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Effect of Curcumin on Beta-Amyloid Plasma Level in Alzheimer Disease: A Systematic Review and Meta-analysis

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Abstract

Alzheimer's disease is known as a most common dementia disorder in the world. The famous hypothesis about the cause of this disease is beta-amyloid (Aβ) accumulation in the brain. There is a widespread neuroinflammation in the patient's brain, leading to neuronal apoptosis and brain atrophy. Curcumin is a well-known anti-inflammation and anti-oxidant ingredient. It can easily cross the blood-brain barrier. There are controversial results about the effects of curcumin on Aβ clearance and metabolism in Alzheimer's disease and the elderly. The aim of this meta-analysis and systematic review was to review the effect of curcumin on Aβ clearance in clinical studies. We performed a systematic review and meta-analysis on the three randomized clinical trials (RCTs) and one pilot study that assessed the effect of curcumin on Aβ plasma level in Alzheimer's disease. For this purpose, we searched PubMed and Scopus databases up to December 2020. Our result showed there was no significant change in serum Aβ level (weighted mean difference [WMD]: 5.3, 95% CI: 0.78-9.97) following curcumin consumption in patients with Alzheimer's disease. Further clinical trials should be done to evaluate the effects of curcumin in Aβ level in Alzheimer's disease.

Keywords: Alzheimer's disease, Beta-amyloid, Curcumin, Meta-analysis

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Introduction

Alzheimer's disease is a common neurodegenerative disease worldwide.[1,2] The most important cause mentioned was the accumulation of beta-amyloid (Aβ) fibril in the central nervous system (CNS).[3] Actually disruption in Aβ homeostasis can lead to the accumulation of Aβ fibrils as plaques in the brain.[4,5] These plaques can be detected by microglia receptors and finally activate signal cascades into microglia that lead to the release of inflammatory factors from microglia.[6,7] So, in brain of patients with Alzheimer's disease, there is a widespread neuroinflammation that can lead to neuronal apoptosis and brain atrophy.[8] The deposition of Aβ protein is a prominent pathological hallmark of brains affected by Alzheimer's disease. For this reason, the inhibition of Aβ production, prevention of Aβ fibril formation and accumulation, destabilization of pre-formed Aβ are considered as attractive therapeutic methods for the treatment of Alzheimer's disease.[9,10] Many animal and clinical studies showed that curcumin as the main constituent of turmeric spice is an effective ingredient in reducing Aβ plaques in the brain models of Alzheimer's disease.[11,12] Curcumin is well-known as an anti-inflammation and anti-oxidant ingredient.[13] It is a lipophilic compound that can easily cross the blood-brain barrier and affect Aβ plaque.[13,14] It can destabilize the Aβ

fibrils and prevent the accumulation of Aβ polymer.[15,16] Many animal studies indicated that curcumin could alter Aβ metabolism in Alzheimer animal models and improve cognition and spatial memory.[17-19] But in clinical studies there is controversial results about its effects on Aβ clearance and metabolism.[20,21] For this purpose, we aimed to review the studies which have been done in this area on the effects of curcumin on Aβ 1-40 plasma level in clinical studies to find how curcumin affects Aβ metabolism.

Methods

Search Strategy

We performed a systematic review and meta-analysis on three randomized clinical trial (RCTs) and one pilot study that assessed the effect of curcumin on Aβ plasma level in Alzheimer's disease. For this purpose, we searched PubMed and Scopus databases up to December 2020, using the following search terms: (curcumin OR diferuloylmethane OR curcuminoids OR turmeric OR "Indian saffron") AND ("Alzheimer disease" OR "Alzheimer's disease" OR "Alzheimer Syndrome" OR "Senile Dementia") AND (amyloid OR "Beta amyloid" OR Aβ) AND (Intervention OR "controlled trial" OR randomized OR random OR randomly OR placebo OR "clinical trial" OR trial OR "randomized controlled trial"

OR "randomized clinical trial"). There was no restriction for time or published language. In addition, the reference list of similar articles were screened to avoid missing any data. Duplicate articles were removed from the reference list after searching.

Inclusion Criteria
Studies with the following characteristics were included in the study: (1) Studies investigating the effects of curcumin on Aβ plasma level in Alzheimer's disease or aged people with dementia, (2) Studies that reported mean ± SD for Aβ, or any other effect sizes from which the calculation of mean ± SD was possible, (3) Only studies that had placebo and intervention groups were selected and the only difference between the two groups was curcumin regime.

Exclusion Criteria
In this meta-analysis, we did not enter letter-to-the-editors, comments, short communications, reviews, meta-analyses and animal studies. In our initial search we found 408 articles in PubMed and Scopus. 64 studies were removed because of duplication. In addition, from 344 articles, 337 studies were removed from our study after screening the full text. Only three studies were eligible to enter our study (Figure 1).

Data Extraction
Data were collected in Excel and included the author's name, year of publication, place of Aβ measurement, number, sex and mean age of the participant in each group, sample size, duration of treatment with curcumin or placebo, study design, dosage of curcumin, methods of measuring outcomes and finally mean ± SD changes of the desired variables. Data were double checked after extraction. Our Aβ data were converted to pg/mL. Finally, in studies that reported data in graphical figures, data were extracted using GetData Graph Digitizer 2.24 from figures.[22] Summary of our data is shown in Table 1.
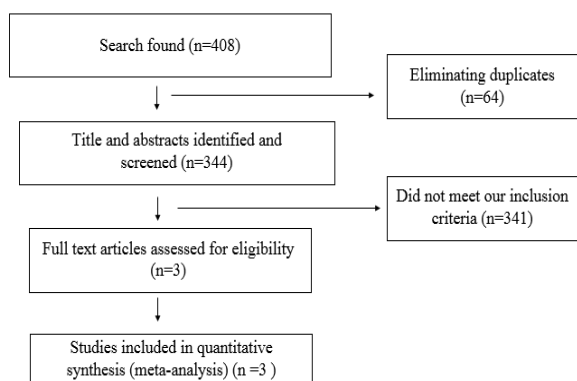

Figure 1. Flow Diagram of Study Selection.

Quality Assessment
Each study was assessed for quality assessment of risk of bias based on the Cochrane risk of bias assessment tool.[23] The quality of each of study was screened by two reviewers for the following items: (1) Random sequence generation, (2) Allocation concealment, 93) Selective reporting, (4) Blinding of participants and personnel, 95) Incomplete outcome data, (6) Other sources of bias. Based on the Cochrane handbook, the methods of the studies were ranked as low (L), or high risk of bias (H) or unclear (U) for each field of bias assessment (Table 2).

Statistical Analysis
Mean change of Aβ 1-40 plasma level was used to calculate effect size. Statistical analysis was performed by STATA, version 13.0 (Stata Corp LP, College Station, TX, USA). We used random effect model for inverse variance. To determine heterogeneity, we used Inconsistency (I^2). I^2 >50% was significant for heterogeneity. The estimates of effect sizes were expressed as weighted mean difference (WMD) and 95% confidence interval (CI).

Results
Systematic Review Findings
The summery of the characteristics of the three RCTs included in the current systematic review and meta-analysis are illustrated in Table 1. The studies were performed in 2008 and 2012. In total 213 participants were analyzed in these studies. The sample size of studies ranged from 8 to 19 participants. Two studies were from the United States[24,25] and one study from Hong Kong.[20] Two studies had a randomized parallel clinical trial design[24,25] and one was pilot study.[20] All studies included both sexes. In all studies there were control or placebo group and intervention group. In one study curcumin was administrated to healthy elderly[25] and in the other two participants had Alzheimer's disease, confirmed by clinical symptoms.

In Ringman and colleagues' study in 2012[24] and in Baum and colleagues' study in 2008,[20] different curcumin dosage and duration of regime was used,; so each regime was considered as an independent study. The dosage of curcumin varied from 80 mg/d to 4 g/d and the duration of intervention ranged from four weeks to 6 months. Mean (SD) age of the participants ranged from 47 (5) to 77.8 (7.7) years. No study had a high-quality based on Cochrane risk of bias assessment tool. One study has a moderate quality which in which one or more domains had an unclear risk of bias.[24] The other two studies had a low quality since they had a high risk of bias for three or more domains (Table 2). In Ringman and colleagues' study,[24] after 24 weeks of treatment with curcumin, Aβ level decreased in both placebo and Alzheimer groups for both doses of 2 g/d and 4 g/d. Also in DiSilvestro and colleagues' study [25] on healthy elderly, Aβ plasma level in the placebo group did not change after four weeks but in

Table 1. General Characteristics of the Included Studies: Randomized Parallel Clinical Trials (R/P)

Author/ Published Year	No. of Intervention Group	No. of Control Group	Study Design	Country	Gender of Participants	Age of Participants in Intervention Group	Age of Participants in Control Group	Dose of Curcumin	Duration of Regime	Health Condition
Ringman et al/ 2012	9	11	R/P	USA	Both	76.7±5.6	70.2±12.4	2 g/d	24 weeks	Alzheimer
Ringman et al/2012	10	11	R/P	USA	Both	75.3±6.9	70.2±12.4	4 g/d	24 weeks	Alzheimer
DiSilvestro et al/2012	19	19	R/P	USA	Both	47±5	48±6	80 mg/d	4 weeks	Healthy
Baum et al/2008	11	8	Pilot study	Hong Kong	Both	73.4±6.6	77.8±7.7	4 g/d	6 months	Alzheimer
Baum et al/2008	8	8	Pilot study	Hong Kong	Both	69±10.9	77.8±7.7	1 g/d	1 month	Alzheimer

Table 2. Assessment of Risk of Bias of Each Included Study

Author/ Published Year	Random Sequence Generation	Allocation Concealment	Selective Reporting	Blinding (Participants and Personnel)	Blinding (Outcome Assessment)	Incomplete Outcome Data	Other Sources of Bias
Ringman et al/2012	L	L	L	L	Not clear	L	L
DiSilvestro et al/2012	L	H	L	H	Not clear	L	L
Baum et al/2008	L	L	L	Not clear	Not clear	H	L

H, high risk ; L, low risk

the curcumin group, Aβ level decreased. In Baum and colleagues' study[20] the Aβ level in intervention groups with different duration of curcumin regime (1 and 6 months) increased significantly after 1 month. In the placebo group, the level of Aβ decreased after 1 month but then after 1 to 6 months, there was no significant change in Aβ levels in both groups.

Meta-analysis Finding

Overall, three studies with total population of 213 adults were analyzed for the effect of curcumin on Aβ plasma level. Our meta-analysis showed that curcumin had no significant effect on Aβ level in these three studies (WMD: 5.3, 95% CI: 0.78-9.97). There is no significant heterogeneity between the studies (I^2= 6.6%, P = 0.369). Also, we did subgroup analysis for healthy conditions and there was no significant change in serum IL-10 levels in in the two methods of measurement (WMD: -0.10, 95% CI:-0.44 -0.24, I^2=0.000%, P = 0.495, Figure 2).

Discussion

Curcumin is a low molecular weight molecule and lipophilic compound that can easily cross the blood-brain barrier.[26] Curcumin has many proinflammatory effects and able to neutralize many toxicity factors on many organs. Nowadays, curcumin was known as an anti-cancer genic compound.[27] Recent animal studies also support the hypothesis that curcumin is beneficial for cognitive disorders.[28-30] Also studies have suggested that dietary curcumin was associated with better cognitive function and lower prevalence of dementia.[30,31] Another

study showed that free curcumin could reduce amyloid plaque burden and insoluble Aβ peptide in the serum,[32] But in clinical studies there is controversial results about the effects of curcumin on dementia diseases. Our results from meta-analysis showed that there was no significant decrease of Aβ on Alzheimer's disease in overall results of clinical studies. In Ringman and colleagues' study,[24] the percent of Aβ decrease was not big. It may be the decrease could become larger with a longer intervention. Also in DiSilvestro and colleagues' study[25] there was no clinical or biochemical evidence of efficacy against Alzheimer's disease and Aβ serum level did not change in the intervention group compared with the placebo group. In Baum and colleagues' study[20] serum Aβ-40 tended to rise in the intervention group; possibly, it may show the ability of curcumin to disaggregate Aβ deposits in the brain, releasing Aβ for circulation and disposal. The variety of severe forms of the disease in patients, duration from onset of the disease, duration of regime and dose of curcumin are important factors that can affect the results. If these factors are equalized between patients, the results will be more reliable. These factors are very important in the final results of the systematic review and meta-analysis.

Conclusion

Based on available data in our systematic review and meta-analysis, there was no evidence about the effects of curcumin to change the Aβ-40 serum level. For further investigation of the effect of curcumin on serum Aβ level, more clinical trials are needed.
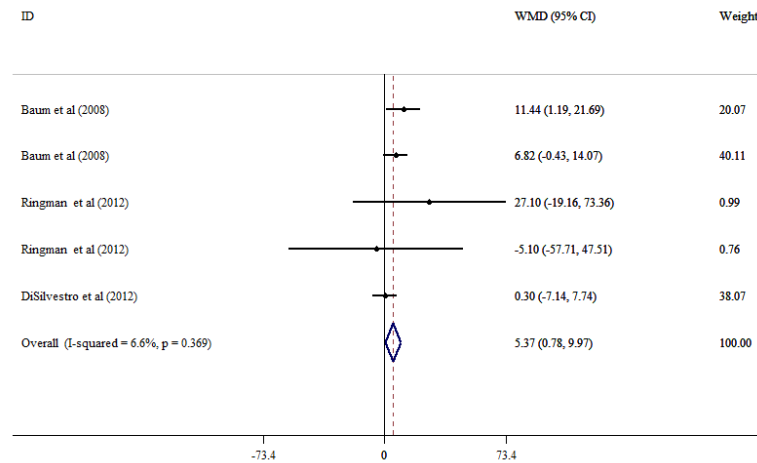
Figure 2. Forest Plots for the Effect of Curcumin on Aβ level in Serum Analysis on Alzheimer's Patient, Expressed as Mean Differences Between Intervention and Control Groups. The area of each square is proportional to the inverse of the variance of the weighted mean difference (WMD). Horizontal lines represent %95 CIs. Diamonds represent pooled estimates from fixed-effects analysis

Conflict of Interest

The authors declare that they have no conflict of interests.

Authors' Contribution

All authors contributed to the conception, design of the study and data acquisition.

Ethical Statement

Not applicable.

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