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Association between Isoflavones Consumption and Cognitive Function and Comorbidities among Older Adults Residing in the State of Johor, Malaysia

Bibi Nabihah AH[1], Suzana S[1] & Hasnah H[2]

[1] *Dietetics Programme,Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia*
[2] *Nutrition Programme,Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia*

ABSTRACT

Introduction: This two-phase longitudinal study sought to determine the association between isoflavones intake on cognitive function and comorbidities among older adults from the state of Johor, Malaysia. **Methods:** Phase 1 involved baseline data collection to examine the association between isoflavones intake and cognitive function among 400 respondents aged 60-years and above, recruited through multistage random sampling. Phase 2 determined the association between isoflavones intake at the baseline and comorbidities at an 18-month follow-up. The baseline data collected included information on socio-demographics, health status, anthropometric measurements, and dietary intake using a dietary history questionnaire (DHQ). Each participant's cognitive function was evaluated using a mini mental state examination (MMSE), digit span, digit symbol, and geriatric depression scale (GDS). **Results:** The daily intake of total isoflavones, daidzein, and genistein were 19.1±19.7, 11.7±12.3 and 7.6±8.1 mg/day, respectively. There was no significant association between isoflavones intake, and specific cognitive function including global, memory, executive functions, and depression. However, there was a significant association (p<0.05) between isoflavones intake r=0.131 (95% CI: 0.064-0.199), daidzein intake r=0.132 (95% CI: 0.064-0.199), and genistein intake r=0.129 (95% CI: 0.062-0.197) with memory (digit span) after adjustment for age, gender, educational level, and body mass index (BMI). No association was found between isoflavones intake and comorbidities (p> 0.05). **Conclusion:** This study found an association between isoflavones intake and memory function, but not with global cognitive, executive functions, depression, and comorbidities. There is a need to promote adequate isoflavones intake in view of its association with memory function.

Key words: Cognitive function, comorbidities, isoflavones, older adults, phytoestrogen

INTRODUCTION

Aging is a complex process related to a multisystem decline of function that affects all systems of the body. Neurodegenerative diseases such as Alzheimer's disease, Parkinsons, dementia, and mild cognitive impairment are some of the most common diseases affecting the elderly (Fratiglioni & Qiu, 2009).

Cognitive impairment is burdensome among older adults since it may increase dependency and reduce quality of life.

* Correspondence: Suzana Shahar; Email: *suzana.shahar@gmail.my*

There are many factors that contribute to cognitive decline such as age, genetics, sex, physical health, lifestyle, dietary pattern, and social interaction. Longitudinal studies report that cognitive decline rate differs among individuals and is also affected by other modifiable factors such as education level, environment, health status, or working status (Gerstorf *et al.*, 2011). Vascular risk factors such as hypertension, type 2 diabetes, hyperlipidemia, or strokes predominantly during middle age are associated with an increased risk of old age dementia (Whitmer*et al.*,2005). Aging may also increase susceptibility of individuals to have various comorbidities such as diabetes, cardiovascular disease, cancer, neurodegenerative diseases, and inflammation (Donmez & Guarente, 2010). These diseases are predominantly influenced by lifestyles and dietary habits.

Isoflavones in soy products have the potential to preserve and improve brain functions (González *et al.*, 2007). A few studies suggest that high isoflavones intake is associated with increased brain function, but no exact level of isoflavones intake has been determined (Zhao & Brinton, 2007). In Japan, the daily dietary intake of isoflavones range from 11 to 47 mg/day (Yamamoto *et al.*, 2001; (Arai *et al.*, 2000). Many studies have also reported that isoflavones have a protective effect against several diseases including cardiovascular diseases, diabetes, pulmonary diseases and cancer (Ikeda *et al.*, 2006). Despite the well documented association between isoflavones with certain diseases, they are seldom considered in the context of comorbidities. Therefore, this study aimed to determine the total isoflavones intake among Malaysian elderly, its association with cognitive function, and also its potential effects in reducing the risk of comorbidities via an 18-month follow up. Our hypothesis was that a high isoflavones intake was associated with better cognitive function and that it might reduce the incidence of comorbidities.

METHODS

This longitudinal study was conducted in ten districts around Johor, Malaysia by multistage random sampling. These subjects were part of the Longitudinal Research Grant Scheme Towards Useful Aging (LRGS TUA) that commenced in July 2013 (Suzana *et al.*, 2015). Written consent was obtained from each subject and the study was approved by the Universiti Kebangsaan Medical Committee's (UKMMC) Ethical Committee (1.5.3.5/244/NN-060-2013).

A total of 400 of 495 elderly subjects were randomly selected and invited to participate for a screening at the respective community centres if they met the inclusion criteria. These were: aged 60-years and above; had no mental illness; no serious physical disability; and had not been on any oestrogen hormone therapy or taken supplements rich in antioxidants three months prior to data collection. Those with chronic kidney diseases and cancer were excluded.

Subjects were interviewed to collect baseline data on their socio-demographics, health, and dietary intake. Anthropometric measurements including height and weight were also taken from which the body mass index (BMI) was calculated. Waist and hip ratio were also measured (World Health Organisation [WHO], 2008). Habitual isoflavones intake was assessed using a dietary history questionnaire (DHQ) (Suzana, Earland & Abdulrahman, 2000).

Neuropsychological ability was assessed using Mini-Mental State Examination (MMSE), Digit Span, Digit Symbol and Geriatric Depression Scale (GDS). The MMSE was used to assess global cognitive function which consists of different tasks such as orientation, registration, attention, calculation, recall, and language with a score range of 0 to 30. A score of 21 or less indicates mild cognitive functional problems (Norlinah *et al.*, 2009). The

Digit Span test was used to assess verbal working memory by involving a series of numbers, both forwards and backwards. In the forward digit span, subjects were asked to recall the given series of increasing numbers (spans of two to nine), and vice versa for the backward digit span.

Memory executive function was assessed using the Digit Symbol test. Subjects were given matched symbols and numbers. The test involved the filling as many blank boxes as possible with a symbol matching each number within 120 seconds. A short form of the GDS test,which consists of 15 questions, is used extensively among older adults to measure depression. Score of four or less indicates a normal state of mental health, while a score of five to nine indicates mild depression and a score of ten and above indicates severe depression (Sheikh & Yesavage, 1986)

A total of 261 subjects were followed up after 18-months to obtain data on co-morbidities (a response rate of 65.3%). Six subjects died during the period of this study while 133 did not participate due to personal or health problems, or relocation to other places. Some refused to participate further.

Analysis of isoflavones

Food intake data from the DHQ was used to estimate isoflavones intake. Weight of soy products was adopted from the Malaysian Food Composition Table (Tee *et al.*, 1997) and Atlas of Food Exchange and Portion Size (Suzana *et al.*, 2009). Isoflavones intake was determined using data from Hasnah *et al.* (2009), Hutabarat, Greenfield & Mulholland (2001), Park *et al.* (2007) and the Unites States Department of Agriculture (USDA) Nutrient Data Laboratory while genistein and daidzein assessments were based on Hasnah *et al.*(2009).

Statistical analysis

The data were analysed using Statistical Package for Social Sciences (SPSS) version 20.0. Descriptive statistics were used to determine the effects of socio-demographic and health status on isoflavones intake. Since the intakes of isoflavones, daidzein, and genistein were not normally distributed, all of the contributions from soy components were transformed using log10. Paired *t*-test was used to determine the difference between the intake of soy isoflavones and sex, while one way analysis of variance (ANOVA) and the Kruskal-Wallis test were performed to determine the mean difference between isoflavones intake by ethnicity as well as test score. Binary logistic regression was used to assess the odds of mild cognitive impairment. The Pearson correlation and Spearman correlation were used to determine the association between continuous data of isoflavones, daidzein and genistein intake with cognitive test score. Binary logistic regression and multiple linear regression were used to determine the association between isoflavones, daidzein and genistein intake, and cognitive test score based on quartiles. Additionally, binary logistic regression was used to analyse the association between isoflavones intake as well as soy protein, daidzein, and genistein intake with comorbidities.

RESULTS

Of the 400 subjects, 42.3% were men with a mean age of 69±5.5 years, and 57.7% were women with a mean age of 69.5±6.4 years. A majority of the subjects were Malay (64.5%), followed by Chinese (33.8%), and Indians (1.7%). Most of the subjects were married; however, more women subjects reported being widowed than men. This concurs with the higher life expectancy of women (77.2 years) compared to men (72.5 years). Men had a higher mean number of years of education (6.0±2.7 years) compared to women (3.7±3.2 years) ($p<0.05$). Most subjects were non-smokers, and only 3.0% were active drinkers. Both sexes were not significantly different in terms of their BMI, waist hip ratio, and

isoflavones intake. The mean intakes of isoflavones, daidzein and genistein were 19.1±19.7 mg/day (range: 0 to94.7 mg/day), 11.7±12.3 mg/day (range: 0-67.4 mg/day), and 7.6±8.1 mg/day (range: 0 to54.7 mg/day),respectively, were not significantly different (p>0.05) between the sexes. This study also found a higher percentage of women (24.5%) with MMSE scores of less than 21 compared to men (6.7%), indicating cognitive impairment (p<0.001) (Table 1).

There was no significant association between isoflavones intake and MMSE, digit span, digit symbol, and GDS as shown in Table 2. However, after adjusting for age, gender, education level, and BMI, isoflavones intake was associated with digit span withr=0.131 (95% CI: 0.064-0.199). There were negative associations between soy protein intake and waist hip ratio, (r= -0.111, p<0.05), as well as genistein intake and waist hip ratio (r= -0.134, p<0.05) (Table 2).

Intakes of isoflavones, daidzein, and genistein had no significant association with comorbidities at the 18-monthfollow up (Table 3). More precise analyses were done to determine the association between each quartile of isoflavones, daidzein and genistein with specific diseases. Only seven diseases were included in this study since there was no recurrence, or reported incidence, of cancer among subjects during the follow up. The diseases analysed were hyperlipidemia, hypertension, diabetes, cardiovascular disease, stroke, chronic kidney disease, and pulmonary disease. There were no significant associations between isoflavones, daidzein,and genistein with the aforementioned diseases as shown in Table 4.

DISCUSSION

This study successfully estimated soy protein intake among a sample of older adults in Malaysia (4.4 g/d of soy protein). This level was much lower compared to the 25 g/d intake of soy protein recommended by the United States Food and Drug Administration(USFDA) (1999) based on its cholesterol lowering properties. Interestingly, the soy intake of other countries is also lower than the USFDA recommendations with the Japanese, Koreans, Indonesians, and Chinese consuming on average of 8.7 g/day, 6.2 to 9.6 g/day, 7.4 g/day, and 3.4 g/day, respectively. Firm tofu was the most popular soy product consumed by the respondents, followed by soybean milk, and *tempeh*. Overall,the isoflavones intake among the respondents was comparable to the level reported among the Asian population (Ho *et al.*, 2007). The Asian population consumes more soy isoflavones(11 to47 mg/day) compared to the western population(0.5 to 0.8 mg/day) (Zamora-Ros *et al.*, 2012). The Japanese have a higher intake of daidzein (18.3 mg/day) and genistein (31.4 mg/day) compared to this study's respondents' intakes of 11.7±12.3 mg/day and 7.6±8.1 mg/day, respectively.

This study found that the dietary intake of isoflavones, daidzein, and genistein was associated with digit span, reflecting temporary storage, and manipulation of information. This verbal working memory is involved in many everyday tasks, such as remembering a telephone number while entering it into the telephone, as well as to understanding long and difficult sentences. A positive association was found between firm tofu and *tempeh* intake and speed of recall among the elderly aged 65-years and above in Indonesia (Hogervost *et al.*, 2011). However, in this study, other cognitive functions, including global cognitive function, processing speed,and depression were not associated with isoflavones intake. Similarly, Kreijkamp-Kaspers *et al.* (2007) also state that neither high nor low levels of isoflavones intake are associated with cognitive functions.

This study also found that daidzein and genistein intakes had no association

Table 1. Baseline characteristics of respondents

	Men (n=169)	*Women (n= 231)*
Age (years)		
Mean+SD	69.4+5.5	69.5+6.4
Ethnicity		
Malay	107 (26.8)	60 (15.0)
Chinese	2 (0.5)	0 (0)
Indian	151 (37.7)	75 (18.8)
Others	5 (1.2)	0 (0)
Religion		
Islam	107 (26.8)	58 (14.5)
Buddhism	2 (0.5)	1(0.2)
Christianity	1(0.2)	150 (37.5)
Hinduism	72 (18.0)	2 (0.5)
Others	5 (1.3)	2 (0.5)
Marital status		
Single	4 (1.0)	147 (36.7)
Married	1 (0.3)	18 (4.5)
Divorce	2 (0.5)	110 (27.5)
Widowed	4 (1.0)	114 (28.5)
Living with		
Alone	11 (2.7)	159 (39.8)
Others	6.0+2.7	18 (4.5)
Years of education*	212 (53.0)	3.7 3.2
Working status		
Working	128 (32.0)	41 (10.3)
Not working/Retired	172 (43.0)	59 (14.7)
Smoking status		
Smoker	51 (12.7)	42 (10.5)
Ex-smoker	307 (76.8)	51 (12.7)
Non smoker	42 (10.5)	307(76.8)
Alcohol intake		
Yes	12 (3.0)	388 (97.0)
No	12 (3.0)	388(97.0)
Family history of dementia		
Yes	9 (2.2)	8 (2.0)
Unsure	152 (38.0)	13 (3.2)
No	19 (4.8)	199(49.8)
BMI (kg/m2)	24.8+4.1	25.1+5.1
Dietary phytoestrogen intake (mg/day)		
Soy protein (4.4 + 4.6)	4.2+4.4	20.2+20.3
Isoflavones (19.1 + 19.7)	12.3+13.0	7.3+7.7
Daidzein (11.7 + 12.3)	4.4+4.7	19.7+19.3
Genistein (7.6 + 8.1)	11.4+11.7	7.8+8.4
MMSE score**	24.2+3.9	21.7+5.4

[1]Values are n(%) and mean+standard deviation (SD)
*p<0.05, **p<0.001, independent t-test, BMI-body mass index, MMSE-mini mental state examination

Table 2. Association between phytoestrogen and cognitive function and anthropometry

	r	*MLRa*		
		Adj b (95% CI)	t stat.	P value
Cognitive function				
Soy protein	0.028			
MMSE	- 0.006			
Digit span	0.013	0.131 (0.064, 0.199)	3.819	< 0.05
Digit symbol	0.012			
GDS				
Isoflavones				
MMSE	0.036			
Digit span	- 0.004	0.131 (0.064,0.199)	3.824	< 0.05
Digit symbol	0 .022			
GDS	- 0.150			
Daidzein				
MMSE	0.030			
Digit span	- 0.015	0.132 (0.064, 0.199)	3.842	< 0.05
Digit symbol	0.032			
GDS	- 0.033			
Genistein				
MMSE	0.031			
Digit span	- 0.009	0.129 (0.062, 0.197)	3.766	< 0.05
Digit symbol	0.006			
GDS	0.005			
Anthropometry				
Soy Protein				
Body Mass Index (BMI)	- 0.022			
Waist Hip ratio (WHR)	- 0.110*			
Isoflavones				
Body Mass Index (BMI)	0.001			
Waist Hip ratio (WHR)	- 0.080			
Daidzein				
Body Mass Index (BMI)	0.002			
Waist Hip ratio (WHR)	- 0.055			
Genistein				
Body Mass Index (BMI)	- 0.016			
Waist Hip ratio (WHR)	- 0.134*			

* P<0.05, indicates significant association between phytoestrogen intake and cognitive test score and anthropometry.

[a] Adjusted for age, sex, BMI, and years of education

Table 3. Phytoestrogen intake and comorbidities at 18-month follow up

	No comorbidities (0 illness) (n= 87)	*With comorbidities (> 1 illness) (n= 174)*	*P value*
Isoflavones			
Quartile 1	21 (24.1)	44 (25.3)	0.612
Quartile 2	23 (26.4)	142 (24.1)	
Quartile 3	17 (19.5)	49 (28.2)	
Quartile 4	26 (29.9)	39 (22.4)	
Daidzein			
Quartile 1	21 (24.1)	45 (25.9)	0.669
Quartile 2	23 (26.4)	41 (23.6)	
Quartile 3	18 (20.7)	48 (27.6)	
Quartile 4	25 (28.7)	40 (23.0)	
Genistein			
Quartile 1	19 (21.8)	45 (25.9)	0.557
Quartile 2	23 (26.4)	43 (24.7)	
Quartile 3	22 (25.3)	44 (25.3)	
Quartile 4	23 (26.4)	42 (24.1)	

*P<0.05, indicates significant association between phytoestrogen intake and comorbidities at 18-month follow up

Table 4. Isoflavones intake and incidence of disease at 18-month follow up

Isoflavones	*N = 261*	*Quartile 1*	*Quartile 2*	*Quartile 3*	*Quartile 4*	*P value*
Hypertension	Yes (n=135)	33 (24.4)	33 (24.4)	38 (28.1)	31 (23.0)	0.933
	No (n=126)	32 (25.4)	32 (25.4)	28 (22.2)	34 (27.0)	
Hypercholesterolemia	Yes (n=105)	26 (24.8)	27 (25.7)	28 (26.7)	24 (22.9)	0.761
	No (n=156)	39(25.0)	38 (24.4)	38 (24.4)	41 (26.3)	
Cardiovascular disease	Yes (n=20)	5 (25.0)	6 (30)	5 (25.0)	4 (20.0)	0.672
	No (n=241)	17 (23.3)	17 (23.3)	16 (21.9)	23 (31.5)	
Diabetes	Yes (n=79)	24 (30.4)	15 (19.0)	25 (31.6)	15 (19.0)	0.298
	No (n=182)	41 (22.5)	50 (27.5)	41 (22.5)	50 (27.5)	
Stroke	Yes (n=2)	0 (0.0)	1 (50.0)	1 (50.0)	0 (0.0)	0.998
	No (n=259)	65 (25.1)	64 (24.7)	65 (25.1)	65 (25.1)	
Chronic kidney disease	Yes (n=4)	1 (25.0)	0 (0.0)	2 (50.0)	1 (25.0)	0.656
	No (n=257)	64 (24.9)	65 (25.3)	64 (24.9)	64 (24.9)	
Pulmonary disease	Yes (n=6)	1 (16.7)	2 (33.3)	1 (16.7)	2 (33.3)	0.716
	No (n=255)	64 (25.1)	63 (24.7)	65 (25.5)	63 (24.7)	

[1] Values are n(%)
* P<0.05 indicates significant association between isoflavones intake and diseases at 18-month follow up

with cognitive function. Huang *et al.* (2006) also report a similar result on associations between genistein intake and cognitive function among middle aged women. However, an interventional study showed significant results (Gleason *et al.*, 2009).

The different finding might be due to difference in isoflavones content in soybeans, which depends on both genetic and environmental factors, including climate, location of plantation, crop year, and storage conditions (Zhu *et al.*, 2005). It was found that isoflavones content in soybeans is higher when planted during the dry season (early in the year in Thailand) compared to when planted during the rainy season (late in the year) (Teekachunhatean, Hanprasertpong & Teekachunhatean, 2013). Teekachunhaten *et al.* (2013) also found a significant

difference in the isoflavones content of soybeans planted in different locations in Thailand. The storage conditions might also affect the isoflavones content; for example, a Korean study shows that longer storage periods (2 to 3-years) significantly reduce isoflavones content regardless of low or ambient storage temperatures (Kim *et al.*, 2005).

A few studies have also found that the prevalence of the equol-producer phenotype is higher among the soy-consuming Asian populationas compared to their western counterparts (Morton *et al.*, 2002; Ozasa *et al.*, 2004; Vedrine *et al.*, 2006). The production of equol may vary presumably due to inter-individual differences of the intestinal microflora composition, which may play a crucial role in the mechanisms of action of isoflavones. Moreover, aging may affect production of equol as the proportion of equol producers decreases with age (Franke *et al.*, 2012). However, the level of equol among the respondents of this study was not assessed as 24-hour urinary excretion and faeces samples were not collected.

With regard to the association between isoflavones intake and cognitive function, the level of oestrogen in the human body plays a role in determining the effectiveness of isoflavones. However, the level of oestrogen was not examined in this study. Additionally, a study by Huang *et al.* (2006) found that genistein intake may show its effectiveness when the level of oestrogen in the body drops. Type of soy products consumed by subjects in different studies might also affect the overall results. For example, natto and miso are the main fermented soy products consumed by the Japanese compared to Malaysians and Indonesians who consume *tempeh*, firm tofu, and soybean milk. It should be noted that fermented soy products have a higher bioavailability and are thus more effective in improving health.

The regularity of isoflavones intake might affect its bioavailability. This study found no significant association due to the fact that this study evaluated habitual isoflavones intake for one week. Another study involving a food frequency questionnaire (FFQ) estimated the annual isoflavones intake, and found a neuroprotective effect during the late pre- and post-menopause period, and an opposite effect in early pre- and post-menopause period (Greendale *et al.*, 2012). Meanwhile, there was no association found in other sample populations treated with phytoestrogens and/or those who consumed very low and infrequent quantities of isoflavones through their diets (Wiseman *et al.*, 2004).The DHQ used in this study only represents the food intake for a short period compared to the capacity of a FFQ, which can assess frequency of consumption of a listed food for a specific time period. AFFQ assesses the foods consumed, their cooking methods, portion size, and can capture a person's usual dietary intake over a longer term.

This study was not able to show longitudinal associations between isoflavones intake and comorbidities. Wong *et al.* (2012) found that a supplementation of 80 mg/day of isoflavones was not associated with hypertension. Meanwhile, Acharjee *et al.* (2015) found that in equol producer subjects with metabolic syndrome who consumed soy, a significant reduction in diastolic blood pressure (7.7%; P=0.02) was observed. Soy isoflavones supplementation at 165 mg/day for two years containing genistein, daidzein, and glycitein in a ratio of 1:1:0.2 may be protective for cardiac health, since it reduces low-density lipoprotein (LDL) cholesterol by 6% (Chilibeck *et al.*, 2013). However, Nanri *et al.* (2010) found no association between isoflavones intake and the incidence of diabetes among both men and women subjects in a longitudinal study among older adults in Japan.

A randomised controlled trial of 105 mg/day isoflavones supplementation reported insignificant results, where

serum lipids or inflammatory markers were not affected (Mangano *et al.*, 2013) In contrast, Kokubo *et al.* (2007) reported that high isoflavones intake is associated with a reduced risk of cerebral infarction by 0.35 (CI: 0.21 to 0.59) and myocardial infarction by 0.37 (CI: 0.14 to 0.98) among post-menopausal Japanese women. This discrepancy might be due to the fermented soy products consumed by the Japanese differing from that consumed by Malaysians. Besides,the Japanese's consumption of isoflavones is much higher at 41.3 mg/day compared to 19.1 mg/day among subjects in this study.

The use of the DHQ required this study's respondents to recall their diets from the past 7 days and may not accurately represent their normal eating habits. The accuracy of food quantities was also questionable as all of the variables were self-reported and some of the subjects might have had poor recall ability. Therefore additional laboratory and clinical data are crucial for future studies to determine the effect of different levels of isoflavones intake on cognition and health. Future research should be done by using a FFQ to obtain habitual intake of isoflavones in detail.

CONCLUSION

The consumption of isoflavones had no significant association with cognitive function except for memory executive function as assessed using digit span. There was no evidence of protective effects of isoflavones towards comorbidities at the 18-month follow up.

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Conflict of Interest

The authors declare no conflict of interest in the running and reporting of this study.

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