Review: The Efficacy of Curcumin in Cognitive Impairment

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Abstract:

Background Dementia is a syndrome characterized by a progressive cognitive decline that can interfere with everyday function. The presence of inflammation is associated with the progression of cognitive decline. Treatment of inflammation-induced cognitive decline has been proposed through the use of anti-inflammatories. One intervention studied is curcumin, a compound extracted from the spice turmeric with anti-inflammatory properties. This paper reviews the efficacy of curcumin in cognitive decline.

Purpose This review seeks to understand how effective curcumin is an intervention for optimizing cognition in older adults ages 55 and older compared to placebo. This study will benefit the naturopathic doctor investigating curcumin's current literature and its efficacy in treating cognitive decline.

Methods A literature search was conducted in accordance with literature review methods. Using the keywords [curcumin OR turmeric] AND [Alzheimer's disease OR dementia], a preliminary search for relevant articles on this topic was conducted on MEDLINE, PubMed, CINAHL, Embase and Cochrane databases screened for article titles containing dementia, Alzheimer's disease and curcumin, and filtering for articles published from 2000 onward and in English.

Results Six studies were found eligible after considering inclusion and exclusion criteria. Of these studies, four of them have shown positive cognition improvements, and two studies have shown no improvement in cognition.

Implications Curcumin may have potential as an intervention for the treatment of cognitive decline. However, due to insufficient studies, more research is warranted to understand better if curcumin is beneficial as an adjunctive treatment for Alzheimer's disease.

Key Messages

- Inflammation plays a potential role in Alzheimer's disease. Curcumin is a compound extracted from the spice turmeric and possesses anti-inflammatory properties.
- Curcumin may be a potential adjuvant in treating mild cognitive impairment, but likely not for those diagnosed with dementia.
- Future research on curcumin use is needed to better address and understand its efficacy on individuals living with mild cognitive impairment and dementia.

Introduction

Dementia is a syndrome characterized by a progressive cognitive decline that can interfere with everyday function.[1] Activities such as planning, bathing, eating and grooming can be affected, requiring assistance when appropriate. Symptoms commonly associated with dementia include progressive memory loss, increasing confusion, reduced concentration, behaviour changes and the eventual loss of ability to do everyday tasks. Six cognitive domains affected by dementia are learning and memory, language, complex attention, executive function, perceptual-motor and social cognition.[1] Dementia is an umbrella term that describes the clinical syndrome of cognitive decline. Under the umbrella of dementia, Alzheimer's disease is the most common type of neurodegeneration, with roughly 60% to 80% of cases of dementia.[1] The remaining subtypes of dementia include vascular dementia, Lewy body dementia and frontotemporal dementia.[1]

Currently, approximately 564,000 Canadians live with dementia and this number is expected to almost double to 937,000 Canadians in 15 years.[2] The Alzheimer's Society reports that there are 25000 new cases of the disease each year.[2] This growth affects social and economic implications on medical costs and burden for families, caregivers and the health system.[3] 1,100,000 Canadians are affected directly or indirectly by dementia, leading to an annual cost of $10.4 billion to care for those living with dementia.[2]

The hallmark of Alzheimer's disease (AD) is the presence of beta-amyloid plaques deposited in the parenchyma of the hippocampus amongst other locations,[4] with one of the earliest documented articles about amyloid being published in 1839.[5] Contained in the amyloid plaques are amyloid-β-peptides resulting from cleavage from the amyloid precursor protein (APP).[6] The significance of accumulation of beta-amyloid plaques is shown to disrupt glial cell function and also responsible for the production of inflammation markers such as IL-1, IL-6, and TNF-α.[7]

A theory now emerging in research is how inflammation influences the pathogenesis of Alzheimer's dementia.[7] Local and circulating inflammatory cytokines can have an impact on the central nervous system.[8] High plasma levels of IL-6, CRP, and TNF-α-related factors have been predictive of cognitive decline in older populations.[9-11] Elevated levels of IL-6 and TNF-α in the blood are also associated with the AD development.[12,13] In mice studies, chronic systemic inflammation has been reported to influence changes that correlate with Alzheimer's disease.[14] These findings of elevated inflammatory markers associated with AD development can suggest a potential intervention using anti-inflammatories.

Curcumin is a compound extracted from the spice turmeric. There is a growing body of evidence that supports the efficacy of curcumin in controlling the treatment of inflammatory conditions.[15] Curcumin modulates inflammation through down-regulation of COX-2, lipoxygenase and inducible iNOS enzymes,[16] inhibition of TNF-α,[17] IL-1,[18,19] IL-2,[20,21] IL-6,[17,22] IL-8,[17,23] and IL-12 production,[24] and down-regulation of mitogen-activated and Janus kinases.[25] Besides its anti-inflammatory action, curcumin is found to have anticarcinogenic, antimicrobial, hepatoprotective, cardioprotective and thrombosuppressive actions.[26]

The proposed research question is: "How efficacious is the use of curcumin in improving memory scores in seniors ages 55 and over compared to placebo?"

Methods

Search Strategy

An electronic bibliographic literature search was conducted in accordance with the preferred reporting items for reviews.[27] Using the keywords [curcumin OR turmeric] AND [Alzheimer's disease OR dementia], a preliminary search for relevant articles on this topic was conducted on the following databases selected to incorporate extensive medical and health care evidence: PubMed, CINAHL, MEDLINE, Cochrane, and Embase. Search articles were organized and screened for the terms dementia, Alzheimer's, and curcumin in the title and abstract; duplicates were manually removed and filtered for articles (1) published from 2000 onward for recency, (2) human studies, and (3) in English.

Screening Process

Article titles and abstracts were screened for the use of curcumin as an intervention for closer review. In addition, abstracts were screened for any use of objective tests to determine cognitive ability, such as MoCA, to quantify efficacy. Characteristics that are crucial in this research are the intervention, population, and outcome.[28]

Selection Process

Full articles were obtained for selected abstracts and reviewed for inclusion. The process of selection is presented in Figure 1. The inclusion criteria for this review were: (a) Curcumin as the intervention, (b) seniors ages 55 and older as subjects, (c) to have an objective measure for memory scores such as MMSE and MoCA at baseline, and (d) controlled trial or clinical trials.

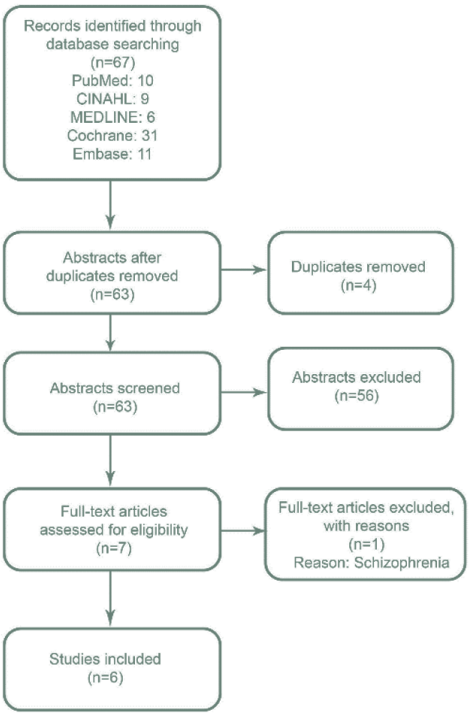
Data Extraction

The author independently extracted data to evaluate and classify the quality of each study. The articles were extracted utilizing the following headers in Appendix A. These include: sample size and key features, intervention, study design, length of study/follow-up period, other interventions, memory test, memory changes, and appraisal findings.

Analysis

Data were extracted from each article and compared and contrasted. Besides the results and amplitude of change of memory scores, points of analysis included the type and dosage of curcumin supplement utilized and their apparent effectiveness in the studies, length of the studies, how the authors reflected on the results, and the variations in sex distribution and the results.

FIGURE 1: PRISMA Chart



Results:

Overview

A total of 67 articles were identified, with four articles removed for duplicates. There were 57 articles excluded, leaving with seven full-text articles. Out of the seven full-text articles, 1 article was excluded because it did not focus on Alzheimer's disease but rather schizophrenia.

A total of six articles were eligible for this review. This included five double-blinded and placebo-controlled randomized control trials and one open-label study. In compiling the studies, the total number of 273 people were studied across the six studies. The sex distribution across the studies ranged from 12.5% to 90% male. The dosages of the studies ranged from 90mg to 4g of curcumin.

The location of the studies ranged from Australia, America, China and Japan. Amongst these studies, several older adults from senior homes, dementia clinics and independent living were sampled. Lengths of studies ranged from four weeks to eighteen months. Each study utilized curcumin as their intervention; however, curcumin can come in many different forms and dosages based on the supplement and the market. The studies selected for this review utilized various curcumin formulations, including C3 Curcumin, Biocurcumax, Longvida Optimized Curcumin and Theracurmin. An extraction chart summarizing the data described in the Methods section under Data Extraction is provided (Appendix A).

Results of the studies were mixed. The primary outcomes observed are that curcumin improved cognitive scores, and curcumin did not improve cognitive scores.

Safety and Adverse Effects

There is previously demonstrated safety and tolerability in human studies for curcumin.[29,30] Gastrointestinal complaints such as nausea and gastritis accounted for most adverse events in the studies.[31,32,35,36] No severe adverse events were observed.

Improvement in Cognitive Scores

In synthesizing the articles, one outcome that arose was that the intervention supported improvement in memory scores—four articles in this review support this theme. The study done by Small et al.[31] recruited 40 non-demented adults and randomized subjects into two groups. Those in the intervention group were given 90mg curcumin in the form of Theracurmin twice daily, and those in the control group received a placebo for 18 months. The study utilized Visual Memory Measures and Measures of Attention to assess for cognition. The verbal memory outcome measure consisted of a long-term recall and found that there was a 28.1% improvement of verbal memory in the curcumin group versus a 2.6% improvement in the placebo group.

Another study that supports this outcome was done by Rainey-Smith et al.[32] The study recruited 96 community-dwelling older adults and randomized them into two groups. Those in the treatment group were given 1500mg daily of Biocurcumax and compared to placebo. This study lasted for 12 months. For eligibility, subjects needed to demonstrate a baseline MoCA score of greater than or equal to 26 out of a maximum score of 30, which is considered normal cognition. Post-treatment, the mean MoCA scores improved by 0.64 points in the treatment group and by 0.09 points in the placebo group compared to their baseline scores.

The third study that supports this outcome was done by Cox et al.,[33] where they enrolled 60 individuals and screened them with the MMSE. Subjects were randomized into two groups: the treatment group was given 400mg of Longvida Optimized Curcumin daily, and the control group was given a placebo. Subjects were tested before the first dose with a serial three subtraction exercise task. One hour after taking the intervention, subjects were subjected to another serial three subtraction task, and again after four weeks. There was a significant effect on the number of correct responses in the curcumin group, increasing by 16% from pre-dose performance versus a 2% increase in the placebo group. This effect continued after four weeks, where the number of correct responses in the curcumin group increased by 17% from baseline versus 3% in the placebo group.

The fourth study that supports this outcome was done by Tabira & Kawamura,[34] where they did an open-label study consisting of 2 trials. The two trials enrolled 19 participants and were given a

supplement containing Huperzine A and curcumin. Subjects were screened with the MMSE and ADAS-Jcog and then subjected to ADAS-Jcog post-supplement at 6-12 weeks and 22-28 weeks. In both trials, the ADAS-Jcog scores improved significantly in both cohorts when compared to baseline.

No Improvement in Cognition

The other significant outcome synthesized in the selected articles is that the intervention showed no improvement in memory scores. Two articles supported this theme. The first article is by Ringman et al.,[35] where they recruited 30 participants with mild to moderate probable Alzheimer's disease screened with the MMSE and obtained a range between 17 and 29, with the mean score 22.5. Participants were randomized into three groups. One group was assigned to take 2 grams of C3 Curcumin daily; a second group was assigned to take 4 grams of C3 Curcumin daily; and a third group was assigned a placebo. The length of the study lasted for 24 weeks, with an open-label extension to 48 weeks. At the end of the period, participants were followed up, and their cognition was measured with the Alzheimer's Disease Assessment Scale – Cognitive Subscale. At 24 weeks, the authors concluded that there was no clinical evidence of efficacy against Alzheimer's disease.

The second article that demonstrated no improvement of cognition was done by Baum et al.,[36] which recruited 34 participants: nine from nursing homes and 24 from dementia clinics. Twenty-two participants completed the study and were randomized into three groups: 4 grams of curcumin daily, 1 gram of curcumin daily, or placebo. This study was conducted for six months. Participants were assessed using the MMSE as baseline and post-treatment. Participants in the 4 gram treatment group exhibited a 0.7 (+/- 1.1) change on their MMSE score, a -0.6 (+/- 1.0) MMSE score change for those in the 1 gram treatment group, and a 1.3 (+/- 0.6) MMSE score change for those in the placebo group. In other words, there was no significant improvement observed in this study.

Baseline and Cognitive Changes

In observing the above results, studies that showed improvement involved community-dwelling older adults with MoCA scores greater than or equal to 26[32] older adults[33] and non-demented older adults with MoCA baseline averaging approximately 26.[31] Whereas the remaining studies by Ringman et al.[35] and Baum et al.[36] did not show any positive outcomes, the samples tested for baseline involved a clinical diagnosis of dementia.

Discussion

This review has outlined five randomized controlled trials and one open-label study using curcumin intervention and observing any changes in cognition and memory scores in participants. Based on the results, four studies demonstrated improvement in cognition, and two studies did not show improvements in cognition. This discussion will interpret these results and evaluate and discuss potential biases that may have affected the studies' findings.

TABLE 1: Baseline Measures and Cognition Changes

Citation	Inclusion Criteria Regarding Dementia	Cognition Result
Cox et al. (2015)	Healthy older subjects	Enhanced cognition
Rainey-Smith et al. (2016)	Elderly subjects	Mean MoCA score increased, but no significant difference between groups
Small et al. (2017)	Non-demented subjects	Significant improvement in memory performance
Ringman et al. (2012)	Mild-to-moderate Alzheimer's disease	No differences
Baum et al. (2008)	Alzheimer's disease	No difference in MMSE
Tabira & Kawamura (2018)	Alzheimer's disease, Lewy Body dementia, Mild Cognitive Impairment	Improvement in ADAS-Jcog

Some studies support the idea that curcumin can be potentially efficacious in treating Alzheimer's disease.[37,38] Three of the four studies that observed improved memory scores involved non-demented or healthy older adults. In deducing from the articles, curcumin as an intervention is potentially effective in healthy individuals for improving cognition and not treating dementia. This may suggest curcumin's role in potentially preventing cognitive decline or that it may likely be a better option for individuals with mild cognitive impairment. Although it is not emphasized as a chronic illness, an expert opinion suggests that there may be a point of no return for Alzheimer's disease.[39] However, with the lack of the number of quality studies, this is not conclusive.

The length of the intervention may affect outcomes. The studies' length ranged from four weeks to 18 months, with four of the five studies taking one year or less. The studies that observed no improvement in cognitive scores had study lengths of 24 weeks and six months; The studies that observed improvements in cognitive scores had study lengths of 4 weeks, 12 months and 18 months. Results are mixed based on the lengths of each study. As dementia is a chronic disease, evidence suggests that the development of dementia takes a significant amount of time, although this varies between patients.[40] Mann, Mohr, Gearing & Chase suggest that this disease progression of dementia ranges from a few years to two decades.[41] If the pathophysiology of Alzheimer's disease takes a great deal of time to develop, then the length of the intervention should reflect and take this process into consideration. The intervention will take time, and may require three to six months to observe subjective or objective improvement in cognition[42] as well as instructions on the length, frequency and intensity of the intervention.

The dosage of curcumin can determine efficacy and if outcomes are dose-dependent. The dosages of the studies ranged from 90mg to 4g of curcumin. Future studies should investigate what an optimal dose of curcumin may be. So far, research can only gauge as to what dose is tolerated. A recent Phase I clinical trial demonstrates that curcumin is safe even at high doses (e.g., 12g/day).[43] Although studies that used the highest dose of curcumin in this review (i.e., 4g daily) exhibited no differences in cognition,[35,36] studies showed cognitive benefits with doses as small as 90mg of curcumin. Dosage may or may not be potentially as important as the formulation, but could be considered for any possible adverse effects such as gastrointestinal symptoms.[29,30]

Besides dosage, the form of the actual curcumin supplementation varied. There are concerns about the bioavailability of curcumin supplementation[44] and whether curcumin can pass the blood-brain barrier for it to take effect. Anand, Kunnumakkara, Newman & Aggarwal explain that although curcumin is safe, humans exhibit low bioavailability, which may be due to poor absorption, rapid metabolism and rapid systemic elimination.[43] In animal studies, no more than 90% of oral curcumin is excreted in the feces.[45] Each study utilized a different supplement, and there was no consistency across the studies with the formulations. Each formulation can exhibit a different bioavailability based on what was incorporated in the proprietary blends. Some studies are attempting to overcome this problem, including the incorporation of piperine, formulating liposomal curcumin, curcumin nanoparticles, and curcumin phospholipid complexes.[46] Some studies did not indicate what kind of curcumin was utilized, and thus results may reflect that.

Additionally, the use of concurrent medications throughout the intervention may pose a challenge. There is an understanding that individuals already diagnosed with cognitive impairment may already be prescribed medication, such as an acetylcholinesterase inhibitor. By taking medications along with curcumin, there will likely be uncertainty about what helps if cognition improves. Interactions between concurrent medications and curcumin could affect outcomes. However, as a part of this review, the participants in studies showing no difference between curcumin and placebo were also on concurrent medications as previously diagnosed. This adds to the suggestion that curcumin may be more beneficial to healthy individuals or those with mild cognitive impairment in maintaining or preventing dementia versus those who are already diagnosed and are unable to function independently.

Limitations

The studies in this review all have small sample sizes. Without a more significant number of participants included in many of these studies, there will not be a good representation and power when it comes to statistical value.

In addition, the samples in some of the studies had disproportionate sex ratios, with the study by Baum et al.[36] having the most significant proportion of female participants and very low rates of inclusion of male participants. This can potentially affect the results if there is no equal distribution of sexes, if sex differences are associated with disease progression or response to intervention.

In discussing representation, this review includes studies from Australia, America, China and Japan. As each group is diverse in their genetics and culture, there is also a need to consider each study's weight in the general population.

Though most of the studies utilized are weak and moderate in strength, as shown in Appendix A, there is not much quality research to answer that curcumin is efficacious. Also included in this review is a weak study that may have further skewed the results of this review. More robust quality studies are warranted in future studies.

This review would be strengthened if the intervention been of the same formulation or brand and consistently administering MoCA as baseline and post-intervention and other cognitive assessments. Future research studies should consider utilizing one specific curcumin supplement that has been identified to have optimal bioavailability consistent with all studies. That will include ensuring that future research includes finding a formulation that will contain a measure of how much curcumin is absorbed into the blood and potentially how long it can stay in the body. All future research can also be strengthened by consistently administering a universal objective measurement of cognition, whether MoCA or ADAS.

There are also limitations to this review. The search did not include all relevant databases, nor were statistical analysis resources utilized for meta-analysis. The author performed all searches independently when there could be many authors to perform a more thorough, unbiased review.

Conclusion

Curcumin shows mixed results as a treatment or preventative intervention for seniors living with or without dementia. The themes presented in this review suggest that curcumin is efficacious in improving memory scores in those without diagnosed dementia compared to those who do have dementia. Thus, it may be more pertinent to suggest for the naturopathic doctor that curcumin may be more reasonable as an intervention for mild cognitive impairment or for use as part of a plan to mitigate the risk of developing dementia from an underlying inflammatory etiology. However, with the lack of studies to date and small sample sizes of the studies in this review, this study warrants the need for more clinical studies to determine the efficacy of curcumin. This review has found mixed results regarding curcumin use and has explored the potential reasons for these results. Future studies involving the use of curcumin should be cognizant of the study period's length, the dosage and the form of supplementation used in the study.

About the Author

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APPENDIX A

TABLE A2: Extraction Matrix

Citation	Sample Size and Key Features	Intervention	Study Design	Length of Study/Follow-Up Period	Other Interventions	Memory Test	Memory Changes	Appraisal Findings
Studies that showed improvement in cognition								
Cox, Pipingas & Scholey, 2015	60 healthy older adults enrolled; Australia Treatment: 40% male Placebo: 33.3% male	400mg Longvida Optimized Curcumin; placebo	Randomized, double-blind, placebo-controlled, parallel-groups	Acute – 1h or 3h Chronic – 4 weeks	No concurrent anticoagulant drugs, anti-cholinergics or acetylcholinester-ase inhibitors or steroid medications	MMSE Screening; Computerized Mental Performance Assessment System (Northumbria University)	1 hour- Increased correct responses of serial three subtraction task; 4 weeks trend towards beneficial effect of correct serial three subtraction	*Overall Quality:* Weak *Strengths:* Consistency of memory testing RCT Relatively equal sex ratio *Limitations:* Small sample size Shortest study length in review
Rainey-Smith, Brown, Sohrabi and Shah, 2016.	96 elderly subjects individuals ingested either placebo (57) or 1500mg of curcuminoids (39); Western Australia Treatment: 33.3% male Placebo: 26.3% male	1500mg/d Biocurcumax or placebo	Randomized, placebo-controlled, double-blind	12 months	None indicated	MoCA scores greater than or equal to 26; Those with 18-25 go through a case-by-case determination of eligibility	Mean MoCA scores improved by 0.64 points in curcumin group and by 0.09 points in placebo group from baseline to 12 months. No significant differences in cognitive test performance between groups	*Overall Quality:* Moderate *Strengths:* Use of MoCA throughout study consistently RCT *Limitations:* Small sample size, but largest amongst review High female proportion
Small et al., 2018	40 subjects; non-demented adults; America Treatment: 43% male Placebo: 47% male	90mg bid curcumin (Theracurmin) or placebo	Randomized, double-blind, placebo-controlled	18 months	None indicated	MoCA baseline 26.7+/-2.6 for curcumin group, 26.9+/-2.5 for placebo group	Significant memory and attention benefits	*Overall Quality:* Moderate *Strengths:* Longest study length within review *Limitations:* Small sample size
Tabira & Kawamura, 2018	10 individuals in Trial 1(9 with AD and 1 with possible DLB), 9 individuals in Trial 2 (3 with AD, 4 with DLB, 3 MCI, 1 vascular dementia)	Trial 1: 6 capsules daily. One capsule includes 60mg curcumin, 25mg H. serrata extract containing 50μg Hup A, 3mg piperine. Trial 2: 2 granules in the sticks. One stick includes 50mg curcumin, 180mg H. serrata extract containing 180μg Hup A.	Open label study	Follow up at 6-12 weeks and 22-28 weeks	Comment on use of lansoprazole due to worsening of chronic gastric ulcers. No other mention of concurrent medication	Trial 1: mean MMSE score 18.8+/- 4.2 and mean ADAS-Jcog score 24.0+/-9.6. Trial 2: Mean MMSE score 23.0 +/- 4.3 and mean ADAS-Jcog score 11.0 +/-4.4.	Trial 1: Most patients showed improvements in ADAS-Jcog scores. Subjective and caregiver comments. Trial 2: ADAS-Jcog scores improved in all cases but for one.	*Overall Quality:* Weak *Strengths:* Use of consistent baseline and post-treatment measure *Limitations:* Very small sample size for both trials Short study length No randomization
Studies that observed no improvement in cognition								
Baum et al. 2008	22 with Alzheimer's disease completed; China. 1g curcumin: 12.5% male 4g curcumin: 27.3% male Placebo: 37.5% male	4g, 1g or 0g curcumin	Randomized, placebo-controlled, double-blind	6 months	Patients permitted to continue with their medications	MMSE scores 15.4+/- 5.8 on 0g 15.4+/-5.0 on 1g 15.6+/-7.9 on4g	MMSE changes 1.3+/-0.6 on 0g -0.6+/-1.0 on 1g 0.7+/- 1.1 on 4g	*Overall Quality:* Weak *Strengths:* Consistency of use of baseline and outcome measures *Limitations:* No indication of the specificity of intervention Very low male sample proportion No use of more substantial cognitive tests such as MoCA
Ringman et al., 2012	36 participants with mild- to moderate probable AD 2g: 33% male 4g: 30% male Placebo: 45% male	2g, 4g, or placebo Curcumin C3 Complex	Randomized, double-blind placebo-controlled trial	24 weeks with an open-label extension to 48 weeks	Acetylcholinester-ase Inhibitors and memantine allowed	MMSE 17-29	No differences between placebo and curcumin, using ADAS-Cog	*Overall Quality:* Moderate *Strengths:* Use of ADAS-Cog, which is preferable *Limitations:* Small sample size Short study period No consistency between baseline and outcome tests

Note: AD – Alzheimer's Disease, DLB – Dementia with Lewy Bodies, MCI -Mild Cognitive Impairment

APPENDIX B

Search String and MeSH terms

Embase	Pubmed	CINAHL	EBM Reviews – Cochrane Central Register of Controlled Trials
1. exp curcumin/ 2. exp dementia/ 3. exp turmeric/ 4. exp cognitive defect/ 5. 2 or 4 6. 1 or 3 7. 5 and 6 8. limit 7 to (full text and (embase or medline) and (clinical trial or randomized controlled trial or controlled clinical trial) and yr="2000 -Current" and article and aged <65+ years>)	1. (curcumin OR turmeric) 2. (dementia OR Alzheimer's) 3. 1 and 2	1. MH "curcumin" 2. MH "Turmeric" 3. MH "Dementia" 4. MH "Alzheimer's disease" 5. S1 OR S2 6. S3 OR S4 7. S5 AND S6	1. Curcumin/ 2. Dementia/ 3. Alzheimer's disease/ 4. 2 or 3 5. 1 and 4

MeSH terms:

Cognitive Dysfunction / prevention & control*
Curcumin / therapeutic use
Dementia / prevention & control*
Dementia / therapy
Healthy Aging
Humans
Inflammation / prevention & control