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RESEARCH ARTICLE

The Efficacy of Curcumin on Cognition, Depression, and Agitation in Older Adults with Alzheimer's Disease

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Abstract: The purpose of this systematic review was to ascertain the current state of science regarding the use of turmeric and its pigment curcumin in individuals with Alzheimer's Disease (AD). A summary of qualitative and quantitative evidence specific to the effect of curcumin on AD is presented in this article. The purpose of the review was to evaluate and summarize findings related to this body of research. Findings indicated a positive correlation between administration of turmeric and improvement AD symptoms; however, long-term benefits need to be researched. Also, experimental research with older adults with mild, moderate, and severe AD should be conducted to determine whether or not turmeric and curcumin improve cognition, depression, and agitation. Specific methodological issues that need to be considered are the dosage and purity of turmeric and curcumin, administration frequency, determination of a suitable placebo, and duration of testing.

Keywords: Curcumin, Cognition, Depression, Older Adults, Alzheimer's Disease, Dementia.

INTRODUCTION

As the aging population grows, dementia is becoming more prevalent, particularly in countries with large middle-class populations [1]. Dementia is a neurodegenerative disease characterized by gradual cognitive decline, behavioral changes, memory loss, personality changes, and impaired reasoning. Although dementia can occasionally affect people under the age of 65, it is more common in older adults [2]. In fact, age is one of the most common characteristics of dementia patients, with rates doubling every five years; it is also more common in Western European countries [3]. Research has frequently shown that dementia is the leading cause of disability and dependency in older adults [4]. Alzheimer's Disease (AD)-a type of dementia-is identified as the sixth leading cause of death in the United States [5]. Approximately 35 million older adults in the United States (US) have dementia as the result of AD [2]. The worldwide impact of dementia has put a devastating financial pressure on the global economy. World Alzheimer's 2015 report has estimated that dementia will cost $1 trillion by 2018 [6].

Nearly 7.7 million new cases of dementia are reported annually; in other words, one new case of dementia is identified every four seconds [7]. While the worldwide prevalence of AD was 26.6 million in 2006, it is anticipated that its occurrence will quadruple by 2050 [8]. The cost of care for individuals with AD is estimated to be $600 billion annually with the United States bearing a share of $236 billion [9].

Given the pervasiveness of the problem, safe and effective alternative and complementary therapies have gained

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attention from the research communities as well as the general public. As a result, a few studies have been conducted to investigate the potential effect of non-traditional therapeutic medicine such as curcumin on AD. Curcumin is a derivative of *Curcuma longa* and is found in the spice turmeric. In this article, we use the term "turmeric" as a source of curcumin. Turmeric is typically used as a culinary curry powder as well as a coloring agent in food. Although curcumin is less known in Western cultures, traditional Indian doctors have been using this compound as a therapy for several chronic conditions such as asthma, diabetic wound healing, and epilepsy [10].

Observational studies on turmeric and one of its essential components, curcumin, on AD have shown that there is a significant correlation between turmeric consumption and incidence of AD. Turmeric has been used in India for over 5,000 years, which may potentially explain why both rural and urban populations have some of the lowest prevalence rates of AD in the world today [11]. Turmeric is a powerful antioxidant that is thought to reduce inflammation of neural tissue associated with AD. Studies indicate that curcuminoids, which are composed of a mixture of curcumin, demethoxy-curcumin, and bisdemethoxy-curcumin, may counteract symptoms of AD by blocking the formation of pathological beta-amyloid plaques [12], by enhancing their clearance in AD patients [13], or by reducing inflammation of neural tissue [13], and which when combined with vitamin D3, further enhances the neuro-restorative process [14]. Additionally, curcumin appears to increase dopamine, norepinephrine, and serotonin in the brain in animal models [15, 16]. Studies report the role of curcumin in reducing the symptoms of depression in the general population [17 - 19]. Studies also suggest that turmeric may have a beneficial effect on cognition, depression, and agitation in older adults with AD [9, 20, 21].

Improved understanding of how turmeric interacts biologically and influences clinical outcomes of AD should assist in determining purity and dosage levels for such a common ingredient being added to a patient's diet. Even at high doses, turmeric is safe in humans; however, this spice may cause gallbladder contraction and is not advised for individuals with biliary problems [22]. The purpose of this systematic literature review was two-fold: a) to summarize and synthesize existing research on the effects of turmeric on cognition, depression, and agitation in older adults with AD; and b) to determine existing gaps in the literature to identify best practices about the use of turmeric in individuals with AD.

METHOD

The purpose of this systematic review was to summarize and synthesize the existing literature on curcumin and AD to identify gaps in the knowledge base. A methodical search was performed in the following databases: AgeLine, Alt Health Watch, CINAHL, Heath Source: Nursing/Academic Edition, Psychology and Behavioral Sciences Collection. The following keywords were used: *turmeric* AND *dementia*, *turmeric* AND *Alzheimer's*, *curry* AND *dementia*, *curry* AND *Alzheimer's, curcumin* AND *dementia*, and *curcumin* AND *Alzheimer's*. Ninety-four articles focusing on dementia and AD were reviewed; however, only a few focused on the effect of curcumin or turmeric on behavioral symptoms in humans.

Table 1. Search process used.

Database	Number of Articles Meeting: Inclusion Criteria	Exclusion Criteria
AgeLine	17	1
Alt Health Watch	37	1
CINAHL	14	0
Heath Source: Nursing/Academic Edition	19	0
Psychology and Behavioral Sciences Collection	7	2

The inclusion criteria consisted of all articles that implemented an appropriate and accurate research design (including quantitative, qualitative, or mixed methods designs), that examined any part of a turmeric and/or curcumin intervention, conducted a study on humans, were primary sources, and were written in English. All secondary sources, such as literature reviews and book chapters, were not included. Additionally, all non-peer reviewed articles, such as conference proceedings and dissertations, did not meet the criteria. Finally, all studies investigating biomarkers and physiological parameters were excluded.

Our search resulted in 300 articles. After reading all articles abstracts, we identified 94 relevant abstracts with words and phrases related to our search criteria. We read each article to determine whether it met our inclusion criteria. Furthermore, we generated an Excel database and created a classification criterion for all relevant studies based on the

following characteristics: (a) purpose, (b) research goal and objectives, (c) human versus animal, (d) research design, and (e) methodology. We conducted a critical assessment of the 94 articles. Four articles were found to meet all the inclusion criteria described above (Table **1**). Each article was read carefully to identify themes and codes for summary analysis.

RESULTS

The four research articles were analyzed through a series of categories and themes, the organization and selection of which was guided by the research question. Several main themes among these research studies were identified. First, the four studies utilized a valid and reliable mental status tool, the Mini-Mental State Examination (MMSE), to systematically assess the participants' mental status. Second, the range of dementia selected for these four studies varied from mild to moderate range. Third, a various methodological approach was chosen, for example, two studies followed an experimental design, one was an observational study, and one was a case study. The observational study with large sample size (n > 1,000) indicated a positive correlation between curcumin consumption and score on MMSE, while the experimental study with considerably smaller sample size than the observational study did not suggest any relationship between curcumin and score on MMSE. A summary of each research article that satisfied the criteria is provided in Table **2** below and includes authors, purpose, design, sample, instruments used, findings, dosage, and the form of curcumin administration.

Table 2. Summary of research evaluating turmeric in older adults with dementia or AD.

Authors	Purpose	Design/Sample/Instruments	Findings	Reported Other Med	Dosage & Duration	Curcumin Administration
1) Ng, Chiam, Lee, Chua, Lim, & Kua [20]	To identify whether or not curry is associated with improved cognitive functioning in older adults who do not have dementia	Survey design, self-report, correlational study Older adults, aged > 60 1,010 observations, Singapore population (n = 1,010) Mini-Mental State Examination (MMSE)	Individuals with high levels of curry consumption had significantly higher MMSE scores than those with low levels of curry consumption. Depression or agitation was not measured in these subjects.	N/A	Self-report consumption in food Duration: Eating Habit	Turmeric in Curry
2) Hishikawa, Takahashi, Amakusa, Tanno, Tuji, Niwa, Murakami, & Krishna [9]	To present three patients with dementia whose, behavioral symptoms improved as a result of taking turmeric	Case Study 3 older adults with dementia (83-year old female, 84-year old female, and 79-year old male) 1) Neuro-Psychiatric Inventory-brief questionnaire 2) Mini-Mental State Examination (MMSE)	1) In one case, the MMSE score was up 5-points, from 12/30 to 17/30. 2) In the other two cases, no statistically significant change was seen in the MMSE; However, substantive improvement was observed in the non-significant improvement cases. Participants were able to recognize their family within 1 year of treatment. Depression and agitation were improved in all 3-participants.	All except one person was taking Donepezil	764 mg/day of turmeric, which contained 100 mg of curcumin. Duration: 12 weeks.	Turmeric
3) Ringman, Frautschy, Teng, Begum, Bardens, Beigi, Gylys, Badmaev, Heath, Apostolova, Porter, Vanek, Marshall, Helleman, Sugar,	To generate data regarding curcumin tolerability and preliminary clinical and biomarker efficacy data in persons with AD	Randomized double-blind, placebo-controlled design, 36 subjects diagnosed with mild-to-moderate AD 1) Mini-Mental Status Examination (MMSE) 2) Alzheimer's Disease Assessment Scale: Cognitive Subscale (ADAS-Cog); 3) Neuropsychiatric Inventory (NPI);	No statistically significant differences between the treatment and control groups. Curcumin was well-tolerated in 33 of the 36 subjects. The study was unable to demonstrate clinical or biochemical efficacy evidence of Curcumin C3 Complex® in AD subjects.	Some were taking acetylcholinesterase inhibitors (AchE-I), but at a stable level.	2 and 4 mg per day Duration: 24 weeks Continued additional 24 weeks as observational study	Curcumin

(Table 2) contd.....

Authors	Purpose	Design/Sample/Instruments	Findings	Reported Other Med	Dosage & Duration	Curcumin Administration
Masterman, Montine, Cummings & Cole [21]		4) Alzheimer's Disease Cooperative Study: Activities of Daily Living Scale (ADCS-ADL); 5) Levels of Ab1 – 40 and Ab1 – 42 in plasma and levels of Ab1 – 42, t-tau, p-tau181 and F2-isoprostanes in cerebrospinal fluid; 6) Plasma levels of curcumin and its metabolites up to 4 hours after drug administration.	They were able to related Curcumin C3 Complex® was associated with lowered hematocrit and increased glucose levels that were clinically insignificant. There were no differences between treatment groups in clinical or biomarker efficacy measures, although preliminary data suggest limited bioavailability of this compound. Depression or agitation was not measured in these subjects.			
4) Baum, Lam, Cheung, Kwok, Lui, Tsoh, Lam, Leung, Hui, Ng, Woo, Chiu, Goggins, Zee, Cheng, Fong, Wong, Mok, Chow, Ho, Ip, Ho, Yu, Lai, Chan, Szeto, Chan, & Mok [22]	To examine the safety and efficacy of curcumin on biochemical (such as side effects, drug absorption) and cognitive measures in AD	Experimental: randomized, double blind, placebo-controlled study 34 subjects recruited from old age homes and dementia clinics, 50 years old or older, ethnic Chinese in Hong Kong with progressive decline in memory and cognitive function for six months with diagnosis of probable or possible AD 1) Mini-Mental Status Examination (MMSE); 2) Plasma levels of isoprostanes iPF_{2a}-III and antioxidants; 3) serum levels Aß and liver and kidney functions; 4) plasma to assay curcumin and metabolites	No statistically significant differences were observed between zero and 6 months among dosage groups for MMSE scores or the plasma levels of isoprostanes iPF_{2a}-III or serum levels Aß. A greater level of curcumin, but not tetrahydrocurcumin, ferulic acid or vanillic acid were noticed in plasma with capsules, but not with powder. Curcumin appeared to be safe. It did not appear to cause adverse side effects in subjects. Depression or agitation was not measured in these subjects.	Gingo bibola	1 g/day or 4 g/day	Curcumin

DISCUSSION

Our analysis identified several gaps in the existing literature that could potentially hinder researchers' ability to predict or explain the effect of curcumin on AD. Although existing literature on the effect of curcumin on animals has demonstrated neurobiological potential, the scarcity of research on human subjects makes it challenging to predict any effect on human behavior. Although some of the studies included in this literature review indicated positive results for the use of turmeric, the findings of these four studies were not conclusive. Also, there were additional concerns related to the generalizability of the studies and their inconclusive results. Some of these concerns include their small size, duration, and curcumin dosage. Three of these four studies had small sample sizes (n = 3 (a case study); n = 36 and n = 34). Most of the studies were conducted for less than six months. One of these three studies was essentially clinically testing a specific product, Curcumin C3 Complex®, which could indicate an insufficient mixture of curcumin and other unproven ingredients in the dosage. The study that utilized a large sample size (greater than 1,000 human subjects) was a correlational study that compared human subjects from three groups who self-reported their curry consumption under the three following categories: never or rarely, occasionally, and often or very often. These subjects had no medical diagnosis of AD nor were the human subjects medically diagnosed as being potentially at-risk for AD. All the subjects were over the age of 59. Mediating variables of known socio-demographic factors, health factors, and other behavioral correlates were considered in the analyses. Using scores from the Mini-Mental State Examination (MMSE), the researchers reported evidence of better cognitive performance in elderly Asians who did not have dementia and consumed greater amounts of curry.

Significant evidence is thus not yet apparent for the role of curcumin in benefitting individuals with AD. The findings of this literature review demonstrate the need for an experimental study with a large sample size over an extended period of time. Additionally, there is a need to identify the most suited form of consumption and the dosage

needed for effective results. Given the lack of significant evidence, it is likely that turmeric and curcumin are not being used as a therapeutic intervention for individuals with mild or moderate AD.

CONCLUSION

This analysis of research articles using human subjects diagnosed with dementia or AD examined the effect of turmeric on cognition, depression, and agitation. Although two of the four studies suggested a correlation between curcumin administration and behavioral symptoms of AD, the long-term effects of curcumin need to be studied. Further research, including experimental designs with human subjects, should be conducted with older adults diagnosed with mild dementia or diagnosed with a potential for AD to determine whether or not curcumin results in improved cognition, reduced depression, and/or diminished episodes of agitation. Specific design issues that need to be considered are the dosage and purity levels of turmeric and/or curcumin as well as the administration frequency rate, the amount of time needed to determine if effects are present, and a suitable placebo that could be used.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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