Use of curcumin in diagnosis, prevention, and treatment of Alzheimer's disease

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Abstract

This review summarizes and describes the use of curcumin in diagnosis, prevention, and treatment of Alzheimer's disease. For diagnosis of Alzheimer's disease, amyloid-β and highly phosphorylated tau protein are the major biomarkers. Curcumin was developed as an early diagnostic probe based on its natural fluorescence and high binding affinity to amyloid-β. Because of its multi-target effects, curcumin has protective and preventive effects on many chronic diseases such as cerebrovascular disease, hypertension, and hyperlipidemia. For prevention and treatment of Alzheimer's disease, curcumin has been shown to effectively maintain the normal structure and function of cerebral vessels, mitochondria, and synapses, reduce risk factors for a variety of chronic diseases, and decrease the risk of Alzheimer's disease. The effect of curcumin on Alzheimer's disease involves multiple signaling pathways: anti-amyloid and metal iron chelating properties, antioxidation and anti-inflammatory activities. Indeed, there is a scientific basis for the rational application of curcumin in prevention and treatment of Alzheimer's disease.

Keywords: *nerve regeneration, curcumin, Alzheimer's disease, senile dementia, early diagnosis, positron emission tomography, magnetic resonance imaging, biological availability, chemical components, neurodegeneration, neural regeneration*
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Introduction

Alzheimer's disease (AD) is a common progressive neurodegenerative disorder prevalent worldwide, yet with no effective cure. It affects about 35 million individuals and cost more than $226 billion in 2016 alone. A conservative estimate of its prevalence is one in nine people aged 65 years and older, being almost three times higher for people aged 85 and older (Alzheimer's Association, 2015). By 2050, a new case of AD is expected to develop every 33 seconds (Lopez, 2011). Indeed, AD is now imposing a tremendous impact on society and is a costly burden that will be a modern epidemic in the near future (Hampel et al., 2011). Consequently, there is an urgent need for global diagnostic, preventive, and therapeutic measures to control the impact of this devastating disease.

Like other chronic diseases, AD develops as a result of multiple factors rather than a single cause. However, its etiology and pathology remain unclear (LaFerla and Green, 2012). Clinically, AD is characterized by memory and cognitive impairments, and personality and behavior changes (Huang and Mucke, 2012). The pathological hallmarks observed in AD brain include extracellular amyloid plaques and intracellular neurofibrillary tangles (NFTs). Amyloid-β (Aβ) is generated a cleavage of the amyloid precursor protein by β- and γ-secretases. This results in native Aβ monomers that have prosurvival effects on neurons and protect mature neurons against excitotoxic death (Giuffrida et al., 2009). In contrast, under pathological conditions, excessive accumulation of monomers results in their assembly into soluble, diffusible toxic oligomeric Aβ species: low-molecular-weight aggregates consisting of 2–30 Aβ peptides. When the oligomers reach a critical concentration, they form insoluble fibrils/aggregates and plaques. It is important to note that soluble Aβ oligomers are more toxic than insoluble deposits (Verma et al., 2015). In particular, Aβ dimers (the major form of soluble oligomers isolated from AD cortex) directly induce tau hyperphosphorylation and neurite degeneration (Jin et al., 2011). NFTs are another hallmark of AD, and are composed of hyperphosphorylated tau, which disrupts microtubules and impairs axonal transport (Beharry et al., 2014; Metaxas and Kempf, 2016; Ye et al., 2017). In addition to these pathologies, extensive neuroinflammation and oxidative damage are also observed at sites of neurodegeneration. Indeed, these pathological factors act together, resulting in progressive neuronal damage and cognitive deficits. Importantly, a vicious cycle develops among Aβ, NFTs, oxidative stress, and inflammation. Aβ and NFTs activate microglia and induce production of reactive oxygen species and inflammatory factors. Conversely, reactive oxygen species and inflammatory cytokines directly act on neurons, further promoting Aβ and NFT formation (Glass et al., 2010; Broussard et al., 2012; Luque-Contreras et al., 2014). Therefore, seeking effective therapeutics with multiple targets is highly desirable (Frautschy and Cole, 2010). Fortunately, accumulating evidence suggests that curcumin (1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) may play a significant role in AD therapy, exerting pleiotropic properties. Curcumin can directly bind to Aβ in the central nervous system and prevent its assembly into neurotoxic species (Kozmon and Tvaroška, 2015; Rao et al., 2015). In addition, curcumin can reduce oxidative stress and inflammatory responses, and has beneficial effects on neuronal and vascular functions (DiSilvestro et al., 2012). Extensive lines of evidence indicate that Aβ oligomer production, oxidative markers, and neuroinflammation are attenuated by administration of curcumin (Hu et al., 2015; Nasir Abbas Bukhari and Jantan, 2015).

Curcumin is a component of the Indian spice turmeric, and is extracted from the rhizome of Curcuma longa, which is widely cultivated in south and southeast Asia, especially China and India (Wanninger et al., 2015). Commercial curcumin refers to curcumin complex, which is composed of curcumin (77%), demethoxycurcumin (17%), and bisdemethoxycurcumin (3%). Curcumin is the major component of three curcuminoids that give turmeric its distinctive yellow color, and is used as a food colorant, flavoring, and additive (Goel et al., 2008). In herbal medicine, turmeric and natural curcuminoids have been used to treat respiratory conditions, abdominal pain, sprains and swelling (Araujo and Leon, 2001). Recent studies indicate that curcumin may have a critical role in management of AD, and is particularly useful as a sensitive diagnostic agent, health-promoting life-long nutraceutical, as well as a multi-target-directed drug (Belkacemi et al., 2011; Goozee et al., 2016).

This review discusses the multifaceted functions of curcumin, including its use in diagnosis, prevention, and therapy at different stages of AD.

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Curcumin: a Sensitive Fluorochrome for AD Diagnosis

Diagnosis of AD in patients is based on clinical examination, which is mainly suitable for late-stage disease (Dubois et al., 2007). Indeed, no definite early diagnostic test at the asymptomatic stage is currently available. The first diagnostic criteria for AD were established in 1984, and included progressive deterioration of language, memory, and cognition, as well as progressive cerebral atrophy detectable by brain imaging (Alzheimer's Association, 2010). However, these criteria were revised as they are too general. The new AD diagnostic criteria now require a gradual onset and fast-progressing cognitive function impairment, which cannot be explained by other diseases (Dubois et al., 2007). Pathological features such as cerebrovascular changes, Aβ, and NFTs, are believed to precede or coexist with AD (Parnetti et al., 2006). Thus, use of biomarkers may increase diagnostic specificity and reliability, which are included in the updated criteria (Reitz et al., 2011). At the time of diagnosis, patients are usually at a mild to moderate stage, which cannot be prevented by current treatments. To overcome this disadvantage, more sensitive diagnostic probes is highly desirable (Bateman et al., 2012; Chase, 2014).

With its recent success as a “multi-anti” agent, curcumin has attracted considerable interest from researchers in the fields of physics, chemistry, biology, and medicine. Curcumin comprises two phenols connected by a linear β-diketone linker, which also induces keto–enol tautomerism. Because of its special structure, curcumin exhibits many interesting photophysical and photochemical properties (Priyadarsini, 2009). Curcumin effectively binds to Aβ plaques and emits a strong fluorescence signal, making it a powerful diagnostic reagent for AD (Garcia-Alloza et al., 2007). During the last two decades, extensive research has been performed to develop curcumin probes for targeting Aβ with available imaging modalities, including positron emission tomography (PET), two-photon microscopy, magnetic resonance imaging (MRI), and near-infrared fluorescence (NIRF) (Tu et al., 2015).

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PET

PET imaging with Aβ-specific tracers has been widely applied in clinical trials, with three Aβ PET tracers approved by the US Food and Drug Administration for clinical use: ^{18}F-flutemetamol (Vizamyl), ^{18}F-florbetapir (Amyvid), and ^{18}F-florbetaben (Neuraceq). Moreover, this approach is an emerging tool for AD research and numerous new PET probes are under development (Mathis et al., 2012). Curcumin derivatives can be labeled with radioactive nuclides (including several radioiodinated ligands and ^{18}F fluoropegylated ligands), making it applicable for PET (Cui et al., 2011). Ryu et al. (2006) synthesized fluoropropyl-substituted curcumin (**Figure 1A**), which shows high binding affinity (Ki = 0.07 nM) to Aβ. Furthermore, its radiolabeled form shows suitable lipophilicity and reasonable brain uptake. These results suggest that ^{18}F

fluoropropyl-substituted curcumin is a promising radioligand for imaging Aβ. In addition, Rokka and coworkers synthesized the [^{18}F]curcumin derivative (**Figure 1A**), with high binding affinity to Aβ plaques in transgenic APP23 mouse brain cryosections. Studies have demonstrated that ^{18}F curcumin derivative can be efficiently removed from blood (1–5 minutes), but has low blood-brain barrier (BBB) penetration, with ^{18}F-radioactivity concentrations of only 0.04% ID/g in mouse brain and 0.03% ID/g in rat brain (Rokka et al., 2014). To overcome this low BBB permeability, Mourtas et al. (2014) designed a lipid-polyethylene glycol (PEG)-curcumin derivative to increase BBB penetration and fluorescence intensity. These nanoliposomes were loaded with curcumin derivative and immobilized to a BBB transport mediator (monoclonal anti-transferrin antibody [MAb]). As anticipated, these multifunctional nanoliposomes were more efficient at labeling Aβ deposits in postmortem tissue of AD patients, with fluorescence was enhanced by almost six times. Uptake of MAb-decorated nanoliposomes loaded with curcumin-derivative was increased (almost two-fold) compared with curcumin-conjugated nanoliposomes (Mourtas et al., 2014). Altogether, these findings indicate that curcumin derivatives entrapped in multifunctional nanoliposomes represent a useful approach in AD diagnosis.

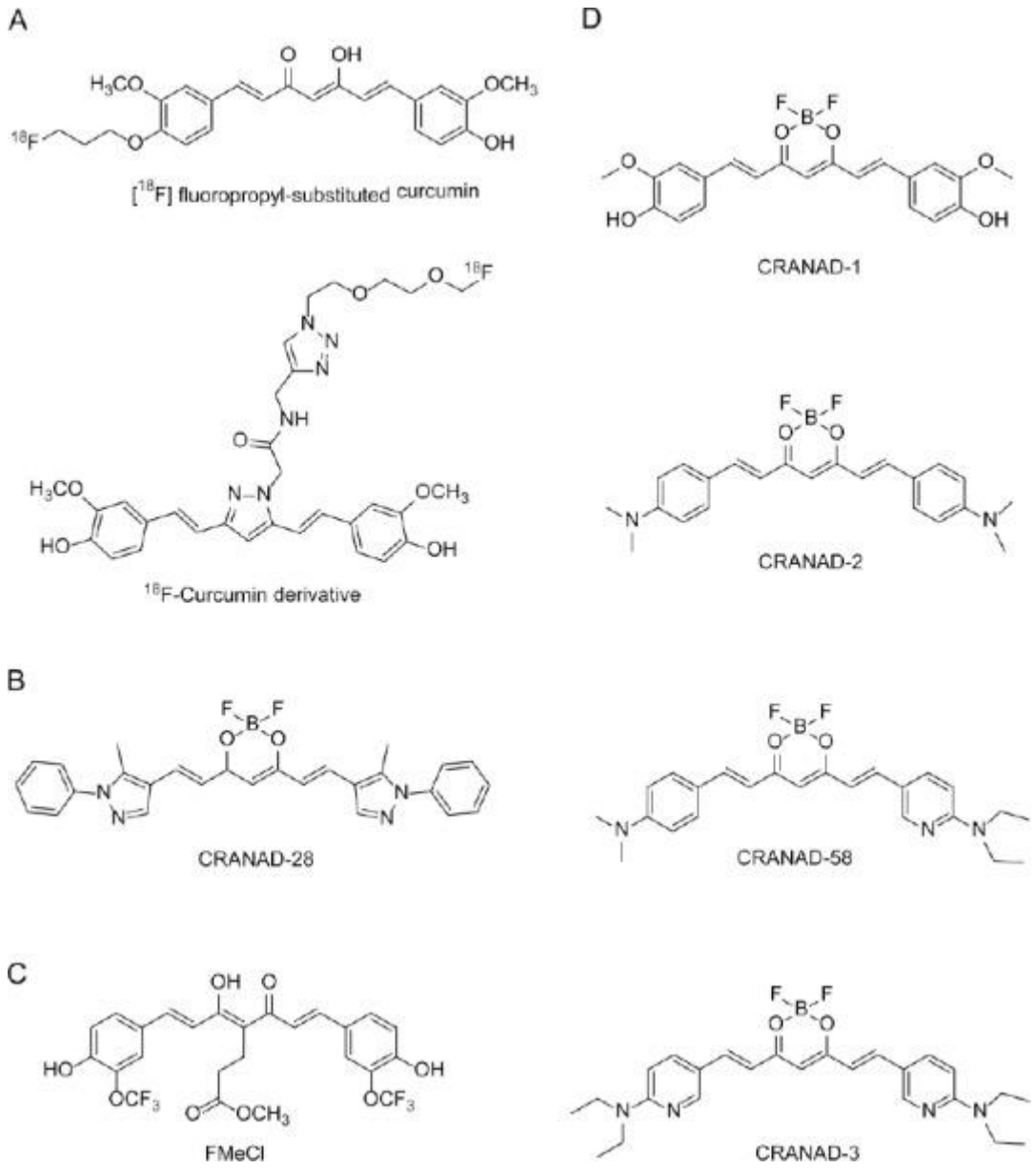

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Figure 1

Curcumin is a sensitive fluorochrome for AD diagnosis.

(A) Curcumin derivatives for PET imaging. [^{18}F] fluoropropyl-substituted curcumin, *K*i = 0.07 nM to Aβ (Ryu et al., 2006); ^{18}F-curcumin derivative (Rokka et al., 2014). (B) Curcumin analogue CRANAD-28 for two-photon microscopy imaging (Zhang et al., 2014). $A\beta_{40}$ monomers: *K*d = 68.80 nM, $A\beta_{42}$ monomers: *K*d = 159.70 nM, $A\beta_{42}$ dimers: *K*d = 162.90 nM, $A\beta_{42}$ oligomers: *K*d = 85.70 nM, $A\beta_{40}$ aggregates: *K*d = 52.40 nM. (C) Curcumin analogue FMeC1 for magnetic resonance imaging (Yanagisawa et al., 2011). (D) Curcumin analogues for near-infrared fluorescence imaging. CRANAD-1, *K*d =38.00 nM; CRANAD-58, $A\beta_{40}$: *K*d = 105.80 nM, $A\beta_{42}$: *K*d = 45.80 nM; CRANAD-3, $A\beta_{40}$ monomers: *K*d = 24.00 nM, $A\beta_{42}$ monomers: *K*d = 23.00 nM (Ran et al., 2009; Zhang et al., 2013, 2015). AD: Alzheimer's disease; Aβ: amyloid-β; PET: positron emission tomography.

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Two-photon microscopy

Two-photon microscopy is an important technique for investigating Aβ species, and provides insight into the dynamics of individual plaque expansion and disruption of the microenvironment (Condello et al., 2011). Zhang et al. (2014) designed and synthesized CRANAD-28 (**Figure 1B**) by introducing a pyrazole ring into curcumin. With this replacement, CRANAD-28 improved tissue penetration because of its longer excitation (498 nm) and emission (578 nm), and displayed high quantum yield in both phosphate-buffered saline (PBS) (0.32) and ethanol (> 1.00). When tested *in vitro* towards different Aβ species, CRANAD-28 showed high affinity, with *K*d values ranging from 52.40 to 162.90 nM. *In vivo* two-photon microscopy clearly demonstrated that CRANAD-28 not only labeled Aβ plaques and cerebral amyloid angiopathies in 9-month old APP/PS1 mice, but also attenuated Aβ crosslinking in brain. These results suggest the potential use of CRANAD-28 in both diagnosis and therapy for AD (Zhang et al., 2014).

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MRI

MRI is cheaper, easier, and nonradioactive in comparison with PET, but its sensitivity needs to be improved before it can be used clinically. Fortunately, recent studies have tested curcumin derivatives as MRI probes for Aβ imaging. Yanagisawa et al. (2011) developed a perfluoro curcumin analog, FMeCl (**Figure 1C**), for ^{19}F MRI to facilitate visualization of Aβ *in vivo*. They found that compared with wild-type mice, ^{19}F MRI showed marked ^{19}F signal levels in the brain of Tg2576 mice after injection of FMeCl (200 mg/kg). Moreover, ^{19}F signal in Tg2576 mice aligned with the distribution of Aβ deposits (Yanagisawa et al., 2011). Interestingly, FMeCl not only labeled Aβ plaques, but also inhibited Aβ aggregates, glial cell activity, and cognitive deficits in APP/PS1 mice (Yanagisawa et al., 2015). Subsequently, a new formulation of FMeCl was developed to increase its bioavailability. Thus, FMeCl may be a promising theranostic agent owing to its dual role in imaging and therapy, similar to CRANAD-28. In addition to curcumin analogues, several curcumin-conjugated nanoparticles have been approved for early diagnosis of AD (Patil et al., 2015). Cheng et al. (2015) used magnetic nanoparticles (MNPs) comprised of super paramagnetic iron oxide conjugated to curcumin to develop a nanoimaging agent (Cur-MNPs). Cur-MNPs show low cytotoxicity (up to 167 mg/mL) and considerable BBB penetration potential. Many dark spots were found by MRI in Tg2576 brain *in vivo*, while almost no such spots were found in control brain. Therefore, Cur-MNPs are another successful example of nanoparticles for Aβ imaging (Cheng et al., 2015).

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NIRF

NIRF is an attractive tool for early AD detection, and presents several advantages including acceptable photon penetration, noninvasive exposure, and inexpensive instrumentation. In past years, Ran's group has designed and synthesized a series of

curcumin analogues (CRANAD-X) as NIRF imaging probes (Ran et al., 2009).First, they synthesized CRANAD-1 (**Figure 1D**) by introducing a difluoroboronate ring into curcumin. With this replacement, CRANAD-1 emission was red-shifted to λmax (em) = 560 nm in methanol, which is not in the NIRF wavelength range (> 650 nm). To further increase emission wavelength, CRANAD-1 was modified by substituting the N,N′-dimethyl group for a phenolic hydroxyl group to yield the compound, CRANAD-2, (**Figure 1D**). As anticipated, CRANAD-2 showed longer emission at λmax (em) = 760 nm. *In vitro*, CRANAD-2 effectively interacted with Aβ (*K*d = 38.00 nM) and increased fluorescence brightness by 70-fold. *In vivo*, CRANAD-2 showed a significant fluorescence difference between 19-month-old wild-type and transgenic mice. However, as a limitation, CRANAD-2 was not able to detect soluble dimeric and oligomeric Aβ species, which are more neurotoxic than insoluble deposits. To overcome this limitation, Ran et all. (2009) designed and synthesized another curcumin analogue, CRANAD-58 (**Figure 1D**), which detects both insoluble and soluble Aβ species. As expected, CRANAD-58 not only displayed sufficient long emission (750 nm), but also exhibited strong binding to soluble Aβ monomers. Notably, CRANAD-58 detected soluble Aβ species in 4-month-old APP/PS1 mice, a younger age than with CRANAD-2. Consequently, CRANAD-58 can be considered the first NIRF imaging probe that is sensitive to both soluble and insoluble Aβ species *in vitro* and *in vivo*. Importantly, Aβ imaging is not only a means for early diagnosis, but also an approach for monitoring the efficacy of therapy. However, none of these NIRF probes have been used for this purpose. To fill this gap, Ran et al. (2009) designed CRANAD-3 (**Figure 1D**) by replacing the two aromatic rings with pyridyls to increase Aβ affinity. *In vitro* spectral testing and *in vivo* NIRF imaging indicated that CRANAD-3, like CRANAD-58, was sensitive to both soluble and insoluble Aβ, but with higher sensitivity than CRANAD-58. Crucially, owing to its excellent ability to detect both soluble and insoluble Aβ, CRANAD-3 can be used to monitor the effectiveness of Aβ-lowering therapeutics, suggesting a dual role of CRANAD-3 in AD (Ran et al., 2009; Zhang et al., 2013, 2015).

Compared with traditional diagnostic agents, synthesized curcumin analogues (CRANAD-58 and CRANAD-3) can detect not only insoluble Aβ plaques but also soluble Aβ oligomers *in vitro* and *in vivo* (Zhang et al., 2013, 2015). Moreover, CRANAD-3 can monitor and evaluate the effectiveness of anti-amyloid interventions, enabling selection of patients for treatment (Zhang et al., 2015). Importantly, curcumin analogues (CRANAD-28 and FMeC1) combine diagnostic and therapeutic properties in a single molecule (Yanagisawa et al., 2011; Zhang et al., 2014), leading to time-saving and cost-effective optimization. Apart from the theranostic role of curcumin for Aβ, curcumin has been reported to detect tau pathology. For example, Mohorko et al. (2010) have shown that curcumin can label tau aggregates in brain sections that coincides with routine thioflavine S and Gallyas silver staining. This suggests curcumin has diagnostic potential in tauopathies. Similarly, Park et al. (2015) designed and synthesized a novel curcumin-based molecular probe by introducing a (4-dimethylamino-2,6-dimethoxy) phenyl moiety to the aromatic rings of CRANAD-2. This probe showed a significant fluorescence response to tau fibrils (quantum yield = 0.32; *K*d = 0.77 μM; λmax(em) = 620 nm), encouraging further development of curcumin in AD theranostics for both Aβ and NFTs.

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Curcumin: a Health-Promoting Nutraceutical for AD Prevention

At present, there is no cure for AD, yet the impact of this disease can be lessened by delaying its onset. Delayed onset of 6 months would result in a reduction of 100,000 cases after 10 years, highlighting the importance of prevention (Brookmeyer et al., 1998). Epidemiological and experimental data suggest that optimal diet, physical exercise, and intellectual activity may promote brain health (Vivar, 2015). In particular, an optimal diet with rich phenolic compounds may provide preventive effects on development of AD (Yamada et al., 2015). Safouris et al. (2015) reported that consumption of a Mediterranean-type diet reduced the incidence of AD. This diet is characterized by a high proportion of plant foods and fish, a moderate proportion of wine, and a low proportion of red meat. They found that higher adherence to the Mediterranean-type diet was associated with lower risk for AD (hazard ratio of 0.60, compared with 0.91 in non-Mediterranean countries) (Safouris et al., 2015). Similarly, Ng et al. (2006) reported that consumption of an Asian-type diet that is rich in soy and turmeric (containing considerable amounts of isoflavones and curcumin, respectively) and high levels of seaweed, also reduced the incidence of AD. These diets are rich in fruits and vegetables, which are primary sources of dietary polyphenols, glucosinolates, and vitamins. Curcumin is a natural phenolic substance with beneficial effects on various chronic conditions including obesity, diabetes, and depression (Arun and Nalini, 2002; Kim and Kim, 2010; Rinwa et al., 2013). Importantly, such chronic diseases may be risk factors for AD, and are linked to the etiology or outcome of AD (Jorm, 2001; Gustafson et al., 2003). For example, diabetes promotes the formation of advanced glycosylation end products, leading to activation of receptors for advanced glycosylation end products on the surface of glial cells, vascular endothelial cells, and neurons. In turn, this induces inflammatory responses and increases Aβ influx, giving rise to further brain damage and ensuing cognitive impairment (Yan et al., 1996). This suggests that curcumin intake may prevent AD progression by reducing AD risk (Reitz et al., 2011). Additionally, curcumin improves memory function in healthy-aged rodents by enhancing synaptic plasticity and neurogenesis (Kim et al., 2008; Dong et al., 2012; Belviranlı et al., 2013). It may also increase docosahexaenoic acid synthesis, resulting in better plasma membrane integrity, which further maintains normal mitochondrial and synaptic function (Pinkaew et al., 2015; Wu et al., 2015). Several studies have examined curcumin supplementation in healthy older people. DiSilvestro et al. (2012) demonstrated that a low dose of lipidated curcumin produced diverse potential health benefits in healthy middle-aged people by increasing nitric oxide levels and lowering soluble intercellular adhesion molecule. Both molecules have relevance for cardiovascular disease risk. Also, curcumin suppressed alanine aminotransferase activity, a general marker of liver injury, and raised plasma myeloperoxidase, an effect associated with inflammation (DiSilvestro et al., 2012). More recently, Cox et al. (2015) showed that supplementation with solid lipid curcumin formulation (80 mg as Longvida®) improved cognitive function, reduced fatigue, and lessened the detrimental impact of psychological stress on mood, which may improve quality of life for the growing elderly population. Therefore, dietary uptake of curcumin may reduce AD risk, enhance cognitive function, and delay and counteract the effect of aging and neurodegenerative disease.

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Curcumin: a Pleiotropic Agent for AD Treatment

Considering the multifactorial etiology and complex pathological mechanisms involved in AD, it is quite reasonable that treatments targeting a single causal or modifying factor will have limited benefits (**Figure 2**). Therefore, growing interest is focused on therapeutic agents with pleiotropic activity, targeting several affected processes (Bajda et al., 2011). Several compounds described here fulfill these properties, with curcumin showing strong anti-Aβ properties and considerable anti-inflammatory and antioxidant activities (Belkacemi et al., 2011).

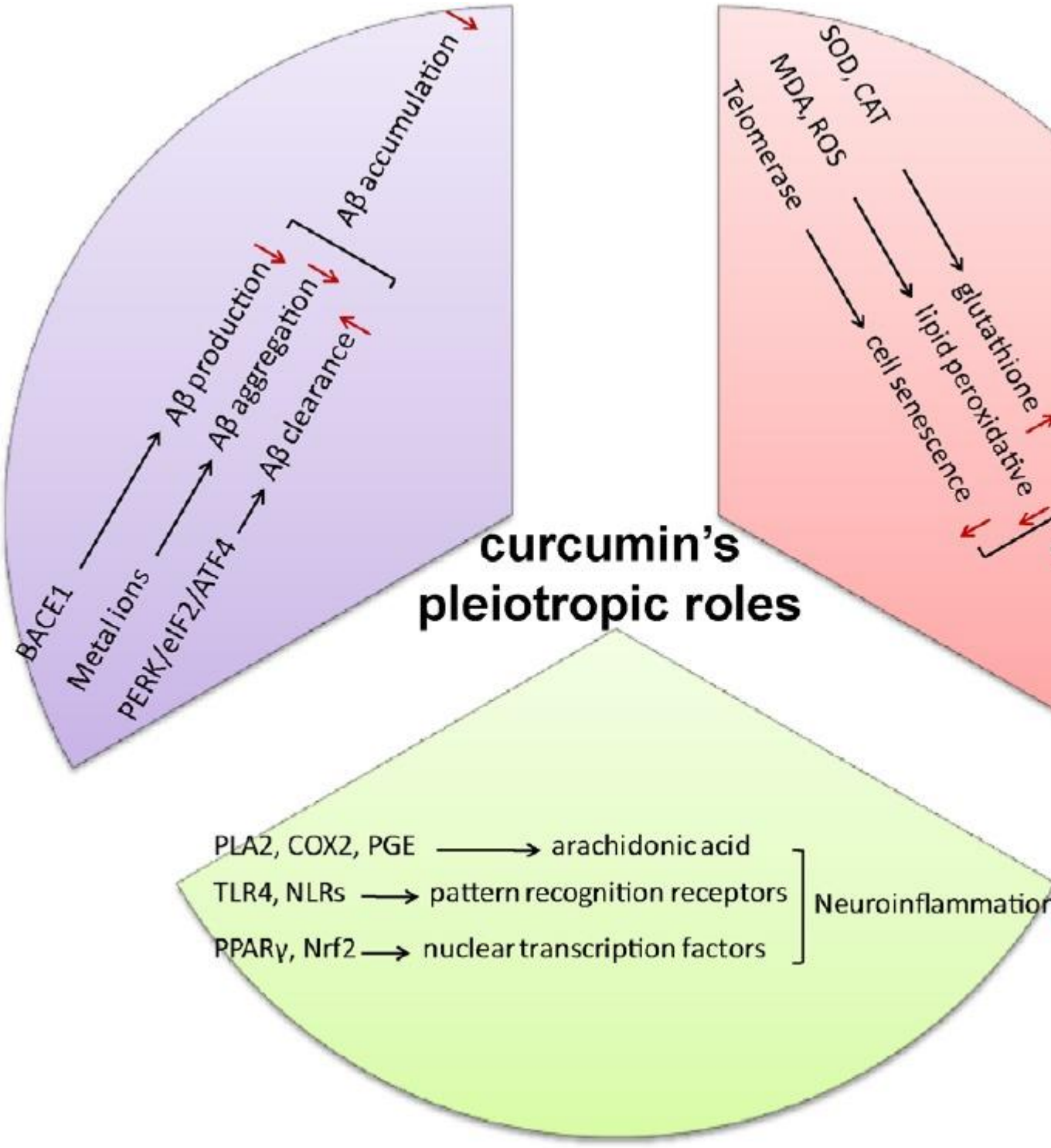

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Figure 2

Curcumin: a pleiotropic agent for treatment of Alzheimer's disease.

Curcumin decreases Aβ production, inhibits Aβ aggregation, and promotes Aβ clearance. Besides, curcumin inhibits inflammatory signal pathways and decreases the production of inflammatory cytokines. Additionally, curcumin reduces oxidative stress and scavenge radicals. Aβ: Amyloid β-protein.

Effect of curcumin on Aβ protein

Over the past decades, the amyloid hypothesis has been widely accepted and been the focus of AD research (Soto, 1999). Consequently, one current strategy for treating AD is anti-amyloid treatments including decreasing Aβ production, inhibiting Aβ aggregation, and promoting Aβ clearance. *In vitro* studies have shown that curcumin lowers Aβ levels by attenuating amyloid precursor protein maturation and suppressing beta-secretase 1 (BACE1) expression, which is the sole β-secretase enzyme (Liu et al., 2010). Moreover, *in vivo* studies using a drosophila AD model have shown that demethoxycurcumin has strong inhibitory BACE-1 activity (IC_{50} = 17 μM), contributing to rescue of morphological and behavioral defects caused by overexpression of amyloid precursor protein maturation and BACE1 (Wang et al., 2014). Recent studies have investigated the molecular mechanism of BACE-1 inhibition by curcumin. Curcumin was found to repress BACE-1 transcription by activating the Wnt/β-catenin pathway, which binds to T-cell factor-4, a repressor of the BACE1 gene (Zhang et al., 2011; Parr et al., 2015). Apart from its role in amyloid precursor protein maturation, studies have indicated that curcumin can attach to Aβ peptides and prevent Aβ aggregation *in vitro* and *in vivo*. *In vitro* curcumin displays high-affinity binding to Aβ aggregates (*K*d = 0.20 nM), with EC50 of curcumin for Aβ destabilization being approximately 1 μM (Ono et al., 2004). In APPswe/PS1dE9 mice, Garcia-Alloza et al. (2007) suggested that curcumin (7.5 mg/kg intravenously, 7 days) clears or reduces the size of senile plaques (Garcia-Alloza et al., 2007). In Tg2576 mice, a daily single dose (500 ppm) of curcumin administered orally for 5 months significantly reduced levels of insoluble Aβ (85%) and Aβ plaques (32.50%) (Yang et al., 2005). Based on comprehensive structure–activity analysis, coplanarity of two phenol rings, length and rigidity of the linker, and substitution conformation of the phenol rings were shown to contribute to the inhibitory potency of curcumin (Reinke and Gestwicki, 2007). Further studies have investigated the atomistic mechanism of curcumin inhibition on Aβ aggregation. By molecular docking and molecular dynamic simulations, Rao et al. (2015) demonstrated that curcumin binding to Aβ-aggregates leads to significant amino acid fluctuations, with a shift in equilibrium towards non-toxic Aβ aggregates. Moreover, curcumin binds to Aβ *via* strong hydrophobic interactions and H-bonding, which disrupts preformed fibrils and prevents oligomerization (Kundaikar and Degani, 2015). Interestingly, alternative theories suggest that curcumin blocks Aβ aggregation by chelating metal ions, such as Cu^{2+}, Zn^{2+}, and Fe^{3+}, likely agonists of Aβ aggregation and oxidative stress (Perrone et al., 2010; Banerjee, 2014). Kozmon investigated interactions between Aβ peptide and Cu^{2+} ions and/or curcumin by molecular dynamic simulations. They found that curcumin not only chelated Cu^{2+} ions, but also directly attached to Aβ, forming curcumin–Cu^{2+}–Aβ and curcumin–Aβ complexes that decrease toxic β-sheet structures (Kozmon and Tvaroška, 2015). Crucially, the effects of curcumin are not limited to modulation of Aβ production and aggregation, and further studies have shown that curcumin accelerates Aβ clearance. Curcumin increases expression of autophagy- and lysosome-related protein markers, such as heat shock proteins, LC3A/B-II, and beclin-1, which are essential for Aβ phagocytosis in neurons (Maiti et al., 2017). Moreover, a curcumin derivative, CNB-001, serves as a 5-lipoxygenase inhibitor, inducing activation of the PERK/eIF2/ATF4 arm of the unfolded protein response and accelerating degradation of Aβ aggregates (Valera et al., 2013). These studies not only indicate that curcumin plays a critical role in the Aβ cascade, but also identify several new targets for AD treatment, such as Wnt/β-catenin and PERK/eIF2/ATF4 of the unfolded protein response.

Effect of curcumin on neuroinflammation

Neuroinflammation is one of the pathological factors in the vicious circle of AD pathogenesis, and is characterized by extensive glial activation and robust cytokine production at the site of damage. Curcumin targets numerous inflammatory signaling pathways, including biosynthesis and metabolism of arachidonic acid, pattern recognition receptor pathways on the surface of glial cells, and nuclear transcription factors (He et al., 2015). For example, IC50 values of curcumin for secretory phospholipase A2, cyclooxygenases-2, lipo-oxygenase, and microsomal prostaglandin E synthase-1 (which are involved in arachidonic acid metabolism) are 11.10, 93.36, 57.77, and 4.88 μM, respectively (Ahmad et al., 2014). Similarly, curcumin serves as a repressor of both toll-like receptors and NOD-like receptors (NLRs), sensors of Aβ and NFTs during neuroinflammation. Curcumin inhibits dimerization of toll-like receptor 4, resulting in marked reduction of proinflammatory cytokines (Youn et al., 2006). Recent studies have suggested that curcumin attenuates neurotoxicity and the related inflammatory response by suppressing nucleotide-binding oligomerization domain (NOD)-like receptor protein 3 (NLRP3) inflammasome activation (Gong et al., 2015; Li et al., 2015). Curcumin may also act as an agonist of both peroxisome proliferator-activated receptor γ and nuclear factor erythroid-2 related factor 2, which regulate expression of various inflammatory cytokines (Innamorato et al., 2008; Wang et al., 2010). *In vitro* studies suggest that curcumin attenuates Aβ-induced inflammatory responses in microglia by suppressing the ERK1/2 and p38 signaling pathways (Shi et al., 2015). Moreover, *in vivo* studies using an AD rat model have shown that curcumin exerts a significant reduction in glial fibrillary acidic protein expression and astrocyte activity, contributing to the rescue of behavioral defects caused by Aβ intracerebral injection (Wang et al., 2013). These results imply that the powerful anti-inflammatory properties of curcumin may be responsible for inhibiting glial cell activation and alleviating Aβ pathology in AD.

Effect of curcumin on oxidative stress

As described, Aβ and phosphorylated-tau aggregation, inflammation, and oxidative stress form a vicious cycle in the brain, contributing to neuronal apoptosis and cognitive decline in AD. Thus, interventions to attenuate oxidative stress have been postulated as another approach in prevention and treatment of AD. Curcumin has excellent antioxidant properties, which elevate superoxide dismutase and catalase activity to conserve glutathione levels and decrease malonyldialdehyde accumulation in mouse models and humans (Soni and Kuttan, 1992; Soudamini et al., 1992; Ak and Gülçin, 2008; Dkhar and Sharma, 2010). A study using a homocysteine-induced rat aging model showed that curcumin (5, 15, or 45 mg/kg) treatment improved learning and memory function by significantly decreasing malonyldialdehyde and super oxide anion levels in the hippocampus (Ataie et al., 2010). However, elevated homocysteine plasma levels also led to abnormal DNA methylation, resulting in decline of cognitive performance (Fux et al., 2005). Curcumin inhibits DNA methyltransferase and may be responsible for its ability to improve cognitive impairment (Fang et al., 2007). Moreover, curcumin inhibits Aβ-induced oxidative stress and cell toxicity, which are dependent on telomerase. Telomerase is a ribonuclear protein complex that synthesizes and elongates telomeric DNA, protecting cells against senescence (Fang et al., 2007). These data suggest that telomerase may be a novel target of curcumin, providing a potential new therapeutic strategy for treating AD.

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Curcumin in the Clinic

Extensive preclinical studies over the past decades have indicated the therapeutic potential of curcumin against a wide range of human chronic diseases. In addition, curcumin directly interacts with numerous cell signaling molecules such as pro-inflammatory cytokines, apoptotic proteins, and phosphorylase kinases. These studies provide a solid foundation for evaluating the efficacy of curcumin in clinical trials (Gupta et al., 2013). Until now, nine human trials of curcumin in AD interventions (including diagnosis, prevention and therapy) have been performed (**Table 1**). In diagnosis, a pilot study using curcumin as a fluorochrome for retinal imaging found that curcumin enabled Aβ visualization with excellent fluorescence properties. The retinal Aβ test was able to differentiate between AD and non-AD with 80.6% specificity (Frost et al., 2014). Additionally, Cox et al. (2015) showed that supplementation with solid lipid curcumin formulation (80 mg as Longvida®) improved cognitive function and reduced fatigue and psychological stress in a healthy older population, suggesting a protective potential of curcumin. Nevertheless, clinical studies on mild cognitive impairment and AD found no significant differences in cognitive function and biomarker measurements between placebo and intervention groups, although curcumin increased vitamin E levels and did not cause any adverse effects at a high dose (Baum et al., 2008). These studies suggest that curcumin may delay disease progression rather than improve biomarkers and cognitive function. It is possible that poor bioavailability of curcumin, selection of cohorts at an advanced stage of AD, and differences in the biology of rodent models and AD patients may be responsible for these failures in clinical trials. It is interesting to note that one clinical trial combining curcumin and Bioperine was terminated, while another trial of high-bioavailability curcumin formulation (Longvida) was not updated, yet both had enhanced bioavailability of curcumin (**Table 1**). Additionally, to the best of our knowledge, none of the existing models fully reproduce the complete pathology and process of AD. Many interventions, although successful in animal models, have failed in clinic trials (LaFerla and Green, 2012). This highlights the urgent need for a next-generation of animal models, which better recapitulate critical aspects of the disease spectrum and facilitate success in preclinical studies and human clinical trials. Thus, it is premature to conclude that there is no effect of curcumin in AD patients. More studies with better bioavailability and delivery strategies, larger numbers of patients at the asymptomatic stage, and longer treatment durations are highly desirable.

Table 1

Clinical trials with curcumin in diagnosis, prevention, and therapy

Study	Cohort	Intervention	Primary endpoint	Main results
ClinicalTrials.gov NCT03085680	24 older adults with physical and/or cognitive impairment	Curcumin (100 mg/d); 3 months	Physical function; cognitive function; pain and inflammation	Not yet recruiting
ClinicalTrials.gov NCT01811381	80 subjects with MCI	Curcumin (800 mg/d) and yoga; 12 months	Blood biomarkers; cerebral glucose metabolism (^{18}F-FDG-PET); cognitive changes; adverse events	Recruiting
ClinicalTrials.gov NCT01383161	132 subjects with age-associated impairment or MCI	Curcumin (180 mg/d); 18 months	Cognitive changes; abnormal accumulation of Aβ and tau (FDDNP-PET); inflammatory markers	Active, not recruiting
ClinicalTrials.gov NCT01001637	26 subjects with AD	Longvida (2 g/d or 3 g/d); 2 months	Cognitive changes; blood concentration of Aβ	Unknown status
ClinicalTrials.gov NCT00595582	10 subjects with MCI	Curcumin (5.4 g/d) and bioperine (900 mg/d); 24 months	MMSE scores; metabolic lesions (PET)	Terminated for various reasons
Baum et al. (2008)	36 subjects with AD	Curcumin (1 or 4 g/d) and ginkgo extract (120 mg/d); 6 months	MMSE scores; blood biomarkers (isoprostane, Aβ, cholesterol, triglycerides, and metals); plasma curcumin levels	Completed, No difference in MMSE scores or blood biomarkers among groups, but vitamin E increased
Ringman et al. (2012)	33 subjects with AD	Curcumin C3 complex (2 or 4 g/d); 6 months	MMSE scores; side effects; plasma and cerebrospinal fluid biomarkers (Aβ, tau, and F2-isoprostanes); curcumin and metabolites in plasma	Completed No differences among groups, and no serious adverse events
Frost et al. (2014)	40 subjects: healthy, MCI, AD	Longvida (20 g/d); 7 days	Diagnostics; curcumin fluorescence retinal imaging of Aβ plaques	Completed Differentiated between AD and non-AD with 80.6% specificity
Cox et al. (2015)	60 subjects: healthy, aged 60–85 years old	Longvida (400 or 800 mg/d); acute: 1–3 hours; chronic: 4 weeks	Cognition; mood and anxiety; blood biomarkers (lipid profile, inflammatory markers, and Aβ)	Completed Cognition and mood were improved. Total and LDL cholesterol were decreased

AD: Alzheimer's disease; Aβ: β-amyloid; MCI: mild cognitive impairment; MMSE: Mini-Mental State Examination; PET: positron emission tomography; LDL: low-density lipoprotein; ^{18}F-FDG: hypometabolism of 2-[18F] fluoro-2-deoxy-D-glucose; FDDNP: 2-(1-{6-[(2-[F-18] fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile; d: day.

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Pharmacokinetic Studies and Commercial Formulations

Curcumin is soluble in organic solvents, but insoluble in water (Wang et al., 1997). Although curcumin is safe and well-tolerated, absorption of curcumin is quite poor. Clinical studies in humans have shown that curcumin is generally safe even at high doses up to 8 g/d (Cheng et al., 2001), but with no detectable levels of the parent compound in the plasma unless patients ingest > 8 g (Lao et al., 2006). Moreover, curcumin availability is lower in the brain than other organs (Vareed et al., 2008). Curcumin undergoes extensive first-pass glucuronidation, resulting in rapid elimination in bile and urine (Ireson et al., 2001). Approximately 75% of curcumin can be detected in feces after a dietary dose (1 g/kg) administered to rats (Sharma et al., 2007). Similarly, curcumin declined rapidly and was unquantifiable within 3–6 hours after intake (Vareed et al., 2008). The main factors limiting curcumin bioavailability are low solubility, poor absorption, and rapid metabolism and elimination. Therefore, numerous studies have been directed at increasing curcumin bioavailability, including use of phospholipid complex formation, loading curcumin into liposomes and nanoparticle encapsulation, and intranasal administration (**Table 2**).

Table 2

Commercial formulations of curcumin

Formulation	Key techniques	Advantages	Reference
Liposomes			
Mimic nanostructured lipid carrier coated with lactoferrin	A low-density lipoprotein-mimic nanostructured lipid carrier was coated with lactoferrin and loaded with curcumin	Mimic nanostructured lipid carrier coated with lactoferrin increased the ratio of brain uptake and accumulation by 1.39 and 2.78 times, respectively, which was mediated by the lactoferrin receptor	Meng et al. (2015)
Solid lipid curcumin particle (SLCP)	Curcumin SLCP was prepared by mixing curcumin extract with phosphatidylcholine, vegetable stearic acid, vitamin C palmitate, and other inert ingredients. It contained 20% curcumin.	SLCP-1 (granular powder) and SLCP-2 (fine powder) formulations were soluble in water, showing 14% and 76% solubility, respectively. SLCP decreased the lipopolysaccharide-induced pro-inflammatory mediators, nitric oxide, prostaglandin E2, and interleukin-6 in a dose-dependent way (10–50 μg/mL)	Nahar et al. (2015)
Wheat germ agglutinin (WGA)-cardiolipin (CL)-nerve growth factor (NGF)-curcumin (CUR)-liposomes	WGA-conjugated and CL-incorporated liposomes (WGA-CL-liposomes) were loaded with NGF and CUR	WGA enhanced permeability of NGF and CUR across the blood–brain barrier by more than two times. WGA-CL-NGF-CUR-liposomes protected cells against apoptosis induced by β-amyloid fibrils	Kuo and Lin (2015)
Nanoparticles			
Poly(lactic-coglycolic acid) (PLGA)-curcumin nanoparticles	PLGA-curcumin nanoparticles were synthesized from PLGA, polyvinyl pyrrolidone and curcumin, then tagged with a moiety-Tet-1 peptide to target neuronal cells	PLGA-curcumin nanoparticles were soluble in water and increased neuronal uptake. In addition, PLGA-curcumin nanoparticles exhibited significant antioxidant and anti-β-amyloid activity	Mathew et al. (2012)
NanoCurc™	A novel polymeric nanoparticle formulation of curcumin (NanoCurc™) was loaded with curcumin, which was polymerized by N-isopropylacrylamide, vinylpyrrolidone, and acrylic acid	NanoCurc™ was water soluble. NanoCurc™ was nontoxic to SK-N-SH cells *in vitro* and protected against reactive oxygen species-mediated acute insult. NanoCurc™ injection increased curcumin levels (0.32 μg/g) *in vivo*, and decreased H_2O_2 (25%) and caspase 3/7 activity (40%) in the brain	Ray et al. (2011)
Nanocurcumin	Nanocurcumin encapsulated curcumin within polyethylene glycol-polylactide diblock polymer micelles using a multi-inlet vortex mixer and flash nanoprecipitation	Nanocurcumin produced a sharp increase in curcumin concentration *in vitro*. Oral administration of nanocurcumin significantly improved memory function *in vivo*. Curcumin concentration in the brain was 6-times higher than ordinary curcumin	Cheng et al. (2013)
Curcumin-loaded poly (lactic-coglycolic acid) nanoparticles	Curcumin-loaded poly(lactic-coglycolic acid) nanoparticles were prepared by the high-pressure emulsification-solvent evaporation method	Prolonged retention time of curcumin increased by 96% in the cerebral cortex and by 83% in the hippocampus	Tsai et al. (2011)
Micelles			
Curcumin micelles	Curcumin micelles contained 93% Tween-80 and 7% curcumin powder	After administration of curcumin micelles, curcuminoid levels in plasma and brain were increased around 10- to 45-fold respectively. Moreover, curcumin micelles proved to be more efficient in preventing mitochondrial swelling than native curcumin	Hagl et al. (2015)
Poly (d,l-lactide-co-glycolide)-b-poly(ethylene glycol)-b-poly(d,l-lactide-co-glycolide) (PLGA-PEG-PLGA) micelles	PLGA-PEG-PLGA triblock copolymer was initially synthesized by an ester linkage ring-opening method. Curcumin micelles were obtained by encapsulating curcumin in PLGA-PEG-PLGA micelles using a dialysis method	Plasma levels of curcumin micelles were increased by 1.31-fold compared with curcumin solution. Brain biodistribution of curcumin micelles was also increased almost 6.28-fold	Song et al. (2011)
Inhalation			
FMeC1	Aqueous solution containing perfluoro curcumin analog (FMeC1) was pumped through a center-flow atomizer to alleviate the problem of trans-blood–brain barrier delivery	Aerosolized FMeC1 modestly improved brain biodistribution of the compound, which bound to β-amyloid in the hippocampus and cortex	McClure et al. (2015)
Gel			
Thermosensitive curcumin nasal gel	Nasal hydrogel was prepared by mixing curcumin ethanol/PEG400 solution with Pluronic F127 and Poloxamer 188	Targeting efficiency of curcumin hydrogel in the cerebrum, cerebellum, hippocampus, and olfactory bulb was 1.82, 2.05, 2.07, and 1.51 times greater, respectively, than after intravenous administration	Chen et al. (2013)

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Conclusions

Curcumin is one of the most studied phytochemical agents in the spice turmeric, displaying complex and multifaceted activities. There have been many reports on curcumin and its roles in AD. This review highlights the unique photophysical, chemical, and biological activities of curcumin as well as its properties throughout the course of AD. It shows high-affinity binding to Aβ and a strong fluorescence signal, making it a powerful diagnostic tool for AD. Many curcumin tracers have been developed to assess Aβ deposits *in vivo*, including the ^{18}F curcumin derivatives, FMeCl and CRANAD-X. These probes have sufficiently long excitation and emission wavelengths for deep brain imaging, reasonable BBB permeability, low toxicity, and reasonable stability. Moreover, CRANAD-58 and CRANAD-3 can detect both soluble and insoluble Aβ species. Further, CRANAD-28 and FMeC1 play a dual role in imaging and therapy. There is concern that reduction of Aβ burden by curcumin derivatives may interfere with Aβ imaging. However, Aβ imaging is performed in the early hours after administration of curcumin derivatives, and its effect on Aβ levels is likely to be minimal at 6 months (Yanagisawa et al., 2011; Zhang et al., 2014). In contrast, prevention and treatment of Aβ requires long-term curcumin administration (Yanagisawa et al., 2015). Curcumin is abundant in an Asian-type diet and may reduce AD risk, consistent with lower AD prevalence in India. Evidence also suggests that curcumin consumption has diverse potential health benefits in the aged population. Apart from its role in diagnosis and prevention, curcumin acts in AD therapies as an antioxidant, anti-inflammatory agent, inhibitor of Aβ aggregation, and chelator of metal ions. Taken together, current research suggests that curcumin is one of the most promising and exciting compounds for development of AD therapeutics.

To date, one clinical study has evaluated the sensitivity and specificity of curcumin fluorochrome in retinal Aβ imaging. This study obtained positive results and has encouraged more clinical trials of curcumin-related Aβ probes in brain imaging. Besides, curcumin shows potential beneficial effects on human health, which may reduce risk factors of AD, and make it a life-long anti-aging nutraceutical. Although curcumin has multifaceted biological activity in AD animal models, its treatment in AD patients remains a challenge, and development of early AD diagnosis and new curcumin formulations are an active area of research.

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