Effect of Curcumin on Clzheimer's disease: a systematic review

Efeito da Curcumina na doença de Alzheimer: revisão sistemática

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ABSTRACT

Alzheimer's disease is a neurodegenerative disease characterized by the accumulation of amyloid plaques, tau fibrils and generalized neuroinflammation, which lead to functional and memory impairment. Without treatment, several adjuvants are used, such as curcumin. In this context, the objective of this systematic review was to evaluate the effects of curcumin on Alzheimer's disease. The search for “curcumin” + “alzheimer’s disease” resulted from 354 articles, of which 6 were included in this review. Despite the scarcity of research in humans, curcumin proved to be an excellent adjunct to the treatment of the disease, evidenced by its benefits in memory and cognitive function,

given by the reduction of the accumulation of senile plaques. In this context, the physiotherapist has full support in recommending periods of administration, provided that they are in safe doses, in order to minimize neurological deficits in these patients.

Keywords: Alzheimer's disease, Curcumin, memory.

RESUMO
A Doença de Alzheimer é uma doença neurodegenerativa caracterizada pelo acúmulo de placas amiloides, fibrilas tau e neuroinflamação generalizada, que levam ao comprometimento funcional e de memória. Sem possuir tratamento, vários adjuvantes são empregados, como a curcumina. Nesse contexto, o objetivo da presente revisão sistemática foi avaliar os efeitos da curcumina na Doença de Alzheimer. A busca "*curcumin*" + "*alzheimer's disease*" resultou de 354 artigos, dos quais 6 foram incluídos nesta revisão. Apesar da escassez de pesquisas em humanos, a curcumina se mostrou como um excelente adjuvante ao tratamento da doença, evidenciado pelos seus benefícios na memória e na função cognitiva, dados pela redução do acúmulo de placas senis. Nesse contexto, o fisioterapeuta possui total respaldo em recomendar períodos de administração, desde que em doses seguras, a fim de minimizar os déficits neurológicos nestes pacientes.

Palavras-chave: doença de Alzheimer, Curcumina, memória.

1 INTRODUCTION

Aging is a natural process that occurs gradually, being a series of progressive changes in the larger organism, being a series of progressive changes predisposed in physiological and worrying reserves, predisposing the individual to a significantly complex risk[1;2]. Currently, there are more than 900 million elderly people in the world and this number is expected to grow by around 56% by 2030 [3;4].

Among the chronic diseases (NCDs), the progressive ones such as dementias stand out, with Alzheimer's disease (AD) being the most common, which is not a disease caused by the accumulation of amyloid plaques, fibrils and generalized neuroinflammation, having as diseases and metabolic , being the most common: diabetes mellitus, dyslipidemia, arterial hypertension, obesity, sedentary lifestyle and an unbalanced diet, thus succeeding the gradual functions of cognitive and behavioral and affective disorders [5;6]. Currently, this population of people with AD in the world will reach 47 million, reaching up to 131 million people with dementia [4;7].

The first manifestation of AD is the loss of short-term memory, progressively evolving and also compromising other types of memory. In addition, brain atrophy causes loss of human functional capacity causing cognitive deficit, in addition to damage to executive and motor functions. Disease progression is accompanied by behavioral

changes such as aggression, depression, hallucinations, anger, and agitation. Such pathophysiological processes present slow and deteriorating manifestations [8;9].

Currently, there are no neuroprotective treatments capable of preventing, reversing or controlling the evolution of the disease that are clinically approved and effective, so it is necessary to know and identify possible potential therapeutic agents to avoid and/or minimize the changes caused by AD [5;10].

In this context, we sought to clarify the potential of the diferulomethane molecule, popularly known as curcumin. This organic compound is extracted from the rhizome of Curcuma longa/saffron, and has become the target of studies since it has been shown to be able to reduce oxidative stress, having as its main advantage its low toxicity rate. Curcumin has a neuroprotective effect in experimental models, mediated by its antioxidant, anti-inflammatory and anti-amyloidogenic properties [8;11;12;13].

Therefore, the aim of the present study was to find current scientific evidence that supports the theory that curcumin acts as a neuroprotector in AD, also seeking to find evidence of its role as an adjuvant in the treatment of this dementia.

2 METHODS

The present study is a systematic review, thus seeking a large number of updated evidence regarding the chosen topic. In the present article, we chose to research and analyze the role of the compound curcumin as a potential neuroprotector and/or as an adjuvant in the treatment of AD, in order to establish a complementary therapy that minimizes the deficits caused by this disease.

The study was developed at the State University of the Midwest, located in Guarapuava - PR. The scientific research that supported the review was based on articles found in the databases Scielo – Scientific Electronic Library Online, PubMed – Publisher Medline, PEDro - Physiotherapy Evidence Database, MedLine - Medical Literature Analysis and Retrieval System Online and LILACS - Literatura Latino- American and Caribbean Health Sciences.

The search for studies in the bases took place during the time period from July 2018 to September of the same year. To guide the search, the descriptors chosen were based on the DeCS - descriptors in health sciences, namely: "alzheimer's disease" and "curcumin", also searched in english as "alzheimer's disease" and "curcumin", respectively.

In order for the findings to be included in the present review, some criteria were considered, which considered: original articles on the curcumin molecule, without being

genetically modified, including study of quantitative, qualitative or mixed approaches, with abstracts and full texts available in full through the medium online.

The time limit established was the last 5 years, in order for the evidence found to be as current as possible, since science is constantly evolving. Review articles, congress abstracts, editorials and letters, as well as case studies, were excluded.

In table 1, the eligibility criteria used for the selection of articles during the searches were better described through the PICOS criteria, structuring and delimiting the research.

Note: Inclusion and exclusion criteria for studies selected for review according to the PICOS criteria.

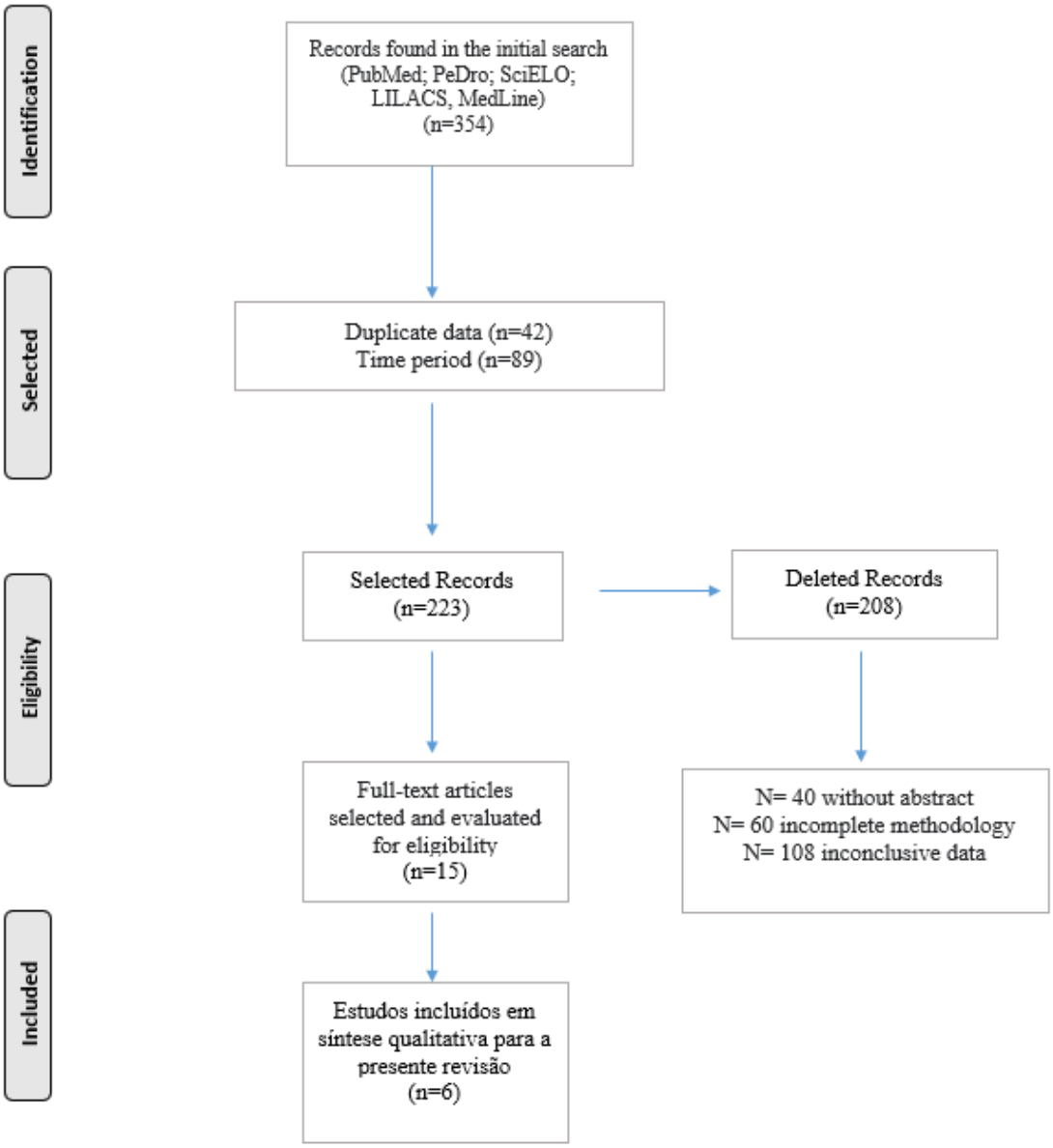
		Inclusion	**Exclusion**
P	*Participate*	Individuals who have a diagnosis of AD; studies involving experimental models of AD;	Individuals with unspecified dementia or no pathological condition;
I	*Intervention*	Curcumin isolated, curcumin in supplements;	Genetically modified molecules, by-products thereof;
C	*Comparison*	With healthy individuals or Control Group without intervention;	-
O	*Outcome*	Attenuation, stabilization or decrease in the evolution of the characteristic dementia condition;	-
S	*Study*	Controlled studies, whether randomized or not;	Review, meta-analysis, abstracts, editorials, case studies;

Studies were evaluated by reading the title and abstract for partial removal of those that evidently did not meet the proposed criteria. Subsequently, the selected articles were read in full, classifying only the eligible ones. A second reviewer independently assisted in the article selection process.

3 RESULTS

Adding the searches in English and Portuguese, the search resulted in 354 records. After excluding duplicates (n=42), time period (n=89) and reading the title, 223 articles were selected for reading the abstract. At this stage, another 208 were excluded, leaving 15 for full reading. Finally, 6 studies composed the present review. The selection process was described in a flowchart (Figure 1).

Figura 1. Fluxograma descrevendo o processo de seleção dos estudos elencados para a presente revisão.



Of the 6 articles selected for the review, only 1 was not carried out in experimental models. Therefore, 1 study had elderly people with AD, 2 studies were carried out with mice and 3 of them with rats. Overall, the final sample ranged between 6 and 72, with an average of n= ±29 participants (Table 2).

Tabela 2. Características gerais dos estudos, sendo: ano de publicação, *n* amostral e características pertinentes à mesma. * *Diagnostic and Statistical Manual of Mental Disorders*

Author	**Year of publication**	**Sample number (n)**	**Sample characteristics**
BASSANI et al.	2017	35	Transgenic Wistar rats with AD model
FENG et al.	2016	72	Transgenic Wistar rats with AD model
LIU et al.	2016	30	Transgenic Wistar rats with AD model
SUN et al.	2017	11	Transgenic Wistar rats with AD model
SUNDARAM et al.	2017	6	Transgenic Wistar rats with AD model
TABIRA et al.	2018	21	Patients diagnosed with AD (DSM-IV criteria*)

With regard to treatment, the administered doses of curcumin varied between 25 and 1000mg/kg/day in animals, with an average dose of 226.6mg/kg/day. In the study with patients, the dose was 60mg per capsule, thus totaling 360mg/day. In all studies with animal models, prophylaxis was performed via the orogastric gavage method. In patients, it was administered as part of a capsule supplement. Intervention time ranged from 4 to 28 weeks, with a mean of ±15 days (Table 3).

In all studies, the effects found after the administration of curcumin had positive effects at the brain level, either at the micro or macroscopic level. However, low doses, such as 25/mg/kg for a relatively short time, 4 weeks, were not effective. Most findings report suppression of neuroinflammation; however, improvements were also found in memory and cognition, as well as in recognition and learning ability (Table 3).

Note: Dose and time of treatment with curcumin and its effects evidenced in each study.

Author	Intervention	Results
BASSANI et al.	25, 50 and 100 mg/kg/day for 4 weeks	Treatment with curcumin at doses of 50 and 100mg/kg prevented deficits in recognition memory, in addition to a small reduction in neuroinflammation.
FENG et al.	100, 200 and 400 mg/kg/day for 24 weeks	Curcumin was effective in regulating brain insulin, in addition to having positive effects on learning and memory capacity. The most effective dose was 200mg/kg
LIU et al.	150 mg/kg/day for 4 weeks	Curcumin significantly alleviated spatial memory deficits as well as improved cholinergic neuronal function and had a suppressive effect on neuroinflammation.
SUN et al.	160 and 1000 mg/kg/day for 24 weeks	Curcumin decreased the expression and excessive phosphorylation of the Tau protein, responsible for much of the damage characteristic of the disease.
SUNDARAM et al.	80 mg/kg/day for 12 weeks	Curcumin had a suppressive effect on neuroinflammation and improved cognitive impairments
TABIRA et al.	60mg of curcumin in each capsule, given 6x daily as part of a supplement for 22 to 28 weeks	The evaluated patients showed improvements in cognitive functions, as measured by the Alzheimer's Cognition Subscale - Japanese version

4 DISCUSSION

The general objective of the study was to provide further explanations on the use of curcumin as a potential neuroprotective agent in individuals predisposed to the development of AD, or in the presence of AD. It is evident, through the search result, the scarcity of research involving patients on the subject, which suggests that it is an area that is not yet in-depth, but with a great neurological effect already proven in animal models.

The advantage of curcumin as a protective agent at the brain level is given by its ease in penetrating the blood-brain barrier. Despite not having a good absorption by the oral route, it was shown in animal models that curcumin has high specificity and affinity with senile plaques, binding them and causing the breakdown of their structure and, consequently, reducing the excessive accumulation of β-amyloid protein[6;18].

The study[3] evaluated the effect of 3 different doses of curcumin in an animal model: 25, 50 and 100mg/kg for 4 weeks. Although doses of 50 and 100mg/kg had a positive effect on preventing deficits in recognition memory, there was no difference in spatial memory in the maze. In addition, there was a small decline in inflammation, but no neurogenic stimulation, resulting in no restoration of the hippocampus. This study limits its results due to the doses and time of administration, as it is believed that larger doses are necessary due to the low absorption of curcumin in the intestine.

Another study[12] was also carried out for 4 weeks, but using doses higher than 150mg/kg/day. The results are significantly better in reducing neuroinflammation, as well as gains in neuronal function. Differing from the previous study, benefits were also evidenced in spatial memory. Thus, studies suggest that small doses cannot reach the brain region as effectively, since higher amounts of curcumin potentiated the effect, possibly because there is more substance available in the brain.

The study[23], conducted in experimental models evaluated the effects of 80mg/kg/day of curcumin for 12 weeks. Measuring the ability of curcumin to regulate pathways that lead to hyperphosphorylation, the results showed that curcumin treatment was able to reduce the rate of progression of β-amyloid aggregation, as well as exhibiting positive effects on the cognition of treated animals.

This result, in addition to the studies described above, suggest that curcumin has effects at high doses (greater than 80mg/kg/day), but that this effect is dependent on the time of administration. Therefore, long periods of administration favor its effect, as evidenced in the literature [20; 18; 3; 23].

The study[8] used doses of 100, 200 and 400mg/kg/day for 24 weeks. All doses had a positive effect on learning ability and memory, but the dose of 200mg/kg/day had a slightly greater effect compared to the other groups.

Another effect of curcumin on the brain was evidenced with respect to insulin regulation in AD. The literature shows that in the early stages of the pathology the disease is accompanied by deficiencies in the use of glucose by the brain and, since glucose is the main source of energy in the brain, its performance and function are considerably impaired. In this study[8], also observed that curcumin can upregulate the signaling pathway to reduce insulin resistance and improve brain glucose metabolism, corroborating the literature[18].

The study[22] justifies the beneficial effects of curcumin by regulating the inflammatory mediator caveolin, which acts as an adjuvant in the clustering of β-amyloid by interacting with its precursor, favoring the development of AD, as evidenced in the literature[9;26]. The study findings suggest that curcumin plays a protective role in AD by attenuating Tau hyperphosphorylation, given by caveolin inactivation. The results were positive at both doses.

Regarding the use of curcumin as a neuroprotector, the literature also shows its role in other neurological diseases, such as stroke and Parkinson's disease, in addition to conditions such as chronic stress and depression[1; 14; 20].

In this context, the data of the present review are in agreement with the findings of another similar study[1], which demonstrated a protective effect on short-term aversive memory by curcumin mediated by the decrease in oxidative stress, reinforcing its role as a protective memory. Similarly, in the study[20] treatment with curcumin was able to reverse deficits in recent memory and delayed memory in stroke models.

The study[14] who investigated the effects of curcumin on PD in an animal model treated intragastrically with curcumin (25, 50, 100 and 200 mg/kg) showed that curcumin was able to improve motor asymmetry. in the cylinder test and memory in the passive avoidance test at all doses.

The only patient study included in this review was developed[24], which included curcumin as part of a supplement. In it, they contained 60mg of curcumin per dose, being administered 6 capsules a day, totaling 360mg/day for 22 to 28 weeks.

Assessed using the Alzheimer's Cognition Subscale – Japanese version, patients showed significant improvements in cognitive functions from the 6th week. However, the limitation of this study is the fact that the supplement is combined, and this benefit may be due to curcumin, other compounds or a combination of them.

It should be added that curcumin is an extremely used component in Indian food as a seasoning and preservative, and it has been considered responsible for the low incidence of AD in India. This statement is supported by the prevalence of AD in India in the elderly, which, in an age group of 70-79 years of age, is 4.4 times lower when compared to the prevalence in the USA [15; 18].

Despite the paucity of research in humans, to date, no studies have reported toxicity regarding the use of curcumin, even when it is used in doses up to 12 g per day. According to health authorities like the Food and Drug Administration (FDA) and the World Health Organization (WHO), curcumin is considered safe. Therefore, although curcumin does not have fully elucidated mechanisms in humans, it is known that it will not cause harm in adequate doses[11; 20; 21].

Although curcumin is not considered a medicine but a supplement, we have full support for its clinical use. 611 of April 1, 2017 and recognized by the Ministry of Health the use and/or indication of freely prescribed substances by the physical therapist is already regulated by the Physiotherapy Council. This agreement, added to the results of the scientific literature, provide us with help and confidence in prescribing the use of curcumin to patients, if necessary.

The findings of our review, in addition to other research, identify that the maximum dose of curcumin is 12mg per day for patients. Although there is no minimum dose, it is known that the effects are dose-dependent, and it is up to the professional to monitor and adjust the dosages. In this way, we seek to enhance the treatment, since it exerts several beneficial effects at the brain and cognitive level. The main limitation of this research is the lack of studies on curcumin in humans, restricting the evidence. Thus, further studies are suggested in the area in order to better elucidate the mechanisms and benefits of curcumin as a neuroprotective agent.

5 FINALS CONSIDERATIONS

Alzheimer's disease is a progressive neurological condition that, to date, has no treatment. Adjuvant therapies have been studied and used in order to minimize the neurological and functional damage caused to these patients. In this context, Curcumin is evidenced as a neuroprotective agent, capable of improving memory, cognitive functions and performance in these patients. Despite the scarcity of studies, safe doses can be used in these patients in order to achieve neurological gains, being an adjuvant therapy to conservative treatment.

In this context, it is up to the physical therapist to assess the need for additional intervention to the treatment, dosages and evolution, aiming to improve the patient's quality of life and functionality.

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