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Role of Curcumin in Treatment of Alzheimer Disease

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Abstract

A lot of research findings support that curcumin (diferuloyl methane) has antioxidant, anti-inflammatory and anti-tumor activity. In India, curcumin has a widespread use as food additive and herbal medicine for human diseases without any side effect. Though curcumin is well established as an anticancer agent but there are a few reports about its promising role against amyloid diseases. According to recent finding curcumin play a crucial inhibitory role in pathophysiology of Alzheimer's disease (AD). Oral administration of curcumin or its metabolites has shown the inhibition of Aβ deposition, Aβ oligomerization and tau phosphorylation in the brain of AD animal model including behavioural improvement. But still it is unknown whether the curcumin is directly involved in those processes or enhance those mechanisms. Thus in this review we want to focus on overall mechanism of curcumin in AD. Some strategies to overcome the problem of low absorption and fast clearance of curcumin nanoparticles have also been proposed.

Keywords: Curcumin; Amyloid disease; Aβ oligomerization

Introduction

Curcumin has been reported historically in ayurvedic medicine especially in India and other oriental countries to have potential to treat many diseases like acute dermatitis, hepatitis, erectile dysfunction, hirsutism, baldness, cancer and neurodegenerative diseases. It is a hydrophobic polyphenol derived from the rhizome of the herb *Curcuma longa* has a wide range of biological and pharmacological activities [1-3]. Traditionally turmeric is used as a curry spice in foods in India. Though curcuminoids have got great attention as it consist major medicinal property of turmeric which is rather mixture of curcumin, a diferuloylmethane (75-80%), demethoxycurcumin (15-20%) and bisdemethoxy-curcumin (3-5%) [4]. There is several reported work where curcumin has shown a prominent beneficial activity with its anti-inflammatory [5-7], antioxidant [8], chemopreventive and chemotherapeutic properties [9-13]. Curcumin also acts as a hepato and nephro-protective [14,15], thrombosis suppressing [16], myocardial infarction protective [17,18], hypoglycemic [19,20] and antirheumatic agent [21]. From drug delivery point of view curcumin is very much safe in some animal model [22] as well as in human studies [23] as it is reported. There are also some reports which have suggested possible beneficial effects of curcumin on the experimental models of Alzheimer's disease (AD) [24]. Based on these results lots of initiatives have been taken to treat Alzheimer using neurorestorative strategy. According to an article in published in nature in 2017, Baker [25] however claims that curcumin is a "deceptive molecule" and has proposed that there's no evidence about its any specific therapeutic benefits, despite thousands of research papers and more than 120 clinical trials. There are many researchers who have given strong evidence concluding a prominent biological activity of curcuminoids. In this review, we tried to focus on role of curcumin and its derivatives as neurorestorative agent for neurodegenerative diseases especially in amyloid diseases.

Amyloid *B* and Tau Protein in Alzheimer's Disease

Amyloid beta (Aβ) has been usually treated as one of the hallmarks of AD pathogenesis. Alzheimer's disease patients generally possess senile plaques, neurofibrillary tangles and extensive neuronal loss in brain (Figure 1). This kind of abnormalities mostly depends on two key proteins, amyloid-β-protein (Aβ) and tau in which Aβ is responsible for senile plaque formation and tau protein responsible for neurofibrillary tangles. In developing countries AD has become highly progressive neurodegenerative disorder characterized by destruction of cognitive function and behavioural changes [26]. In AD brain a high amount of Aβ fibril deposition leads to neuropathology including loss of neuron and impairment of neuronal functions [27-30]. According to earlier report amyloid protein precursor gene cloning and its co-localization at chromosome 21 coupled with earlier recognition that trisomy 21 invariably leads to the neuropathology of AD [31,32]. It also depicts the primary event of Aβ deposition in AD pathogenesis. Some incidence of mutation are also reported near the Aβ region of the coding sequence of APP gene [33,34] which further degraded by the enzyme proteases called α-, β- and γ-secretases [35]. Therefore alternation in APP metabolism through secretases or aberrant nature of APP metabolism might be a key for AD pathogenesis.

Similarly same kind of mutation in gene coding region of tau protein are also associated in severe tau deposition in neurofibrillary tangles in the brain causing fronto-temporal dementia with parkinsonism without any Aβ deposition [36,37]. From this observation we can conclude that Aβ deposition in brain is first pathological event causing AD.

Though Aβ has two species named Aβ40 and Aβ42. These two species differs from each other depending on the presence of C terminus of Aβ end at 40th or 42nd amino acid respectively [38].

According to previous report, Aβ42 can manifest plaque formation in early age of about 12 years whereas plaque formation of Aβ40 is detected later at least after 20 years [39]. Further studies have shown that Aβ42 aggregation is much faster than Aβ40 [40] and for amyloid deposition in parenchyma and vasculature Aβ42 [41] is highly required.

Bioavailability and Potency of Curcumin and Its Metabolites

Due to low intrinsic activity, poor absorption, high rate of

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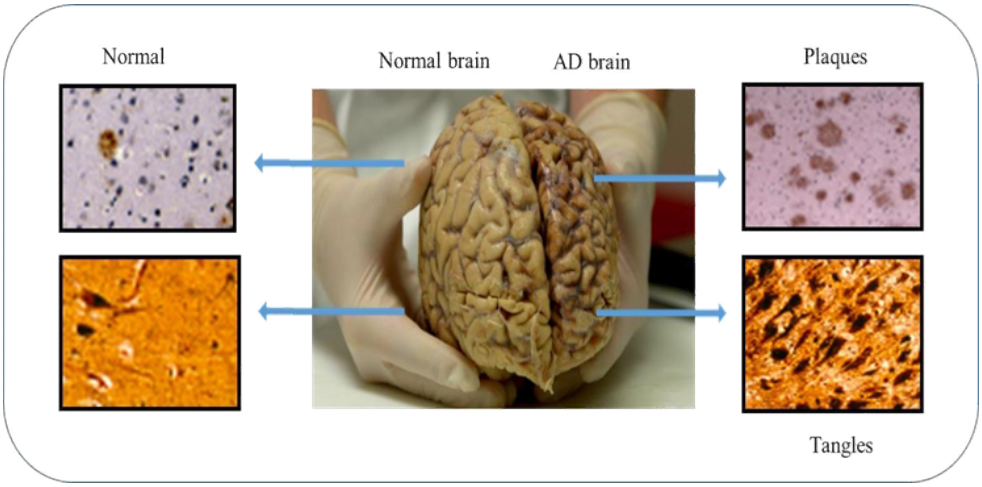

Figure 1: Diagramatic representation of brain showing senile plaques and tangles at one side and normal morphology on another side.

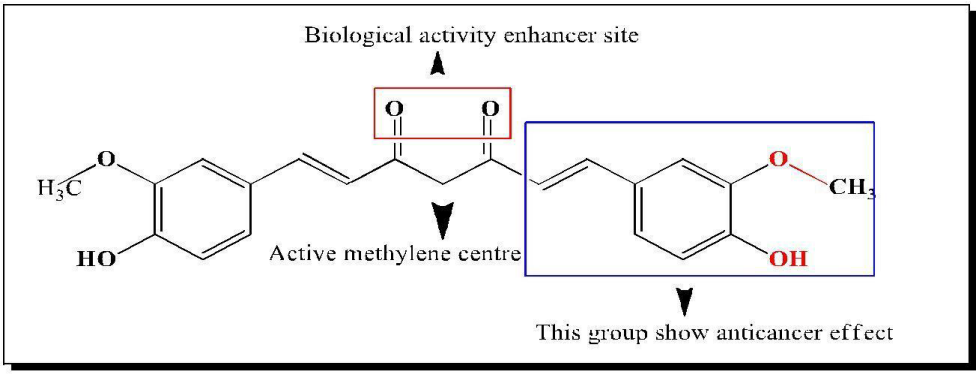

Figure 2: Curcumin (diferuloyl methane) with bio active site.

metabolism, inactivity of metabolic products, rapid elimination and clearance from the body, an agent primarily show the reduced bioavailability. Thus to be a good agent every experimental molecule need to maintain its intrinsic efficacy. According to previous reports curcumin has shown a poor absorption and rapid metabolism that is the demerit using curcumin as bio friendly drug. Furthermore there are some factors mainly responsible for this reduced bioavailability including limited tissue distribution, low serum levels, apparent rapid metabolism and short half-life. Wahlstrom and Blennow in 1978 using Sprague-Dawley rats have shown a poor absorption of curcumin in blood plasma after oral administration of 1 g/kg of curcumin [42]. Another group of researcher, Rabindranath and Chandrasekhara have shown that there was no curcumin in heart blood after oral administration of 400 mg of curcumin to rats [43]. In 1998, Shoba et al. have reported that a maximum serum concentration of 1.35 (± 0.23) μg/mL was observed at time 0.83 h when curcumin was orally administered to a rat at a dose of 2 g/kg whereas a same kind of dose of curcumin to human has given either untraceable or very low (0.006 μg/mL at 1 h) serum level [44].

According to Rabindranath and Chandrasekhara, orally administered 400 mg of curcumin to rat only a very small amount of unchanged drug was found in kidney and liver. Though at the beginning (within 30 min) around 90% of curcumin was observed compare to 24 h interval when only 1% of curcumin was found in stomach [43]. Another group of researcher using a mouse model have shown a maximum amount of curcumin in the intestine (117 μg/g) with curcumin dose of 0.1 g/kg via i.p. route around 1 h after dosing and a moderate curcumin amounts of 26.1, 26.9 and 7.5 μg/g, respectively in spleen, liver and kidney but in brain tissue it showed only a trace amount (0.4 μg/g) [45]. In another study malignant as well as colorectal tissue of patient were treated with 600 mg of curcumin (concentration 7.7 and 12.7 nmol/g, respectively) and those doses have shown pharmacological activity in colorectum measured by effects on level of COX-2 protein [46].

Majority of research supports that curcumin itself as a whole is more potent than its metabolites. When curcumin is taken orally it is conjugated with glutathione, glucuronate or sufate to give water soluble compounds in liver and intestine or alternately reduced to Hexahydrocurcumin (HHC) and Tetra Hydrocurcumin (THC) when taken through intraperitoneal injection. Again these metabolites are less bioactive than curcumin itself (Figure 3). Holder et al reported that THC and HHC are the major metabolites of curcumin while dihydroferulic acid together with traces of ferulic acid are minor ones [47]. In some cases sulfate conjugate were observed in addition to glucoronidase in curcumin treated rat urine [43]. On the other side Pan et al, based on hydrolysis of plasma samples with glucoronidase have shown 99% of curcumin as glucoronide conjugate [45]. *In vivo* study

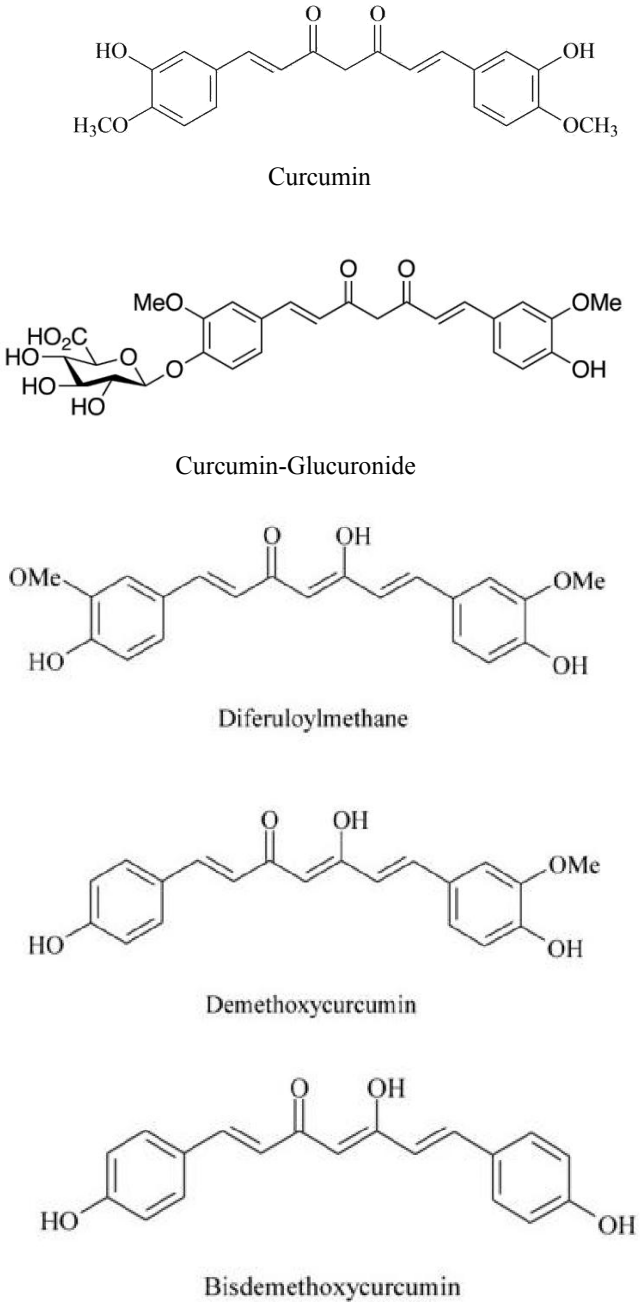

Figure 3: Major curcumin metabolites.

also proved that the major metabolites of curcumin are curcumin-glucuronoside, dihydrocurcumin–glucuronoside, Tetrahydro-Curcumin (THC) – glucuronoside and THC [45]. Later Ireson et al. justified those finding after examination on rat and human [48].Though there have some contradiction in between curcumin and curcumin derivative in comparison to activity.

Curcuminoids in turmeric roots are a mixture of three main bioactive components viz., Curcumin, Demethoxycurcumin (DMC) and Bisdemethoxycurcumin (BDMC) where curcumin constitutes about 80%. It has two tautomeric forms, the bis-keto form is predominantly found in neutral and acidic conditions and in a solid phase and enolate form is found in alkaline condition (Figure 4).

Half-life of curcumin is crucial in biosystem for elimination or clearance point of view. According to Wahlstrom and Blennow when 1 g/1 kg curcumin were orally given in rat, a trace amount of curcumin found in rat urine and almost 75-80% was excreted in the faeces [42]. In another study it has been shown that the absorption and elimination half-life of curcumin, orally administered with 2 g/2 kg dose in rat shown 0.31 and 1.7 h respectively, but in human it was almost undetectable [44]. Though these finding are not enough to conclude about the factor controlling the curcumin activity and need further study to address this issue.

Strategies to Increase Bioavailability of Curcumin

In respect to poor bioavailability of curcumin, some new strategies have come up to overcome this problem including complex formation with nanoparticle, liposome, micelle and phospholipids which are capable to keep up longer circulation, better permeability and resistance to metabolic processes. Nowadays nanoparticle based systems are widely applied for targeted drug delivery system. There are some reports about nanocurcumin which were synthesized for cancer therapy. They are mostly polymer based nanoparticle of curcumin with less than 100 nm size having promising effect on pancreatic cell line compared to that of free curcumin. Both free curcumin and nanocurcumin have shown pro-inflammatory cytokine interleukins and TNF-R reduction as well as inhibit activation of transcription factor NFκB. Though there is not much report of *in vivo* effect of nanocurcumin in mice or its biodistribution to show any efficacy comparison between nanocurcumin and free curcumin [49]. Later Tiyaboonchai et al. has reported curcuminoid loaded Solid Lipid Nanoparticle (SLNs) having 450 nm sizes showing prolonged *in vitro* release of curcuminoids. Thereafter *in vivo* study with healthy volunteers showed improved efficacy of SLNs loaded curcuminoid over free curcumin [50]. According to recent research nanoparticle based system has gained great attention due its targeted and promising delivery nature. Though our recent focus is on Alzheimer diseases utilizing sugar based nanocurcumin and enhance the permeability of nanosystem through blood brain barrier.

In other cases liposomes are excellent agent in drug delivery system. Li et al., has demonstrated liposomal curcumin activity against human pancreatic carcinoma via *in vitro* and *in vivo* analysis where curcumin liposome inhibits pancreatic carcinoma growth and exhibit anti-angiogenic activity [51]. Ruby et al. also investigated the antitumor and antioxidant activities of neutral unilamellar liposomal curcuminoids in mice [52]. Furthermore Preclinical studies are reliable to show the increase bioavailability of liposomal curcumin over free curcumin.

Micelle and phospholipid complexes also have significant role to improve gastrointestinal absorption of natural drugs maintaining higher concentration at plasma level and lower rate of elimination. On the basis of pharmacokinetic analysis, Ma et al. reported that a polymeric micellar curcumin can show approximately 60 fold more biological half-life in rats, compared to curcumin solubilised in a mixture of DMA, PEG and dextrose [53]. Moreover phospholipid complex help to formulate some natural drugs named silymarine [54] and dolichol [55]. This drug has higher and improved bioavailability. In other cases structural modification of curcumin can enhance the biological activity (Figure 2). Depending on curcumin structural properties Mosley et al. reported several studies mentioning the biological efficiency relationship of curcumin and its derivative [56]. Other possibilities include metal

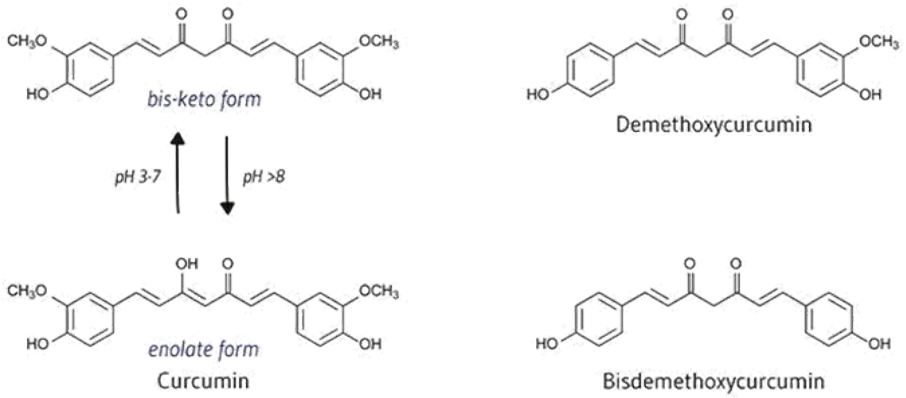

Figure 4: Major turmeric derived curcuminoids, the bioactive forms of curcumin.

chelation of curcumin might be a key delivery system. Based on this technique John et al has shown an efficient antitum or activities of curcumin, piperonylcurcumin, 2-hydroxy napthyl-curcumin, cinnamyl-curcumin and their copper complexes. In comparison to activity, copper complex with curcumin and its derivative has shown better efficacy than parent compound [57]. Another study done by Sui et al illustrated the activity of curcumin an *in vitro* inhibitor of HIV-1 and HIV-2 proteases where curcumin complex with boron showed 10 fold enhancement compare to curcumin alone. Curcumin boron complex also lowered the IC50 values significantly [58]. Again a group of researchers has reported that curcumin manganese complex has more reliable neuroprotective activity than curcumin itself both *in vitro* and *in vivo*. Further they concluded that the complex might be useful as a neuroprotective agent to treat acute brain pathologies associated with NO-induced neurotoxicity and oxidative stress induced neuronal damage like epilepsy, stroke and traumatic brain injury [59,60].

Bioconjugate can also help to improve curcumin bioavailability. According to previous report curcumin bioconjugate containing glycine, alanine and piperic acid has shown an improved biological activity with increased cellular uptake or reduced metabolism of those biocojugate showing increased concentration inside the infected cell compared to free curcumin [61].

Inhibition of *B*-Secretase and Acetylcholinesterase Activity

As mentioned earlier, β-secretase helps in cleaving of Aβ protein from APP gene. Curcumin is reported to suppress Aβ-induced β-site APP-cleaving enzyme 1 (BACE-1) upregulation at a concentration of 3-30 μM and curcumin depreciates the production of Aβ-induced reactive oxygen species at 1-30 μM concentration whereas 20 μM cucumin halted the structural changes in Aβ towards βsheet-rich secondary structure [62]. Another group of researcher showed that curcumin with concentration about 20 μM depreciated the over expression of APP and BACE-1 mRNA levels, which was increasing when treated with copper or manganese ions (50-100 μM) in a time and concentration dependent pattern [63] .

Following the new therapeutic approach for AD, researchers found Acetylcholinesterase (AChE) activity have some impact on neuropathology. Some researcher found that AChE inhibitors remain the major class of drug for providing symptomatic relief [64].Though *in vitro* assay have shown AChE inhibition by curcumin with an IC50 value of 67.69 μM but *ex vivo* study showed no significant response [65]. Despite of those contradictory results we need to explore different strategy to combat those loop hole to treat AD pathogenesis.

Curcumin can Reduce Aβ-Induced Inflammation in AD Pathogenesis

According to previous reports, inflammation has a good impact on AD pathogenesis [66,67] and further finding have shown that anti-inflammatory drug therapy suppress the incidence and progression of AD [68]. Though defective phagocytosis of Aβ may leads to the down regulation of β-1,4-mannosyl-glycoprotein 4-β-Nacetylgluc osaminyltransferase (MGAT3) and prevent MGAT3 transcription. Transcription of Toll like receptor (TLR)-3, TLR-5, TLR-7, TLR-8 and TLR-9 and TLR-10 are drastically downed in mononuclear cells of AD patients on Aβ impassion in comparison to control one [69]. Bisdemethoxycurcumin, a curcuminiod compound can effectively enhance the defective phagocytosis of Aβ *as well as* the transcription of MGAT3 and TLRs and the translation of TLR2-4. These finding suggest that bisdemethoxycurcumin can correct the immune defects in AD patients [69].

In Vitro and *In Vivo* Studies using Curcumin

Either free curcumin or curcumin derivatives show remarkable activity in regression of AD pathogenesis. The primary goal is to reduce the burden of Aβ deposits in brain. Multiple mechanisms have been proposed to interpret the role of curcumin and its active components in neurorestorative activity in amyloid diseases. Different researchers have different observations on their findings treating AD with curcumin in different concentrations. According to a study using liquid chromatography technique coupled with tandem mass spectrometry, the maximum concentration (C_{max}) and the time to reach maximum concentration (T_{max}) of plasma curcumin in rat were 0.06 (± 0.01) μg/mL or 0.16 (± 0.03) μM and 41.7 (± 5.4) min after when 500 mg/kg of curcumin were orally registered in rat and the elimination half-life were 28.1 (± 5.6) min and 44.5 (± 7.5) min for curcumin oral (500 mg/kg or 1.36 mmol/kg) and intravenous (10 mg/kg or 0.03 mmol/kg) administration respectively [70]. Moreover it has been investigated that curcumin crosses the blood-brain barrier and labels senile plaques and CAA in AD model mice using *in vivo* multiphoton microscopy [71]. In a study Tg2576 AD mice model which indicate a 695 amino acid residue spliced from human APP modified by the Swedish FAD double mutation K670N-M671L [72] and curcumin are highly effective to induce inflammation and

oxidative damage in brain and a low dose around 160 ppm (0.43 μmol/g) of curcumin administered orally for 6 month decreased the level of insoluble and soluble Aβ and plaque burden in many affected brain regions but high dose of 5000 ppm (13.6 μmol/g) were unable to change Aβ level [73]. Furthermore curcumin also plays a key role to suppress phosphorylated C-JUN N-Terminal Kinase (JNK) and insulin receptor substrate-1 (IRS-1) and in the AD animal model. Though there are also several data on this issue. Based on those data we can conclude that curcumin can play a potential therapeutic agent for the treatment of AD pathogenesis.

Human Trials using Bioactive Curcumin to Treat AD

To check the effect of curcumin in human as pre-clinical trials with pharmacokinetics as well as safety measurement are already reported. In Taiwan, curcumin was orally administered in patients with neurodegenerative diseases at dosage ranging from 500-8000 mg/g (1.36-2.17 mmol/day) for 3 months among 25 patients and no toxicity was observed at any dose [74]. Another preclinical study was performed in USA where 24 healthy volunteer were administered a single dose of curcumin ranging from 500 to 12000 mg (1.36-32.6 mmol) and only 7 of 24 (30%) experienced minimal toxicity (diarrhoea, headache, rash and yellow stool), which was not dose-related [75]. From this study they conclude that the curcumin can be introduced safely to patients at a single dose of 12,000 mg (32.6 mmol) and at dosages of up to 8000 mg/day (21.7 mmol/day) for 3 months [75]. In china a clinical trial on 34 AD patients were randomized to 4 (10.9 mmol), 1 (2.7 mmol) (plus 3 g placebo), or 0 g curcumin (plus 4 g placebo) once daily showed no significant differences in changes in Mini-Mental State Examination scores or plasma Aβ40 levels between 0 and 6 months. At the same time cognitive as well as Aβ40 and Aβ42 are being measured in plasma and CSF along with tau and p-tau 181. Though no significant differences in cognitive function were found between placebo and curcumin groups or in plasma or CSF biomarkers and any adverse events were reported either [76]. Thus these experiments are not enough to justify the curcumin activity in AD pathogenesis. So we need to perform some additional experiment from a large sample data with longer time interval to conclude anything on this matter.

Conclusion

According to several report Curcumin has shown different biological properties including antioxidant, anti-inflammatory and anti-tumor activity as well as anti-Aβ aggregation and inhibition of β-secretase, AChE and Aβ-induced inflammation *in vitro*. Long term oral administration of curcumin might be promising in reducing Aβ deposition, oligomerization and tau phosphorilazation in the AD brain. These findings conclude that curcumin and its derivative might prove to be the key agent to combat AD pathogenesis. In clinical trials, Curcumin has been used either alone or in combination with other agents. Various formulations of curcumin, including emulsions, encapsulation in liposomes, nanoparticles, microparticles, tablets and capsules have been examined. As reported in literature, curcumin shows therapeutic potential against a number of human diseases. In every case it has been proved to be safe, nontoxic even at a high dose of 12 g/day. The underlying mechanism for curcumin's clinical efficacy though not clear but could be due to modulation of numerous signalling molecules of one or more of its bioactive components. From the findings of the completed clinical trials, it may be concluded that curcumin's clinical efficacy leaves no doubt. However, this polyphenol has not yet been approved for human use due to limited bioavailability and fast clearance rate. Further clinical trials may reveal more of curcumin's mechanism of action and can contribute as novel therapeutics.

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