Table 1. Efficacy measures of randomised controlled trials

Author	Aim and Recruitment	Study Population	Intervention	Methodology	Efficacy	Study Design
Baum L, et al.[7]	Aim: To examine safety and effects of curcumin on biochemical and cognitive measures in AD	Probable AD (N=34) placebo (0g curcumin; n=8): (3M:5F,77.8±7.7, MMSE 15.4±5.8) 1g curcumin (n=8): (M:7F,69.0±10.9, MMSE 15.4±5.0) 4g curcumin (n=11): (3M:8F,73.4±6.6, MMSE 15.6±7.9)	1*4g curcumin (or placebo) per day orally Duration: 6month Follow up: at 0,1,6 months	Cognitive and clinical assessments: MMSE Biochemical measures: Antioxidants, plasma glutathione, peroxidase, superoxide dismutase activity, ascorbic acid, uric acid, vitamin A and E Kidney function test (Sodium, potassium, urea, creatinine, protein) Liver function test (albumin, bilirubin, alkaline phosphatase, alanine, aminotransferase, glutamic-pyruvic, transaminase) Pharmacokinetic analysis ELISA, HPLC, mass spectrometry, gas chromatography, serum A□, plasma isoprostanes, IpF_2[alpha]-3, A□40. [curcumin, desmethoxy curcumin, bis demethoxy curcumin, tetrahydro	Serum Aβ40 levels did not differ among doses at 0,1 or 6 months Between baseline and 6 months, serum A□40 changed from 30±6ng/L to 26±3 on 0g and from 28±6 to 35±7 on 4g Change in serum Aβ40 between baseline and 1 month did not differ between patients taking curcumin as capsules or powder Change in plasma isoprostanes between baseline and 6 months did not differ among doses (P=0.23, -11±10% for 0g, 12±10% for 1g, and 6±8% for 4g Vitamin E levels changed, 1±3% with curcumin (8±2% for capsules vs -4±5% for powder; P=0.05) versus -21±5% with 0g (P=0.001) and the percent change of vitamin E levels correlated positively with the total curcuminoids level (P=0.01, pearson correlation), during one month. Level of curcumin peaked at 250 n M at 1.5 hours with food and at 270 n M at 4 hours with only water. At 24 hours, the level fell to 60 n M There were no significant differences in levels of any curcuminoids or of total curcuminoids between 1- and 4-g groups Total curcuminoids levels tended to be greater with 4g than with 1g (P=0.15) Patients taking capsules (taken fasting with water: 10 patients) had greater levels of CDB than did patients taking powder (with a little food; 12 patients) Total 7 withdrew: (withdrawal group) 3 due to gastrointestinal complaints 3 due to falls or dizziness 1 for respiratory tract infection	Double-blind, randomised placebo-controlled trial.

				curcumin, feluric acid, vanillin is measured in plasma]		
Lee MS, et al.[16]	Aim: To investigate the effects of acute-on-chronic curcumin treatment on cognitive function, mood, blood biomarkers and ability to cope with mental challenge in healthy older adults Recruitment: Health check-up program at Tri-Service General Hospital, National Defence Medical Centre in Taiwan	Newly diagnosed untreated pre-diabetes (N=48, 1M:1F, median age 71±4, MMSE 26.7±1.5 (max30), pre-mean WM 2.50±0.11 (out of 3), BMI (18.5-30) kg/m^2, fasting glucose (100-125) mg/DI) Mean BMI=25kg/m^2 (not different between the groups) Average impaired fasting glycaemia= 117 mg/100 MI	Randomised groups: ingested at a white bread (119g) breakfast group1: placebo (n=12) group2: cinnamon 2g (n=12) group3: turmeric 1g (n=12) group4: cinnamon 2g + turmeric 1g (n=12) Follow up: Baseline 0,2,4 and 6 hours	Cognitive measures: post-pre-prandial WM, MMSE Questionnaires: S-FFQ, FFQ Analytic methods: Radioimmunoassay, RT-PCR [Dry chemistry plasma insulin, blood mononuclear cell (MNC)] was measured. Biomarkers: (APP, PS1, PS2, GSK-3β) Nucleic acid extraction [m RNA expression- c DNA transferred] Biochemical measures: Homeastatic model assessment, DEXA (truncal fatness), (smoking, drinking, hyper lipidemia, hyper tension, BMI, fasting glucose, fasting insulin)	No interaction was found between turmeric and cinnamon in regard to WM Significance negative correlation between the insulin responses (AUC) and the change in WM, which also applied to the AUC for the insulin: glucose ratio although not for the AUC for glucose The AD biomarker AUC were significantly inter correlated notably with APP for PS1, PS2 and GSK-3β but these were not correlated with WM BMI had a non- significant negative correlation with the change in WM (-0.282), truncal fat had an r of -0.407 ($p<0.05$) 3 Subjects were excluded [1 fasting glucose was frankly diabetic,1 grossly discordant normal MMSE, 1 abnormal WM score]	Double blind, randomised placebo controlled metabolic study
Ringman JM, et al. [21]	Aim: To obtain tolerability and preliminary clinical and biomarker efficacy data on curcumin in persons with AD.	Patients with mild to moderate AD Three groups (N=36) Placebo group (n=11) (5M:6F, 70.2±12.4yrs, MMSE 23.2±2.3, ADAS-Cog Score	4*500mg capsules twice daily with fatty meal placebo or curcumin Follow up: 24week Duration:48week	Pharmacokinetics results: HPLC, tandem mass spectrometry, plasma and CSF levels (LC/MS/MS) Clinical measures: Alzheimer's Disease Assessment Scale (ADAS-Cog),	The difference in joint pain occurrence as linear function of curcumin dose, a 2.5% trend towards decrease in joint pain per gram of curcumin was found ($p=0.07$) No differences between treatment groups in change in ADAS-Cog, NPI, ADCS-ADL, or MMSE scores using repeated measures When the 2gm/day and 4gm/day curcumin groups were combined, there was a trend for	Double blind, randomised, placebo-controlled study

	Recruitment: Mary S. Easton Centre for Alzheimer's Disease Research at UCLA.	18.2±4.9, NPI 8.5±12.4, ADCS-ADL 66.7±3.6) Curcumin group 2g/day (n=9) (M:2F,76.7±5.6yrs, MMSE 21.4±3.2, ADAS-Cog score 20.9±7.4, NPI 8.9±9.6, ADCS-ADL 60.3±10.9) Curcumin group 4g/day (n=10) (3M:7F, 75.3±6.9 yrs., MMSE 22.8±3.4, ADAS-Cog score 19.3±3.4, NPI 11.7±16.9, ADCS-ADL 61.0±8.4)		Neuropsychiatric Inventory (NPI), Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS-ADL) Biomarkers: Levels of Ab_{1-42}, total tau (t tau), tau phosphorylated at threonine 181, p-tau_{181}, CSF isoprostanes (F_{2-} IsoPs), Ab_{1-40}, Ab_{1-42}, CSF Ab_{1-42}, CSF tau, p tau, F_{2-} IsoPs	treated subjects to do worse than placebo-treated subjects on the MMSE (P=0.08) No significance effects of treatment group on change in plasma AB_{1-42}, CSF Ab_{1-42}, CSF $_{tau}$ or p tau or F_{2-} IsoPs Overall adverse events occurred in 91.7% among placebo treated subjects And 100% among curcumin treated subjects 11.4% drop out (4/35) Placebo group 1 subject withdrew (worsened memory) 2gm/day curcumin group 3 subjects withdrew (2 GI side effect + 1 difficulty swallowing pills) 4gm/day curcumin 2 subjects withdrew (1 GI side effect + 1 difficulty swallowing pills)	
Rainey-Smith SR, et al.[20]	Aim: To investigate the effects of acute-on-chronic curcumin treatment on cognitive function, mood, blood biomarkers and ability to cope with mental challenge in healthy older adults Recruitment: Community-dwelling older adults	Cognitively healthy older adults (N=96) Curcumin group(n=39) (67.2±7.2 yrs, M:2F, YOE 13.4±3.5, BMI 26.7±3.9, Diastolic BP 78.0±9.9mm Hg, Systolic BP 128.8±17.8mm Hg, IPAQ 5100±3805 (MET min/week), hypertension 30.8%, Depression 20.5%, Anxiety 12.8%, CCRT score 38.1±5.7) Placebo group(n=57) (65.2±6.1yrs, 15M:42F, BMI 25.8±5.3, Systolic BP 127.6±19.5 mmHg, Diastolic	Curcumin treatment group: 1*500mg BCM-95®CG(Biocurcumax™) capsules three times a day after meals with water Placebo treatment group: 1 placebo capsules three times a day after meals with water Duration: 12month	Cognitive measures: MoCA, RAVLT list A trial 1-5 total, RAVLT short term recall, RAVLT delayed recall, Wechsler Digit Symbol Scale, COWAT, Cog State, GML, IPAQ Memory function measures: DASS-depression, DASS-anxiety, DASS-stress, PRMQ Questionnaires: SF-36 physical health, SF-36 mental health Biomarker: APOE genotyping (APOE ε4 allele carriage)	Placebo group performed significantly better at baseline in the digit symbol task (t=2.98, P<0.01), the MoCA (t=2.10, <0.05) and cognitive composite (non-computerised) scores (t=2.40, P<0.05), the latter of which was mainly driven by the MoCA and digit symbol scores No significant interactions of the time * treatment group from measures of physical health, mental health, mood and self-reported memory function Mean MoCA score improved by 0.64 point in the curcumin group and by 0.09 point in the placebo group from baseline to 12 months No significant interaction between time and treatment groups was observed (F=136, P=0.25), considering baseline and 12-month MoCA performance only No other difference in cognitive test performance were observed across the treatment groups Decline in function was observed among placebo group at 6 months but similar association was	Double-blind, randomised placebo-controlled study

		BP 74.9±11.8 mmHg, IPAQ 4272± 2599, hypertension 26.3%, depression 24.6%, Anxiety 14%, CCRT score 39.2±5.7)		Physiological measures: Blood pressure, medical history hypertension	not observed among curcumin treatment group Significant effect of curcumin on cognition was observed after 4 weeks of treatment. 23 participants (gastrointestinal complaints) accounted for major adverse events 8 participants excluded because of low intervention compliance rates (<70%) Compliance rates were based on returned capsule counts and participants capsule logs	

Cox KHM, et al.[9]	Aim: To investigate the effects of acute-on- chronic curcumin treatment on cognitive function, mood, blood biomarkers and ability to cope with mental challenge in health older adults Recruitment: Australia	Free from a history of neurological conditions or psychiatric disorders(N=60) curcumin group(n=30) (11M:19F Age:68.5±5.7 yrs.) Placebo group(n=30) (11M:19F,68.5±5.7 yrs.)	Curcumin group: 400mg Long Vida® Optimized Curcumin capsule once daily (approximately 80mg curcumin in a solid lipid formulation) Placebo group: Placebo capsules [containing dextrin and a small amount (approximately 4mg/capsule) of tartrazine (E102) for colouring to visually match the active treatment] Duration:4week Follow up: acute (1 and 3hour after a single dose) chronic (4 week) acute or chronic (1 and 3h after a single dose following chronic treatment)	Cognitive measures: Global cognitive function, Cognitive array, Cognitive battery, Cognitive results, Cognitive status, MMSE, NART score Mood measures: Mood results, Trait anxiety STAT-T depressive symptom, depression, Anxiety and stress scale, Beck Depression Inventory-2 BDI-2, Bond-Lader Visual Analogue scales Biochemical measures Blood biomarkers Questionnaires: National adult Reading Test, modified Telephone Interview for cognitive status	1hr after dose administration there was a significant beneficial effect of acute curcumin treatment on number of correct responses during serial three subtraction task Correct responses provided by participants in the curcumin group increased by 16% from pre-dose performance compared with an increase of just 2% in the placebo group Significant benefit was observed in digit vigilance task of curcumin over placebo at 1- hour post dose assessment but was not apparent 3h after acute dose administration Chronic curcumin treatment was associated with significantly lower levels fatigue compared with placebo (Mood results) Follow up curcumin group showed an average 11% reduction in fatigue from baseline compared with decrease of just 2% in placebo group CSF subscale examination revealed this effect was specific to physical fatigue where the curcumin group showed an average 11% decrease and placebo group a 4% No significant effect of Acute treatment on change in mood following mental challenge Excellent retention rate,100% of participants who received treatment finished the trial	Double bli randomise placebo-controlled parallel- g trial