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Research Paper

Short-term Efficacy of Commercial Curcumin Nanomicelle on Cognition, Oxidative Stress and Choline Esterase in Alzheimer's Disease

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ABSTRACT

Introduction: Alzheimer's disease (AD) is a progressive neurodegenerative disease accompanied by cognitive dysfunction. Preclinical changes can precede the onset of clinical symptoms by decades, highlighting the need for preventative and therapeutic strategies to mitigate or delay disease progression. This pilot clinical trial aimed to investigate the effects of commercially available curcumin nanomicelles on oxidative stress pathways and serum cholinesterase levels in patients with AD.

Methods: Fifteen volunteers with mild-to-severe AD and 15 age-matched healthy controls were enrolled. Participants with AD received 80 mg of thermodynamically stable 10 nm curcumin nanomicelles on alternate days for two months. Cognitive function, as assessed by the mini-mental state examination (MMSE), did not exhibit significant changes in patients with AD following curcumin nanomicelle administration (19.8 versus 20.6). Serum levels of oxidative stress biomarkers, including catalase (CAT), superoxide dismutase (SOD) inhibition, malondialdehyde (MDA) concentration, and cholinesterase activity, were evaluated before and after intervention.

Results: The results showed no significant differences in cognition improvement, CAT activity, SOD inhibition, MOD concentration, or cholinesterase activity between patients with AD and healthy controls or before and after curcumin nanomicelle administration.

Conclusion: Although curcumin nanocarriers did not enhance antioxidant biomolecule levels, they did not provoke lipid peroxidation. Therefore, this study suggests that optimizing nanocarrier parameters, including concentration, particle size larger than 10 nm, and blood-brain barrier (BBB)targeting, warrants further investigation in a long-term study to explore their potential as supplemental therapies for AD.

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Highlights

- Commercial curcumin nanomicelles do not change the score of the MMSE questionnaire.
- Commercial curcumin nanomicelles do not induce lipid peroxidation.
- Commercial curcumin nanomicelles do not enhance oxidative stress biomarkers or cholinesterase activity in AD.
- No difference is observed between the levels of oxidative stress biomarkers and cholinesterase activity in healthy and AD patients.
- Optimal concentration and particle size larger than 10 nm may improve the outcomes.

Plain Language Summary

With the increase in the number of aged people, we expect a high rise in brain diseases such as Alzheimer's disease (AD). It is predicted that, by 2050, over 100 million people will be suffered from AD. Therefore, it is important to find new ways to prevent or slow down AD. One natural compound that has shown promise in lab studies is curcumin, which is one of the primary ingredients in turmeric. Curcumin is known for its ability to fight inflammation and act as an antioxidant, and has the potential to reduce the harmful protein clumps (Aβ plaques) often found in the brains of AD patients. This study aimed to see if nano-sized curcumin (called nanomicelles) can help people with mild to severe AD. Our findings showed that, after two months of taking 80 mg of 10 nm nano-curcumin, there was no significant change in either the memory and thinking abilities or in blood markers compared to the pre-treatment phase or healthy controls. It may be due to the form and dose of curcumin or the duration of consumption. The product did not induce adverse effects. This helps guide future research, preventing others from repeating the study and encouraging them to explore different approaches, such as higher doses, longer treatment periods, or various forms of curcumin and particle size, or to focus on other potential treatments for AD.

1. Introduction

Dementia encompasses a constellation of clinical symptoms, including impairments in memory, problem-solving, cognitive abilities, communication, eating, and mobility. Alzheimer's disease (AD) constitutes a significant proportion of dementia cases, accounting for an estimated 60-780% of all dementia diagnoses (Silva et al., 2019). Epidemiological projections estimate that 6.2 million individuals will be affected by AD in the US by 2021 (Association, 2010). Furthermore, AD is considered the sixth leading cause of mortality in the US. In Iran, the mortality rate attributed to AD was 25.34 per 100000 individuals in 2019 (Balooch Hasankhani et al., 2022). The annual cost of care for patients with AD in the US was estimated at 15.3 million hours and 256.7 USD billion in 2020, increasing to 355 billion USD in 2021 (Wiley, 2021). The prevalence of AD in India is significantly lower (4.4 times) than in the US, potentially attributable to the frequent consumption of spices, such as turmeric, in the Indian diet (Ege, 2021). In Iran, an estimated 2%-3% of the population aged 67-78 years' experience AD, with healthcare costs for these individuals exceeding those of the general population by a factor of three (Navipour et al., 2019). In other words, the cost of AD healthcare in Iran ranges from 434 to 2480 USD, depending on the stage of the disease (Aajami et al., 2019). Notably, the age-standardized incidence rate for AD is decreasing in men, while the Age-Standardized Mortality Rate is increasing in women in Iran (Balooch Hasankhani et al., 2022).

AD is a progressive neurodegenerative disorder characterized by selective neuronal loss and cognitive decline. Degenerative physiological changes can begin several decades before the manifestation of clinical symptoms (Wiley, 2021). Consequently, preventative strategies aimed at mitigating or delaying the onset of AD symptoms are of significant importance. The molecular hallmark of AD is the accumulation of tau protein tangles within neurons and Aβ plaques in the extracellular space of the brain, leading to neuronal death (Wiley, 2021). While reactive oxygen and nitrogen species are essential for normal cellular function at basal levels, aberrant changes in their levels can contribute to cellular and neural damage, as observed in AD. For instance,

reactive lipid species generated by lipid peroxidation and peroxynitrite (ONOO-) accumulate in the brains of patients with AD, contributing to neuronal damage. Malondialdehyde (MDA), a product of polyunsaturated fatty acid peroxidation, is another marker of oxidative stress in patients with AD (Tavakol et al., 2022).

Cells employ various biomolecules, including catalase (CAT) and superoxide dismutase (SOD), to counteract the detrimental effects of oxidative stress. Mitochondrial SOD (MnSOD) and CAT are responsible for scavenging superoxide radicals and H_2O_2 (Lee et al., 2012). Consequently, SOD levels are crucial for mitigating oxidative stress in neurons and potentially slowing AD progression. Overexpression of SOD in transgenic mice of AD model improves spatial memory and CAT activity, while decreasing oxidized and amyloid proteins (Dumont et al., 2009). Beyond oxidative stress homeostasis, the levels of cholinergic proteins, such as acetylcholine (ACh), are crucial for transmitting synaptic signals. Degeneration of cholinergic neurons in the basal forebrain and increased acetylcholinesterase (AChE) activity surrounding amyloid plaques contribute to amyloid toxicity and AD progression (Melo et al., 2003).

Despite extensive research efforts in neuropharmacology and pharmacology, effective treatment of neurodegenerative diseases and disorders remains a significant challenge (Hamidpour et al., 2024; Tavakol et al., 2014, Tavakol et al., 2022, Tavakol et al., 2017; Tavakol et al., 2023). While therapeutic agents are crucial, preventative strategies that delay disease progression are highly desirable. Curcumin, a polyphenolic compound derived from turmeric root, possesses anti-inflammatory, antioxidant, and anti-amyloid properties (Tavakol et al., 2019). Both curcumin and its nanoformulation have been explored as potential alternatives to anti-amyloid antibodies for labelling amyloid-beta (Aβ) plaques in imaging studies, offering advantages over conventional dyes such as Congo red and thioflavin-S (Maiti et al., 2016). However, curcumin's clinical application is hindered by several limitations, including rapid metabolism, poor solubility and bioavailability, sensitivity to light, metal ions, alkaline conditions and heat, physicochemical instability, and rapid degradation (Flora et al., 2013; Karthikeyan et al., 2020).

While a comprehensive search of ClinicalTrials.gov website reveals a substantial number of registered studies (2759) about AD, only five specifically investigate the effects of curcumin on AD. Four additional clinical trials evaluating curcumin's impact on AD have been reported in the literature but are not currently registered on ClinicalTrials.gov website (Brondino et al., 2014). To the best of our knowledge, only one clinical trial has been identified to date that evaluated the efficacy of nano-curcumin in patients with AD, utilizing solid lipid nanoparticles (NPs) (NCT01001637). Despite promising preclinical findings in animal models (Chen et al., 2018), a long-term, 6-month study involving curcumin consumption in AD patients did not demonstrate significant improvements in clinical symptoms (Baum et al., 2008). This lack of efficacy is attributed, in part, to curcumin's poor water solubility, physicochemical instability, and high Log P value, resulting in limited bioavailability.

To overcome these limitations and enhance curcumin's water solubility and bioavailability, encapsulation into nanocarriers, such as nanomicelles, has emerged as a promising strategy. Several studies have investigated the efficacy of nano-curcumin in AD. For instance, PEGylated curcumin NPs made from polylactic acid have been shown to inhibit the production and depolarization of Aβ plaque fibers in PC12 cells (Yang et al., 2021). Moreover, the encapsulation of curcumin in poly-lactide-co-glycolide (PLGA)-selenium NPs reduced Aβ load and memory deficits in a mouse model of AD (Huo et al., 2019). Furthermore, encapsulation of curcumin into PLGA NPs has been shown to exhibit an anti-amyloid effect via the Wnt/β-catenin pathway in rat models of AD (Tiwari et al., 2014).

This study employed commercially available curcumin nanomicelles, characterized and subsequently administered to patients with AD. This study focused on assessing the impact of curcumin nanomicelles on cholinesterase activity. Given curcumin's established role in mitigating oxidative stress within cells, this study further examined the effects of curcumin nanomicelles on enzymes implicated in oxidative stress pathways, including SOD, CAT, and MDA.

2. Materials and Methods

General experimental procedures

Nano curcumin (Sina curcumin) from Exir Nano Sina Company (Tehran Province, Iran), as well as CAT, MDA, and SOD kits were purchased from ZellBio GmbH (Germany). A cholinesterase assay kit was purchased from Pars Azmon Kit (Karaj City, Tehran Province, Iran). The dynamic light scattering instrument was from ZetaSizer, Malvern, UK.

Nanocurcumin characterization: Particle size and zeta potential, entrapment efficacy and drug release studies in water, simulated gastric fluid (SGF), and simulated intestinal fluid

Commercial nano-curcumin (Sina curcumin) was a gift from Exir Nano Sina Company (Tehran Province, Iran). Hatamipour et al. characterized the nanomicelles of Sina Curcumin as follows. In brief, the hydrodynamic particle size was determined using dynamic light scattering (ZetaSizer, Malvern, UK) at a wavelength of 633 nm under normal and accelerated conditions (Hatamipour et al., 2019).

The entrapment efficacy of the nanomicelles was determined using ultrafiltration. The molecular weight of the centrifugal filter was 12 KD. The diluted nanomicelles with 5% dextrose were added to a centrifugal filter and centrifuged at 4000×g for 30 minutes. High-performance liquid chromatography (HPLC) was used to determine the amount of free curcuminoids that crossed the filter. The percentage of entrapment efficacy formula was calculated as follows (Equation 1):

1. *Entrapment efficacy % = (Total drug concentration-Supernatant drug concentration/Total drug concentration)×100*

The release profiles of curcuminoids from nanomicelles were evaluated in SGF and simulated intestinal fluid (SIF). The pH of SGF and SIF was adjusted to 2.2 and 6.8, respectively. The release profile was studied for 72 h, and the number of released curcuminoids was evaluated using HPLC. All characterization experiments were performed in triplicate. The mean and SD were reported and analyzed (Hatamipour et al., 2019).

Clinical trial study

Participants

Fifteen subjects with mild to severe probable AD were enrolled at the Neurology Clinic of Firoozgar Hospital (Tehran, Iran). In addition, 15 healthy subjects were age-matched and served as the control group.

Inclusion and exclusion criteria

The inclusion criteria for the intervention group included male-female aged >65 years, diagnosed with AD using a Mini-Mental State Examination (MMSE) questionnaire and neurologist confirmation, liver problems, and not being treated with aspirin and anticoagulants. However, the inclusion criteria for the control group included a range of intervention groups and the absence of AD.

The exclusion criteria for the intervention group included death, discontinuation of treatment for more than a week, instability of patients with curcumin, and allergic reactions to nano curcumin.

Intervention

Patients took medications prescribed by their physician during the study and used nano-curcumin as a supplement. Patients with AD took a Sina curcumin (80 mg) capsule for eight weeks on even days (three times a week).

MMSE questionnaire for cognition evaluation consumption and Smoke

The age, weight, and height of patients were studied in both groups. The MMSE is a relatively easy and quick assessment tool that evaluates cognition. It was performed before and after curcumin administration in patients with AD over two months. Briefly, the MMSE assesses orientation to time and place, registration, attention and calculation, recall, repetition, language (including reading and writing), and copying. MMSE scores were evaluated and compared before and after curcumin consumption in patients with AD.

Blood collection

At the time of enrollment and after the study's termination, 5 mL of blood was collected from patients to prepare serum. Blood was centrifuged, and the serum was isolated and stored at -80 ˚C until analysis.

Oxidative stress analysis

CAT activity

CAT is an antioxidant heme enzyme found in the peroxisomes of human tissues. It breaks down hydrogen peroxide into water and hydrogen. Therefore, it protects tissues from the disruptive effects of reactive hydroxyl radicals (Goyal & Basak, 2010). CAT activity was measured using a Zell-Bio GmbH (Germany) assay Kit. This was performed using a manual kit. In brief, serum was diluted with assay buffer at a ratio of 1:5. The standards were then diluted with assay buffer (1:20). Then, 25 µL of serum was mixed with 25 µL of hydrogen peroxide reagent in duplicate wells and incubated at room temperature for 30 minutes. Then, 25 µL of the substrate and 25 µL of horseradish peroxidase (HRP) reagent were added to each well and incubated at room temperature for 15 minutes. Absorbance was measured using a microplate reader at a wavelength of 560 nm. The activity (U/mL) was calculated using a formula derived from the standard curve. CAT activity was analyzed in duplicate, and the values provided are the normalized Mean±SD.

SOD inhibition

Superoxide is a harmful byproduct of cellular oxygen metabolism. SOD catalyzed the dismutation of superoxide to hydrogen peroxide and molecular oxygen (Younus, 2018). A SOD colorimetric assay kit was purchased from ZellBio GmbH (Germany). Briefly, standards were prepared using a manual kit. Ten microliters of serum, 50 µL of the substrate working solution, and 25 µL of xanthine oxidase were added to each well and incubated at room temperature for 20 minutes. The absorbance was measured using a microplate reader at 450 nm. The concentration was calculated using the following formula (Equation 2):

2. SOD inhibition = (Mean OD of sample/Mean OD of zero standard) ×100

SOD inhibition was analyzed in duplicate, and the values provided are the normalized Mean±SD.

MDA concentration

MDA is the final byproduct of polyunsaturated fatty acid peroxidation and arachidonic acid. Therefore, it is considered an index of oxidative stress (Maurya et al., 2021). An MDA/thiobarbituric acid reactive substance colorimetric assay kit was purchased from ZellBio GmbH (Germany). Analysis was performed according to the manufacturer instructions. In brief, 50 µL of serum, 50 µL of sample diluent, and 50 µL of TBA substrate were added to each well and incubated at 37 ˚C for one h with shaking. The absorbance was read using a microplate reader at 535 nm. The concentration (µM) was calculated using the formula derived from the standard curve. MDA concentration was analyzed in duplicate, and the values provided are the normalized Mean±SD.

Choline esterase activity

Choline esterase is an enzyme involved in the degradation of choline-based esters, which are crucial for neurotransmission (Kondapalli & Sruthi, 2020). The choline esterase activity (U/L) was determined using the butyryl thiocholine technique with a Pars Azmon kit (Karaj, Tehran, Iran). Briefly, two reagents, A and B, and serum were added to the wells. After incubation, absorbance was measured at 405 nm using a microplate reader. Cholinesterase activity was analyzed in duplicate, and the values provided are the normalized Mean±SD.

Statistical analysis

SPSS software, version 23 was used to analyze the data related to oxidative stress and cholinesterase. A paired t-test was used to compare the results before and after the intervention with those of the control and patients. Statistical significance was set at $P<0.05$.

3. Results

Nanoparticle characterization

Hatamipour et al. characterized the nanomicelles of Sina curcumin. They reported that the particle size of the nanomicelles was 9.5±0.1 nm and that it remained unchanged during the 24-month incubation period under both normal and accelerated conditions for 6 months. The percentage of entrapment efficacy was 100±0% (Hatamipour et al., 2019).

The drug release study in SGF showed an 18% release of curcumin from the micelles by 72 h, while the curcumin release from the nanomicelles was 11% when they were kept in SIF. Moreover, curcumin release from the nanomicelles was 2% after six h in both SGF and SIF (Figures 1a, 1b, and 1c) (Hatamipour et al., 2019).

Cognitive function score

Table 1 presents the demographic information. The MMSE questionnaire was administered to patients with AD to evaluate the effect of curcumin nanomicelles on cognitive impairment. The scores showed that curcumin naomicelles did not significantly change the MMSE scores in patients with AD (P=0.730). No change was observed in orientation to time (P=1.00) and place (P=0.644), registration (P=0.541), recall (P=0.756), nomination (P=1), repetition (P=1), conception (P=0.517), reading (P=1), writing (P=1), copying (P=0.726) or attention (P=0.796) (Table 2).

Oxidative stress response before and after intervention

CAT activity

CAT activity as an oxidative stress index was evaluated in patients before and after the intervention. The results indicated no significant difference in CAT activity among patients with AD who received nanocurcumin treatment (P=0.268). In contrast, no significant difference was observed in the CAT activity between the control and intervention groups eight weeks posttreatment with nanocurcumin in patients with AD (P=0.745) (Figure 2a).

Table 1. Demographic data in the control and AD patients' groups

Variables	n=15	Minimum	Maximum	Mean±SD
Age (y)	AD	65	80	72.8667±5.06905
	Control	65	92	70.666±8.8533
Weight (kg)	AD	47	90	65.3333±12.99267
	Control	52	85	70.666±9.05276
Height (cm)	AD	154	185	165.2±8.95385
	Control	157	185	168.26±7.62952

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SOD inhibition

SOD inhibition, as an oxidative stress index, showed no significant difference in SOD inhibition before and after nanocurcumin administration (P=0.787). Furthermore, no significant difference was observed in SOD inhibition between the control and intervention groups at eight weeks posttreatment with nanocurcumin in patients with AD (P=0.621) (Figure 2b).

MDA concentration

As a final byproduct of lipid peroxidation, the results derived from MDA concentration showed no significant difference in the amount of MDA in patients with AD when they took nanocurcumin in the short term (P=0.924). However, no significant difference was observed in the amount of MDA between the control and intervention groups by eight weeks posttreatment with nanocurcumin in AD patients (P=0.957) (Figure 2c).

Table 2. MMSE scores before and after curcumin nanomicelle consumption in AD patients

Criteria	Mean	
	Before (n=15)	After (n=15)
Orientation to time	3	3
Orientation to place	3.8	4
Registration	2.6	2.8
Recall	0.4	0.5
Nomination	2	2
Repetition	0.8	0.8
Conception	2.7	2.8
Reading	0.8	0.8
Writing	0.7	0.7
Copying	0.4	0.5
Attention	2.3	2.5
Total score	19.8	20.6

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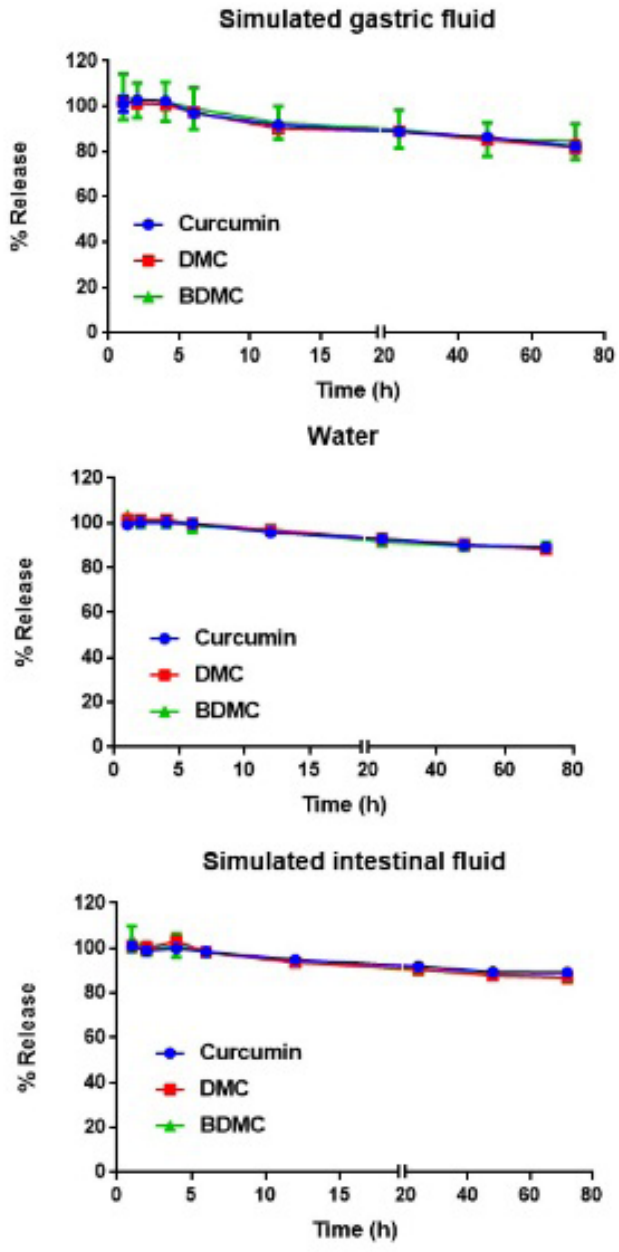

Figure 1. Release profile of curcumin and its ingeridents

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a) Release profiles of demethoxycurcumin (DMC), Bisdemethoxycurcumin (BDMC) and curcumin in SGF, b) Water, c) SIF at 0, 1, 2, 4, 6, 12, 24, 48 and 72 h

Note: The figure was reused from (Hatamipour et al., 2019), and permission was received.

Choline esterase activity

Choline esterase is an enzyme involved in choline degradation, and butyrylcholine esters were evaluated. The data showed no significant difference between choline esterase activity in AD patients before and after the prescription of nanocurcumin (P=0.549). Moreover, no significant difference was observed between cholinesterase activity in the healthy control and AD patient groups (P=0.088) (Figure 3).

4. Discussion

AD is a progressive neurodegenerative disorder typically diagnosed when degenerative physiological changes in the brain have been underway for approximately three years (Beason-Held et al., 2013). To effectively design and select an ideal therapeutic agent, a thorough understanding of the underlying cellular mechanisms beyond disease pathology is essential. The brain, consuming approximately 20% of the body's total oxygen,

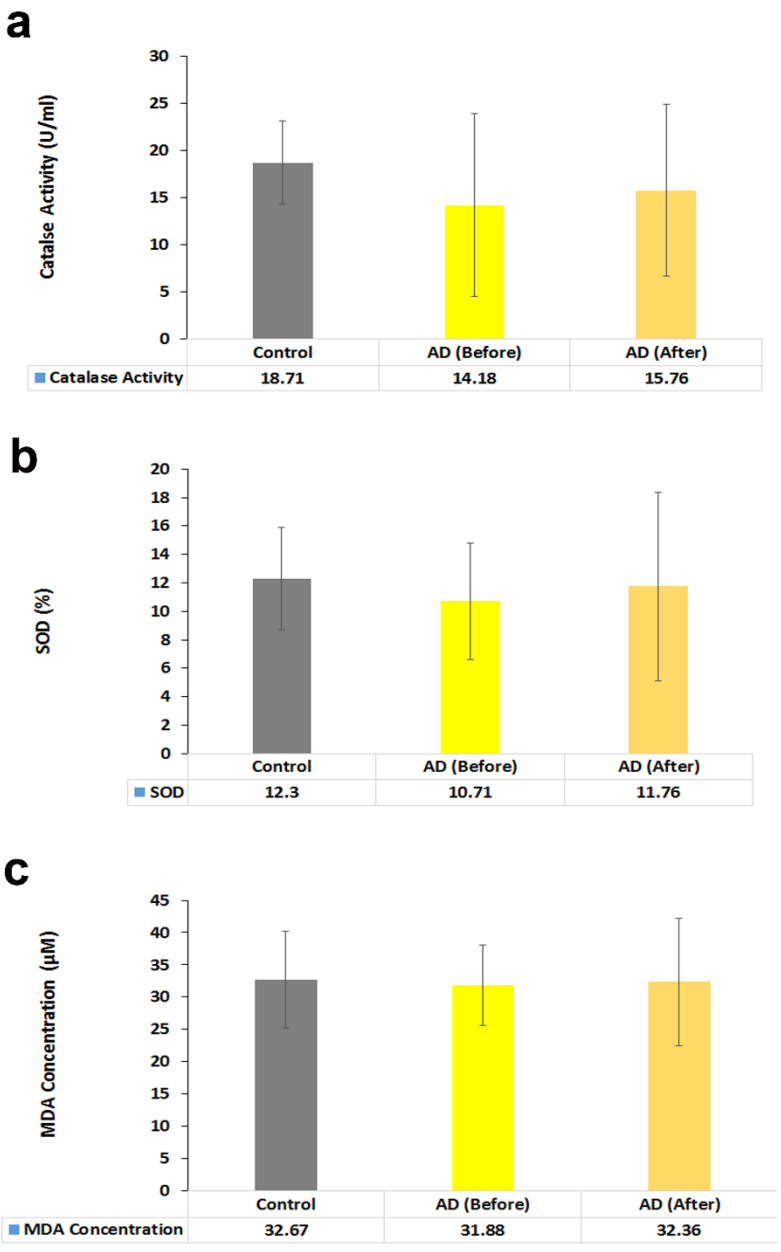

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Figure 2. CAT activity, SOD inhibition, and MDA concentration in the serum of healthy controls and AD patients before and after nano-curcumin administration

a) CAT activity in the serum of AD patients before and after nanocurcumin administration indicating the non-significant difference before and after of the nanocurcumin prescription; in addition, no significant difference was observed between the healthy control and patients.

b) SOD inhibition in the serum of AD patients before and after nanocurcumin administration indicating the non-significant difference before and after of the nanocurcumin prescription; in addition, no significant difference was observed between the healthy control and patients.

c) MDA concentration in the serum of AD patients before and after nanocurcumin administration; nanocurcumin did not induce a significant difference in SOD, indicating the non-significant difference before and after of the nanocurcumin prescription; In addition, no significant difference was observed between the healthy control and patients.

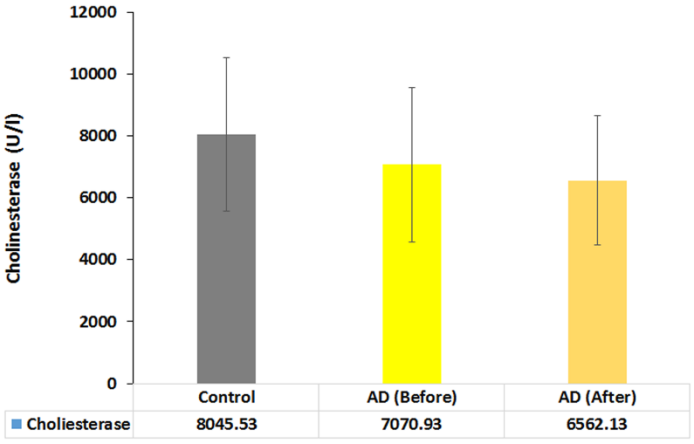

Figure 3. Cholinesterase activity in the serum of AD patients before and after nanocurcumin administration

Note: Nanocurcumin did not induce a significant difference in cholinesterase activity. In addition, no significant difference was observed between the healthy control and patients.

is particularly susceptible to oxidative damage. CAT and SOD play crucial roles in scavenging the byproducts of oxidative stress.

Our results revealed no significant changes in cognitive scores following the administration of curcumin nanomicelles to patients with AD. Furthermore, no significant differences were observed in cholinesterase, SOD, or CAT levels after curcumin nanomicelle administration in patients with AD. These data suggest that 10 nm curcumin nanomicelles, administered at a concentration of 80 mg every two days, did not significantly alter SOD and CAT activity over two months. The concentration of MDA, a byproduct of lipid peroxidation, remained unchanged. This indicates that curcumin nanomicelles did not induce or exacerbate lipid peroxidation, suggesting their potential safety in terms of extra lipid peroxidation.

Curcumin exhibits antioxidant properties and has a high affinity for Aβ plaques, effectively inhibiting plaque aggregation (McClure et al., 2017; Mei et al., 2020; Yanagisawa et al., 2011). However, the efficacy of these actions hinges on the ability of curcumin to cross the blood-brain barrier (BBB) and maintain its concentration within the target brain regions. Research has demonstrated that NP size, targeting functionalization, and payload drug concentration within the brain are critical factors for efficient drug delivery in AD. As mentioned earlier, the present study employed 10 nm nanocarriers. While studies have indicated that the optimal particle size for BBB passage is approximately 40 nm or less, nanocarriers smaller than 10 nm may be filtered by the kidneys, hindering their optimal retention in the brain (Danaei et al., 2018).

The optimal concentration of curcumin in the brain is another critical consideration. Studies have demonstrated that curcumin concentrations of 500 nM and 100 μM in the brain can promote and inhibit neurogenesis, respectively, in animal models of AD (Begum et al., 2008). Therefore, both excessively high and low curcumin concentrations may be ineffective. The encapsulation of curcumin within nanocarriers has been shown to significantly enhance its payload in the brain, resulting in notable improvements in cognitive function (90%) and AChE inhibition (52%) (Kakkar et al., 2013). Nanoencapsulation of drugs enhances both the bioavailability and retention time of curcumin in the brain (Tsai et al., 2011). Certain nanocarrier systems, such as curcumin lipid NPs, demonstrate an enhanced affinity for Aβ plaques compared to free curcumin, leading to a decline in Aβ aggregation (Maiti et al., 2018). To achieve successful delivery of nano-curcumin to the brain, targeted delivery strategies are recommended. Lactoferrin, T807 molecules, insulin, transferrin, and integrin receptors, Tet-1 peptide, B6 peptide, odorranalectin, and N-trimethyl chitosan are all potential targeting agents for functionalizing nanocarriers to facilitate BBB crossing (Ege, 2021). For example, functionalization of pegylated poly(lactic-co-glycolic acid) (PLGA) NPs with the B6 peptide (Orlando et al., 2012) or transferrin-Tet-1 has been shown to significantly enhance brain uptake of curcumin compared to their non-targeting counterparts (Ramalingam & Ko, 2015).

Although several successful preclinical studies have been conducted related to the improvement of cognition using curcumin NPs, clinical findings have been controversial regarding the effectiveness of curcumin

in patients with AD and healthy subjects, in part owing to structural changes in the BBB or involved signalling pathways in patients with AD, indicating the necessity of targeted delivery to the brain (Goozee et al., 2016; Voulgaropoulou et al., 2019). In a clinical trial, 1500 mg of curcumin (Biocurcumax™) and a placebo were administered to 160 individuals without cognitive impairment. The results at six months indicated that the intervention group did not show a decline in cognition, while the placebo group showed a decline in cognitive function (Rainey-Smith et al., 2016). In other words, although curcumin did not improve cognition, it stabilized cognition for six months as a protective agent (Reddy et al., 2018). Evaluation of cognitive function, working memory, and sustained attention in healthy older individuals who were administered solid lipids of curcumin (Longvida®, 80 mg/day) showed that on the one hand, four weeks after consuming Longvida®, working memory, sustained attention, and mood improved. However, these results were not significant three h post-treatment (Cox et al., 2015). Another study on healthy individuals showed that administrating curcumin (Theracurmin®, 90 mg twice a day) for 18 months decreases amyloid and tau accumulation in the brain, while improving short-term memory, attention, visual, and verbal functions (Small et al., 2018).

A clinical trial involving individuals with AD demonstrated that administrating curcumin (2-4 g/day) for six months did not result in significant changes in cognitive function, tau levels, or Aβ concentrations in the plasma and cerebrospinal fluid of patients with mild to moderate AD (Ringman et al., 2012). Similarly, *Baum et al. (2008)* reported that administering 1 or 4 g of curcumin to individuals with progressive cognitive impairment did not significantly alter MMSE scores after six months despite an observed enhancement in vitamin E levels compared to the placebo group. Furthermore, serum Aβ1-40 levels did not significantly increase. This study is the first pilot clinical trial to evaluate the efficacy of curcumin nanomicelles on cognitive function and oxidative stress. These results align with previous research investigating the efficacy of curcumin in patients with AD, indicating that no significant differences were observed in MMSE scores.

5. Conclusion

The ageing global population is projected to lead to a significant increase in neurodegenerative diseases, including AD. Projections indicate that the number of individuals affected by dementia and AD will reach 152 million and 106.8 million, respectively, by 2050. Therefore, identifying preventative and therapeutic agents capable of inhibiting or slowing AD progression remains a critical research priority. Curcumin, with its established antioxidant, anti-inflammatory, and anti-Aβ plaque properties, holds promise as a potential therapeutic agent. However, its poor solubility and bioavailability pose significant challenges. Encapsulating curcumin within nanocarriers has emerged as a promising strategy to address these limitations. Our study suggests that further optimization of nanocarrier parameters, including particle size and administration duration, is crucial for achieving clinical efficacy. Specifically, the development of curcumin nanoparticles exceeding 10 nm in size, functionalized with BBB-targeting biomolecules, such as transferrin and Tat-1, warrants further investigation. Additionally, identifying the optimal concentration of curcumin NPs that induce neurogenesis, exhibit antioxidant and anti-Aβ plaque activity, and possess anticholinesterase potential is essential. Although there seems to be a long way to go to optimize curcumin NPs for treating AD in the clinic, it is not far off. The results of our study serve as a beacon for future research, highlighting the need to optimize particle size, targeting agents, concentration, and duration of administration of curcumin nanocarriers.

Ethical Considerations

Compliance with ethical guidelines

The Ethics Committee approved this controlled clinical trial by the Department of Toxicology and Pharmacology, Faculty of Pharmacy and Pharmaceutical Sciences, Tehran Medical Sciences Branch, Islamic Azad University, Tehran, Iran (Code: IR.IAU.PS.REC.1396.98). The protocol was explained to all participants, and they enrolled after providing written informed consent.

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Authors' contributions

Material preparation, data collection, and analysis: Samira Kazemi and Narges Hesni Langroudi; Writing and providing technical assistance: Kamran Tavakol and Sepide Arbabi Bidgoli; Analyzing MMSE questionnaire: Peyman Hasani Abharian; Data analysis: Mohammad Taghi Joghataei; Supervision, study design and data interpretation: Sepide Arbabi Bidgoli and Shima Tavakol.

Conflict of interest

The authors declared no conflict of interest.

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