Turmeric- From spice rack to medicine cabinet?

An analysis of the effectiveness of turmeric in treating Alzheimer's patients

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Image Source: http://www.homeremediesweb.com/images/product_turmeric.jpg

Abstract

Background: Alzheimer's disease ("AD") is a terminal, neurodegenerative disorder that affects the elderly. Numerous research studies show the existence of a number of markers of inflammation in the AD brain, suggesting that AD is an inflammatory response and that it significantly contributes to it's own pathogenesis [1]. Anti-inflammatory pharmaceuticals have been shown to limit inflammation but not without side effects. A natural source of an anti-inflammatory exists in the Indian herb turmeric. The lowest rates of validated AD are found in rural India, a population known for its turmeric consumption [2].

Objective: This review intends to synthesize the best available evidence associating the therapeutic potential of turmeric with the successful treatment of AD in the elder (<60) population.

Methods: A literature review was conducted and relevant peer-reviewed journal articles from CINAHL, PubMed and ScienceDirect were collected and prioritized based on inclusion criteria. Two independent researchers assessed the articles for relevancy and the inter-rater reliability was 100%.

Results: A total of 12 studies were included for review and results were relatively consistent among them. The literature shows a clear association between turmeric and a significant reduction in the psychological and behavioral symptoms of this form of dementia. In experimental studies turmeric has been shown to successfully reduce the beta-amyloid plaque burden as well as other AD proteins.

Conclusion: Since the turmeric plant itself cannot be patented, it's benefits are difficult to put into practice and thus epidemiological research is limited. Available research synthesized in this review has generated results indicating that naturally occurring turmeric has beneficial potential for the treatment of Alzheimer's patients. Further human studies is needed to positively ascertain these results, with consideration of bioavailability, safety and tolerability in the target populations.

Introduction

What is AD?

This neurodegenerative disease manifests through clinical symptoms such as cognitive dysfunction, agitation, depression, delusion, hallucination, insomnia, and wandering. The disease progresses from memory loss to dementia and eventually death, normally within 8 years of onset [3]. The clinical biomarkers associated with AD pathogenesis are: extracellular accumulation of amyloid protein in the form of senile plaques and accumulation of hyperphosphorylated tau in the form of neurofibrillary tangles [4]. It's incidence is increasing from 1% between the ages of 60 and 70 to 6-8% by age 85 [4]. When compared to western populations the prevalence of AD is 4.4 times lower in Indian and Asian populations [5].

Why consider the spice turmeric?

Current FDA-approved medications are associated with various side effects and low effectiveness. Turmeric, specifically it's active compound curcumin, has been used in traditional Indian medicine for centuries, based on its anti-inflammatory, anti-oxidant, anti-amyloidgenic, metal- chelating and anti-proliferative properties [4]. Results from a large prospective epidemiological study, the Indo-US Cross National Dementia Study, showed that there is a lower incidence and prevalence of AD in the rural Indian population when compared to the US reference population, which is in part attributable to the consumption of turmeric [2].

Research Question

In the elderly (<60) population does the consumption of turmeric effectively treat the clinical symptoms of Alzheimer's disease?

Methodology

Keywords: Turmeric and Alzheimer's

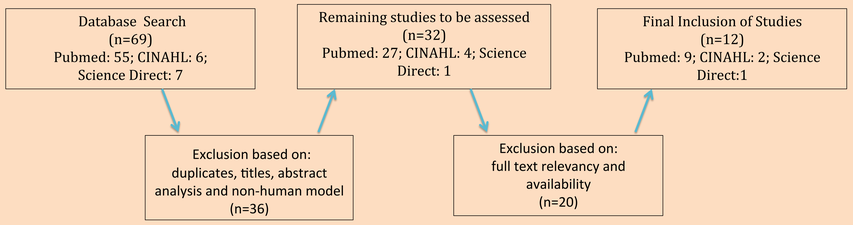

Figure 1. Methodology flow chart for the structured literature review.

Inclusion Criteria:

- Peer-reviewed journal
- AD as the main topic
- Human models or *in vitro* studies
- Between 1995-2015
- English Language

Two independent raters evaluated the articles based on the inclusion criteria and inter-rater reliability was 100% with a Cohen's kappa of κ= 1.0.

Results

Authors	Study Design	Primary Findings	Limitations
		Human Studies	
[6] Baum, L. et al. (2008)	Six-month randomized placebo controlled double blind pilot clinical trial	- Serum Aβ40, the main component of amyloid plaques, did not differ significantly among doses. Serum Aβ40 tended to rise on curcumin possibly reflecting an ability of curcumin to disaggregate Aβ deposits in the brain, releasing them for circulation and disposal. -Between baseline and 6 months, serum Aβ40 (mean ± SE) changed from 30± 6 ng/L to 26± 3 on 0 g and from 28± 6 to 35 ± 7 on 4 g (P = 0.15). - Oral cucurmin did not show any adverse side effects.	- Small sample size (n=34) with only 27 completing the 6 month trial. - The mean age of the sample was 78 years old and participants were selected based on probable or possible AD and of Chinese ethnicity. This is subject to selection bias, or specifically Berkson bias as the participants were sampled from old age homes.
[7] Hishikawa, N. et. al. (2012)	Case Study	-Three cases of AD were shown to significantly improve with turmeric treatment, specifically the behavioural and psychological symptoms of dementia (delusions, hallucinations, apathy, agitation, anxiety, irritability and depression). -With the curcumin treatment, the astrocytic marker, glial fibrillary acidic protein, was reduced and insoluble and soluble Aβ and plaque burden was significantly decreased by 43-50%.	- Very small sample size (n=3), low power. -No description on the methodology of how patients were chosen or for length of treatment- possibly subject to selection bias and much of the results are based on qualitative data rather than quantitative. - Did not look at core symptoms (memory loss).
[8] Ringman, J. M, et al. (2012)	24 week double-blind placebo controlled	-Unable to demonstrate clinical or biochemical evidence of efficacy against AD. There were non-significant trends for both MMSE score and the ADAS-cog score to worsen slightly in the curcumin treated groups relative to the placebo group.	-Lack of follow-up biomarker data for subjects who discontinued, small sample size (n=24) and short duration. -Variability in the baseline disease severity may have masked effects, particularly if the intervention was effective in the subgroup.
		Experimental Studies	
[9] Taylor, M. et, al. (2011)	Experimental Study	- This study compared the effects of nanoliposomes associated with curcumin on the aggregation of the amyloid-β1-42 (Aβ1-42) peptide. All nanoliposomes with curcumin, or the curcumin derivative, were able to inhibit the formation of fibrillar and/or oligomeric Aβ in vitro. Of the three forms of curcumin liposomes tested, the click-curcumin type was by far the most effective (p=0.01).	- Only three nanoliposomes were tested and all were tested in vitro. This study, though promising, is not relatable to the human population.
		Reviews	
[3] Ahmed, T. & Gilani, A. (2014)	Review Article	- Curcuminoids enhance Aβ uptake, inhibits fibril formation and extension and down regulates Aβ-induced BACE-1.	- Did not explain their methodology and thus could not identify biases from the inclusion/exclusion criteria.
[4] Belkacemi, A. et. al. (2011)	Expert Review	- Curcumin has been shown to display complex and multifaceted activities as an antioxidant and an anti-inflammatory agent and in the inhibition of β-secretase and Aβ aggregation. It therefore represents one of the most promising compounds for the development of AD therapies. - Using nanotechnology, some studies demonstrate higher efficacy and bioavailability with sustained release.	- Did not explain their methodology and thus could not identify biases from the inclusion/exclusion criteria.
[10] Chin, D. et al. (2013)	Comprehensive Review	- Turmeric has not been very successful in clinical trials due to it's poor bioavailability. - In vitro and animal models have shown that curcumin is anti-amyloidogenic, reduces plaque burden and reverses amyloid pathology and possesses anti-inflammatory effects.	- There have been few clinical trials to date, to summarize and review and much of the research is ongoing.
[11] Howes, M., & Perry, E. (2011)	Review Article	- In 1010 people aged 60-90 years frequent or occasional curry consumers had significantly higher MMSE scores than rare or non-consumers. - The mechanistic effects of curcumin include neuroprotection from Aβ as a result of antioxidant effects and suppression of Aβ induce BACE-1 up-regulation. - Curcumin reduces metal-induced amyloid aggregation or oxidative neurotoxicity in AD.	- Did not explain their methodology and thus could not identify biases from the inclusion/exclusion criteria.
[12] Lee, W. et.al. (2013)	Review Article	- Stability of curcumin is crucial to maintain it's physiological activities. The decomposition is pH dependent and it degrades more rapidly at neutral to basic conditions, like physiological pH. This is a significant disadvantage to its therapeutic use. - Out of 214 anti-oxidant compounds tested in preventing fibril formation curcumin demonstrated the strongest inhibitory effect.	- Did not explain their methodology and thus could not identify biases from the inclusion/exclusion criteria.
[5] Mishra, S. & Palanivelu, K. (2008)	Overview	- A growing body of evidence indicates that oxidative stress, free radicals, beta amyloid, cerebral deregulation caused by bio-metal toxicity and abnormal inflammatory reactions contribute to the key event in Alzheimer's disease pathology. - AD patients, enrolled in a study in UCLA, had their macrophages treated with curcumin and when compared with patients whose macrophages were not treated with curcumin, they showed an improved uptake and ingestion of the plaques.	- Did not explain their methodology and thus could not identify biases from the inclusion/exclusion criteria.
[13] Ray, B., & Lahiri, D.K. (2009)	Review	- Curcumin has 'pleotropic' properties like many other naturally derived compounds. - A role of curcumin has already been established in pre-clinical trials to alter inflammatory responses, however, curcumin has had disappointing results in clinical trials due to it's poor bioavailibity.	- There have been few clinical trials to date, to summarize and review and much of the research is ongoing.
[14] Ringman, J.M., et. al. (2005)	Literature Review	- Curcumin inhibited the formation and extension of Aβ fibrils and destabilized preformed Aβ- fibrils in a dose-dependent fashion at a range between 0.1 and 1 micro-molar concentration. - Turmeric is listed as generally safe, but curcumin itself is not listed and has been given a temporary acceptable daily intake level of 0.1 mg/kg of body weight pending further study.	- Lack of human studies data.

Discussion

- As evidenced by our results, most of the data concerning turmeric's beneficial effects on AD is relatively recent. All human studies (n=3) have been conducted in the last 7 years and thus clinical and epidemiological evidence is lacking.
- It is surprising to see that there has been so few randomized control trials (RCT), as turmeric seems to be a safe and natural alternative to current pharmaceutical offerings. However, when looked at from an economic point of view one must remember that turmeric is a naturally occurring spice so it is not patentable. This would limit it's profitability.
- The RCT's that have been conducted were not rigorous or large-scale, they were limited by a small number of patients, short period of follow up, and no real statistical analysis was presented. It is also difficult to administer turmeric through the oral route or measure its consumption due to its poor aqueous solubility and low systemic bioavailability, bringing clinical efficacy into question.
- Every study reviewed commented on its low bioavailability, and identified this as the largest barrier to turmeric's success as an AD drug. Rapid metabolism and quick elimination has also been noted in most studies as potential limiting factors.
- All studies that commented on turmeric's safety found it to be well tolerated, even at high doses. What makes this spice an even more attractive candidate is it's multifaceted neuroprotective ability and lipophilic character that allows it to cross the blood brain barrier. It has been shown to be effective in the reduction of plaque burden, reversal of amyloid pathology and decrease of soluble phosphorylated tau (Figure 2).
- Several other compounds have been isolated from turmeric in addition to curcumin, those being curcuminoids. Recent studies have shown the curcuminoids also possess potential roles in the treatment of AD - specifically demethoxycurcumin (curcumin II), bisdemethoxycurcumin [3][4][13]. The fact that turmeric possesses a number of active and non-active compounds suggests that the presence of potent drug candidates could have been unaccounted for.

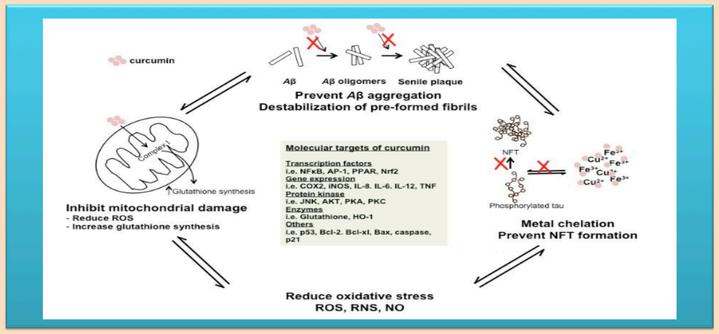

Figure 2. Molecular targets of curcumin against AD. Adapted from [12].

Limitations

- This structured review was subject to non-differential misclassification bias, which lies within the data collection and was consistent throughout each database that was searched.
- The review was based on two keywords: turmeric and Alzheimer's. We acknowledge these keywords are limiting in scope, however, when other keywords were added very similar search results were found and this search ascertained the most specific results.
- Only English studies were included which leads to a potential inclusion bias. Only three prominent databases searched which could result in some articles being missed.
- An executive decision was made by the researchers to only include titles that included in vitro and human studies excluding animal models (i.e rats) as these studied were not relevant to our research question.

Conclusions

- Based on the results of this review, it is not advisable to have patients (<60) replace their AD medications with turmeric. However, due to it's safety and potential beneficial effects, it would not be harmful to have the patient consume more turmeric in their diet unless they have gall bladder problems.
- An emphasis on RCT's and longitudinal studies would prove very beneficial to the crusade for turmeric as an AD treatment.
- Clinical efforts should be directed toward facilitating it's carrier mediated transport and/or nanotechnology [9][13] based delivery system to increase the bioavailability.