

A preliminary study of the safety, feasibility and cognitive efficacy of soy isoflavone supplements in older men and women

CAREY E. GLEASON^{1,2}, CYNTHIA M. CARLSSON^{1,2}, JODI H. BARNET³, SARAH A. MEADE^{1,4},
KENNETH D. R. SETCHELL⁵, CRAIG S. ATWOOD^{1,2}, STERLING C. JOHNSON^{1,2}, MICHELE L. RIES¹,
SANJAY ASTHANA^{1,2}

¹Section of Geriatrics and Gerontology, Department of Medicine, University of Wisconsin, Madison, WI 53705, USA

²Geriatric Research, Education and Clinical Center (GRECC), William S. Middleton Memorial Veterans Hospital, Madison, WI 53705, USA

³Department of Biostatistics and Medical Informatics, University of Wisconsin, Madison, WI 53792-4675, USA

⁴Wisconsin Alzheimer's Institute, University of Wisconsin, Madison, WI 53719, USA

⁵Department of Pathology and Laboratory Medicine, Cincinnati Children's Hospital Medical Center; and Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH 45267, USA

Address correspondence to: C. E. Gleason, Madison VA GRECC (11G), 2500 Overlook Terrace, Madison, WI 53705, USA.
Tel: (+1) 608 256 1901, Ext. 11518; Fax: (+1) 608 280 7165. Email: ceg@medicine.wisc.edu

Abstract

Background: a small number of reports exist on the cognitive effects of soy isoflavones, the findings from which are mixed. Isoflavone efficacy is dependent upon conversion of glycosides contained in soy foods and supplements to the biologically active aglycons. Of particular interest is the production of the metabolite, equol, which is dependent upon intestinal microflora and an integrous digestive system, both being altered by age and age-associated conditions. Unfortunately, few studies enrolled adults over the age of 70, and none included older men.

Objective: we examined safety, feasibility and cognitive efficacy of soy isoflavone administration in older nondemented men and women (age 62–89 years).

Design and Methods: in this randomised, placebo-controlled, double-blind pilot study, subjects ingested either 100 mg/day soy isoflavones (glycoside weight) or matching placebo tablets for 6 months.

Results: active and placebo-treated subjects exhibited a comparable side-effect profile. Plasma levels of genistein and daidzein ($P < 0.001$), but not equol, increased with isoflavone administration. While similar at baseline, the two groups differed across 6 months of treatment on 8 of 11 cognitive tests administered. Isoflavone-treated subjects improved on tests of visual-spatial memory ($P < 0.01$) and construction ($P = 0.01$), verbal fluency ($P < 0.01$) and speeded dexterity ($P = 0.04$). Placebo-treated participants were faster than isoflavone-treated subjects on two tests of executive function ($P < 0.05$).

Conclusions: these data suggest that administration of 100 mg/day of isoflavones was well tolerated. Plasma genistein and daidzein levels, but not equol, increased with isoflavone administration. Finally, data support the potential cognitive effects of soy isoflavones in older adults.

Keywords: cognitive ageing, phytoestrogen, isoflavone, equol, genistein, daidzein, elderly

Introduction

Interest in estrogenic isoflavones in soy products increased in both scientific and lay communities after findings from the Women's Health Initiative (WHI) [1, 2] revealed potential cognitive harm associated with two forms of hormone therapy (HT) [3]. Like HTs, the cognitive effects of soy isoflavones have been investigated, and the findings are

mixed. Evidence of positive neurobiological effects supports the potential cognitive benefits of isoflavones [4], and six of nine human studies conducted thus far suggested cognitive benefits with soy isoflavone administration [5–10]. However, few studies included individuals over 70 years of age, and none included older men, even though older adults are as likely as younger cohorts to use nonallopathic therapies [11]. Moreover, only one study [12] measured

plasma isoflavones levels, an estimate of actual exposure to isoflavones.

It is well documented that there are large inter-individual variations in the extent of intestinal metabolism of soy isoflavones, even in younger populations and even when intake is standardised [13]. Isoflavones in foods and supplements occur as highly water-soluble glucosides, which must undergo hydrolysis by intestinal β -glucosidases to release bioactive *aglycons* (daidzein, genistein and glycitein). Daidzein undergoes further metabolism to obtain the estrogenic and biologically active metabolite, equol [14]. While data on older adults' ability to metabolise daidzein to equol are scant, the proportion of equol producers decreases with age [15]. The fact that isoflavone metabolism and absorption are heavily dependent upon intestinal metabolism [16] and that ageing and selected medications may compromise the integrity of gastrointestinal function, necessitates examining whether older adults can metabolise isoflavone glycosides to the biologically active *aglycons*. To clarify the feasibility and potential cognitive efficacy of a soy isoflavone supplement in older adults, we conducted a randomised, placebo-controlled, double-blinded pilot study in 30 men and women (age 62–89 years), using purified glycosidic isoflavones (100 mg/day), in addition to measuring plasma levels of genistein, daidzein and the metabolite equol, and cognitive function over the course of 6 months of treatment.

Methods

Subjects

Thirty-four participants, recruited from the community, provided informed consent for study participation. See Appendix 1 in the supplementary data at *Age and Ageing* online for details of study enrolment. Thirty subjects completed the study. Three subjects were excluded following screening, and one subject withdrew consent after baseline. At entry all participants were over 60 years of age, cognitively healthy and free of major medical, neurological and psychiatric illnesses. All women were postmenopausal, and had not used HT for a minimum of 6 months prior to enrolment. All subjects completed extensive laboratory, cognitive and medical evaluations to assess eligibility and ensure safety; female subjects underwent mammographic examination to screen for pre-existing pathology. The Health Science Institutional Review Board reviewed and approved all study procedures and consent forms, assuring adherence to principles outlined in the declaration of Helsinki [17].

Study design and data collection

At baseline, subjects were randomised to receive either capsules containing 100 mg/day of purified glycosidic isoflavones (~85% daidzein and genistein; Novasoy[®] brand isoflavones; Archer Daniels Midland Co., Decatur, IL, USA) or matching placebo capsules containing maltodextrin and caramel food colour in this double-blind, parallel-group

design study. Specific contents of isoflavone and placebo capsules are included in Appendix 2 provided as supplementary data at *Age and Ageing* online.

Baseline assessment included neuropsychological evaluation; collection of blood samples for isoflavone and hormone assays, and safety laboratory testing; symptom interview and brief medical evaluation. Subjects also completed a standardised and validated food frequency questionnaire (FFQ [18]), estimating weekly intake of dietary soy isoflavones. Study procedures were repeated at months 1, 3 and 6. Subjects were provided with 3-month supplies of study medication at baseline and again at month 3. Two months following termination of study medication, subjects returned for a final visit, limited to neuropsychological evaluation and safety laboratory tests.

At the start of their research visit, subjects' nonfasting blood samples were drawn for analysis of isoflavones (genistein, daidzein and equol), oestrogen (17 β -oestradiol), luteinising hormone (LH) and safety laboratory tests (amylase, lipase and phosphate). To reduce variability in measurements, subjects were instructed to take tablets with low-fat, carbohydrate-based meals 4 h before appointments. Measurement of hormones and safety laboratory tests was performed by Clinical Laboratory Improvement Amendments certified laboratories, using standard reagents.

Plasma isoflavone and serum hormone measurement

Isoflavone assays were performed on blood samples collected at baseline and at months 1 and 6. Concentrations of total daidzein, genistein and equol in plasma (0.5 ml) were measured after enzymatic hydrolysis of glucuronide and sulphate conjugates, using stable-isotope dilution GC-MS method, previously described [19]. Concentrations were expressed as nmol/l. Assays were conducted under Good Laboratory Practice procedures, including within- and between-batch plasma samples quality-control specimens. Using serum collected at baseline and at month 6, 17 β -oestradiol was measured using an enzyme immunoassay [EIA kit (Alpco Diagnostics, Salem, NH, USA)]; serum LH were measured using an enzyme-linked immunosorbent assay (Hope Laboratories, Belmont, CA, USA)].

Neuropsychological battery

At every visit, a trained psychometrician administered a battery of neuropsychological measures, sampling memory, attention and executive function (higher order cognitive abilities, such as planning, organising and reasoning), following standardised testing procedures. Tests included measures of *verbal and visuospatial memory* (Buschke Selective Reminding test, Paragraph Recall, Rey Complex Figure test, Visual Spatial Learning test); *language* (Boston Naming test); *language fluency* (FAS, animal fluency); *visual-motor function* (Rey Complex Figure test copy, Grooved Pegboard) and *executive function* (Stroop Color Word test, Mazes and Trail Making Test B). Citations for tests listed here are provided in Appendix 3 (available in *Age and Ageing* online).

Statistical analyses

To examine the feasibility of isoflavone administration in adults over 60 years of age, plasma levels of isoflavones following 1 and 6 months' administration of 100 mg/day purified glycosidic isoflavone tablets are presented along with data on side-effects, safety laboratory tests and study and medication adherence estimated by FFQ and pill count. To examine cognitive efficacy, neuropsychological data were compared for an effect of soy administration across visits. In particular, changes from baseline (delta-scores) on neuropsychological measures were compared between isoflavone and placebo groups. The effect of soy isoflavone withdrawal was also examined by comparing neuropsychological performance at months 6 and 8.

Nonparametric methods, more powerful and appropriate statistical methods for small sample sizes, were employed for all comparisons. *P*-values were computed for categorical subject characteristic variables (e.g. sex) using Pearson's chi-square test, and for continuous subject variables (e.g. age) using the nonparametric Wilcoxon rank-sum test. *P*-values, adjusted for age and education, for treatment effect across time corresponding to the cognitive outcome measures were computed using nonparametric Wilcoxon score general linear models [20].

Results

Subjects

Thirty older men and women completed the study. Subject characteristics at the time of study entry were similar for the two randomisation groups (isoflavone vs. placebo-treated). Table 1 summarises participant characteristics. All participants were self-identified as White and non-Hispanic. There were no differences between the intervention groups with regard to age, education, Mini-Mental State Exam [21] score or Geriatric Depression Scale [22] score.

Sixteen participants consumed soy isoflavones prior to study entry with the mean consumption of 38.1 mg/week, compared to 14 subjects consuming no soy prior to enrolment. The 16 subjects with prior exposure to soy isoflavones were evenly distributed between groups with 9 being randomised to receive placebo. One subject consumed 412.67 mg/week of isoflavones. Exclusion of this subject from analyses did not substantively change the results reported below.

Feasibility of soy isoflavone administration in older adults

Table 1 lists reported adverse symptoms; study procedure and medication adherence as measured with FFQ data and pill count, and a summary of safety laboratory data at month 6. Overall, subjects reported few adverse symptoms. There were no differences between groups in number or type of symptoms reported, and no subject withdrew due to adverse events. Analysis of FFQ data suggested that par-

ticipants were similar in amount of soy consumed during the study, and that they were able to comply with instructions to avoid dietary soy. Pill counts revealed that subjects correctly self-administered study medication. To monitor for possible side-effects, reported to have occurred with high doses of soy isoflavones [23, 24], changes from baseline scores for amylase, lipase and phosphate levels were compared for groups at each time point. The placebo-treated group evidenced slight increases in amylase at month 3 ($P = 0.05$), and in lipase at months 1 ($P = 0.03$) and 3 ($P = 0.05$). There were no between-group differences in the change from baseline phosphate, LH or oestrogen levels. (See Table 1 for month 6 values.)

Isoflavone assays

Plasma levels of total isoflavones, genistein and daidzein increased significantly from baseline at months 1 and 6 for subjects treated with isoflavone supplements (see Table 2).

Of note, between-subject variability was large for plasma genistein and daidzein levels and even greater for equol levels, despite chronic administration of a standardised dose. Mean changes in plasma levels of equol did not differ between treatment groups with none of the subjects being significant producers of equol [25], following administration of a purified glycoside isoflavones. Only one subject had equol levels >10 nmol/l during treatment; none had levels >25 nmol/l.

Relationship between treatment with soy isoflavones and cognitive variables

Table 3 summarises findings comparing the effect of treatment across visits as measured by change-from-baseline scores on neuropsychological variables. The isoflavone-treated group differed across visits from the placebo-treated group on 8 of the 11 tests administered. With an alpha level of 0.05, we acknowledge that 1 in 20 comparisons will by chance reach significance. Of the 18 variables examined, 10 were statistically significant and 2 showed a trend towards significance. As noted, exclusion of a subject from analyses whose background use of soy was unusually high did not markedly alter means reported in Table 3.

Subjects on soy isoflavone supplement performed better on several cognitive tests compared with those receiving placebo, including immediate and delayed recall of the Complex Figure Test, category fluency (months 3 and 6 only) and grooved pegboard test. There was a trend for improved performance for isoflavone-treated subjects on time to complete mazes. During the last two treatment visits, subjects on placebo were faster than those on isoflavones on two tests of executive function, Trail Making Test part B and Stroop Color-Word test. The isoflavone- and placebo-treated groups differed on the learning trials of the Visual Spatial Learning test. The pattern of results suggested that the placebo group was more accurate in recalling correct stimuli, but that the isoflavone group was more accurate in rejecting incorrect designs (months 3 and 6 only). The two groups did not differ in performance on two tests of verbal learning and recall,

Table 1. Subject characteristics at entry into study: safety and adherence profile; vital signs, and safety and hormone laboratory tests

	Placebo treated (<i>n</i> = 15)	Isoflavone treated (<i>n</i> = 15)	<i>P</i> -value
Subject baseline characteristics			
Age mean (SD) (years)	74.3 (6.3)	73.0 (7.9)	0.62
Women (%)	53.3% (<i>n</i> = 8)	46.7% (<i>n</i> = 7)	0.72
Education mean (SD) (years)	16.5 (3.3)	17.1 (3.0)	0.69
Total isoflavone intake at baseline ^a mean (SD)	6.3 (13.9)	34.3 (106.4) ^b	0.65
Mini-Mental State Examination mean (SD) points/30	29.5 (0.7)	28.7 (1.5)	0.13
Geriatric Depression Scale mean (SD) points/15	4.9 (3.9)	3.1 (3.0)	0.17
Symptoms reported during study (<i>n</i>)			
Breast or abdominal tenderness	2	2	1.00
Excessive fatigue	2	4	0.36
Loss of appetite	1	2	0.54
Muscle weakness	3	3	1.00
Nausea	2	3	0.62
Pedal oedema, calf tenderness, redness or swelling	3	2	0.62
Study adherence			
Ave dietary soy intake during 6 months of study (SD) (g/week)	19.9 (34.7)	4.9 (10.9)	0.76
Pill Count -% of expected number of pills used (SD)	97.5% (2.2%)	98.1% (5.7%)	0.68
Changes at 6 months in vital signs and laboratory tests			
Systolic BP mean (SD) (mmHg)	2.7 (14.1)	-5.8 (19.2)	0.06
Diastolic BP mean (SD) (mmHg)	-0.6 (11.5)	-5.0 (11.3)	0.23
Amylase level mean (SD) (U/l)	5.7 (26.1)	-6.7 (38.3)	0.52
Lipase level mean (SD) (U/l)	5.4 (31.0)	-0.4 (39.4)	0.42
Phosphate level mean (SD) (mmol/l)	0.03 (0.3)	0.11 (0.5)	0.59
17β Estradiol levels for women mean (SD) (pg/ml)	3.25 (16.6)	-0.29 (2.9)	0.86
17β Estradiol levels for men mean (SD) (pg/ml)	0.4 (6.4)	-0.9 (6.7)	0.95
LH levels for women mean (SD) (mIU/ml)	-0.6 (5.1)	2.8 (5.3)	0.36
LH levels for men mean (SD) (mIU/ml)	0.2 (1.8)	0.1 (1.3)	1.00

^aEstablished with Food Frequency Questionnaire (FFQ).

^bWhen outlier who consumed 412.67 mg isoflavones per week was excluded, new total for baseline intake of isoflavone-treated subjects was 7.2 (19.8) mg/week (SD) with a *P*-value of 0.87.

Note: CVs for all hormone assays were ≤10%.

Table 2. Plasma levels of soy isoflavones at baseline, month 1 and month 6

	Placebo treated (<i>n</i> = 15)	Isoflavone treated (<i>n</i> = 15)	<i>P</i> -value
Baseline plasma isoflavone levels ^a			
Total plasma isoflavones (nmol/l) (SD)	16.0 (5.5)	21.1 (15.7)	0.541
Plasma genistein (nmol/l) (SD)	4.2 (1.6)	6.0 (5.8)	0.965
Plasma daidzein (nmol/l) (SD)	4.3 (2.0)	5.7 (4.5)	0.160
Plasma equol (nmol/l) (SD)	7.5 (3.1)	9.4 (7.5)	0.541
Month 1 plasma isoflavone levels ^b			
Total plasma isoflavones (SD) (nmol/l)	8.4 (2.7)	334.6 (188.6)	0.000
Plasma genistein (SD) (nmol/l)	2.8 (1.6)	173.5 (115.0)	0.000
Plasma daidzein (SD) (nmol/l)	2.8 (1.3)	157.6 (88.8)	0.000
Plasma equol (SD) (nmol/l)	2.8 (3.7)	4.7 (5.6)	0.089
Month 6 plasma isoflavone levels ^c			
Total plasma isoflavones (SD) (nmol/l)	8.6 (3.8)	345.8 (183.5)	0.000
Plasma genistein (SD) (nmol/l)	3.1 (2.5)	186.5 (105.3)	0.000
Plasma daidzein (SD) (nmol/l)	2.9 (1.5)	154.9 (84.4)	0.000
Plasma equol (SD) (nmol/l)	2.7 (0.2)	3.4 (3.7)	0.471

^aFor one subject from the placebo-treated group, plasma isoflavone data were unavailable at baseline.

^bFor one subject from the placebo-treated group, plasma isoflavone data were unavailable at month 1.

^cFor one subject from the soy isoflavone-treated group, plasma isoflavone data were unavailable at month 6.

Note: CVs for all isoflavone measurements range from 8 to 11% at a concentration of 70 ng/ml.

Table 3. Change from baseline in cognitive performance over course of 6 months of treatment

	Change at month 1		Change at month 3		Change at month 6		Adjusted <i>P</i> -value*
	Isoflavone	Placebo	Isoflavone	Placebo	Isoflavone	Placebo	
<i>Verbal and visuospatial memory</i>							
Buschke Selective Reminding Test							
Total of learning trials-words	1.2 (9.1)	-0.5 (4.3)	1.9 (9.0)	1.4 (4.7)	3.1 (7.9)	1.4 (9.3)	0.42
Learning slope-trial 5 vs. trial 1	0.8 (2.2)	-0.2 (2.1)	-0.3 (1.1)	1.1 (2.3)	-0.3 (2.4)	0.1 (1.8)	0.73
Delayed recall-words	0.9 (2.3)	-0.0 (1.5)	0.7 (2.1)	0.1 (1.3)	0.9 (2.0)	-0.2 (1.5)	1.00
Paragraph Recall Test							
Total immediate recall-points	0.4 (15.6)	-3.0 (12.0)	0.9 (9.8)	-0.2 (13.7)	1.3 (14.0)	-1.1 (10.9)	0.51
Total delayed recall-points	-3.0 (15.3)	-4.0 (9.2)	-0.9 (10.0)	3.1 (10.5)	-0.4 (14.0)	-2.0 (10.7)	0.33
Rey Complex Figure Test							
Immediate recall-points	3.9 (4.9)	-2.8 (6.1)	0.9 (4.3)	-0.5 (5.5)	2.1 (6.5)	-1.3 (5.3)	0.00
Delayed recall-points	2.4 (4.4)	-3.1 (4.8)	0.7 (4.9)	0.4 (5.0)	1.1 (5.8)	-0.1 (5.3)	0.00
Visual Spatial Learning Test							
Total correct positions + designs	-2.5 (4.8)	3.1 (7.4)	-0.1 (5.7)	2.7 (7.7)	-1.0 (5.5)	1.1 (5.2)	0.04
Learning slope position + design (trial 5 vs. trial 1)	-0.4 (2.0)	0.6 (2.7)	-0.4 (2.5)	0.5 (2.5)	0.1 (1.4)	-0.3 (2.3)	0.01
Learning slope incorrect designs ^a (trial 5 vs. trial 1)	0.1 (1.6)	0.1 (1.2)	-0.6 (1.6)	0.30 (1.9)	-0.8 (1.8)	0.5 (2.1)	0.00
<i>Language</i>							
Boston Naming (10-item version)							
Number correct	-0.4 (4.2)	0.0 (7.2)	0.0 (5.6)	0.8 (5.0)	-0.4 (4.8)	1.6 (4.8)	1.00
<i>Language fluency</i>							
Fluency							
Letter fluency-total	0.9 (7.9)	-0.4 (7.3)	0.3 (7.3)	1.3 (6.4)	1.1 (9.7)	3.3 (6.2)	0.07
Category fluency-total	0.6 (6.0)	1.3 (9.2)	3.2 (5.9)	-0.2 (7.8)	1.4 (5.8)	-1.9 (5.8)	0.00
<i>Visual-motor function</i>							
Rey Complex Figure Test							
Copy-points	2.3 (3.4)	-1.0 (5.1)	0.1 (2.6)	0.3 (4.1)	0.8 (3.6)	-0.6 (4.9)	0.01
Grooved Pegboard							
Ratio of dominant to non-dominant nand-time ^a	-0.16 (0.5)	-0.03 (0.1)	-0.1 (0.5)	-0.1 (0.2)	-0.23 (0.5)	-0.02 (0.1)	0.04
<i>Executive function</i>							
Stroop Color Word Test							
Color word time ^a	0.3 (5.0)	0.4 (7.2)	-2.1 (5.8)	-3.0 (7.9)	-2.1 (6.5)	-3.5 (5.1)	0.02
Trail Making Test B							
Time to complete ^a	-5.4 (22.4)	10.2 (13.6)	5.6 (24.9)	2.9 (15.0)	-1.2 (18.5)	-5.8 (18.7)	0.01
Mazes							
Time to complete ^a	-21.6 (44.8)	-11.7 (46.1)	-22.1 (59.2)	-15.5 (44.0)	-23.1 (50.6)	-19.3 (48.6)	0.09

^aNegative value suggests improvement.

**P*-values for treatment effect across time were adjusted for age and education.

Buschke Selective Reminding test and Paragraph Recall test, nor on a confrontation naming test, Boston Naming test.

The effect of withdrawal of isoflavones was examined by comparing the performance of the two groups on study medication (month 6) to their performance 2 months after having stopped study medications (month 8). There were no significant between-group differences on any cognitive measure across these two visits.

Discussion

These findings from a randomised controlled clinical study using soy isoflavones (100 mg/day) revealed important factors related to the feasibility of conducting similar studies enrolling older participants. Unlike previous investigations of isoflavone's cognitive effects, our study sample was markedly

older and included both men and women. Plasma genistein and daidzein levels in our study were elevated with daily administration of the dietary supplement. However, confirming earlier reports [13], there was substantial variability in levels achieved even with chronic use of a stable dose, and standardised time for blood collection (4 h post-dosing). While there may be quantification differences between laboratories [26], genistein levels achieved in our study (170–180 nmol/l) were noticeably lower than those obtained in the only other investigation of cognitive effects [12] (615.1 nmol/l) that measured plasma isoflavone levels. Data from this study highlight the need to clarify factors affecting the bioavailability of these compounds as we attempt to understand their cognitive efficacy in older adults.

Another important finding was that none of our older subjects could be characterised as equal producers. This is unexpected based on estimates that 20–25% of adult

Westerners are so-called equol producers [25], but in-line with reports that the proportion of equol producers decreases with age [15]. It has been proposed that equol production in adults is associated with greater effectiveness of soy [27], and that differences in the proportion of equol producers enrolled in various studies could partly explain disparate findings [28]. Our healthy older adults appear less likely to convert daidzein into equol, perhaps due to alterations in gut motility, absorption or kidney clearance. Overall, these findings suggest that older adults using common over-the-counter soy supplements are less likely to demonstrate equol-associated benefits.

Interestingly, our data suggested that the isoflavones, genistein and daidzein, may offer a combination of cognitive effects for older men and women with improvements in the areas of visual-spatial memory, construction, category fluency, speeded dexterity and motor planning. A number of small intervention studies also indicated that administration of isoflavones enhanced cognition [5–10]. In particular, these studies described improvements in cognitive abilities characterised as frontal lobe functions, such as verbal fluency, planning and cognitive flexibility, and on tasks such as mental rotation and other visuospatial skills. Our data partially supported these findings, such that isoflavone-treated subjects showed improvement on a visual construction and memory test, verbal fluency and mazes, an executive function task assessing planning and working memory. Unexpectedly, our data suggested the placebo-treated subjects improved to a greater extent than isoflavone-treated subjects on speeded tests of divided and selective attention. These surprising findings need further clarification. Lastly, our cognitive data were consistent with previous reports finding no enhancement of verbal memory [8, 10].

In contrast to studies suggesting beneficial cognitive effects, three investigations did not find cognitive improvements associated with either soy isoflavone supplementation [12, 29] or soy milk intervention [30]. Differences in participants' characteristics and background diet could contribute to discrepant findings from various studies. The present study differs from previous research on cognitive effects of soy isoflavones in its inclusion of older participants of both sexes. Trials examining the cognitive effects of soy isoflavones have primarily enrolled postmenopausal women in their 50s or 60s. The highly limited data related to age and sex differences in response to soy isoflavone treatment suggest that these exist [9, 10], such that isoflavones may act as phyto-selective oestrogen receptor modulators (phytoSERMs) with both oestrogen-agonist and antagonist actions [31]. Moreover, background diet of all but one of our participants included little or no isoflavones. The individual and combined effect of these factors may affect outcomes by influencing metabolism of an isoflavone intervention. Unfortunately, most studies did not measure plasma levels of isoflavones. Given inter-individual differences in isoflavone metabolism, it is imperative to examine cognitive change in association with estimates of biological exposure to isoflavones.

There are limitations inherent in our small sample size. Consequently, the study was not powered to examine the effect of subject characteristics such as sex and background diet. Rather, these data offer preliminary support for future investigations of this well-tolerated nutritional supplement's influence on cognitive function in older adults. The selection of isolated glycoside isoflavone tablets, as opposed to a whole food intervention, may also be a limitation of the study. The use of an isolate may fail to adequately mimic isoflavones found in whole foods, and thus fail to achieve biologically relevant levels of metabolites. However, considering the feasibility of a dietary intervention in an elderly population, newer *aghycon* supplement formulations may offer reasonable alternatives to whole foods.

These novel data describe the feasibility of a soy isoflavone supplement targeting cognitive outcomes, obtained exclusively from older adults, a growing population likely interested in cognition-enhancing supplements. Our findings revealed that soy isoflavone administration elevated plasma genistein and daidzein, but not equol levels in our older population. Further, our data revealed the necessity of measuring plasma isoflavone levels when conducting intervention trials with older adults, given the variability in genistein and daidzein plasma levels observed with stable dosing. Our data also emphasise the need to clarify factors affecting isoflavone metabolism and equol production in older adults and influencing cognitive efficacy of isoflavones, such as age and gender.

Key points

- A 100 mg/day dose of soy isoflavones was well tolerated in a group of older adults. Soy isoflavone- and placebo-treated subjects exhibited a comparable side-effect profile.
- Plasma levels of genistein and daidzein ($P < 0.001$), but not equol, increased with isoflavone administration in our older subjects.
- Isoflavone-treated subjects improved on tests of visual-spatial memory ($P < 0.01$) and construction ($P = 0.01$), verbal fluency ($P < 0.01$), and speeded dexterity ($P = 0.04$). Placebo-treated participants were faster than isoflavone-treated subjects on two tests of executive function ($P < 0.05$).

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Conflicts of interest

The authors report no financial or other contractual agreements that might cause conflicts of interest or be perceived as causing conflicts of interest.

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Ethical approval

As discussed in the body of the manuscript, all subjects provided informed consent to participate in the study, and the University of Wisconsin's Health Science Institutional Review Board reviewed and approved all procedures, materials and consent forms used when conducting the study.

Supplementary data

Supplementary data are available at *Age and Ageing* online.

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A longitudinal analysis of older Australian women's consultations with complementary and alternative medicine (CAM) practitioners, 1996–2005

JON ADAMS¹, DAVID SIBBRITT², ANNE F. YOUNG³

¹School of Population Health, University of Queensland, Queensland, Australia

²CCEB, University of Newcastle, Newcastle, Australia

³Research Centre for Gender and Health, University of Newcastle, Newcastle, Australia

Address correspondence to: J. Adams. Tel: (+61) 7 336 55116; Fax: (+61) 7 336 55540. Email: jadams@sph.uq.edu.au

Abstract

Objective: to determine the factors associated with complementary and alternative medicine (CAM) use among older Australian women over time.

Methods: a longitudinal analysis of postal questionnaires completed in 1996, 1999, 2002 and 2005 as part of the Australian Longitudinal Study on Women's Health.

Results: the percentage of women who consulted a CAM practitioner in the years 1996, 1999, 2002 and 2005 were 14.6%, 12.1%, 10.9% and 9.9%, respectively. Use of CAM increased as the number of reported symptoms increased and physical health deteriorated, for non-urban residents compared to urban residents.

Conclusion: use of CAM amongst older women appears to be strongly influenced by poor physical health. There is also a suggestion that lack of access to conventional health care providers increases CAM use. There is also an overall decline in the use of CAM among older women as they age.

Keywords: *complementary and alternative medicine, complementary therapies, longitudinal studies, older women, elderly*