WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 10, Issue 6, 347-373. Review Article ISSN 2277– 7105

CURCUMIN AS A NATURAL APPROACH FOR TREATMENT OF ALZHEIMER'S DISEASE

Saurabh Sharma[a]*, Prasanta Kumar Biswal[a], Varsha Pandey[b], Ashutosh Kashyap[b]

[a]Gayatri College of Pharmacy, Odisha, India.

[b]School of Pharmaceutical Sciences, RGPV, Bhopal, India.

Article Received on
26 March 2021,

Revised on 15 April 2021,
Accepted on 06 May 2021

DOI: 10.20959/wjpr20216-20482

***Corresponding Author**
Saurabh Sharma
Gayatri College of Pharmacy,
Odisha, India.

ABSTRACT

Alzheimer's disease a major neurodegenerative disorder that is affecting more that 30 million individuals worldwide. The major pathway associated with this disease are tau phosphorylation, neuroinflammation and oxidative stress. For over a decade many research are been carried out for the early diagnosis and treatment of this neurodegenerative disorder. Curcumin the phytochemical agent present in spice turmeric, have been found to be novel and natural approach in diagnosis and treatment of Alzheimer's disease. This review is focused on the activities of curcumin that can prove potential approach in diagnosis and treatment of Alzheimer. Various challenges related to use of curcumin as therapeutic drug and approaches to overcome these challenges. Findings suggest that newer drug therapy associated with curcumin could become a promising therapy for Alzheimer's disease.

KEYWORDS: Alzheimer Disease, Neurodegenerative, amyloid plaques, intracellular neurofibrillarytangles, amyloidogenic pathway, lipid peroxidation.

INTRODUCTION

1. Alzheimer's Disease

Alzheimer Disease (AD) is an age related progressive and irreversible neurodegenerative disorderthat is marked by non-cognitive and cognitive memory impairment **(Palareti *et al.*, 2016) (Giuffrida *et al.*, 2009).** Age is one of the major risk factor associated with Alzheimer's disease. According to a study conducted on patients diagnosed with Alzheimer's purports that with diagnosis of every 1275 new cases of Alzheimer per year per 100,000 patients older than age of 65 years, the progression of disease doubles every 5 years after 65

years of age **(Hirtz *et al.*, 2007)**.Report on centenarians appears to support that Alzheimer's disease is not essentially the result of aging, but the chances of positive diagnosis of Alzheimer's reaches one in three after the age of patients exceeds 85 **(den Dunnen *et al.*, 2008).**

By the end of three or four decades, the new cases of Alzheimer's are expected to be developed inevery 33 seconds all-round the globe. As a matter of fact Alzheimer's disease is constraining a tremendous impact on the society and expenses to deal with it suggest that modern epidemic is in near future. The increasing numbers of patients suffering from Alzheimer's disease according to the study clearly indicates the increasing numbers of elderly population in low and middle incomecountries. Subsequently, it is anticipated that the number of individuals with dementia will rise from 2001 to 2040 by 80–190% in Europe, North America and the created Western Pacific locale, whereas in Latin America, India, China, North Africa andthe Center Eastern Bow a soak increment of more than 300% is forecasted **(Hampel *et al.*, 2011).**

The neurodegenerative insignia of Alzheimer is associated with presence of senile plaques (SPs),neurofibrillary tangles, persistent neuronal loss, deposits of β (Aβ) amyloid plaques and intracellular neurofibrillary tangles (NFTs) in the limbic region and neocortical regions **(Querfurth and Laferla, 2018).** Formation of senile plaques and amyloid fibrils that are hallmarkof this neurodegenerative disorder causes damage to the neuronal structure and its synaptic connections (Cheng *et al.,* 2013)**.** Senile plagues and hyper-phosphorylation of tau proteins occurs as a results of aggregation of insoluble alpha-beta amyloid proteins as multiple sites of neurofibrillary tangles **(Oddo *et al.*, 2003).**

The two hallmarks of Alzheimer's disease specifically amyloid plaques and neurofibrillary tangles(NFTs) have been extensively studied broadly in order to understand the basic cause and the potential treatment of this disease condition. Still diagnosis of Alzheimer's disease is possible bypost mortem or else clinical diagnosis is only possible long after the onset of the disease pathology.This obstruct the easy detection of disease, a key to prevention and also to potential successful therapeutic intervention of Alzheimer's disease **(Hampel *et al.*, 2011**).

Senile plaques (SPs) are mainly formed due to the aggregates of fibrillar Aβ, amyloid-β peptide (Aβ) and tau proteins act as hallmark proteins in Alzheimer's disease condition. Enzymatic proteolysis of mammalian transmembrane protein which is amyloid precursor

protein (APP) leads to formation of this amyloid- β peptide. Nonamyloidogenic and amyloidogenic pathway leads to the proteolysis of APP **(Nunan and Small, 2000).** In amyloidogenic pathway cleavage of amyloidprecursor protein occurs due to β-secretase at the N-terminal of the amyloid-β protein leading to formation of sAPPβ, similarly γ-secretase enzyme causes cleavage of C99 fragment at the C- terminal of Aβ, which allow breakdown of APP intracellular domain (AICD) and secretion of Aβ species of variable length into lumen **(Seubert *et al.*, 1993)**. Subsequently in non-amyloidogenic pathway, cleavage of APP occur by the enzyme α-secretase leading to formation of soluble APPα (sAPPα) along with it formation of short membrane bound C-terminal fragments (CTF), α-CTF or C83 occurs **(Panegyres, 2001)**. C83 protein fragment formed are again cleaved by γ-secretase leading to secretion of p3 peptides along with AICD into cytoplasm **(Black *et al.*, 1997)**.

In contrast to this low molecular weight aggregates consisting of 2-30 Aβ peptides, diffusible harmful oligomeric Aβ peptides occurred as an aggregates from the excessive accumulation of monomers. Indiffusible fibrils and plaques are formed when this oligomers reaches to a critical concentration. These Aβ oligomers formed are soluble in body fluids and are much more harmful as compared to the insoluble aggregates formed **(Verma *et al.*, 2015)**. Extensive neuroinflammation and oxidative damages are also found at the site having neurodegenration in case of Alzheimer's disease and other neurodenegerative disorders which may be the causative factor other than Aβ dimers and NFTs. All these pathological factors collectively leads to progression in neuronal damage and mental impairment. As a result a catastrophic cycle begins between Aβ, NFTs, oxidative stress and inflammation and at last it give rise to activated microglia, increased production of reactive oxygen and inflammatory factors **(Broussard *et al.*, 2012)**. Production of many other factors like nitric oxide (NO), ROS, proinflammatory cytokines, chemokines and prostaglandins are increased along with activation of microglia due to accumulation of these Aβ aggregates **(Glass *et al.*, 2010)**.

1.1 Role of The amyloid-β cascade and neuroinflammation in AD

Proteolysis of the mammalian transmembrane amyloid precursor protein (APP) causes production of amyloid-β protein aggregates. These APP undergo proteolysis through two methods either amyloidogenic or non amyloidogenic pathway **(Nunan and Small, 2000).** For reduction of the amyloid-β aggregates formed which act as the hallmark in case of AD, the APP secretase has beenchoosen as the most successful target which can stimulate α-secretase

cleavage. So that the APP is processed through the nonamyloidogenic pathways thus reducing the β- or δ-secretase cleavage and finally leading to reduction in amount of Aβ produced. Therefore in recent researches on AD many such γ- and β-secretase inhibitors or modulators have been designed so as to reduce formation of Aβ aggregates **(De Strooper et al., 2010)**. Aβ proteins and oxidative stress are found to play an important role in progression and development of AD much before Aβ pathology and neurofibrillary tangles but various research indicated that during myocardial infarction the lipid peroxidation that occurs in brain found to cause oxidative damage that could have comparatively major role in pathogenesis of AD. Levels of lipid peroxidation are found to be very high during AD in hippocampus and frontal cortex of brain that are dependent apo-lipoprotein E (ApoE) genotype and levels of protein in brain region **(Ramassamy *et al.*, 1999) (Ramassamy *et al.*, 2000).**

Levels of F-2 Isoprostanes, a prostaglandin like compounds are found to be very high during diagnosis in plasma, urine and cerebrospinal fluid in case of patients suffering from Alzheimer disease which are derived from the free radical catalyzed peroxidation of arachidonic acid **(Pratic ☐ *et al.*, 2000)**. Oxidative stress which is another important factor found with elevated levels along with a byproduct of lipid peroxidation, acrolein, in hippocampus and temporal cortex.

1.2 Oxidative stress another major factor in Alzheimer's disease

Oxidative stress is found to be one of the major factor that play an important role in the pathogenesis of major brain disorders like ischemia and neurodegenerative disorders. Brain is much more prone toward such oxidative damage in case of increase consumption of oxygen, increased levels of polyunsaturated fatty acids, reduced levels of antioxidants in body and high levels of redox transition metallic ions **(Moreira *et al.*, 2009)**.

Oxidative stress mainly occurs due to DNA oxidation, lipid peroxidation, and protein oxidation and 3-nitrotyrosine formation as observed in several cases of Alzheimer's disease. Recent researchers have found that the methionine residue 35 are highly critical to oxidative stress and neurotoxic activities. Formation of 4-hydroxy-2-nonenal (HNE) or Isoprostanes have found to occur due to Amyloid-β protein aggregates (1-42) to neuronal cultures which are the products of lipid peroxidation **(Mark *et al.*, 1997) (Mark et al., 1999).** Increased levels of compounds like thiobarbituric acid reactive substances, Isoprostanes and neuroprostanes demonstrate the increase in lipid peroxidation in Alzheimer's disease. In such cases vitamin E found to act as preferable antioxidant that can inhibit the lipid peroxidation

induced by these Amyloid-β protein aggregates**(Butterfield *et al.*, 2001**).

Other than lipid peroxidation increased levels of reactive oxygen species (ROS) known to be key factor in neurodegeneration in Alzheimer's disease. Amyloid-β protein aggregates which known to be the main causative agent in pathogenesis of Alzheimer's disease have found to induce free radical oxidative stress like ROS and reactive nitrogen species (RNS) causing neurodegeneration as observed in Alzheimer's. Proinflammatory genes like induced nitric oxide synthase (iNOS), interleukin-1β (IL-1β), tumor necrosis factor- α (TNF-α), nuclear factor-κB (NF-κB) activation occur by reactive oxygen species and reactive nitrogen species where they act as the signaling molecule for activation and causes chronic inflammation. And in turn this chronic inflammation again increases more production of ROS and RNS and increase the neurodegenerative damage **(Sarkar and Fisher, 2006)**.

2. CURCUMIN

2.1 Background

Curcumin is yellow coloured extract obtained from turmeric that is insoluble in ethanol, water and acetone. It has a melting point of 183°C and molecular formula $C_{21}H_{20}O_6$ **(Aggarwal and Harikumar, 2009)**. It is the primary phytoconstituents found in turmeric along with other curcuminoids like demethoxycurcumin (curcumin II), all these phytoconstituents are recently identified as cyclocurcumin. Commercial curcumin contains 77% curcumin I, 17% in demethoxycurcumin form, 3% as bis demethoxycurcumin **(Darvesh *et al.*, 2012).** Turmeric (curcuma longa) belongs to the genus Zingiberaceae. Curcuma longa is a tropical herbaceous, short stemmed, rhizomatous, perennial plant naturally grown throughout the Indian subcontinent and all over tropical Asia. These rhizomes are dried and powdered to extract an orange-yellow powder that are extensively used as spice and for flavouring in foods and recipes. The synonyms for turmeric are 'haldi' in Hindi, 'chiang huang' in Chinese, 'ukon' in Japanese, 'haridra' or 'gauri' in Sanskrit and 'kurkum' in Arabic.

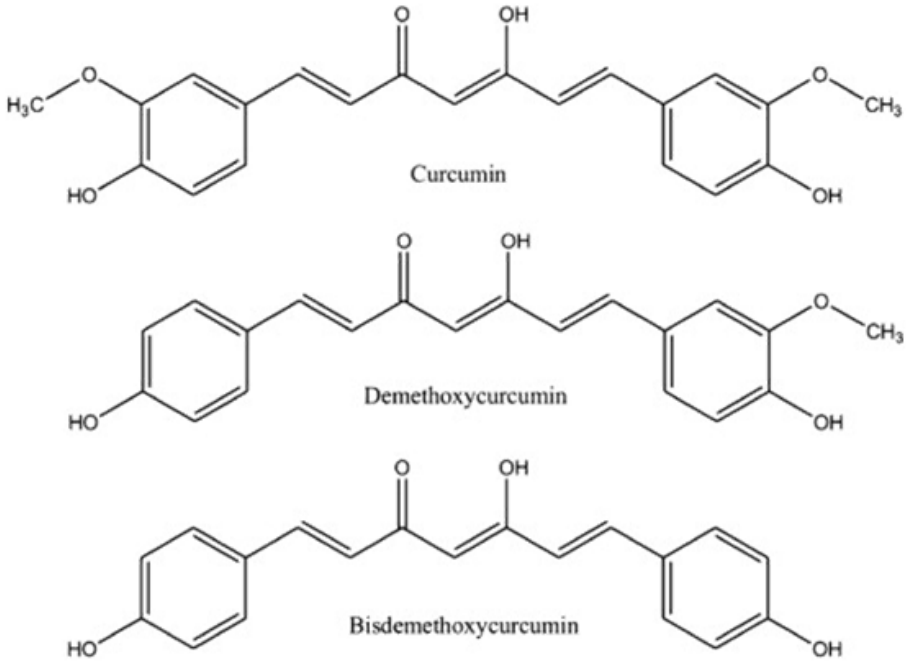

Fig: Structure of curcumin, Demethoxycurcumin and Bisdemethoxycurcumin.

Curcumin a phenolic compound with yellow colored pigment extracted from turmeric, it has an aromatic smell due to the presence of volatile oils which is been extensively used as a natural therapeutic agent because of its various pharmacological activities like antitumor activity, antimicrobial activity, anti-inflammatory activity and antioxidant properties **(Liu *et al.*, 2012)**. Despite of its pharmacological activities usage of curcumin is limited in treatment of various disease condition owing to its less absorption, rapid metabolism in body and limited permeabilityacross the blood brain barrier. Although curcumin has least solubility and poor absorption but various researches have indicated that curcumin is safe and well tolerated even at a high concentration upto 8g/day. Recent researches have been focused on improving the oral bioavailability of curcumin by the used of phospholipid complex formation, loading of curcumin on to novel drug delivery system such as quantum dots, nanoparticles **(Li *et al.*, 2012).**

In recent researches curcumin have been found to be effective in preventive and treating various neurological disorders including Alzheimer's disease. In various animal study model for evaluating the therapeutic action of curcumin, it found to act as a powerful antioxidant. In presence of curcumin the concentration of circulating free radical end product found to decrease because of the potent scavenging activity of curcuminoids on superoxide and hydroxyl radicals **(Soni and Kuttan, 1992)**. Along with this curcumin inhibit the generation

of reactive oxygen species thus protecting brain, liver, lungs, kidney and heart from oxidative agents **(Joe et al., 1995)**.

2.2 Curcumin as a Diagnostic agent in Alzheimer's disease

Currently early diagnosis of Alzheimer's disease based on clinical examination is not possible at an asymptomatic stage. First diagnosis of Alzheimer's disease was established in 1984 based on progressive deterioration of language, memory and progressive cerebral damage detectable by brain imaging **(Association, 2015)**. Gradual diagnostic criteria has been changed as the criteria included in early diagnostic methods were too general, later diagnostic criteria includes gradual onset and fast progression of cognitive function impairment, which is not seen in case of other disease condition **(Dubois *et al.*, 2007).** At this stage of diagnosis patients usually reaches to a mild and moderate stage, where treatment with help of current therapeutic agents are not easy. To overcome this delayed diagnostic methods more sensitive diagnostic probes are desired that couldbe able to diagnose at an early stage **(Bateman *et al.*, 2012)**.

In addition to therapeutic activities of curcumin, its fluorescent ability and property to bind to amyloid β aggregate made it a potential imaging agent for the diagnosis of Alzheimer's disease. Due to its properties to bind with amyloid β aggregate many research has been performed to makeuse of curcumin as probe for targeting amyloid β aggregate with various imaging techniques like positron emission tomography (PET), magnetic resonance imaging and near infrared fluorescence(NIRF) **(Tu et al., 2015).** Interest of researcher from the field of physics, chemistry, biology and pharmacy has considerably increased toward application of curcumin as a diagnostic agent. Curcumin consist of two phenolic group connected by linear β-diketone linker, that induces keto- enol tautomerism which enables curcumin to exhibit many photophysical and photochemical properties **(Priyadarsini, 2009)**.

2.2.1 Positron Emission Tomography

Positron Emission Tomography (PET) with tracers specific to amyloid β aggregate have been widely applicable for diagnostic purpose of Alzheimer's disease. PET related diagnostic approach is emerging as a potential approach in diagnosis of Alzheimer's disease with new researches related to newer PET probes **(Mathis *et al.*, 2012)**. Curcumin labelled with various radioactive nuclide probed to be applicable for diagnostic purpose using PET, like fluoropropyl substituted curcumin found to show improved binding affinity towards amyloid β aggregate (Ryu *et al.*, 2006). Some other curcumin derivatives like lipid-polyethylene glycol

(PEG) - curcumin derivative found to increase BBB penetration and fluorescence intensity. These nano-liposome loaded with curcumin derivative could help in more efficiently labelling of amyloid β aggregate. Mab loaded with curcumin on nano-liposome were more efficient in labelling and fluorescence found to improve by six times **(Mourtas *et al.*, 2014)**.

2.2.2 MRI

Recent research have found to use of curcumin derivatives as MRI probes for imaging of amyloid β aggregate. Perfluoro curcumin analog found to be a potential approach in MRI imaging that facilitate visualization of amyloid β aggregate in *invivo* studies **(Yanagisawa *et al.*, 2011)**. Super paramagnetic iron oxide in conjugation with curcumin used to formulate magnetic nanoparticles proved to be potential nanoimaging agent for early diagnosis of Alzheimer's disease. Various *Invivo* diagnostic studies found the curcumin conjugated nanoparticles showed less cytotoxicity along with increased blood brain barrier penetration activity in MRI studies on Tg2576 brain. Thus Curcumin-MNPs can prove to be an important approach in early diagnosis of Alzheimer by amyloid-β imaging **(Chen *et al.*, 2001)**.

2.2.3 Near-infrared fluorescence (NIRF)

Near Infrared fluorescence (NIRF) is a newer attractive molecular imaging technique in the field of diagnosis of Alzheimer's disease that could promise early and non-invasive diagnosis. NIRF requires fluorescence imaging agents that can excite at a wavelength of near infrared when accumulated in the tissues under diagnosis. Thus excited imaging agents generate fluorescence that can produce a 2-dimesional image demarking the tissue deposition of NIRF imaging agents. Recent research on such NIRF imaging agents like CRANAD-58, synthesized by introducing a difluroboronate ring into curcumin, which was considered to the first NIRF imaging agent that could possibly detect both soluble as well as insoluble Aβ species. Other than CRANAD-58, some other curcumin derivative like CRANAD-3 could monitor and evaluate the effectiveness fo anti- amyloid intervention which could enable the selection of patient for treatment **(Zhang *et al.*, 2013)(Chongzhao *et al.*, 2009).**

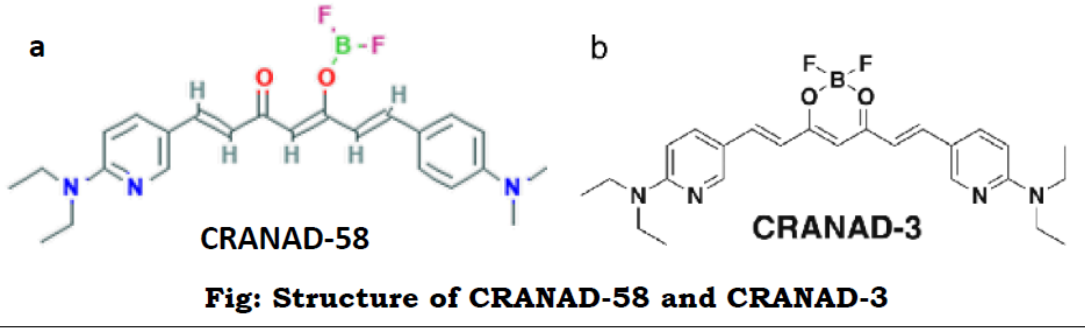

Fig: Structure of CRANAD-58 and CRANAD-3

2.3 Curcumin in treatment of Alzheimer's disease

The best approach in treatment of Alzheimer's disease is the inhibition of amyloid-β aggregates formation and clearance of Aβ aggregates. Strong anti-inflammatory activity of curcumin makes a potential approach in treatment of Alzheimer's other than its diagnostic properties. Moreover curcumin helps in breakdown of amyloid-β aggregates and also prevents further protein aggregation thus slowing down the progression of disease condition **(Baum *et al.*, 2004)**. Inflammation and oxidative damages caused by ROS are the main contributory pathway in progression of AD, which could be slowed down by the help Vitamin E therapy in due course of time. As curcumin possess stronger antioxidant properties and anti-inflammatory property than vitamin E therefore much more effective in slowing down the progression of disease **(Cummings,2015)**. These fact have been cleared in various researches which conclude that in rural India where use of turmeric in quite very common, show only 1% prevalence of Alzheimer's disease **(Chandra*et al.*, 1998)**.

2.3.1 Anti-inflammatory of curcumin in Alzheimer's disease

Various studies have showed that curcumin possess anti-inflammatory property as it causes inhibition of transcription factor NF-κB. Inhibitory property of curcumin on transcription factor make it a potential approach in treatment of Alzheimer's disease as NF-κB play an important role in transduction of signal involved in inflammation. Other than inhibition of transcription factor NF-κB, curcumin shows anti-inflammatory activity due to its free radical scavenging ability as reactive oxygen species or free radicals also play a key role in causation of inflammation **(Singh and Aggarwal, 1995)**.

Some of the pathological factor involved in inflammation like Interleukin-1β (IL-1β), Interleukin-6 (IL-6), Tumor necrosis factor-α are inhibited by curcumin in a dose dependent manner thus reducing inflammation **(Cho *et al.*, 2007).** Furthermore in addition to action of curcumin on these factors, effects of curcumin on prostaglandin E2 and nitric oxide release

have also been seen in report of various researches, curcumin found to reduce the expression of iNOS and cyclooxygenase-2 (COX-2) mRNA **(Jin *et al.*, 2007)**. Similar action is seen in metabolism of arachidonic acid through lipoxygenase pathway. Research on murine macrophages cell and HT- 29 human colon cancer cells reported that curcumin found to inhibit the catalytic activity of 5- LOX and blocks the phosphorylation of cytosolic phospholipase. Its inhibitory action seen on thecatalytic activity of 5-LOX in case of murine macrophages and HT- 29 human colon cancer cells**(Hong *et al.*, 2004).** Curcumin shown to also inhibit proinflammatory pathway by enhancing Peroxisome proliferator-activated receptor (PPARγ) when seen in case of Aβ25−35- treated astrocytes **(Wang *et al.*, 2010)**.

2.3.2 Curcumin on Amyloid β aggregate

Amyloid β aggregate formation is one of the major pathway in progression of AD. Inhibition of Amyloid β aggregate formation could be the best possible approach to reduce the toxic effect of Aβ and thus reducing the progression of Alzheimer's disease **(Necula *et al.*, 2007)**. Recent studies found to show that curcumin act as the strongest inhibitor of Amyloid β aggregate formation out 214 antioxidant tested, curcumin found to bind with the Aβ and thus inhibits its aggregation **(Kim*et al.*, 2005)**. Curcumin found to have a dose dependent effect on inhibition of Aβ seen in case of primary cortical neurons in AD transgenic mice, reduces levels of Tau phosphorylation, and attenuate inflammation and reduce oxidative damage and thus reduce both Aβ fibrils and (amyloidβ-(A4) protein precursor APP maturation **(Zhang *et al.*, 2010)**.

Recent studies suggested that despite of its low bioavailability, curcumin can cross blood brain barrier using substrate binding site of efflux transporter P-glycoprotein **(Romiti *et al.*, 1998)**.

Curcumin after crossing blood brain barrier, binding with Aβ was demonstrated using multiphotonimaging system through *invivo* study. A low dose of 160 ppm and a high dose of 5000 ppm was given through parenteral route shown 30% reduction in Aβ plaque within 1 week of injection. Andshown significant reduction in Aβ plaque along with reduced levels of oxidized protein and proinflammatory cytokine after 6 month of curcumin administration **(Garcia-Alloza *et al.*, 2007)**.

2.4 Challenges associated with curcumin as a treatment for Alzheimer

Despite of its fluorescent properties for diagnosis of Alzheimer by Aβ aggregates and Aβ

binding ability, curcumin are associated with various challenges that prevent the use of curcumin in treatment of Alzheimer's disease. Limitation in use of curcumin in treatment is associated with the pharmacokinetic properties of curcumin. Curcumin have a low bioavailability, very short half-life and nearly insoluble in various solvents including water. Rapid metabolism of curcumin occurs after oral administration by conjugation, sulfation and glucoronidation making it a challenge in administration of curcumin for treatment through oral route. Potential use of curcumin in treatment is also limited because of its classification as PAINS (pan-assay interference compounds). PAINS are compounds that usually show false activity in multiple assay or those show false positive results in high throughput screens. Activity of curcumin with multiple assay occurs not by interaction with specific target, but by interfering with the assay readout. PAINS type characteristic shown by curcumin like redox activity, metal chelation properties, auto fluorescence and covalent protein labeling activity **(Parsamanesh *et al.*, 2018)**.

Other than above mentioned limitation, some other limitations associated with the use of curcuminis the clinical trial for the formulation to know the efficacy of curcumin containing formulation. Alzheimer's disease is multi stage progressive neurodegenerative disorder that involves various pathological markers. And proper diagnosis of Alzheimer can only be done post-mortem which makes it much more difficult for evaluating the efficacy of any formulation in clinical trials. Patients involved in clinical trials are often selected based on the score in Mini-Mental State Examination that explains the severity of dementia, thus allowing the classification of dementia into non cognitive impairment, mild cognitive impairment and severe cognitive impairment. Thus to overcome these challenges associated with pharmacokinetic properties of curcumin and improve therapeutic efficacy of curcumin, new strategies have been applied like alternate drug delivery, variation in the route of administration, nanotechnology based drug delivery such as nanoparticles,liposomes, quantum dots **(Serafini *et al.*, 2017)**.

2.5 Approaches to overcome challenges associated with curcumin.

Combination of curcumin with some other co-adjuvants is a potential approach in administration of curcumin. In some of the *invivo* studies it was demonstrated that piperine shown to significantly improve the spatial memory due to its cytoprotective action and inhibition of Acetylcholine esterase in hippocampus **(Srinivasan, 2007**). Thus piperine combined with other nutraceuticals like curcumin, vitamin C, B vitamin, epigallocatechin

gallate, α-lipoic acid found to showimproved cortical and hippocampal- dependent learning in case of transgenic mouse when treated for over 6 months. Their performances were distinguishable from the non-transgenic mouse **(Chonpathompikunlert *et al*,. 2010) (Ruggles *et al*,. 2014).**

Prodrug can be another approach in improvement of bioavailability of curcumin during administration as a treatment for Alzheimer's disease. Prodrug are pharmacologically inactive derivative of active constituent of drug that can be bio-transformed either through chemical reaction or enzymatic reaction thus producing active drug that gives therapeutic action. This prodrugs can improve pharmacokinetic properties as well as bioavailability of drug. For improvement of bioavailability of curcumin, attachment of phenolic hydroxyl groups of curcumin to various promoieties through biodegradable linkage can be a common approach (Ratnatilaka NaBhuket *et al.*, 2017).

Some of the curcumin prodrug were formulated as mono and diesters of amino acids that found to show significant antibacterial effect, along with slow metabolism, enhanced water solubility and improved cellular uptake **(Dubey *et al.*, 2008)**. A lipidic prodrug of curcumin was formulated as di-O-decanoyl curcumin which showed a release upto 24 hrs during *invivo* studies on male Wistar rat with a dose of 1 mg/kg, elimination half-life found to be extended to approximately 7 hrs and AUC found to be increased fourfold higher as compared to active curcumin when administered through IV route **(Han *et al.*, 2011).** An ethyl succinate ester of curcumin, Curcumin diethyl disuccinate formulated and evaluated for biological activities found to shown higher cytotoxic effect in Caco-2 cells as compared to curcumin. On IV administration of this compound to male Wistar rat, plasma concentration of curcumin found to achieve highest level of 676 lg/L after 5 min of administration. The plasma level of curcumin was much higher in case of prodrug as compared to direct curcumin administration along with increase in volume of distribution and mean resident time **(Bangphumi *et al.*, 2016)**.

Another possible approach in improvement of bioavailability can be utilization of molecule that can block the metabolism of curcumin. Administration of 20mg/kg piperine (a UDP-glucuronosyltransferase) along with 2g/kg of curcumin demonstrated improved bioavailability by 154% and 2g curcumin administered along with piperine in healthy human found to improve bioavailability by 2000% and two fold increase in AUC of curcumin when co-administered with piperine as compared to curcumin administered alone **(Shoba *et al.*, 1998)**

(Cai *et al.*, 2013). Oral bioavailability of curcumin found to increase by formulation of self-emulsifying drug delivery system (SMEDDS) containing UGT inhibitors like piperine, quercetin, tangeretin and silibinin. SMEDDS containing curcumin loaded with silibinin found to significantly increase curcumin plasma level and improve bioavailability by 3.5 fold as compared to curcumin administered alongloaded on SMEDDS during *invivo* study on mouse.

Sl. No.	Delivery system	Targeted Therapy	Test component	Outcome	Reference
1.	Oral curcumin	Study based on curcumin activity toblock β-amyloid aggregation and fibril formation *invitro* and *invivo* observed under electron microscope	Study on groups ofAPPsw Tg2576 transgenic mice.	Suppression in aged animalsof amyloid beta oligomers and fibril formation as well as with combined antioxidant, anti- inflammatory and antiamyloid in two animalbody.	(Yang *et al.*, 2005)
2.	Polymeric nanoparticle encapsulated curcumin	Study on prevention of neuronal cells from oxidative stress caused by H2O2 in both cell culture and *invivo.*	Cell line study on SK-N-SH cells and *invivo*study on 5–6 weeks old athymic CD1 athymicmice.	The Nanocur ameliorates theROS mediated damage in both human cell culture and animal model which can implicate neurodegenerativedisorders including Alzheimer's disease.	(Ray *et al.*, 2011)
3.	Curcumin loaded PLGA-PEG-PLGA triblock copolymeric micelles	Study on penetrationof drug in brain	*Invitro* and *invivo* on Kunming mice with body weights rangingfrom 18 to 22 g.	This formulation increasedthe permeation of drug in lungs and Brain than any other organ hence can be used for delivering drug inbrain for treatment of several neurodegenerativedisorder.	(Song *et al.*, 2011)
4.	PEG-PLA Nanoparticle	Prevention of Amyloid β aggregation thus improvement in radial arm maze (RAM) and contextual fear conditioning (CFC)tests.	Radial arm maze (RAM) and contextualfear conditioning (CFC) tests performedfor Nanocurcumin (NC), unformulated curcumin, or placebo was gavaged once a week for 3 months to 9-month-old Tg2576 mice.	Oral administration of curcumin nanoparticles to Tg2576 AD model mice shown significant improvements even at a lowdose (23 mg/kg per week) over placebo control in working and cue memory. Improvedbioavailability, greater plasma concentration and six fold higher AUC andMRT in brain.	(Cheng *et al.*,2013)
5.	Curcumin Loaded-PLGA Nanoparticles Conjugated with	To study the antiamyloid andanti-oxidative properties of the	*Invitro* uptake study and cytotoxic study on GI-1 glioma cells.	Tagging the PLGA curcumin nanoparticle with Tet-1 neuropeptide greatly	(Mathew *et al.*,2012)

	Tet-1 Peptide	nanoparticles and toanalyse the *invitro* uptake of the nanoparticles.		increases its in vitro neuronaltargeting efficiency.	
6.	Oral curcumin	Study on tolerability and preliminary clinicaland biomarker efficacy data on curcumin in persons with AD.	Thirty-six subjects with mild-to- moderateprobable AD were enrolled at the Mary S. Easton Center for Alzheimer's Disease Research at UCLA.	Curcumin behave as antioxidant, anti-inflammatory, antiamyloid ithas many other properties studied invitro and invivo models of mice but its efficacy is less due to its low bioavailability.	(J.M. *et al.*, 2012)
7.	curcumin intranasal thermosensitive hydrogel	To improve brain targeting efficiencyfor curcumin and thus improve bioavailability.	Invitro ,invivo, Controlled, Male Sprague-Dawley rats weighing about 250 g	Thermo-sensitive nasal curcumin in-situ gel showed favourable gelation time, sustained release, enhanced brain uptake of compared to i.v.administration.	(Chen *et al.*, 2013)
8.	Curcumin Micelle containing tween 80 and curcumin powder	ameliorate mitochondrial dysfunction	Invitro and *invivo* study on 7 female NMRI mouse of 8 to 24 months of 170 gm.	Curcumin micelles as goodprotective agent for preventing mitochondrial dysfunction.	(Hagl *et al.*, 2015)
9.	Aerosolize a curcumin derivative, FMeC1	Study on binding of FMeC1 to amyloid plaques expressed inthe hippocampal areas and cortex confirmed by immunohistochemist ry data	Study on The C57BL/6 and 5XFAD mice (8ndash;12months)	Aerosols are more prominent than i.v for bioavailability of curcuminfor therapy of Alzheimer disease.	(McClure *et al.*,2015)
10.	Intraperitoneal injection of curcumin	Regulation of AMP Kinase was studies by curcuminto evaluate the prevention of neuraltissue against Endoplasmic Reticulum stress.	*Invivo* study on Male ICR mice (6–8 weeksof age) and Sprague– Dawley rats (200–250g)	Curcumin shown to inhibitTXNIP/ NLRP3 inflammasome activation by suppression ofER stress, and thereby protected neuronal cell survival from glutamate neurotoxicity. Inflammasome and neurotoxicity is also apathway in AD.	(Li *et al.*, 2015)

11.	Nanostructured lipid carrier (NLC) modified with lactoferrin (Lf) and	Enhance uptake of curcumin across theblood brain barrier.	Invivo study on Sprague-Dawley (SD)rats (180-220 g) and ICR mice (18-22 g).	The brain coronal sections displayed a higher accumulation of Lf–mNLC in the cortex and the third	(Meng *et al.*, 2015)
	loaded withcurcumin			ventricle than that of NLC.The pharmacodynamic studies revealed that Lf- mNLC could efficiently control the progression ofthe AD.	
12.	Solid lipid curcumin particle	Study on effect of novel curcumin formulation on nitricoxide (NO) and prostaglandin E2 (PGE2)	Cell line study and MTTassay on SK-N-SH cells	SLCP-1(commercially available as Longvida®) wasslightly more effective in inhibiting the anti- inflammatory response than SLCP-2.	(Nahar *et al.*,2015)
13	di-O-demethylcurcumin	Study based on underlying mechanisms and effects of di-*O*- demethylcurcuminin preventing Aβ-inducedapoptosis	Invitro, Controlled, The SK-N-SH cells were cultured in MEMsupplemented with 10% heat inactivated FBS, 100 units/ml penicillin, and 100 μg/ml streptomycin inhumidified 95% air, at37 °C and 5% CO2 inan incubator.	Study showed that di-*O*-demethylcurcumin protected against neuronal death through its suppression of the apoptosis mediated by mitochondrial death and ERstress pathway.	(Pinkaew *et al.*,2015)
14.	Curcumin	Study made on effectof curcumin on Aβ42-induced microglia activation and MAPK pathways.	Study on 1–3 day oldneonatal Balb/C mouse,	Curcumin could effectively inhibit A-stimulated microglia activation via ERK1/2 and p38 pathways. Curcumin may be used as aneffective agent in further therapeutic applications for AD	(Shi *et al.*, 2015)
15.	FMeC1, and FMeC2 (curcumin derivatives)	Study about curcumin derivativeon various AD pathology	Study on APPswe/PS1dE9 double transgenic (APP/PS1) mice with aC57BL/6 background were obtained	Both curcumin and FMeC1 modulated the formation of Ab aggregates,but increase in the keto formof FMeC1 resulted in relatively weak binding	(Yanagisawa *etal.*, 2015)

				activity to Aβ aggregates. Whereas FMeC2 bearing the methoxycarboxy group substitution at the C-4 position showed no effect on Aβ aggregates	
16.	Curcumin	Study on effect of curcumin on	Study on hippocampal neurons were	Study showed that curcumin appears	(Stankowska *et al.*, 2017)
		hippocampal neuronsfrom ET-1 mediated cell death and examine the involvement of c-Junin this pathway.	harvested from albino Sprague–Dawley rats.	to have neuroprotective effects by protecting primary hippocampal neurons from ET-1 mediated cell death possiblythrough blocking an increase in c-Jun levels, decreasing activation of caspase 3 and caspase 7 andpreventing from ET-1 mediated cleavage of procaspase-3 and fodrin.	
17.	Novel efficient curcumin analogues, steroidmolecule with curcumin moiety.	Effect of novel curcumin derivativeon levels of Ach, Glutathione, paraoxenase and BCL2 in brain	*Invivo* study on Femalealbino rats (70 rats), weighing 200–220 g, and aged 16– 18weeks.	All the tested compounds have been shown to possessanti-Alzheimer's disease properties in AD model by enhancing Ach synthesis, GSH level, paraoxenase level and BCL2 lymphoma level with respect tountreated group.	(Elmegeed *etal.*, 2015)
18.	Intraperitoneal Injection of curcumin	Inflammasome	Invitro, Controlled, 6- to8-wk-old C57BL/6 mice	Curcumin found to show anti-inflammatory activityby dose dependent inhibition of NLRP3 inflammasome activation and the subsequent releaseof mature IL-1.	(Gong *et al.*, 2015)
19.	Intra-cerebroventricular Injection	HippocampalNeurogenesis	Invivo study on 3-4 months old male Wistarrats weighing 300-340 g	There was a positive effectof hippocampal neurogenesis. Curcumin showed poor absorption hence poor	(Bassani *et al.*,2017)

				bioavailability.	
20.	Solid lipid curcumin particles	To study and investigate the role of curcumin on heat shock proteins (HSPs) and Autophagy lysosomal pathways(ALPs), *In vitro*, after exposure to Aβ.	Cell line study on Human cortical neurons(SH-SY5Y) and mouse neuroblastoma (N2a) cells.	Curcumin can improve dysregulation of molecular chaperones and autophagy lysosomal pathways as a means of protecting neuronsfrom Aβ42-induced cell death and thus improving Alzheimer condition.	(Maiti *et al.*, 2017)
21.	Oral curcumin	Study made on effects of curcumin	Cell line study on Wild type mouse Neuro-2a	Curcumin plays a protective role in AD through	(Sun *et al.*, 2017)
		on the expression ofhyper-phosphorylation of Tau, Caveolin-1and GSK-3β	(N2a/WT) cells and N2a/APP695swe cellsand *invivo* study on APP/PS1 double transgenic mice.	attenuating the hyper- phosphorylation of Tau viainactivating the Caveolin-1/GSK-3β pathway, which might provide a novel idea for ADtreated with curcumin	
22.	Biocurcumax^{TM} Capsules	Randomised, placebo-controlled,double-blind study	Study performed on 160 participants between age group of 60-85 years.	studies have demonstrated positive effects of curcuminon Aβ, tau, inflammation and oxidative stress	(Rainey-Smith *et al.*, 2016)
23.	Curcumin-loaded self- nanomicellizing solid dispersion	Oral bioavailability enhancement of curcumin to preventAmyloid-β aggregation	*Invitro* study, MTT assay and cellular uptake study conductedon SH-5Y695 human neuroblastoma cells.	Formulation showed better efficacy against the cytotoxicity induced by copper metal ion, H_2O_2, andAβ42 oligomer in cell line. Oral administration of formulation for 3 months reversed the behavioural deficit in APPSwe/PS1deE9 mice which were confirmed fromthe open field, NORT, Y-maze, and MWM tests.	(Parikh *et al.*,2018)

*WGA- wheat germ agglutinin, CL- cardiolipin, FMeC1- 1,7-Bis(40- hydroxy-30-trifluoromethoxy- phenyl)-4 ethoxycarbonylethyl-1,6-heptadiene-3,5-dione, ET-1 - Endothelin-1

3. CONCLUSIONS

Curcumin is a minor constituent yet most studied phytochemical agent used as a traditional medicine present in turmeric. Many research have been conducted for their potential effect as anticancer, treatment for neurodegenerative disease like Alzheimer's disease. Despite of such potential activities of curcumin, use of curcumin in various disease condition are limited due to various limitations related to pharmacokinetic properties and bioavailability of curcumin. This review highlights the potential properties of curcumin over treatment of Alzheimer's disease and approaches to overcome various challenges related to it. Curcumin shows affinity towards binding to Aβ, anti-inflammatory property, antioxidant properties on ROS, fluorescent properties for diagnostic purpose related to Alzheimer's. Low solubility, reduced bioavailability has limited thepotential use of curcumin. Some of the novel approach of using co adjuvants and other enzymatic inhibitor have found to improve the bioavailability of curcumin thus improving the plasma concentration and the therapeutic action of curcumin.

4. AUTHOR CONTRIBUTION

All the author mentioned, have been given equal efforts in completion of this review article. Nofunding agencies were involved in completion of the paper.

5. CONFLICT OF INTEREST

None of the authors have any conflict of interest.

6. REFERENCES

1. Aggarwal, B. B. and Harikumar, K. B. 'Potential therapeutic effects of curcumin, theanti-inflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases', *International Journal of Biochemistry and Cell Biology*, 2009; 41(1): 40–59. doi: 10.1016/j.biocel.2008.06.010.
2. Association, A. '2015 Alzheimer's disease facts and figures', *Alzheimer's and Dementia*. Elsevier Ltd, 2015; 11(3): 332–384. doi: 10.1016/j.jalz.2015.02.003.
3. Bangphumi, K. *et al.* 'Pharmacokinetics of Curcumin Diethyl Disuccinate, a Prodrug of Curcumin, in Wistar Rats', *European Journal of Drug Metabolism and Pharmacokinetics*. Springer International Publishing, 2016; 41(6): 777–785. doi: 10.1007/s13318-015-0308-z.
4. Bassani, T. B. *et al.* 'Effects of curcumin on short-term spatial and recognition memory, adult neurogenesis and neuroinflammation in a streptozotocin-induced rat model of dementia of Alzheimer's type', *Behavioural Brain Research*. Elsevier B.V., 2017; 335:

41–54. doi: 10.1016/j.bbr.2017.08.014.

5. Bateman, R. J. *et al.* 'Clinical and Biomarker Changes in Dominantly Inherited Alzheimer's Disease', *New England Journal of Medicine*, 2012; 367(9): 795–804. doi: 10.1056/nejmoa1202753.
6. Baum, L. and Ng, A. 'Curcumin interaction with copper and iron suggests one possible mechanism of action in Alzheimer' s disease animal models', 2004; 6: 367–377.
7. Black, R. A. *et al.* 'A metalloproteinase disintegrin that releases tumour-necrosis factor-Ø from cells', *Nature*, 1997; 729–733. doi: 10.1038/385729a0.
8. Broussard, G. J. *et al.* 'The role of inflammatory processes in Alzheimer's disease', *Inflammopharmacology*, 2012; 20(3): 109–126. doi: 10.1007/s10787-012-0130-z.
9. Butterfield, D. A. *et al.* 'Evidence of oxidative damage in Alzheimer's disease brain: Central role for amyloid β-peptide', *Trends in Molecular Medicine*, 2001; 7(12): 548–554. doi:10.1016/S1471-4914(01)02173-6.
10. Cai, X. *et al.* 'Bioavailability of Quercetin: Problems and Promises', *Current Medicinal Chemistry*, 2013; 20(20): 2572–2582. doi: 10.2174/09298673113209990120.
11. Chandra, V., Ganguli, M. and Pandav, R. (1998) 'Prevalence of Alzheimer ' s disease and other dernentias in rural India The Indo-US study'. doi: 10.1212/WNL.51.4.1000.
12. Chen, A. L. *et al.* 'Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions', *Anticancer Research*, 2001; 21(4 B): 2895– 2900.
13. Chen, X. *et al.* 'Enhanced brain targeting of curcumin by intranasal administration of a thermosensitive poloxamer hydrogel', *Journal of Pharmacy and Pharmacology*, 2013; 65(6): 807–816. doi: 10.1111/jphp.12043.
14. Cheng, K. K. *et al.* 'Highly stabilized curcumin nanoparticles tested in an in vitro blood-brain barrier model and in alzheimer's disease Tg2576 Mice', *AAPS Journal*, 2013; 15(2): 324–336. doi: 10.1208/s12248-012-9444-4.
15. Cho, J. W., Lee, K. S. and Kim, C. W. 'Curcumin attenuates the expression of IL-1β,IL-6, and TNF-α as well as cyclin E in TNF-α-treated HaCaT cells; NF-κB and MAPKs as potential upstream targets', *International Journal of Molecular Medicine*, 2007; 19(3): 469–474.doi: 10.3892/ijmm.19.3.469.
16. Chongzhao, R. *et al.* 'Design, synthesis, and testing of difluoroboron-derivatized curcumins as near-infrared probes for in vivo detection of amyloid-β deposits', *Journal of theAmerican Chemical Society*, 2009; 131(42): 15257–15261. doi: 10.1021/ja9047043.
17. Chonpathompikunlert, P., Wattanathorn, J. and Muchimapura, S. 'Piperine, the main

alkaloid of Thai black pepper, protects against neurodegeneration and cognitive impairment in animal model of cognitive deficit like condition of Alzheimer's disease', *Food and Chemical Toxicology*. Elsevier Ltd, 2010; 48(3): 798–802. doi: 10.1016/j.fct.2009.12.009.

18. Cummings, J. L. 'Alzheimer Disease', 2015; 287(18): 2335–2338.
19. Darvesh, A. S. *et al.* 'Curcumin and neurodegenerative diseases: A perspective', *Expert Opinion on Investigational Drugs*, 2012; 21(8): 1123–1140. doi: 10.1517/13543784.2012.693479.
20. Dubey, S. K. *et al.* 'Design, synthesis and characterization of some bioactive conjugates of curcumin with glycine, glutamic acid, valine and demethylenated piperic acid and study of their antimicrobial and antiproliferative properties', *European Journal of Medicinal Chemistry*, 2008; 43(9): 1837–1846. doi: 10.1016/j.ejmech.2007.11.027.
21. Dubois, B. *et al.* 'Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria', *Lancet Neurology*, 2007; 6(8): 734–746. doi: 10.1016/S1474- 4422(07)70178-3.
22. den Dunnen, W. F. A. *et al.* 'No disease in the brain of a 115-year-old woman', *Neurobiology of Aging*, 2008; 29(8): 1127–1132. doi: 10.1016/j.neurobiolaging.2008.04.010.
23. Elmegeed, G. A. *et al.* 'Synthesis of novel steroidal curcumin derivatives as anti-Alzheimer's disease candidates: Evidences-based on in vivo study', *Steroids*. Elsevier Inc., 2015; 101: 78–89. doi: 10.1016/j.steroids.2015.06.003.
24. Garcia-Alloza, M. *et al.* 'Curcumin labels amyloid pathology in vivo, disrupts existing plaques, and partially restores distorted neurites in an Alzheimer mouse model', *Journal of Neurochemistry*, 2007; 102(4): 1095–1104. doi: 10.1111/j.1471-4159.2007.04613.x.
25. Giuffrida, M. L. *et al.* 'B-Amyloid Monomers Are Neuroprotective', *Journal of Neuroscience*, 2009; 29(34): 10582–10587. doi: 10.1523/JNEUROSCI.1736-09.2009.
26. Glass, C. K. *et al.* 'Mechanisms Underlying Inflammation in Neurodegeneration', *Cell*. Elsevier Inc., 2010; 140(6): 918–934. doi: 10.1016/j.cell.2010.02.016.
27. Gong, Z. *et al.* 'Curcumin suppresses NLRP3 inflammasome activation and protects against LPS-induced septic shock', *Molecular Nutrition and Food Research*, 2015; 59(11): 2132–2142. doi: 10.1002/mnfr.201500316.
28. Hagl, S. *et al.* 'Curcumin micelles improve mitochondrial function in neuronal PC12 cells and brains of NMRI mice - Impact on bioavailability', *Neurochemistry International*. Elsevier Ltd, 2015; 89: 234–242. doi: 10.1016/j.neuint.2015.07.026.

29. Hampel, H. *et al.* 'The future of Alzheimer's disease: The next 10 years', *Progress in Neurobiology*, 2011; 95(4): 718–728. doi: 10.1016/j.pneurobio.2011.11.008.
30. Han, Y. R. *et al.* 'A simple RP-HPLC method for the simultaneous determination of curcumin and its prodrug, curcumin didecanoate, in rat plasma and the application to pharmacokinetic study', *Biomedical Chromatography*, 2011; 25(10): 1144–1149. doi: 10.1002/bmc.1584.
31. Hirtz, D. *et al.* 'How common are the "common" neurologic disorders?', *Neurology*, 2007; 68(5): 326–337. doi: 10.1212/01.wnl.0000252807.38124.a3.
32. Hong, J. *et al.* 'Modulation of arachidonic acid metabolism by curcumin and related β-diketone derivatives: Effects on cytosolic phospholipase A2, cyclooxygenases and 5-lipoxygenase', *Carcinogenesis*, 2004; 25(9): 1671–1679. doi: 10.1093/carcin/bgh165.
34. Ii, I. 'BB Biochi ~ m ~~ a', 1995; 1282: 14–16.
35. J.M., R. *et al.* 'Oral curcumin for Alzheimer's disease: Tolerability and efficacy in a 24-week randomized, double blind, placebo-controlled study', *Alzheimer's Research and Therapy*, 2012; 4(5). pagination. Available at: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed14&NEWS=N&AN =52282479.
36. Jin, C. Y. *et al.* 'Curcumin attenuates the release of pro-inflammatory cytokines in lipopolysaccharide-stimulated BV2 microglia', *Acta Pharmacologica Sinica*, 2007; 28(10): 1645–1651. doi: 10.1111/j.1745-7254.2007.00651.x.
37. Kim, H. *et al.* 'Effects of naturally occurring compounds on fibril formation and oxidative stress of β-amyloid', *Journal of Agricultural and Food Chemistry*, 2005; 53(22): 8537–8541. doi: 10.1021/jf051985c.
38. Li, F. *et al.* 'In vitro antioxidant and anti-inflammatory activities of 1-dehydro-[6]-gingerdione, 6-shogaol, 6-dehydroshogaol and hexahydrocurcumin', *Food Chemistry*. Elsevier Ltd, 2012; 135(2): 332–337. doi: 10.1016/j.foodchem.2012.04.145.
39. Li, Ying *et al.* 'Curcumin attenuates glutamate neurotoxicity in the hippocampus by suppression of ER stress-associated TXNIP/NLRP3 inflammasome activation in a manner dependent on AMPK', *Toxicology and Applied Pharmacology*, 2015; 286(1): 53–63. doi: 10.1016/j.taap.2015.03.010.
40. Liu, J. P. *et al.* 'The in vitro protective effects of curcumin and demethoxycurcumin in Curcuma longa extract on advanced glycation end products-induced mesangial cell apoptosis and oxidative stress', *Planta Medica*, 2012; 78(16): 1757–1760. doi: 10.1055/s-0032-1315257.

41. Maiti, P., Rossignol, J. and Dunbar, G. L. 'Curcumin Modulates Molecular Chaperones and Autophagy-Lysosomal Pathways In Vitro after Exposure to Aβ42', *Journal of Alzheimer's Disease & Parkinsonism*, 2017; 07(01): 1–12. doi: 10.4172/2161-0460.1000299.
42. Mark, R. J. *et al.* 'A role for 4-hydroxynonenal, an aldehydic product of lipid peroxidation, in disruption of ion homeostasis and neuronal death induced by amyloid β-peptide', *Journal of Neurochemistry*, 1997; 68(1): 255–264. doi: 10.1046/j.1471-4159.1997.68010255.x.
43. Mark, R. J., Fuson, K. S. and May, P. C. 'Characterization of 8-epiprostaglandin F(2α)as a marker of amyloid β- peptide-induced oxidative damage', *Journal of Neurochemistry*, 1999; 72(3): 1146–1153. doi: 10.1046/j.1471-4159.1999.0721146.x.
44. Mathew, A. *et al.* 'Curcumin loaded-PLGA nanoparticles conjugated with Tet-1 peptide for potential use in Alzheimer's disease', *PLoS ONE*, 2012; 7(3). doi: 10.1371/journal.pone.0032616.
45. Mathis, C. A. *et al.* 'Development of positron emission tomography β-Amyloid plaque imaging agents', *Seminars in Nuclear Medicine*. Elsevier Inc., 2012; 42(6): 423–432. doi: 10.1053/j.semnuclmed.2012.07.001.
46. McClure, R. *et al.* 'Inhalable curcumin: Offering the potential for translation to imaging and treatment of Alzheimer's disease', *Journal of Alzheimer's Disease*, 2015; 44(1): 283–295. doi: 10.3233/JAD-140798.
47. Meng, F. *et al.* 'A novel LDL-mimic nanocarrier for the targeted delivery of curcumininto the brain to treat Alzheimer's disease', *Colloids and Surfaces B: Biointerfaces*. Elsevier B.V., 2015; 134: 88–97. doi: 10.1016/j.colsurfb.2015.06.025.
48. Moreira, P. I. *et al.* An integrative view of the role of oxidative stress, mitochondria and insulin in Alzheimer's disease', *Journal of Alzheimer's Disease*, 2009; 16(4): 741–761. doi:10.3233/JAD-2009-0972.
49. Mourtas, S. *et al.* 'Multifunctional nanoliposomes with curcumin-lipid derivative and brain targeting functionality with potential applications for Alzheimer disease', *European Journal of Medicinal Chemistry*. Elsevier Ltd, 2014; 80: 175–183. doi: 10.1016/j.ejmech.2014.04.050.
50. Nahar, P. P., Slitt, A. L. and Seeram, N. P. 'Anti-Inflammatory Effects of Novel Standardized Solid Lipid Curcumin Formulations', *Journal of Medicinal Food*, 2015; 18(7): 786–792. doi: 10.1089/jmf.2014.0053.
51. Necula, M. *et al.* 'Small molecule inhibitors of aggregation indicate that amyloid β

oligomerization and fibrillization pathways are independent and distinct', *Journal of Biological Chemistry*, 2007; 282(14): 10311–10324. doi: 10.1074/jbc.M608207200.

52. Nunan, J. and Small, D. H. 'Regulation of APP cleavage by a-, b- and g-secretases', *FEBS Lett*, 2000; 483(1): 6–10.
53. Oddo, S. *et al.* 'Triple-transgenic model of Alzheimer's Disease with plaques and tangles: Intracellular Aβ and synaptic dysfunction', *Neuron*, 2003;; 39(3): 409–421. doi: 10.1016/S0896-6273(03)00434-3.
54. Palareti, G. *et al.* 'Comparison between different D-Dimer cutoff values to assess the individual risk of recurrent venous thromboembolism: Analysis of results obtained in the DULCIS study', *International Journal of Laboratory Hematology*, 2016; 38(1): 42–49. doi: 10.1111/ijlh.12426.
55. Panegyres, P. K. 'The functions of the amyloid precursor protein gene', *Reviews in the Neurosciences*, 2001; 12(1): 1–39. doi: 10.1515/revneuro.2001.12.1.1.
56. Parikh, A. *et al.* 'Curcumin-loaded self-nanomicellizing solid dispersion system: partII: in vivo safety and efficacy assessment against behavior deficit in Alzheimer disease', *Drug Delivery and Translational Research*, 2018; 8(5): 1406–1420. doi: 10.1007/s13346-018-0570- 0.
57. Parsamanesh, N. *et al.* (2018) *Therapeutic potential of curcumin in diabetic complications*, *Pharmacological Research*. Elsevier Ltd. doi: 10.1016/j.phrs.2018.09.012.
58. Pinkaew, D. *et al.* 'Di-O-demethylcurcumin protects SK-N-SH cells against mitochondrial and endoplasmic reticulum-mediated apoptotic cell death induced by Aβ25- 35', *Neurochemistry International*, 2015; 80: 110–119. doi: 10.1016/j.neuint.2014.10.008.
59. Pratic, D. *et al.* 'Increased 8,12-iso-iPF2?-VI in Alzheimer's disease: Correlation of a noninvasive index of lipid peroxidation with disease severity', *Annals of Neurology*, 2000; 48(5): 809–812. doi: 10.1002/1531-8249(200011)48:5<809::aid-ana19>3.0.co;2-9.
60. Priyadarsini, K. I. 'Photophysics, photochemistry and photobiology of curcumin: Studies from organic solutions, bio-mimetics and living cells', *Journal of Photochemistry and Photobiology C: Photochemistry Reviews*, 2009; 10(2): 81–95. doi: 10.1016/j.jphotochemrev.2009.05.001.
61. Querfurth, H. W. and Laferla, F. M. 'Alzheimer's Disease', 2018; 329–344.
62. Rainey-Smith, S. R. *et al.* 'Curcumin and cognition: A randomised, placebo- controlled, double-blind study of community-dwelling older adults', *British Journal of Nutrition*,

2016; 115(12): 2106–2113. doi: 10.1017/S0007114516001203.

63. Ramassamy, C. *et al.* 'Oxidative damage and protection by antioxidants in the frontal cortex of Alzheimer's disease is related to the apolipoprotein E genotype', *Free Radical Biology and Medicine*, 1999; 27(5–6): 544–553. doi: 10.1016/S0891-5849(99)00102-1.
64. Ramassamy, C. *et al.* 'Oxidative insults are associated with apolipoprotein E genotype in Alzheimer's disease brain', *Neurobiology of Disease*, 2000; 7(1): 23–37. doi: 10.1006/nbdi.1999.0273.
65. Ratnatilaka Na Bhuket, P. *et al.* (2017) 'Enhancement of Curcumin Bioavailability Via the Prodrug Approach: Challenges and Prospects', *European Journal of Drug Metabolism and Pharmacokinetics*. Springer International Publishing, 42(3), pp. 341–353. doi: 10.1007/s13318-016-0377-7.
66. Ray, B. *et al.* 'Neuroprotective and neurorescue effects of a novel polymeric nanoparticle formulation of curcumin (NanoCurc^{TM}) in the neuronal cell culture and animal model: Implications for Alzheimer's disease', *Journal of Alzheimer's Disease*, 2011; 23(1): 61–77. doi: 10.3233/JAD-2010-101374.
67. Romiti, N. *et al.* 'Effects of curcumin on P-glycoprotein in primary cultures of rat hepatocytes', *Life Sciences*, 1998; 62(25): 2349–2358. doi: 10.1016/S0024-3205(98)00216-1.
68. Ruggles, D. R., Freyman, R. L. and Oxenham, A. J. 'Influence of musical training on understanding voiced and whispered speech in noise', *PLoS ONE*, 2014; 9(1). doi: 10.1371/journal.pone.0086980.
69. Ryu, E. K. *et al.* 'Curcumin and dehydrozingerone derivatives: Synthesis, radiolabeling, and evaluation for β-amyloid plaque imaging', *Journal of Medicinal Chemistry*, 2006; 49(20): 6111–6119. doi: 10.1021/jm0607193.
70. Sarkar, D. and Fisher, P. B. 'Molecular mechanisms of aging-associated inflammation', *Cancer Letters*, 2006; 236(1): 13–23. doi: 10.1016/j.canlet.2005.04.009.
71. Serafini, M. M. *et al.* 'Curcumin in Alzheimer's disease: Can we think to new strategies and perspectives for this molecule?', *Pharmacological Research*. Elsevier Ltd, 2017; 124: 146–155. doi: 10.1016/j.phrs.2017.08.004.
72. Seubert, P. *et al.* 'Secretion of β-amyloid precursor protein cleaved at the amino terminus of the β-amyloid peptide', *Nature*, 1993; 361(6409): 260–263. doi: 10.1038/361260a0.
73. Shi, X. *et al.* 'Curcumin inhibits Aβ-induced microglial inflammatory responses in vitro: Involvement of ERK1/2 and p38 signaling pathways', *Neuroscience Letters*, 2015; 594: 105–110. doi: 10.1016/j.neulet.2015.03.045.

74. Shoba, G. *et al.* 'Influence of Piperine on the Pharmacokinetics of Curcumin', *Planta Med*, 1998; 353–356. Available at: https://pdfs.semanticscholar.org/2c1d/b67216db08e105d6fb1f7ec30e7275c681f1.pdf.
75. Singh, S. and Aggarwal, B. B. 'Activation of transcription factor NF-κB is suppressedby curcumin (diferulolylmethane)', *Journal of Biological Chemistry*, 1995; 270(42): 24995–25000. doi: 10.1074/jbc.270.42.24995.
76. Song, Z. *et al.* 'Curcumin-loaded PLGA-PEG-PLGA triblock copolymeric micelles: Preparation, pharmacokinetics and distribution in vivo', *Journal of Colloid and Interface Science*. Elsevier Inc., 2011; 354(1): 116–123. doi: 10.1016/j.jcis.2010.10.024.
77. Soni, K. B. and Kuttan, R. 'Effect of oral curcumin administration on serum peroxidesand cholesterol levels in human volunteers', *Indian Journal of Physiology and Pharmacology*, 1992; 36(4): 273–275.
78. Srinivasan, K. 'Black pepper and its pungent principle-piperine: A review of diverse physiological effects', *Critical Reviews in Food Science and Nutrition*, 2007; 47(8): 735–748. doi: 10.1080/10408390601062054.
79. Stankowska, D. L. *et al.* 'Neuroprotective effects of curcumin on endothelin-1mediated cell death in hippocampal neurons', *Nutritional Neuroscience*, 2017; 20(5): 273–283.doi: 10.1080/1028415X.2015.1119377.
80. De Strooper, B., Vassar, R. and Golde, T. 'The secretases: Enzymes with therapeutic potential in Alzheimer disease', *Nature Reviews Neurology*. Nature Publishing Group, 2010; 6(2): 99–107. doi: 10.1038/nrneurol.2009.218.
81. Sun, J. *et al.* 'Curcumin Decreases Hyperphosphorylation of Tau by Down-Regulating Caveolin-1/GSK-3β in N2a/APP695swe Cells and APP/PS1 Double Transgenic Alzheimer's Disease Mice', *American Journal of Chinese Medicine*, 2017; 45(8): 1667–1682. doi: 10.1142/S0192415X17500902.
82. Tu, P., Fu, H. and Cui, M. 'Compounds for imaging amyloid-β deposits in an Alzheimer's brain: A patent review', *Expert Opinion on Therapeutic Patents*, 2015; 25(4): 413–423. doi: 10.1517/13543776.2015.1007953.
83. Verma, M., Vats, A. and Taneja, V. 'Toxic species in amyloid disorders: Oligomers or mature fibrils', *Annals of Indian Academy of Neurology*, 2015; 18(2): 138–145. doi: 10.4103/0972-2327.144284.
84. Wang, H. M. *et al.* 'PPARγ agonist curcumin reduces the amyloid-β-stimulated inflammatory responses in primary astrocytes', *Journal of Alzheimer's Disease*, 2010; 20(4): 1189–1199. doi: 10.3233/JAD-2010-091336.

85. Yanagisawa, D. *et al.* 'In vivo detection of amyloid β deposition using 19F magnetic resonance imaging with a 19F-containing curcumin derivative in a mouse model of Alzheimer's disease', *Neuroscience*. Elsevier Inc., 2011; 184(19): 120–127. doi: 10.1016/j.neuroscience.2011.03.071.
86. Yanagisawa, D. *et al.* 'Curcumin derivative with the substitution at C-4 position, but not curcumin, is effective against amyloid pathology in APP/PS1 mice', *Neurobiology of Aging*. Elsevier Ltd, 2015; 36(1): 201–210. doi: 10.1016/j.neurobiolaging.2014.07.041.
87. Yang, F. *et al.* 'Curcumin inhibits formation of amyloid β oligomers and fibrils, binds plaques, and reduces amyloid in vivo', *Journal of Biological Chemistry*, 2005; 280(7): 5892– 5901. doi: 10.1074/jbc.M404751200.
88. Zhang, C. *et al.* 'Curcumin decreases amyloid-β peptide levels by attenuating the maturation of amyloid-β precursor protein', *Journal of Biological Chemistry*, 2010; 285(37): 28472–28480. doi: 10.1074/jbc.M110.133520.
89. Zhang, X. *et al.* 'Design and synthesis of curcumin analogues for in vivo fluorescence imaging and inhibiting copper-induced cross-linking of amyloid beta species in alzheimer's disease', *Journal of the American Chemical Society*, 2013; 135(44): 16397–16409. doi: 10.1021/ja405239v.