, Guido Shobha et al, concluded that curcumin could not be used. In this experiment, curcumin was combined with piperidine, a potent inhibitor of hepatic and intestinal glucuronidation, to assess its effects on the bioavailability of curcumin on healthy human volunteers. The study demonstrates that piperidine has no adverse effects while increasing the serum concentrations, degree of absorption, and bioavailability of curcumin in both rats and humans [47].

Using a transgenic model that expresses human wild-type tau (h tau) on a mouse tau knockout, Ma et al. (2013) found that synaptic and cognitive impairments, NFTs, and neuronal death start to appear around 11–12 months and reach their peak at 17 months. The mice were 15 to 16 months old at the start of the study and were given either a meal without curcumin or one with 500 ppm of curcumin. The bioavailability of free curcumin in the brain is higher in solid lipid curcumin particles than in other curcumin formulations. This study discovered that curcumin improved behavioral assessments and decreased the number of tau dimers. In contrast to untreated h tau mice, curcumin administration enhanced spatial memory and cognition as measured by an MWM. Additionally, employing the Novel Object Recognition Test (NORT), curcumin-treated h tau mice demonstrated normalization of recognition memory toward wild-type measurements [48].

The different types of animal models used in various studies were shown in table 1.

Conclusion:

Concerning substantial data from reputed journals and research, curcumin has different biological properties, including anti-inflammatory, anti-amyloid, potent immunomodulatory effect, cholesterol-lowering effect, and possible anti-tau properties. These findings conclude that curcumin might be a key agent in combating AD pathogenesis by inhibiting tau hyperphosphorylation by inhibiting GSK and JNK pathways. As reported in the literature, curcumin has poor absorption, rapid metabolism, and excretion, reflecting bioavailability. To increase its bioavailability and permeability to the CNS, it is recommended that additional long-term clinical studies be carried out using fresh doses and elaborated methodologies. In brief, tau targeting is a promising treatment strategy, but various challenges, including lack of selectivity and specificity towards tau protein, is not been extensively studied as beta-amyloid protein in AD.

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Abbreviations:

AD: Alzheimers disease
NMDA: N- methyl -D-aspartate
AQP4 : Aquaporin water channel
ROS: Reactive oxygen system
CDK: Cyclin dependant kinase
GSK: Glycogen synthase kinase
JNK: c-Jun N-terminal kinase
MAPK: Mitogen-activated protein kinase
IC 50: Half-maximal inhibitory concentration
NFTs: Neurofibrillary Tangle
NF kB: Nuclear factor kappa beta
NO: Nitric oxide
TNF: Tumor necrosis factor
IL: Interleukin
CpG: Cytosine- phosphate- guanine dinucleotide
CSF: Cerebrospinal fluid
ERK: Extracellular regulatory kinase
PPAR: Peroxisome proliferated activated receptor
LXR: Liver x receptor
ABCA1: ATP- binding cassette transporter A1
NPI-Q: Neuropsychaitric-a brief questionnaires
MAO: Monoamine oxidase
GFAD: Glial fibrillary acidic protein
MSC: Mesenchymal stem cell
LDL: Low-density lipoprotein
MWM: Morris Water Maze
NORT: Novel Object Recognition Test