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Neurocognitive Effects of Curcumin in Alzheimer's Disease

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ABSTRACT

Background: *The rise in population ageing has led to an increase in neurodegenerative diseases and dementia such as Alzheimer's Disease (AD). Alterations in cognitive processes occur underpinning memory, attention, perception and problem-solving processes [1]. AD affects approximately 50 million people and is more prevalent in Western Europe rather than Asia and Africa [2]. It remains a complex disease with environmental and genetic factors accounting for its pathogenesis. It is manifested either sporadically (95%) or hereditary (5%) with gene mutations in the Amyloid Precursor Protein (APP) or presenilin genes (PS1, PS2) [3].*

Keywords: Aβ- amyloid, Tau proteins, Pathogenesis, Neurocognitive, Alzheimer's disease

INTRODUCTION

AD histological studies have due Aβ mutations, c) calcium dysregulation hypothesis due to ageing, oxidative stress or presenilin dysfunction and d) tau shown the presence of amyloid plaques and neurofibrillary tangles being responsible for neuronal inflammation. These plaques have two protein components; Aβ-amyloid (Aβ) and tau proteins that promote plaque destabilisation [4]. Aβ protein is produced from the amyloid precursor protein (APP) cleavage by β- and γ-secretases. The accumulation of small Aβ peptides causes synaptic dysfunction in AD [5] Moreover, tau protein aggregation (a neuronal actin microtubule stabilising protein) occurs due to abnormal regulation of its phosphorylation. In AD, hyperphosphorylated tau in neurofibrillary tangles is observed. These proteins activate microglia, astrocytes and cytokines are produced including the tumour necrosis factor (TNF-a) and interleukins (IL-6); leading to an inflammatory cascade driving neuronal death [6]. Figure 1 summarizes the AD pathogenesis hypotheses

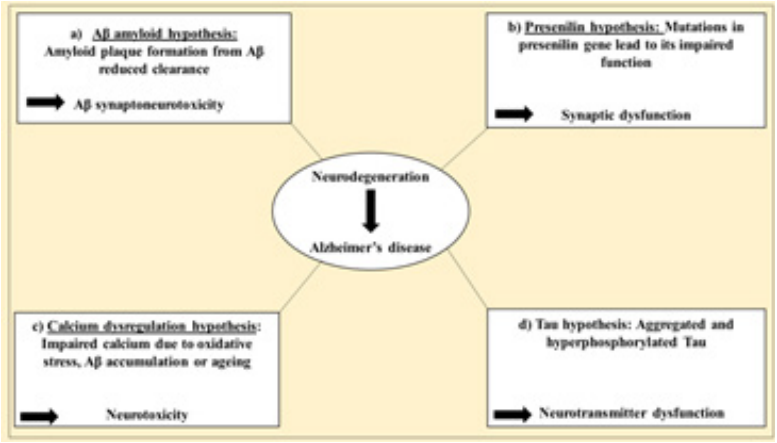

Figure 1: (Modified from (Kocahan and Doğan 2017): AD pathogenesis hypotheses leading to neurotoxicity and neurodegeneration. Specifically, a) Aβ- amyloid hypothesis with Aβ overproduction or reduced clearance, b) presenilin hypothesis with impaired presenilin function hypothesis due to aggregated and hyperphosphorylated tau

Although substantial investment is placed in AD pharmacotherapy (cholinesterase inhibitors-donepezil, NMDA receptor antagonists- memantine and monoamine oxidase inhibitors), there are limitations relating to drugs' side effects, administered dose and patients' response. Polyphenol compounds such as curcumin have been in the spotlight as possible candidates for treating AD. Curcumin is an antioxidant and herbal remedy polyphenolic compound present in the Indian curry spice turmeric [7]. Figure 2 summarizes curcumin's role in AD.

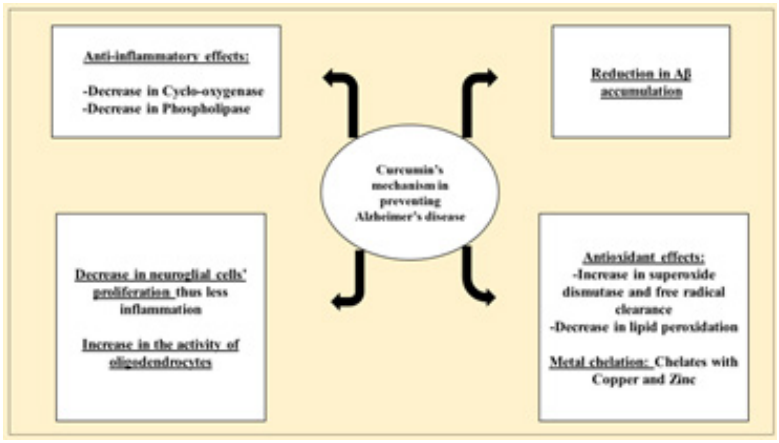

Figure 2: (Mishra and Palanivelu, 2008): Curcumin's mechanism of action in AD. It acts as an anti-inflammatory agent decreasing the activity of cyclo-oxygenase enzymes and phospholipase and reduces the production of Aβ plaques. Also, decreases neuroglial cells' proliferation while increases the activity of oligodendrocytes participating in cognitive processes. It has antioxidant properties by decreasing brain lipid peroxidation and the free radical formation by enhancing superoxide dismutase enzyme. It participates in metal chelation with copper and zinc

Transgenic mice studies with curcumin supplementation have shown memory improvements and reduction in inflammatory markers [8]. In vitro and in vivo studies have demonstrated curcumin's potential to reduce Aβ fibril formation by interfering with abnormal conformational changes of the Aβ 1-42 C-terminal region [9]. Moreover, animal studies have shown curcumin to suppress brain lipid peroxidation leading to a reduction in free radical formation and neuronal stress. Curcumin can inhibit the cyclo-oxygenase enzyme (COX-2) and nitric oxide synthase (iNOS), involved in brain inflammation [10]. Its mechanism of action is compatible with resveratrol a plant secondary metabolite- produced in response to stress [6] and ibuprofen- a non-steroidal anti-inflammatory drug. Curcumin does not cause toxicity at low doses and gets easily absorbed [11]. The use of long chain Ω3 fatty acids (PUFAs) including EPA and DHA might enhance curcumin's efficacy in reducing neuroinflammation [12].

AD brain slices show increased levels of Histone Acetyltransferases (HAT) and DNA methyltransferases (DNMT1), that control gene expression [13]. Curcumin acts as an inhibitor of DNMT1 and HAT, restoring histone post-translational modifications [6]. Evidence of curcumin's mechanism in preventing cognitive decline in human AD is still under research. Curcumin formulations are being explored for being capable to cross the blood brain barrier and enhance cognition [1]. Finally, the gut microbiome is currently being investigated for potential interaction with curcumin's systemic neuroprotective role. The following review aims to provide supportive evidence for curcumin's role in cognition and disease.

HYPOTHESIS/AIM

Dementia is the leading cause of Alzheimer's disease in the elderly. Although pharmacotherapy treatment is promising in alleviating AD symptoms, current emphasis is placed on the role of diet in cognitive decline. Curcumin, belonging to the polyphenol family has been explored for its anti-inflammatory and neuroprotective effects. Although several in vitro and In vivo studies have demonstrated curcumin's promising role in enhancing cognition, there are lots of inconsistencies. This review essay aims to investigate the current existing evidence from animal and human randomised controlled trials for filling the gap of curcumin's impact in cognitive improvement. The investigated hypothesis would be to conclude whether there is a positive link between curcumin's consumption in lowering

cognitive impairment in AD pathogenesis. There are two outcomes when it comes to test the above hypothesis. The primary outcome relates to improvements in cognition and memory processes and the secondary outcome aims to examine any significant differences in biochemical biomarkers (inflammatory markers) and brain activity upon curcumin administration. The following review provides supportive evidence for these arguments and aim to evaluate them in order to fill up the gaps in the presented literature. Finally, in the discussion section, strengths and limitations of the presented studies are highlighted and suggestions for improvements are given, allowing a better control in the experimental design.

ABOUT THE STUDY

To investigate the hypothesis of curcumin's role in improving cognition in AD, a systematic literature search was performed using 2 online databases (PubMed and Cochrane library online sites). Figure 3 highlights the steps of the methodical approach used to select scientific journals.

Step 1 Identifying the journal articles: The Cochrane Library and PubMed online websites were opened. In the search tab different phrase combinations were typed including: "curcumin and cognition", "curcumin and dementia", "curcumin and memory", "curcumin and Alzheimer's disease", "curcumin", "Alzheimer's disease".
Step 2 Journal screening: In the online databases menu, the year range was selected as the more recent (>2010). In PubMed the controlled clinical trial and review options were selected as well. Finally, approximately 17 journals were found in the Cochrane library and 120 in the PubMed.
Step 3 Journal selection: The title and the abstract of the above journals were reviewed as well as the study sample size, whether they were human/animal studies and their study design (*)
Step 4 Final result: From approximately 140 journals identified online, 5 animal and 5 human studies met the criteria of step 1 and were related to the topic being studied. A thorough screen of the journal contents was performed.

Figure 3: Workflow of the methodology used in the literature search (*) Journal selection criteria: The journals in the datasets were screened as to whether the study populations were elderly animals (e.g. rats, nematodes, mice) or elderly humans that either had symptoms of mild cognitive impairment or early-late onset AD. Human studies involving AD patients reported patients taking anti-inflammatory drugs and each study administered a different curcumin dose. Informed consent was obtained from all human patients in the beginning of the study

In the literature search, both human and animal studies were used because despite their physiological and cognitive differences, the latter provide substantial evidence of curcumin's mechanism in cognition which is further referred in the discussion section.

In this essay, an equal number of animal and human studies was used for discussion. Once the clinical studies were selected, two tables were designed in the results section (animal and human studies) in order to evaluate the investigated hypothesis. It should be mentioned that from the literature search, animal experiments and human controlled trials or reviews have been selected. There were not as many meta-analyses studies, which s standardized cognitive tests (mini mental test) and PET scans were used to assess cognitive function. The primary aim of the human studies was cognitive improvement upon curcumin administration while the secondary aim was a significant reduction in biochemical markers including tau protein, anti-inflammatory markers or changes in brain structures regulating to cogindicated further research is needed to that field. In animal studies, the use of the Morris Water maze test and in human studienitive processes, measured by neuroimaging techniques. The presented studies were used for formulating evaluating and improvement comments for supporting the hypothesis.

ANIMAL STUDIES

Scientific evidence and discussion

Animal studies allow to investigate curcumin's mechanism in cognition (Table 1). There were no significant differences in the results in all five studies. For instance, when 12-month-old mice were administered either 150 ppm or 1000 ppm curcumin dose for 6-months, a significant reduction in Aβ42 generation and improvements in working and spatial memory occurred in the highest curcumin dose [14]. Similar studies have demonstrated improvements in memory

performance in the highest curcumin dose followed by a reduction in inflammatory biomarkers [15]. Interestingly, in a study using 18 aged rats, acetylcholinesterase inhibition occurred when curcumin and donepezil AD drug were administered [16].

Table 1: Modified from Sarker and Franks: Summary of animal studies investigating the impact of curcumin in cognition

Author	Sample size	Curcumin dose	Biochemical result	Behavioural result
Wang et al. 2014	12 month old male and female APP/ PSI transgenic mice	150 and 1000 ppm for 3 months	Reduced AP42 generation (in higher doses) . Increased autophagy in the hippocampus. . Decreased expression of the AKT and PBK genes Significant improvement in spatial memo in the 1000 ppm curcumin group after using the Monis Water Maze test	Improvements in working and spatial mem01y at higher doses.
Miyasaka et al, 2015	56-60 C.elegans with transgenic human tau	10 µg/plate and 100 µg/plate	In the 1OOµg/curcumin plate group, a significant reduction in neuronal loss occurred. No effect on tua phosphorylation Increase in tubulin for microtubule stability	At high curcumin dose, a reduction in neuronal morphological abn01malities
Dong et al, 2012	15 rats (12-monthsyears old)	480 ppm for 6 and 12 weeks	The longer period of curcumin administration increased neurogenesis in the dentate gyrus In the 12-week curcumin group significantly higher social recognition and spatial memo1y skills occurred after using the Monis water maze task	Both periods had better social recognition index.
Sarker et al, 2015	19 male mice (15-months years old)	1000 ppm for 12 weeks, placebo or restricted cal01y diet (70% energy)	Decrease in the plasma CRP and IL-6 in the curcumin group Improved cognitive capacity linked to spatial memory in the hippocampus and c01tex after 8 weeks in the curcumin group after using the Moris Water Maze	Significant improvement in executive neuronal function
Naqvi et al, 2019	18 male rats	1000 mg/ kg for 7 days or donepezil at 1 mg/kg for 7 days	Both in the curcumin and donepezil groups, memorry in1provement (measured by the Moris Water Maze task) and acetylcholinesterase inhibition occuned although these effects were more potent in the curcumin group	Significant memorry improvement in the curcumin group

Human studies

Table 2 summarizes the human clinical trials with the primary outcome being cognitive function alterations and the secondary outcome changes in brain activity or blood biomarkers [18]. Although animal studies (Table 1) reflected no significant result inconsistencies, human randomised control trials showed mixed results. For instance, randomised control trials administering [19]. This is counteracted with studies using patients with mild AD patients different curcumin doses concluded no significant differences in cognition between the control and curcumin groups. However, the biochemical markers of vitamin E (antioxidant) and cholesterol levels dropped in the curcumin group (Baum dementia who showed memory improvements after curcumin dose. This reveals that in contrast to animal studies, curcumin in humans more potently improved memory in patients with mild dementia but in patients with mid/late AD no significant improvement occurred.

Table 2: Modified from Gooze et al, 2015 and Hamaguchi et al, 2010: Summary of human clinical studies investigating the role of curcumin in cognition [17-18]

Author	Sample size	Curcumin dose	Biochemical result	Side effects
Baum et al, 2008 (Randomized control trial)	34 AD patients for 6 months taking gingko leaf extract as a treatment	1000-4000 mg/day or placebo	• No difference in cognition between the placebo and the curcumin group after 6- month • Vitamin E levels increased in the curcumin group	3 patients withdrew due to minor GI problems

Hishikawa et al, 2012 (case study)	3 AD geriatric patients followed for 1year	100 mg/day or placebo	• After 12 weeks, mood improvement in the curcumin group and a decrease in dementia occurred. • Improvements in the Mini-Mental State • examination (MMSE) up to 5 points overall	Anxiety
Ringman et al, 2012 (randomized parallel control trial)	36 patients with mild and moderate AD taking acety!cholinesterase inhibitors and memantine	2000 or 4000 mg/day for 24 weeks	No difference in cognition between both groups after using the AD Assessment Cognitive scale after 24 and 48 weeks	Diarrhoea, joint pain but no other side effect reported
Cox et al, 2015 (randomized control trial)	60 healthy patients with no diagnosed dementia	400 mg or placebo	• One hour after curcumin administration , significant improvement in memory and mood occurred • Reduced total and LDL cholesterol	No reports
Small et al, 2018 (randomized control trial)	40 middle-aged patients with mild cognitive impairment	2 x 90 mg or placebo for 18 months	• Significant improvements in memory as measured by visual and verbal standardized tests occurred in the curcumin group • Mixed results regarding the change in the PET signals in both groups for the hypothalamus and 4 brain lobes.	No reports

DISCUSSION

Curcumin has drawn attention for its role in cognition. Although animal models provide substantial information regarding curcumin's role in cognitive improvement, it is difficult to compare with humans. Animal studies fail to show the exact mechanism of neuronal death that is manifested in humans, due animals' limited lifespan and the highly controlled experimental environment used. Although C. elegans and mice genome shows similarities to humans and transgenic gene expression can be conducted with the human presenilin gene, sporadic AD cannot be investigated which is the main human AD form. Rat magnetic resonance studies (MRI) reflected similarities in Aβ plaques and tau compared to humans but their response to AD treatment was different. This allows to explore different organisms' cognitive reactions upon curcumin administration. The use of animal studies for unlocking curcumin's mechanism costs both ethically and financially but allows investigation of the impact of diet in improving cognitive signalling pathways.

Inconsistencies in human experimental trials might be partly explained due to differences in response rates and the AD complexity in humans compared to animals. Also, curcumin absorption plays a significant role in its detection in plasma due to its poor bioavailability. Curcumin is hydrophobic and needs to be conjugated to pass the blood brain barrier [12]. Two studies found minimal curcumin amounts in plasma indicating its systemic clearance [20,19]. Curcumin formulations are being researched to overcome this challenge including piperidine (in black pepper), possibly enhancing curcumin's bioavailability [18]. Moreover, it would be interesting to compare curcumin's cognitive impact with other polyphenol foods (e.g. blueberries) in order to assess their potency. Alternatively, curcumin might enhance the activity of Ω3 long chain poly-unsaturated fatty acids (PUFAs) including EPA and DHA which are important for synaptic plasticity. In vitro curcumin administration was found to increase DHA levels in rodents' brains, but further testing is needed to elucidate curcumin's potential enhancing DHA; essential in brain function and memory [19].

Another explanation for the mixed results in human studies relate to their small size (underpowered) To overcome this, large human clinical trials are needed with adequate sample size and longitudinal (>2 years) with adequate follow-ups due to AD late onset. Another difference spotted between animal and human studies lies on curcumins side effects. In two studies of Table 2 when 4000 mg/day curcumin was used, gastrointestinal side effects occurred,

highlighting curcumin's toxicity at higher doses in humans. This explains the high drop-out rate that influenced study's statistical power [12]. Additional testing is needed to investigate curcumin's therapeutic window in people and its toxicity dose needs to be well defined. Moreover, the choice of the cognitive test being used (cognitive battery test) might be sensitive in testing episodic memory and that is why standardized computerized cognitive tests are designed. In animal studies, the Morris Maize Water navigation test used to investigate behaviour skills, does not fully reflect the spatial learning human skills.

The notion that curcumin improved cognition in elderly patients with mild dementia significantly higher than AD patients might relate possibly to curcumin's interaction with AD medication; making it very difficult to mediate its function. An animal study found donepezil and curcumin to have similar mechanism [21]. This indicates that curcumin might compete with certain AD drugs for the same receptor for absorption; possibly competitive inhibition [12]. AD patients without taking medication during the study should be preferred, for excluding drug's interference in curcumin mechanism. Additional testing is underway investigating curcumin's interaction with cholinesterase inhibitors [22]. Despite showing a decrease in inflammatory signalling cascades (IL-6, CRP) and reactive radical species generation in curcumin animal studies, AD human trials found no significant reduction in these markers when curcumin was given. This is explained by curcumin's efficiency in reducing neuroinflammation and Aβ plaque formation in early but not late AD [12].

Ongoing investigation is placed for curcumin's role to act as a vasodilator in cerebral circulation. Given the fact that patients who are prone to inflammation develop neurocognitive disorders, the inclusion of patients with chronic diseases (e.g. obesity) will allow to investigate curcumin's potential to suppress neuroinflammation. Curcumin has the potential to improve the diabetes associated lipid biomarkers which might lead to neurotoxicity and AD vascular dementia [23] and can positively affect apoE phenotypes [1]. A better clarification of the study dose and its therapeutic window need to be defined. In the presented studies, oral curcumin was used and there might be differences in curcumin's bioavailability if given intravenously or along with adjuvant therapies. Overall, despite animal studies being informative for curcumin's mechanism, are less consistent to reflect the sporadic human AD.

CONCLUSION

Alzheimer's disease (AD) is a neurodegenerative disease manifested during ageing. Although pharmacotherapy is currently in the frontline for treating its pathogenesis, dietary and lifestyle factors play a crucial role in its aetiology. Curcumin, a polyphenolic compound is known to have neuroprotective effects. The aim of this essay review was to investigate and evaluate curcumin's role in cognition during ageing and disease particularly in AD. Animal and human clinical studies provide conclusive evidence not only for unlocking curcumin's mechanism of action by acting as a potent neuroprotective agent but also for spotting the differences in response rates either in different organisms or within the human population. Although curcumin shows promising anti-inflammatory effects and improvements in spatial and episodic memory in animal studies, humans show pleiotropic results. It has been very difficult to generalise whether curcumin can reduce cognitive impairment in human AD due to substantial heterogeneity across clinical trials, differences in dose and formulation used. It is hypothesized that curcumin improves memory in elderly patients with mild dementia in early AD but there are no significant differences in late human AD studies. This can be explained by individual variability, disease onset, lifestyle factors, curcumin interaction with AD drugs and curcumin's bioavailability. So, the original hypothesis of curcumin's role in improving cognition in human AD is accepted for the early disease onset but additional testing is needed for late AD. To overcome the challenge of curcumin's therapeutic effects in human AD cognition, further clarification and attention should be given in the clinical study design by increasing sample size and long-term experimentation since human AD is mostly sporadic (manifested late in life) and prolonged period is needed to investigate curcumin's therapeutic effects. This cannot be fully studied in animal studies since model organisms have decreased lifespans, simplified physiology and certain cognitive aspects cannot be investigated. Although, there are phylogenetic differences between humans and vertebrates, animal studies remain in the forefront for investigating curcumin's physiological mechanism as an inflammatory agent in reducing oxidative neuronal stress and enhancing neurotransmitter release. Curcumin's dose being used should be properly defined and its therapeutic window needs to be established for possible human toxic effects. Further clarity is needed in the anti-inflammatory biomarkers being studied and better standardization is needed in the cognitive-memory tests used. Neuroimaging techniques should be used to further explore curcumin's impact in brain activity and the possible changes in the brain associated cognitive areas upon curcumin administration. Further research is currently underway

for investigating the role of curcumin formulations and other polyphenol foods including anthocyanins and quercetin in enhancing its bioavailability and efficiency as well as the impact of gut microbiota in curcumin's absorption. Overall, AD is a multifactorial disease and investigation of both drug therapy and diet is needed in restoring the faulty brain circuit processes involved in the neural plasticity underpinning memory. Such conclusions will further support the investigated hypothesis, favouring curcumin's neuroprotective role in AD.

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