Original Article

Turmeric improves post-prandial working memory in pre-diabetes independent of insulin

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Background and Objectives: Cognitive impairment develops with pre-diabetes and dementia is a complication of diabetes. Natural products like turmeric and cinnamon may ameliorate the underlying pathogenesis. **Methods:** People ≥60 years (n=48) with newly-recognised untreated pre-diabetes were randomised to a double-blind metabolic study of placebo, turmeric (1g), cinnamon (2g) or both (1g & 2g respectively), ingested at a white bread (119g) breakfast. Observations were made over 6 hours for pre- and post-working memory (WM), glycaemic and insulin responses and biomarkers of Alzheimer's disease (AD)(0,2,4 and 6 hours): amyloid precursor protein (APP), γ-secretase subunits presenilin-1 (PS1), presenilin-2 (PS2), and glycogen synthase kinase (GSK-3β). Differences between natural product users and non-users were determined by Students *t* and chi square tests; and between pre-test and post-test WM by Wilcoxon signed rank tests. Interaction between turmeric and cinnamon was tested by 2-way ANOVA. Multivariable linear regression (MLR) took account of BMI, glycaemia, insulin and AD biomarkers in the WM responses to turmeric and cinnamon. **Results:** No interaction between turmeric and cinnamon was detected. WM increased from 2.6 to 2.9 out of 3.0(p=0.05) with turmeric, but was unchanged with cinnamon. WM improvement was inversely associated with insulin resistance (r=-0.418, p<0.01), but not with AD biomarkers. With MLR, the WM responses to turmeric were best predicted with an R^2 of 34.5%; and with significant turmeric, BMI and insulin/glucose AUC beta-coefficients. **Conclusions:** Co-ingestion of turmeric with white bread increases working memory independent of body fatness, glycaemia, insulin, or AD biomarkers.

Key Words: cognition, Alzheimer's disease, curcumin, cinnamon, insulin resistance

INTRODUCTION

The increased risk of cognitive impairment and dementia in diabetes encourages efforts to identify the phenomenon as early as possible and to abort or at least lessen its course.[1-15] There is, however, evidence that one may serve as a risk for the other and that a vicious cycle may develop, making early intervention more of an imperative.[16] Increasing evidence points to diet[17] and exercise[18] as the most likely useful strategies. There is no clear evidence that current pharmacotherapy alters the risk of dementia in diabetes, with the possible exception of metformin:[11] even here, there is controversy as to whether the risk of vitamin B-12 deficiency with metformin may diminish its potential value.[19] While as yet unproven, there are indications epidemiologically[20,21] and experimentally[22] that turmeric or its curcumin content may reduce the risk of dementia and that its aromatic turmerone content

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may induce neural stem cell proliferation.[23,24] The question is then whether it might be possible to reduce the risk of cognitive impairment seen in association with hyperglycaemia, in diabetes or pre-diabetes.[25] Since cinnamon has mild anti-hyperglycaemic properties,[26] and may reduce the risk of neurodegeneration through inhibition of neurofibrillary tangle formation and promotion of their disassembly,[26,27] it is a possible adjunct to any role that turmeric might have in hyperglycaemic states. This is especially so, since a clinical trial in Thailand has shown that turmeric curcumin reduces the risk of Type 2 diabetes in those with pre-diabetes and improves beta-cell function.[28] Blood concentrations of the curcuminoid metabolites of turmeric are measurable within a short time of ingestion, so that their presence in a meal might be metabolically and cognitively beneficial.[29] Curcumin metabolites appear in plasma and urine[30] and can be found in brain in association with amyloid.[31] In the case of cinnamon, the taste and smell are mainly due to cinnamaldehyde which, together with lesser components cinnamic acid and cinnamyl alcohol, is converted to sodium benzoate; but there other components , notably coumarin.[32-35] Benzoate itself has neuroprotective properties.[34] It is also known that changes in biomarkers for neurodegeneration can be detected during insulin infusions[36] and that body compositional disorders like obesity alter their profile.[37]

Pre-diabetes is itself associated with cognitive impairment[12,38] and given its comparable if not greater prevalence than diabetes, is a point in an individual's health history to target with measures that could arrest both the trajectories towards diabetes and dementia. Working memory (WM) is a simple yet effective measure and predictor of those cognitive processes to do with central executive roles and attention.[39-41] We therefore hypothesized that, in pre-diabetes, a refined carbohydrate meal might compromise cognitive function as reflected in WM; that it would be possible to improve WM after a meal with turmeric or cinnamon; that biomarkers of neurodegeneration would respond in concert with WM; and that these biomarkers would explain in part the natural product effects on WM. To these ends, we studied apparently healthy and independent community-based people aged 60 years or over with newly-recognized pre-diabetes and before the implementation of any management plan.

METHODS

Participants

A total of 48 participants aged 60 years or older with newly diagnosed untreated pre-diabetes were recruited from a health check-up program at Tri-Service General Hospital, National Defense Medical Center in Taiwan, during September 2012 to July 2013, for a randomised double blind metabolic study of the effects of turmeric and cinnamon on WM. The selection criteria were that they were aged ≥60 years, had a body mass index (BMI) within 18.5-30 kg.m-2, and a fasting glucose between 100-125mg/dl, but had no history of medication usage for diabetes, no severe chronic disease and no recent acute illness or hospitalisation in the preceding two months. They were also excluded if there was a history of heavy drinking in the previous two weeks, they supplemented their diet with ginseng or garlic, had an eGFR ≥45, or had been exposed to contrast medium within three days.All participants provided informed consent. The study protocol was approved by the ethics (IRB) committees of the Tri-Service General Hospital National Defense Medical Center and the National Health Research Institutes (NHRI) of Taiwan.

Study design

Participants were randomized into 4 groups using block randomization combined with gender stratification as a basis for this double blind, placebo controlled metabolic study.

The treatments were Group1: placebo (n=12), Group2: Cinnamon 2g (n=12), Group3: Turmeric 1g (n=12) and Group4: Cinnamon 2g + Turmeric 1g (n=12).

Participants were asked to fast over-night from 10pm. On the morning of the study, a questionnaire was administered, MMSE (mini-mental state examination)[42] and WM recorded and anthropometric measurements (weight, height and abdominal circumferences) and blood pressure taken prior to breakfast. BMI (Body Mass Index in (kg)/height (m^2) was calculated. After a finger prick glucose and venipuncture, each participant ate a standard breakfast together with one of the treatments in capsule form (placebo or natural product) at 0800h. There were 4 sampling time points: baseline, 2, 4and 6 hours. At 2-hourly intervals, we monitored the blood glucose by finger prick and obtained venous blood. WM was repeated at 6 hours.

Three subjects were excluded after randomisation, one because the fasting glucose on the day was frankly diabetic (placebo group), one who had eaten breakfast before attendance at the study centre (cinnamon group), and one because of a grossly discordant normal MMSE (mini-mental state examination) and abnormal WM score (1 out of 3 (combined turmeric and cinnamon group).

Study materials

Breakfast comprised 2 slices of white bread (119g) and water. The natural products studied were turmeric, species *Curcuma longa*, a member of the ginger family, Zingiberacea (a Taiwanese cultivar supplied by Dr Mei-Shang Ho of Academia Sinica) and imported cinnamon powder (Kirkland Ground Saigon Cinnamon, species *Cinnamomum loureiroi*, closely related to *Cinnamomum cassia*, from Vietnam, with a high essential oil cinnamaldehyde content). These were given to participants in opaque gelatin capsules with identical appearance to the placebo (corn starch).

Working memory (WM)

Short-term mental storage and manipulation operations are collectively called working memory. WM is widely thought to be one of the most important mental faculties, critical for cognitive abilities such as planning, problem solving, and reasoning and is used in many cognitive and neuroscience research laboratories. We used a modification of the n, n-1, n-2 back WM test with n=10 digits.[43,44] Participants were presented serially with a random order for the ten digits and asked to recall one digit by its order. This was repeated three times so that the maximum score was three. Each participant performed the WM test twice,

pre-test before the meal and post-test 6 hours later. The impact of interventions was assessed by comparing pre-test and post-test scores in various treated groups.

Questionnaires

Participants were administered two questionnaires after the study, one to do with socio-demographic characteristics, personal behaviours (physical activity, smoking, drinking alcohol, betel nut chewing), clinical history and medication usage; and the other a semi-quantitative food frequency questionnaire (S-QFFQ).The FFQ paid particular attention to the use of culinary herbs and spices.

Analytical methods

Whole blood glucose was measured by dry chemistry Plasma insulin was measured by radioimmunoassay. The mRNA expression of biomarkers was measured in peripheral blood mononuclear cells by RT-PCR to reflect both amyloid plaque formation and neurofibrillary tangle formation. For blood mononuclear cell (MNC) isolation and total RNA extraction, blood was collected into an EDTA anticoagulant tube for each participant and layered on Ficoll-Paque medium. This was centrifuged and MNC separated out at the interface between plasma and the medium. Total RNA was extracted from isolated MNC by using MagCore® automated Nucleic Acid Extractor (RBC Bioscience, Taipei, Taiwan) and a Total RNA Whole Blood Kit according to the manufacturer's protocol. All of the extracted RNA was stored immediately at -80℃ for further experiments.

The mRNA expression of *APP, PS1, PS2,* and *GSK-3β* was measured in MNC by RT-PCR using QuantiTect® reverse transcription kit (Qiagen GmbH, Hilden, Germany) and transferred into cDNA. Real-time PCR was performed using Rotor-Gene® QPCR system, SYBR Green PCR master mix (Qiagen GmbH, Hilden, Germany), and primers designed to amplify the target genes

. The reaction solution (25 μL) contained SYBR Green PCR master mix (12.5 μL), cDNA (1μL), and 1μL aliquots of primers; real-time PCR conditions included denaturation at 95℃ for 5 min followed by 40 cycles at 95 ℃ for 5 s, annealing temperature at 55 ℃for 10 s (Table 1). All values were normalized to the expression of a housekeeping gene *β*-actin.

Statistical analysis

The differences between natural products users and non-users were determined by Students *t* test and the chi

Table1. Participant characteristics by intervention

	Turmeric			Cinnamon		
	User (n=23)	Non-user (n=22)	*p*-value	User (n=22)	Non-user (n=23)	*p*-value
Gender (Women, %)	52.2	45.5	0.65	50.0	47.8	0.88
Age, mean (SD), years	71.3 (5.59)	74.7 (6.45)	0.14	74.0 (6.71)	72.8 (5.61)	0.73
Education, mean (SD), years	11.1 (4.36)	11.4 (4.05)	0.85	10.5 (4.45)	11.9 (3.86)	0.28
Employment (%)			0.27			0.19
Employed	17.4	13.6		18.2	13.0	
Retired	73.9	59.1		54.5	78.3	
Other	8.7	27.3		27.3	8.7	
Fresh ginger use (%)			0.46			0.46
Never	26.1	13.6		13.6	26.1	
Sometimes	73.9	86.4		86.4	73.9	
Cook with ginger (%)			0.91			0.46
Never	65.2	63.6		59.1	69.6	
Sometimes	34.8	36.4		40.9	30.4	
Curry consumption (%)			1.00			0.14
Never	17.4	18.2		27.3	8.7	
Sometimes	82.6	81.8		72.7	91.3	
Ginger flavoring (%)	87.0	95.5	0.61	86.4	73.9	0.46
Cinnamon use (%)			1.00			1.00
Never	86.4	81.8		85.7	82.6	
Sometimes	13.6	18.2		14.3	17.4	
Exercise, mean (SD), times/week	4.0 (2.5)	3.7 (2.6)	0.68	4.0 (2.5)	3.7 (2.6)	0.68
Smoking (%)	0.0	13.6	0.11	13.6	0.0	0.11
Drinking (%)	39.1	40.9	0.90	50.0	30.4	0.18
Hyperlipidemia (%)	34.8	27.3	0.59	40.9	21.7	0.17
Hypertension (%)	56.5	63.6	0.63	63.6	56.5	0.63
BMI, mean (SD), kg/m^2	25.1 (2.76)	25.0 (4.49)	0.93	25.1 (3.70)	25.0 (3.72)	0.92
Fasting glucose, mean (SD), mg/dL	117 (17.9)	117 (10.8)	0.98	117 (14.1)	117 (15.6)	0.97
Fasting insulin, mean (SD)	1.10 (1.30)	0.89 (0.78)	0.514	0.89 (0.92)	1.10 (1.21)	0.517
HOMA-IR, Mean (SD)	0.32 (0.38)	0.26 (0.25)	0.53	0.27 (0.29)	0.31 (0.35)	0.59
Insulin AUC† (SD), $mg.hr.L^{-1}$	9.7 (6.6)	12.36 (8.84)	0.29	10.9 (7.6)	11.0 (8.0)	0.98
MMSE, mean (SD)	28.2 (2.06)	26.7 (4.25)	0.14	27.6 (2.46)	27.4 (4.10)	0.85
WM pretest (SD)	2.61 (0.58)	2.59 (0.59)	0.92	2.50 (0.60)	2.70 (0.56)	0.26
Hypoglycaemic event (%)	0	0	-	0	0	-

†Over six hours

BMI: body mass index; HOMA-IR: homeostasis model assessment of insulin resistance; AUC: area under curve; MMSE: mini-mental state examination; WM: working memory.

square test. The differences between pre-test and post-test WM for natural products users and non-users were determined by Wilcoxon signed rank test. Possible interaction between turmeric and cinnamon was evaluated with the 2-way ANOVA test. Multivariable linear regression (MLR) models were used to take account of BMI, glycaemia, insulin and AD biomarkers in the evaluation of WM responses to turmeric and cinnamon. $P<0.05$ was considered statistically significant. All statistical analyses were performed using SPSS software version 20 for Windows.

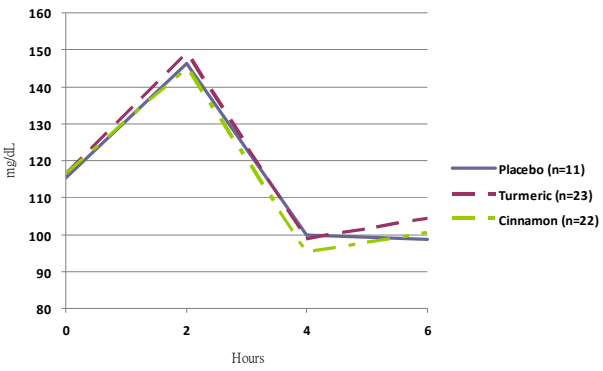
RESULTS

Participants who used or did not use turmeric or cinnamon at breakfast are shown in Table1. Since no interaction was found between turmeric and cinnamon in regard to WM, users include those who used the natural product alone or in combination. Men and women were studied in equal numbers; the median ages were 71-75 years; and the educational level comparable between the groups. Judged from the FFQ, about 80% used turmeric-containing curry sometimes and only about 16% used cinnamon at all. The background diet was of Chinese cultural orientation, generally rice and noodle-based with regular consumption of green leafy vegetables, root vegetables, mushrooms, tofu of various kinds, pork, chicken, occasional beef, fish and crustaceans more than once a week, seasonal fruits and assorted small side dishes of condiments like chilli, garlic and soy sauce. Participants exercised an average of about 4 times per week. There were few smokers (<15%), but more than a third drank alcohol sometimes or regularly. More than half were known to be hypertensive. The mean BMI was 25kg/m^2 and not different between the groups. As the entry requirement, all had impaired fasting glycaemia with an average of 117mg/100ml. Hyperlipidaemia had been recognised in more than 20% of participants. The mean MMSE on the day of study was between 26.7 and 28.2 (maximum 30), depending on group, but not significantly different between groups. The mean pre-test WM was 2.50-2.61 (out of 3) by group, but also not significantly different between groups. No hypoglycaemic episodes were experienced during the studies.

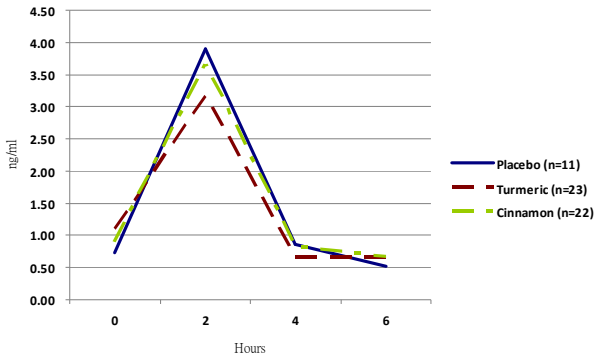
The glycaemic and insulin responses to breakfast are shown in Figures 1A and 1B, respectively. Use of turmeric or cinnamon made no difference to the responses. However, WM improved in the turmeric users over the 6 hours of observation by comparison with the non-users (Figure 2), but such was not the case with cinnamon.

There were significant negative correlations between the insulin responses (AUC, area under the curve) and the change in WM, which also applied to the AUC for the insulin: glucose ratio although not for the AUC for glucose (Table 2). The AD biomarker AUCs were significantly inter-correlated, notably with APP for PS1, PS2 and GSK-3β, but these were not correlated with WM (Table 2). Although BMI had a non-significant negative correlation with the change in WM (-0.282), truncal fat had an r of -0.407($p<0.05$) (data obtained by DEXA and not shown).

Using MLR, we modelled the WM responses to the natural products and found the best equation for turmeric



(A) Glycemic responses to natural products (turmeric and cinnamon)



(B) Insulin responses to turmeric and cinnamon

Figure 1.

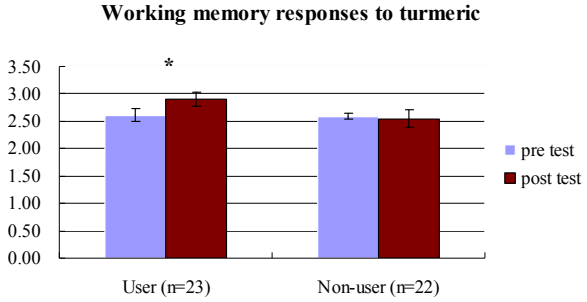


Figure 2. Working memory responses to turmeric. Error bars are the SEs of the working memory mean score. *p = 0.05 level (2-tailed).

users to include turmeric, BMI and the AUC for the insulin: glucose ratio which had significant beta coefficients of 0.296 ($p<0.05$), -0.052 ($p<0.05$) and -3.234 ($p<0.05$) respectively with an R^2 of 35%. In the case of cinnamon, while it was not significantly predictive of WM, each of BMI and AUC insulin: glucose was predictive with its use (Table 3). The AD biomarkers were not independently or conjointly predictive of WM (data not shown).

DISCUSSION

Post-prandial working memory

We found that a modest addition of 1g turmeric to a rather nutritionally-bland breakfast of white bread improved working memory (WM) over 6 hours in older people with pre-diabetes. This was not the case for 2g cinnamon. With neither natural product were the glycaemic or insulin responses to the bread altered .These glycaemic responses were consistent with previous reports

Table 2. Pearson correlation matrix for working memory, glycemic, body composition and biomarkers (APP, PS1, PS2, GSK3B) (n=45)

		(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
(1)	WM_pre	1									
(2)	WM_post	0.284	1								
(3)	APP_AUC†	-0.051	0.081	1							
(4)	PS1_AUC†	0.105	0.153	0.667**	1						
(5)	PS2_AUC†	0.134	0.088	0.414**	0.312*	1					
(6)	GSK3B_AUC†	-0.041	0.036	0.661**	0.855**	0.154	1				
(7)	GLU_AUC†	-0.151	-0.119	0.134	-0.009	0.049	-0.109	1			
(8)	Insulin_AUC†	-0.171	-0.365*	0.080	0.081	0.146	0.152	0.260	1		
(9)	Insulin/glucose ratio AUC†	-0.162	-0.418**	-0.022	0.019	0.091	0.107	0.084	0.968**	1	
(10)	BMI	-0.107	-0.282	0.369*	0.209	0.013	0.181	0.291	0.087	-0.001	1

†Over six hours
AUC: area under curve; WM: working memory; APP: amyloid precursor protein; PS1 and PS2: protease subunits; GSK3B: glycogen synthase kinase 3-beta; GLU: glucose; BMI: body mass index.
** Correlation is significant, $p < 0.01$ level (2-tailed).
* Correlation is significant, $p < 0.05$ level (2-tailed).

Table 3. Multi-linear regression of working memory responses taking account of body fatness and insulin resistance

	Model 1		Model 2		Model 3	
	R^2 (%)	B	R^2 (%)	B	R^2 (%)	B
Turmeric	10.3	0.368*	18.5	0.372*	34.5	0.296*
BMI				-0.045*		-0.052*
AUC rInsulin/Glucose†						-3.234*
Cinnamon	0	-0.012	8.0	-0.007	26.6	-0.048
BMI				-0.045		-0.045*
AUC rInsulin/Glucose†						-3.720**

†Over six hours
BMI: body mass index; AUC rInsulin / Glucose: the Insulin to Glucose AUC ratio.
Model 1: natural products (turmeric and cinnamon)
Model 2: Model 1+BMI
Model 3: Model 2+rInsulin/glucose
**Regression coefficients are significant, $p < 0.01$ level (2-tailed).
* Regression coefficients are significant, $p < 0.05$ level (2-tailed).

from a Swedish group for turmeric (6g in healthy subjects) although their insulin response was greater from 30-60 minutes[45] and for Cinnamomum cassia and Cinnamomum zeylanicum,[45,46] but for the cinnamon cassia variety (between 1and 3g) the insulin response was reduced by 120min.[45,47] The extent to which turmeric improved WM was dependent on the participants' body fatness and insulin resistance, suggesting that the benefits of turmeric might be enhanced where these characteristics were less abnormal. At the same time, we cannot necessarily extrapolate the findings to euglycaemic individuals or to those with diabetes, as likely as that might be. While we do not have the sample size to stratify by gender, we have included by design both men and women in similar numbers in this study so that our findings may be of relevance irrespective of gender.

Turmeric is used widely in Asia for culinary purposes. The characteristic yellow color is due to curcumin which accounts for 3% to 6% of turmeric. Experimental studies have shown that curcumin can decrease neurotoxicity and may serve as a potent anti-inflammatory agent in the CNS, partly because of its antioxidant activity. Our findings with turmeric are consistent with these observations, insofar as they appear to influence cognitive function where there is disordered energy metabolism and insulin resistance.

Relevance and plausibility of natural product effects on working memory

Although the assessment of WM is simple and convenient, it has considerable utility in the appraisal of cognition and in the prognostication of future impairment and dementia.[41] The prospect of acute change in WM has been apparent from observations during glycaemic response tests using white bread.[14,48] In these it has been possible to mininise any adverse effect by reducing the glycaemic and insulin responses. Similarly, t has also been possible to reduce cognitive decline with concerted efforts to improve glycaemic control in diabetes.[49] Coupled with the knowledge that curcumin metabolites appear in peripheral blood within hours of ingestion of turmeric, it was appealing to test its post-prandial effects on cognition.[29] Likewise, the immediate taste recognition of both turmeric and cinnamon, along with growing evidence that taste and olfactory receptors are present beyond the mouth and nose , elsewhere in the gut[52]and body,[50] makes their possible acute effects on the nervous system plausible.[51,52] However, in this study natural product capsules were given so that acute effects will have been initiated beyond the oropharynx, in the gut or systemically.

Duration of exposure - acute versus medium-term or chronic effects

Whatever the explanation for these acute findings, they are consistent with the time-course for generation of curcumin metabolites after turmeric ingestion.[29] Moreover, they have utility insofar as they represent a method for improving cognition in the course of daily life, at least for those whose WM is less than perfect by the simple test used and in a patient group at risk of cognitive impairment. The trajectories of mild cognitive impairment are known and could be examined in the presence of regular turmeric consumption.[53]

Neuroprotective mechanisms of turmeric

Even though the effects of turmeric on WM were predicated on the degree of body fatness (particularly truncal fatness assessed by DEXA in this study) and insulin resistance, they were independent of these characteristics. Thus, the question is begged as to how turmeric might work, and how it might have benefit in the short term. Epidemiological support for neuroprotection by turmeric is notably absent although there are regional variations in intake in Asia which would lend opportunities to address this possible association.[54] Animal studies available would generally represent the equivalent of medium-term effects in humans.

To this extent, there might be favourable effects on mitochondrial function.[55-57] There is also experimental evidence that curcumin can inhibit formation of amyloid plaques,[31] protect the hippocampus[58] and the prefrontal cortex.[22] It is intriguing that benefit is seen in the face of pre-diabetes, and that it is evident independent of insulin resistance,although curcumin can prevent diabetes.[28] Moreover, even though cinnamon can alter insulin receptor expression and improve glycaemic status, there was no evidence of its interaction with turmeric.[59-61]

We had postulated that the kinetics of AD biomarkers might represent a pathway for turmeric through amelioration of amyloid plaque (for APP, PS1 and PS2) or neurofibrillary tangle formation (for GSK-3β*)*, but, while the biomarkers showed active correlations among themselves during the 6 hours study, these did not account for the link between turmeric and WM. Thus, we must consider the possibility that less-well understood pathways, activated or modulated by turmeric, might be available to alter the course of neurodegeneration in pre-diabetes and, probably, diabetes. Again, the separate AD biomarker inter-correlations may in themselves indicate the extent of accessibility of APP, presenelins, γ-secretase and pathways to the natural products examined.

The mechanisms available, but not directly canvassed in the present study, are improvements in neuronal function by way of synaptic transmission, mitochondrial activity,[55] anti-inflammatory effects, immuno-modulatory effects and lipid transport with apoE (whose apoE4 isoform is a recognised risk factor for Alzheimer's disease).[20,35,62-67] The gut microbiome might also be involved as curcumin can increase microbial diversity in the direction of what is considered gut-protective. [68]

The relatively strength of insulin resistance and, to a lesser extent, body fatness in modulating the effect of turmeric on WM in our models, places some emphasis on measures to improve these variables by the known approaches of diets and exercise. Moreover, insulin can favourably affect the AD biomarkers[36] and enhance memory.[69] Consistent with this, obesity surgery has also been found to reduce AD biomarkers[37] and we did find an association between body fatness and the APP mRNA response.

Cultural and practical considerations

The breakfast we used was not typical for the population studied, although bread, usually soft white, is becoming more usual as the first meal of the day, especially among elderly people with chewing difficulties. But the findings should be relevant to the more traditional rice porridge breakfast to which various spices and chopped plant and animal foods are added. The reasons we chose white bread were that we could standardise it, because its nutritional profile was restricted, and that it was likely to be eaten by all participants.

Nevertheless, it was consumed against a Chinese cultural background diet which may have affected the outcome by any one of a number of biological phenomena which becomes established with a food culture, such as the gut microbiome.[51]

We deliberately used whole turmeric rather than curcuminoids or turmeric extracts. We wanted to examine the commodity used in daily life and with which there are generations of experience and presumptive safety across Asian food cultures – south, north-east and south-east Asia, albeit in a range of cuisines. The amounts used were also within the usual household range. Taken alone, these approaches do not guarantee safety. It is noteworthy that curcumin itself has safety constraints on account of cytotoxicity, mitochondrial and DNA damage and chromosomal aberrations.[70,71] Moreover, with some dietary practices, like the use of pepper, the bioavailability and toxicity of curcumins may increase.[72] That said, the bioavailability of curcumins is low, so that most of the in vivo concerns about toxicity, and some of the potential beneficial effects, have been to do with the gut prior to absorption. It may be that the effects of curcumins to restore disordered gut microbial ecology seen in experimental animals [68] might play a role in gut-brain axis health although for these to be post-prandial would seem unlikely, but not impossible.

It is of interest that gut disorders like the autonomic neuropathy of gastroparesis may be seen early in the development of diabetes. If the effect of turmeric in pre-diabetes on WM were dependent on the presence of related gut dysfunction, then the extrapolation to other groups would need to be circumspect.

In any case, we must keep in mind that our findings are in older people of dominantly Chinese ancestry and culture and in a clinical sub-group which currently does not receive targeted health care. This means that, although the target group is large and increasing, the preventive and therapeutic protocols into which turmeric might fit are poorly developed.[73]

Implications for the diabetes-vulnerable, diabetes care and dementia prevention

Notwithstanding the cultural considerations with our study, the global burden of diabetes-predisposing conditions is increasing markedly with aging demographics,

because of impaired energy regulation,[74,75] and of body compositional disorders[76] as well as diabetes itself. Together, these are increasing the risk of cognitive impairment.[77,78] Diabetes itself increases the risk of dementia 2-3-fold.[11] It can be expected that the already substantial prevalence of dementia will increase further as a consequence.[79,80] While a Cochrane review was equivocal about the prospects for altering the course of cognitive decline in diabetes[81] and drug trials negative,[82] it has been demonstrated that improvement in glycaemic control can reduce the risk of cognitive impairment as reflected in WM.[83] Dietary measures promise to ameliorate diabetes-linked cognitive impairment as reported for the Mediterranean diet.[17] Not only that, but the increased mortality risk associated with cognitive impairment may also be reduced with a diverse diet.[82] Metformin, as anti-hyperglycaemic therapy, has been shown to decrease the risk of dementia and other neurodegenerative disease.[11,85,86] Thus, it may be possible to interrupt a vicious cycle of an increasing burden of disease by early intervention.[16] Since pre-diabetes is itself associated with cognitive impairment,[12,38] the present findings in pre-diabetes with turmeric provide a possible approach to reduction of the burden of cognitive impairment, at least for brief periods of time and which could translate into longer benefit. They add support to the otherwise limited evidence for natural products like turmeric and cinnamon in the management of cognitive impairment.[61,63] We would expect that if body fatness and insulin resistance were optimised, the cognitive benefits of turmeric would be enhanced, on the basis of our evidence. In particular, since GSK-3β is a marker of both insulin resistance and the risk of tau hyper-phosphorylation, it might be sufficiently responsive to longer-term cinnamon consumption to be of cognitive advantage. Some encouragement for longer -term benefits of turmeric come from experimental observations that curcumin is anti-amyloidogenic.[87]

Study limitations

Although we have used a meaningful outcome, WM, to evaluate the changeability of impaired cognition at mealtime, the scale is narrow from 1-3 and the ability to detect change with small numbers limited. We have, nevertheless, been able to consider two rather different natural products with putative benefit, but with different relevant mechanisms of action including anti-oxidative, anti-inflammatory and anti-proliferative properties in the case of turmeric[54] and pro-insulin-sensitivity along with mitochondrial function in the case of cinnamon.[88] The first was effective and the second not. As it turned out, we could not impute a mechanism for the turmeric finding except that it was unlikely to be related to body fatness, insulin resistance or short-term effects on indices of amyloid plaque or neurofibrillary tangle formation.[89]

We would rather have studied each participant with the different interventions to increase the sensitivity of our design to recognise change, but, in Chinese culture, there is a reluctance to have repeated blood sampling because the amount of blood is seen as a measure of life. Therefore, understandably, ethics clearance was provided for one intervention per subject.

The post-prandial findings may not translate into longer term benefit, but there is likely to be value for mealtime turmeric usage. We do not know how much longer than 6 hours the effect may be seen. It is possible, though, that this may attenuate with time or across the day.
There may be palatability barriers to the use of turmeric at breakfast, although this is not likely with traditional Asian rice porridge meals.

Notwithstanding these limitations, the findings add impetus to the quest to address the growing burden of cognitive impairment and dementia.[82]

Conclusion

Turmeric, a traditional culinary herb, yellow on account of its curcumin pigment, can improve post-prandial working memory in people with pre-diabetes who are prone to cognitive impairment. While it does this independently of body fatness, insulin resistance and known biomarkers of Alzheimer's disease pathogenesis, its efficacy is dependent on energy balance and insulin status. We did not find the same for cinnamon. Our findings may be relevant in the longer term, in diabetes, in those vulnerable to diabetes, and in others with cognitive impairment, although those possibilities need evaluation in their own right.

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AUTHOR DISCLOSURES

No Author has a conflict of interest.

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Original Article

Turmeric improves post-prandial working memory in pre-diabetes independent of insulin

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薑黃改善糖尿病前期患者餐後工作記憶之代謝研究

背景：認知功能失調伴隨糖尿病前期與失智症是糖尿病的併發症之一。天然食品如薑黃及肉桂可改善此致病機轉。本研究為評估薑黃肉桂如何影響糖尿病前期患者認知功能之代謝研究。方法：對象為三軍總醫院參加老人健檢者，納入條件為其空腹血糖介於 100-126 mg/dL，共計 48 位參與者。經由雙盲性別分層隨機分派至服用口服降血糖藥物或其組合、薑黃、肉桂或其組合及控制組共 4 組，每組 12 名，男女各半。參與者須於報到後抽取空腹血液、實施工作記憶前測及測量基本體位資料。再於 8 時服用早餐及受試藥物，各組分別為安慰劑、薑黃 1 克、肉桂 2 克、肉桂 2 克與薑黃 1 克等。隨後每隔 2 小時採集血液，共 4 次，於最後 1 次抽血完畢後，再測工作記憶分數。利用 RT-PCR 技術測得 APP、PS1、PS2、GSK-3βmRNA 表現量。利用 t 檢定及卡方檢定比較天然食品使用者及非使用者平均值之差異；魏克森符號等級檢定工作記憶前測及後測的分數。利用雙因子變異數分析檢定薑黃與肉桂兩植物成分之交互作用。複迴歸模式分析校正身體質量指數、血糖、胰島素濃度、阿茲海默症相關之生物標記後，薑黃肉桂對工作記憶之影響。結果：薑黃與肉桂兩植物成分並無交互作用產生。有服用薑黃者工作記憶平均分數由 2.6 增加至 2.9 分，為邊緣性顯著(p=0.05)，服用肉桂者工作記憶前後測平均分數沒有顯著差異。工作記憶分數之改善與胰島素阻抗呈負相關 (r=-0.418, p<0.01)，但與阿茲海默症之相關生物標記無顯著相關。複迴歸分析結果顯示服用薑黃、BMI 及胰島素阻抗為工作記憶分數最佳預測因子。結論：本研究觀察到的薑黃改善認知效果，可能並非透過假設之降血糖途徑或降低生物標記基因表現量而來，推測薑黃有其他保護神經元機制。

關鍵字：認知功能、阿茲海默症、薑黃素、肉桂、胰島素阻抗