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Does the Administration of Curcumin, Compared to Placebo, Change Cognitive Function in Adults Older than 40?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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Abstract

OBJECTIVE: The objective of this selective EBM review is to determine whether or not the use of curcumin, versus a placebo, is effective in changing cognitive function.

STUDY DESIGN: Review of 3 randomized control trials with blinding in English from 2008 to present.

DATA SOURCES: Articles were selected from Cochrane and PubMed databases based on relevance to the selected research question and patient-centered outcomes.

OUTCOME(S) MEASURED: The outcome measured is cognitive change, evaluated by mean score changes in the Mini Mental Status Examination (MMSE) or the Montreal Cognitive Assessment (MoCA).

RESULTS: Two of the studies demonstrated no change in cognitive function measured with the MMSE (Ringman JM, Frautschy SA, Teng E, et al. *Alzheimers Res Ther*. 2012;4(5):43. doi: 10.1186/alzrt146. and Baum, L, Lam CW, Cheung SK, et al. *J Clin Psychopharmocol*. 2008;28(1):110-113. doi: 10.1097/jcp0b013e318160862c), while the third article also did not demonstrate a change in cognitive function, as measured by the MoCA (Rainey-Smith SR, Brown BM, Sohrabi HR, et al. *Br J Nutr*. 2016;115(12):2106-2113. doi: 10.1017/S0007114516001203).

CONCLUSIONS: The studies are unable to demonstrate that curcumin is more effective than placebo in preventing cognitive changes.

KEY WORDS: Cognition, curcumin, placebo, aging, RCT

INTRODUCTION

Cognitive decline is a common and heartbreaking symptom, typically caused by certain diseases or organic changes in brain structures over time. It can vary in symptomology, ranging from short-term memory loss to permanent dementia. In 2011, over 16 million people in the United States lived with some degree of cognitive impairment. The most studied and influential risk factor for cognitive changes is increasing age. Today, the US population is living longer due to the large "Baby Boomer" generation.[2] It follows that clinicians will be seeing and treating more dementia-related diagnoses than ever before.

Diseases that cause cognitive decline, such as Alzheimer's disease or vascular dementia, are considered to be the 3rd most costly diseases to treat in the US. In 2010 alone, the US spent $3.2 billion for nursing home residents with Alzheimer's disease, not including the estimated $144 billion in expenses for family and volunteer care.[1] Healthcare for people with cognitive decline costs more than that of heart disease and cancer combined in this country.[2] People with cognitive impairment are more likely to use healthcare resources, including the emergency department and family practices, more frequently and more inappropriately than those with other diagnoses.[2] These patients also utilize family members to care and advocate for them, causing an emotional, physical, and monetary cost that, while not easily described, is significant and potentially overwhelming for many caregivers.

The definitive cause of cognitive decline, especially in its most common form of Alzheimer's disease, is still unknown. However, some researchers hypothesize that structural brain changes over time and the formation of beta-amyloid plaques, neurofibrillary tangles, and tau proteins are to blame for the cognitive symptoms and mood disorders commonly associated with dementia.[3] Declines in cognitive function are unfortunately nonspecific, but typically

include symptoms like memory loss, vision change, mood or behavior change, and decreased recognition or memory recall. There are currently no medications approved by the FDA to treat dementia.[4] However, some off-label therapies that are commonly used to treat Alzheimer's disease are cholinesterase inhibitors, benzodiazepines, lifestyle changes, and treatment of any underlying organic cause.[4]

Currently, there are not many effective, safe, or well-studied options for treating or reversing idiopathic cognitive changes. This reality forces patients and family members to find treatment and relief with more natural substitutes. A diet change is one of the more popular alternatives to medication for people with cognitive changes. One of these dietary alterations is to increase parenteral intake of a spice known as curcumin. More commonly known as turmeric, it is found in many eastern diets including Indian curry and Thai soups. Turmeric has colloquial benefits reported from these cultures for many different illnesses and symptoms. Curcumin has also been shown to have important antioxidant and anti-inflammatory effects, while also having a positive influence on cognition, especially in animal studies.[5,6] This systematic review evaluates the ability of the spice curcumin to change cognitive function and reverse cognitive decline in older adults.

OBJECTIVE

The objective of this selective evidence-based medicine (EBM) review is to determine if the administration of curcumin, compared to placebo, change cognitive function in adults older than 40?

METHODS

The studies used in this EBM review were found and selected using PubMed and Cochrane Library databases. The objective was to find three randomized control trials (RCTs) from peer-reviewed journals that included adults over the age of 40 with changes in cognitive function. They had to be relevant to clinical practice and had to measure patient-oriented outcomes. Inclusion criteria for the searches were studies published after 2008, randomized control trial, written in English or Spanish, and using human subjects. The exclusion criteria were review articles and publication before 2008.

In each study, the spice curcumin was the intervention of choice. The study by Rainey-Smith et al.[6] used 500 mg Biocurcumax-95 curcumin capsules three times daily, Baum et al.[7] utilized 1 g curcumin powder via capsule or packet once daily, and Ringman et al.[5] chose to use Curcumin C3 Complex 2 g or 4 g divided into two daily doses. The interventions were compared to a placebo that matched the spice's form and administration method in each study. The major outcome measured in these studies was change in cognitive ability measured via the Mini Mental Status Examination (MMSE) and Montreal Cognitive Assessment (MoCA).[5,6,7] The articles also measured outcomes including adverse effects of the spice and bioavailability via plasma and CSF levels of curcumin after ingestion; these outcomes, however, are not being evaluated in this paper, as they were not universally studied.[5,7] Table 1 contains an exhaustive list of inclusion and exclusion criteria for the study subjects, as well as more detailed epidemiologic data. Each article reported their findings and statistics as p-values from ANOVA of the mean changes in baseline scores on the MMSE[5,7] or MoCA.[6]

Table 1. Demographics & Characteristics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Ringman, et al. (2012)[5]	RTC	36	59-73	Presence of dementia, probable AD, age >49, MMSE scores 17-29, English speaking, presence of study partner	Systemic illness, GI bleeding, aspirin >325mg, coumadin, heparin, gingko biloba, antioxidants, and NSAID use >3 days/week	6	2 or 4 g Curcumin daily in 2 doses
Rainey-Smith, et al. (2016)[6]	RTC	160	58-82	Age 40-90, good health and no CVD, no significant cognitive or ADL impairments	Dementia, hx of CVA, depression, psych disorders, blood thinners/ coagulopathy, biliary obstruction, non-English speakers	49	Curcumin as 500 mg capsule TID
Baum, et al. (2008)[7]	RTC	34	59-84	Age >50, ethnic Chinese in Hong Kong, progressive decline in memory/ cognition, probable AD, written consent	Coagulopathy/ blood thinners, smoking, severe illness	7	1 g of Curcumin powder QD

OUTCOMES MEASURED

Each study measured changes in cognitive abilities using either the MMSE[5,7] or the MoCA,[6] given before the clinical trial began and again at the end of the clinical trial. The MMSE is a quick and simple exam given by a health practitioner to quantify a person's cognitive function and over time, evaluate cognitive loss. It measures several aspects of cognition such as orientation, naming, attention, calculation, language, motor skills, and recall. The highest score possible on the MMSE is 30 points. The MoCA is another exam that health care workers use to evaluate the cognitive function of patients. It measures executive and visuospatial function, in addition to the cognitive functions the MMSE tests for, with a total score possible of 30 points. Both are well-known and accepted screening tools for many diseases that cause cognitive decline.

Two of the trials reevaluated scores after six months[5,7] and one performed evaluations additionally at twelve months.[6] The individual scores were then calculated into means for each group, with the appropriate standard deviations; ANOVA and its corresponding p-value was then calculated as well.[5,6,7] Changes in cognition were also analyzed by changes in activities of daily living (ADCS-ADL) and by the ADAS-cog which is an exam specifically for Alzheimer's disease. However, these findings are not compared in this study because they were not utilized among all three trials.[5]

RESULTS

Three randomized control trials compared curcumin supplementation vs. placebo in similar form and administration. Two of the studies used subjects who had clinical dementia or cognitive deficits,[5,7] while the third excluded people with diagnoses of dementia or cognitive decline.[6] All three studies required the subjects to be at least 40-50 years old, since dementia is

an age-related disease. Additionally, the studies each excluded subjects on blood thinners, aspirin, or frequent NSAID use because curcumin could potentially interact with these drugs. The trial subjects were able to continue to live at home, whether independently or in a care-home setting throughout the study. They had to present to the study headquarters for medication refills and health questionnaires during either the six or twelve months, depending on the study. Only one study, by Ringman et al.,[5] retained enough subjects to have a losses-to-follow-up ratio of less than 20%. A majority of patients withdrew due to gastrointestinal adverse effects in all three of the randomized control trials and there were no serious adverse effects experienced by participants in any of the three trials.[5,6,7]

In the study by Ringman et al.,[5] thirty-six subjects with mild to moderate cognitive dysfunction were randomized into three different groups; one group received placebo (n=11), while the other two received either 2g (n=9) or 4g (n=10) of curcumin intervention for twenty-four weeks.[5] The outcomes measured were drug tolerability and cognitive changes, via subject interviews or MMSE scores, respectively.[5] Six of the subjects withdrew; one due to significant memory changes and the other five withdrew because of adverse effects of the intervention medication.[5] Each group had roughly equal numbers of men and women, education levels, and current use of memantine for dementia.[5] Interestingly, the placebo group (70.2 yrs.) was five to six years younger than either intervention group (76.7 and 75.3 yrs.).[5] There was no significant difference in change in MMSE scores using ANOVA calculations.[5] However, when both the 2 g and 4 g curcumin groups were combined and compared to the placebo group, there was a trend for the intervention groups to perform worse than the placebo group.[5] While being an interesting trend, the change is not significant with a p-value of 0.08, nor does it exist when each individual curcumin group is compared to placebo, as seen in table 2.[5]

Table 2. MMSE Results Measuring Cognitive Change for Ringman et al.[5]

Mean Baseline Score (4 g curcumin)	Mean Baseline Score (placebo)	Mean Post-Intervention Score (C)	Mean Post-Intervention Score (P)	Mean Change from Baseline (C)	Mean Change from Baseline (P)	P-Value
22.8	23.2	19.9	22.7	-2.90	-0.45	0.08

The Rainey-Smith et al.[6] RCT enrolled 160 community-dwelling older adults without a current diagnosis of dementia or cognitive dysfunction and randomized them into two groups receiving placebo or 1.5 g of curcumin in divided doses daily for 12 months.[6] The study included results of only ninety-six participants, as forty-nine withdrew due to adverse effects and fifteen others were non-compliant with their regimen.[6] There were no significant differences between the two groups in terms of demographic information, including age, sex, medical history, or education level.[6] At baseline, the placebo group performed better on the MoCA significantly, as indicated by a p-value < 0.05. At six and twelve months, the score changes were analyzed by repeated-measures ANOVA.[6] Interestingly, at six months, the placebo group had a score decrease that was then annulled at the twelve-month reading, which was not seen in the treatment group.[6] Therefore, the time x treatment analysis shows a significant improvement for the curcumin group with a p-value < 0.05.[6] When comparing only the baseline scores to the final twelve-month scores and isolating the time variable, however, there was no significant change, as seen in table 3.[6]

Table 3. MoCA Results Measuring Cognitive Change for Rainey-Smith et al.[6]

Mean Baseline Score (1.5 g curcumin)	Mean Baseline Score (placebo)	Mean Post-Intervention Score (C)	Mean Post-Intervention Score (P)	Mean Change from Baseline (C)	Mean Change from Baseline (P)	P-Value
25.8	26.4	26.5	26.5	0.64	0.09	0.25

Baum et al.[7] created a study that enrolled 34 subjects with mild cognitive decline to take either placebo, 1 g of curcumin, or 4 g of curcumin for six months. While the subjects were matched across the three groups regarding medical history, there were more females enrolled and the placebo group was significantly older than either intervention group at 77.8 years of age.[7] All participants were of Asian descent.[7] Seven of the participants withdrew due to gastrointestinal complaints, falls, or respiratory tract infections.[7] Mean change in MMSE scores was not significant, as shown in table 4.[7] Even when combining the two intervention groups' data and comparing that average to that of the placebo group, there was still not a significant change with p=0.39.[7]

Table 4. MMSE Results for Baum et al. Study[7]

Mean Change from Baseline (C=1 g)	Mean Change from Baseline (C=4 g)	Mean Change from Baseline (P)	P-Value
0.7	-0.6	1.3	0.43

DISCUSSION

Cognitive decline, whether due to vascular dementia, Alzheimer's disease, or Parkinson's disease, is a significant and debilitating symptom affecting a person's ability to think, move, and live independently. Unfortunately, there are no FDA approved drugs or treatment regimens for cognitive decline.[4] Current recommendations include trials of grade 2A cholinesterase inhibitors such as donepezil or rivastigmine, followed by memantine for more significant dementia or decline.[8] Diet additives like ginkgo biloba, vitamin B, and omega-3 fatty acids have unproven benefits for dementia and are patient-specific.[8] Trials of new dietary supplements or medications continue to be necessary until a proven treatment for cognitive decline is found.

Curcumin, also known as turmeric, is an inexpensive and well-known spice that is currently being researched for its efficacy. It has been shown to have anti-oxidant and anti-

inflammatory benefits, and some people have relief from arthritis and muscle pain with its use.[9] The Joint United Nations and World Health Organization Expert Committee on Food Additives reports the acceptable daily intake (ADI) of curcumin to be 0-3 mg/kg, and considers curcumin to be a safe additive, with minor side effects including nausea, diarrhea, or headaches at high intake levels.[9] All three articles researched for this paper had some level of adverse effects consistent with diarrhea, nausea, or other gastrointestinal upset for subjects on the intervention drug.[5,6,7] Compared to anticholinergics or benzodiazepines, with high side effect profiles and sedating qualities, curcumin seems to be a more attractive alternative for many patients.

While these articles were randomized and all were at least single-blinded, there are some aspects of validity that are concerning. The Baum[7] study had a placebo group older than the experimental group, while the Ringman[5] study had a significantly younger placebo group compared to the experimental group. Since age is the greatest risk factor for cognitive decline, it makes it difficult to accept the final results of the studies if there are significant age differences between subject groups. The two studies do not show opposing results even though their control group ages were different. This could mean 5-7 years difference in age is not a significant variable, or it could be damaging to validity.

Only two of the trials, by Ringman[5] and Baum[7] included patients with existing cognitive decline. However, their results did not differ from the trial that only included healthy subjects, see tables 2-4.[5,6,7] The Ringman[5] study was the only one to maintain a loss-to-follow-up ratio less than 20% and have a relatively large sample size with 160 subjects randomized. Much potential data was lost because of poor subject compliance that could have affected the final results in all three trials. Unfortunately, none of the articles offered “worst-case” analysis for the subjects that were lost. Additionally, none of the articles mentioned how they controlled for normal dietary

intake of curcumin in the control groups. This variable could have had significant impacts specifically in the Baum study because all the subjects were Hong Kong Chinese and most likely use turmeric regularly in their diets.[7]

The most significant factor affecting these studies, however, is that curcumin has low bioavailability and poor gastric absorption.[5] Even though each article used a different version of curcumin powder, it was still a generally pure derivative of curcumin without other additives or chemical components.[5,6,7]

CONCLUSIONS

The three clinical trials analyzed do not establish that curcumin is effective in reducing cognitive decline when compared against placebo. Each study showed similar cognitive changes when analyzing MMSE or MoCA score changes after six or twelve months.[5,6,7] However, this does not mean that curcumin should be rejected as a potential treatment for cognitive changes. Each article showed low plasma absorption of curcumin, which further demonstrates that curcumin alone is not absorbed well by humans.[5,6] While finding subjects for medical trials is difficult, futures studies should do a better job accounting for losses to follow up, creating groupings that are demographically similar, and demonstrating control over variables from daily life that could influence results. In the future, researchers should try an intervention that supplements curcumin to enable better absorption, such as piperine or turmeric, the spice from which pure curcumin is derived from.[9] It would be beneficial to also evaluate if long-term use of curcumin in healthy young adults can prevent future cognitive decline, unlike many current study patterns. Creating more studies that utilize a bioavailable version of curcumin or that evaluate long-term use of curcumin could potentially ameliorate cognitive decline or prevent it from occurring in the first place.

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