
John E. Lewis

JOHN E. LEWIS[1]*, STACY E. CUTRONO[2], ANGELICA B. MELILLO[1], EDUARD TIOZZO[1], JOHANNA LOPEZ[1], SARAH ADWAN[1], LAWRENCE CHEN[1], SUSANNA LEONARD[1], MARK HOWELL[3], JANELLE DIAZ[3], JUDI M. WOOLGER[4], JANET KONEFAL[1], ELAINE PATERSON[5], DAVID BARNES[5]

Corresponding Author*

1. Department of Psychiatry & Behavioral Sciences, University of Miami Miller School of Medicine, 1120 NW 14th Street, Miami, FL, 33136, USA

2. Sylvester Comprehensive Cancer Center/UMHC, University of Miami Miller School of Medicine, 1475 NW 12th Avenue, Miami, FL, 33136, USA

3. UHealth Fitness and Wellness Center, University of Miami Miller School of Medicine, 1120 NW 14th Street, 9th Floor, Miami, FL, 33136, USA

4. Department of Medicine, University of Miami Miller School of Medicine, 1120 NW 14th Street, 9th Floor, Miami, FL, 33136, USA

5. Standard Process, Inc., 1200 W. Royal Lee Drive, Palmyra, WI, 53156, USA

Dietary supplementation on quality of life in adults

KEYWORDS: Dietary supplementation, quality of life, depressive symptoms, ginkgo biloba, elderly adults

Abstract

Background: Declining quality of life (QOL) is increasingly prevalent among the elderly. Certain nutrients may be effective at improving QOL.
Objective: The purpose of this clinical trial was to evaluate (a) Ginkgo Synergy® and Choline and (b) OPC Synergy® and Catalyn,® compared to placebo, on QOL among healthy older adults.
Design: Participants were randomly assigned to one of three groups and followed for 6 months. Outcomes included quality of life, depression, and anxiety.
Results: The Ginkgo Synergy® and Choline arm showed significant improvements on vitality and depressive symptoms.
Conclusion: Our study showed modest effects of a ginkgo biloba and choline-based formula on QOL and mental health. However, the results of the study may not be generalizable to the entire population of healthy older adults, as our sample was predominantly white, non-Hispanic, and well-educated.

INTRODUCTION

In the United States, the elderly population (>65 years of age) is expected to increase by 20%-50% by the year 2030 (1). Aging is usually accompanied with decreasing overall quality of life (QOL) (2), which was defined by the World Health Organization in 1995 as "the individuals' perceptions of their position in life in the context of the culture and value system in which they live, and in relationship to their goals, expectations, and standards" (3).

Conventional Western medicine has not delivered a wholly effective preventative strategy for maintaining physical and mental health among the elderly. Therefore, many consumers have turned to nutritional therapies with total sales of dietary supplements estimated at more than $30 billion in 2010 (4). Interestingly, according to results from the Third National Health and Nutrition Examination Survey conducted between 1988 and 1994, the usage rates among elderly may be even higher (5). Among males and females 60 and older, the rate of dietary supplement use was approximately 42% and 54%, respectively, whereas males and females between 20 and 59 years of age averaged 35% and 47%, respectively. Dietary supplements typically contain a range of bioactive components that are purported to have health benefits and thus impact QOL. For example, ginkgo biloba may impact QOL, but the relationship has not been studied extensively. One study showed significant improvements in QOL in 50 to 65 year-old healthy adults who supplemented with 240 mg/day of a ginkgo biloba extract (EGb 761), as compared to those who took a placebo (6). Another study did not show improvement in QOL in healthy older adults after supplementation with a formula containing 160 mg ginkgo biloba, 68 mg Gotu kola, and 180 mg docosahexaenoic acid taken daily for 4 months (7). However, the baseline SF-36 scores for both the physical and the mental/emotional domains in that study were above average compared to population norms (8), thus reducing the likelihood that QOL scores would improve. Ginkgo biloba also has been reported to have an antidepressant effect (9-10). Thus, given that behavioural symptoms such as depression may negatively affect QOL, ginkgo biloba may affect QOL through its antidepressant effect. Further investigations are warranted to evaluate the benefit of ginkgo biloba supplementation on QOL and mental health.

Other nutrients may also have an impact on QOL. For example, grape seed extract contains high concentrations of flavonoids (11-12), and it has been shown to have antioxidant properties in laboratory studies. Supplementation with 300 mg twice daily lowered total cholesterol and improved inflammatory markers in obese Type 2 diabetics, but the effect on QOL was not evaluated (11). Vitamin D is produced endogenously in response to sun exposure and obtained in the diet, and receptors have been found in numerous tissues throughout the body. Thus, vitamin D supplementation has recently been investigated for its potential impact on depression, fracture prevention, immune function, cardiovascular disease risk, and cognitive function (13-14). A case review found that QOL improved after 3-month supplementation with vitamin D among outpatient veterans with chronic pain (15).

Our study extends the evaluative process of nutritional therapies through a randomized, double-blind, placebo-controlled, clinical trial assessing a regimen of dietary supplements' efficacy and safety in enhancing QOL and mental health in a sample of healthy older persons.

METHODS

Study participants

The study was conducted with the approval of the University of Miami Institutional Review Board for human subjects research, and each subject signed informed consent and HIPAA forms before enrolling in the study. Potential participants (n=144) were identified through referrals from clinical offices and centres at the University of Miami Miller School of Medicine and local community centres in Miami-Dade, Broward, and Palm Beach counties during May 2010 to December 2011. Twenty-three participants failed the screening inclusion and exclusion criteria, and out of 121 eligible participants for the study 97 were enrolled at baseline.

Study Design

Inclusion and exclusion criteria

Potential study candidates were identified as individuals who expressed an interest in a study assessing the efficacy of a dietary supplement on QOL and mental health. Inclusion criteria consisted of: (a) 60 years of age and older (One 58 year-old and three 59 year-old subjects were enrolled, as they were eligible otherwise and expressed an interest to participate.); (b) English speaking; (c) not living in a skilled or intermediate care level nursing facility; (d) no use of similar dietary supplements two weeks before enrolling in the study and during the length of the trial; and (e) a Mini-Mental State Exam (MMSE) score ≥ 23 (16). Exclusion criteria consisted of: (a) a cognitive deficit greater than that indicated according to the MMSE score; (b) a clinical diagnosis of Alzheimer's disease and/or related disorders; (c) a psychiatric diagnosis of schizophrenia, other psychotic disorders, bipolar disorder, major depression with psychotic features, delirium, and alcohol or substance abuse/dependence; (c) bleeding disorders; (d) aphasia or sensory, motor, and/or visual disturbances that would have interfered with psychometric tests; (e) gastrointestinal disorders causing impaired absorption of the study supplements; (f) insulin-dependent diabetes; (g) major conditions such as cardiovascular, pulmonary, renal, thyroid, hepatic, gastrointestinal, or seizure; (h) hematologic or oncologic disorders treated with chemotherapy in the previous two years; (i) active chemotherapy or radiation treatment for cancer; (j) current cigarette smoking; (k) more than three major medical or psychiatric hospitalizations in the past year; (l) diagnosis of a terminal illness; (m) a T score >70 on the Global Severity Index of the Brief Symptoms Inventory (BSI) (17); (n) a score ≥ 29 on the Beck Depression Inventory-II (BDI) (18); (o) prescription and over-the-counter (OTC) sympathomimetic amines and antihistamines within two days of an assessment visit; (p) cognition enhancing drugs such as Donepezil, Rivastigmine, Galantamine, and Tacrine; (q) Coumadin, tricyclic antidepressants, antipsychotics, and anticonvulsants; and (r) participating in a concurrent trial for drugs, dietary supplements, or treatment that affects behaviour.

Screening

Potential subjects were pre-screened for the inclusion and exclusion criteria and given a brief introduction to the nature and purpose of the study. All eligible participants completed the Short Portable Mental Status Questionnaire (SPMSQ) (19) and the Wechsler Memory Scale III Story A (WMS-III-A) (20). Subjects were allowed only two errors on the SPMSQ. Furthermore, if they scored less than 6 points on story A for the WMS-III-A, they were given a second opportunity and had to score a 4 or greater on story B. If all pre-screening criteria were achieved, subjects were then scheduled for the remainder of the screening (MMSE, BSI, and BDI) and the baseline assessment.

Mental status was assessed with the MMSE, the most popular brief cognitive assessment, providing a rapid screen of orientation, registration, attention and calculation, recall, and language domains. Persons who scored 22 or less on the MMSE were excluded from the study, as this implies cognitive impairment in those with more than eight years of education. Participants were also evaluated using the BSI and BDI, respectively, to measure overall stress and depressive symptoms. A T score of >70 on the Global Severity Index on the BSI and a BDI score ≥29 resulted in exclusion from the study.

Baseline assessment and randomization

Participants who passed the screening process and completed the baseline assessment were randomly assigned to one of the three conditions: (a) dietary supplements consisting of Ginkgo Synergy® and Choline, (b) dietary supplements consisting of OPC Synergy® and Catalyn®, or (c) placebo. Assignment of subjects into one of the three treatment groups was accomplished with a computer-generated table of random permutations, designed to balance the number of subjects in each group. The table was prepared in advance and the predetermined list of treatments served to prepare the numbered supplement containers (used in order) and the envelopes to be opened in case of an emergency. All subjects and investigators were blind to the treatment condition, and only the Coordinator of Product Development at Standard Process knew the assignment.

Outcomes and assessments

Each participant completed a basic sociodemographic and medical history questionnaire and reported their list of medications at baseline. The outcome assessments were completed at baseline and 3 and 6 months follow-up. Almost all assessments were performed at either our office at the University of Miami or at a private office in several different community centres. In several cases, we performed assessments at participants' homes for convenience of the participant who had no reliable transportation. The administration of the battery typically required 30 minutes.

Quality of life and mental health measures

Outcomes included QOL, functional status, and symptoms of depression and anxiety. The Medical Outcomes Study Short Form 36 (SF36) was the primary outcome measure and used to assess health-related QOL, as it is arguably the most widely used and validated functional measure. The SF-36 provides eight different scales with a t-score for each scale ranging from 0-100 with higher scores representing greater perceived QOL (21). The Quality of Well-Being Scale (QWBS) is a comprehensive measure of health-related QOL, and it has been extensively used in previous clinical trials. The QWBS is a preference-weighted measure with three different scales of functioning that are

The most attractive isn't always the most extractive.

"Beauty's only skin deep." What's true for people is even more so for natural raw materials like acerola berries. That's why we not only search around the world for the best varieties, we thoroughly test what we find for the highest levels of vitamins and other nutrients. And we keep these levels high throughout the extraction process. Are there easier ways? Probably. But that's not how you get to be a global leader in naturally sourced ingredients.

To discover how our products can help make yours better, we invite you to visit our website: www.nexira.com. Or call us at +33 2 32 831818..

nexira
Innovation Inspired by Nature

Acerola Berry *(Malpighia glabra linne)*

scored from 0.0 (death) to 1.0 (full health) (22). The screening values of the BDI and the Beck Anxiety Inventory (BAI) were used at baseline and were administered again at 3 and 6 months follow-up to assess changes in depressive and anxiety symptoms over the course of the intervention (18-23).

Intervention

For the 6-month intervention period, participants enrolled in the study received: (a) Ginkgo Synergy® (2 capsules/day providing 120 mg/day ginkgo biloba leaf, 80 mg/day ginkgo biloba whole extract, 40 mg/day grape seed extract, Gotu kola leaf (*Centella asiatica)*, dried buckwheat leaf juice, buckwheat seed, and soybean lecithin powder) plus Choline (4 tablets/day providing 700 mg/day), (b) OPC Synergy® (2 capsules/day providing 100 mg/day grape seed extract, 50 mg/day green tea extract [60% catechins], 50 mg/day bilberry fruit (25% anthocyanins), dried buckwheat leaf and juice, green tea leaf powder, and dried carrot root) plus Catalyn® (4 tablets/day providing 312 IU/day vitamin D, 1,600 IU/day vitamin A, 5.3 mg/day vitamin C, 0.3 mg/day thiamine, 0.3 mg/day riboflavin, 1.3 mg/day vitamin B6, defatted wheat germ, carrot (root), calcium lactate, nutritional yeast, bovine adrenal, bovine liver, magnesium citrate, bovine spleen, ovine spleen, bovine kidney, dried pea (vine) juice, dried alfalfa (whole plant) juice, mushroom, oat flour, soybean lecithin, and rice bran), or (c) placebo (cellulose, lactose, and beet powder) provided by the manufacturer (Standard Process, Palmyra, WI). Supplements were given to each participant at the baseline and 3-month follow-up assessments to promote greater compliance. Subjects were not advised to modify eating or physical activity habits or prescription medication use. They were instructed not to consume other dietary supplements containing vitamin B complex nutrients, vitamin E, ginkgo biloba, or any other similar nutrients for two weeks prior to having the baseline assessments and until after the 6-month intervention period. Finally, each subject was compensated $35 per assessment at baseline and 3 and 6 months follow-up.

Statistical analysis

Data were analyzed using SPSS 19 (IBM Inc., Chicago, IL) for Windows. Frequency and descriptive statistics were calculated on all variables. Analysis of variance and chi-square were utilized to determine the presence of differences in background contextual variables by study arm assignment. We utilized linear mixed modelling (LMM) to assess the fixed effect of time by randomization (study arm) on changes in our outcome variables from baseline to 6 months follow-up. If the type III test of the fixed effect of time by randomization was significant, then we used pairwise comparisons to determine the unique differences in effects over time by study arm between baseline and follow-up at 3 and 6 months. LMM with heterogeneous compound symmetry covariance allowed us to account for subject attrition, inter-correlated responses between time points, and non-constant variability. The criterion for statistical significance was $\alpha = 0.05$.

RESULTS

Safety and tolerability

During the entire study period, one subject from the placebo group reported a week of insomnia and heightened energy at night and had to withdraw from the study. A second subject from the Ginkgo Synergy® and Choline study arm reported joint aches that were not alleviated by titrating the dose by 1/3 and then increasing the dose by 1/3 every 3 days. A third subject from the OPC Synergy® and Catalyn® study arm was diagnosed with ulcerative colitis shortly after enrolling in the study, and her physician advised her to stop taking all dietary supplements and withdraw from the study. No other adverse events were reported.

Sociodemographics, health risk, and medication use

Table 1 presents the sociodemographic variables by study arm assignment for age, gender, race/ethnicity, education, and marital status. The sample comprised of 72% females (n=70) and 28% males (n=27) with a mean age of 68.8 years (SD=7.2; R=58, 93). The racial/ethnic distributions of the subjects were as follows: 82.5% white, non-Hispanic (n=80), 15.5% Hispanic (n=15), and 2% black, non-Hispanic (n=2). Only race/ethnicity showed a difference, as more Hispanics were assigned to the Ginkgo Synergy® and Choline study arm ($X2(4)=14.2$, $p<0.01$). The most commonly prevalent diseases and disorders among this sample, including cancer, high blood pressure, thyroid problems, arthritis, depression, and low back pain/herniated disc, were not significantly different by study arm assignment. Table 2 displays the prevalence of current prescription medications and OTC remedies. A higher percentage of subjects in the OPC Synergy® and Catalyn® study arm were taking some type of medication for dyslipidemia or high cholesterol ($X2(2)=6.3$, $p=0.04$). No other proportions were significantly different. Of note, almost 70% of our sample was taking some type of vitamin/mineral dietary supplement.

Outcome variables

On the SF-36, the fixed effects for time, randomization, and time by randomization were non-significant for the physical functioning, role-physical, role-emotional, mental health, and bodily pain scales. For general health, the fixed effect for time ($F[2,119.9]=5.2$, $p<0.01$) was significant, but the effects for randomization and time by randomization were non-significant. For vitality (Figure 1), the time by randomization effect was marginally significant ($F[4,109.4]=2.3$, $p=0.06$). Post-hoc comparisons revealed that the baseline vitality score for the OPC Synergy® and Catalyn® study arm was significantly higher than the Ginkgo Synergy® and Choline arm (mean difference=16.1; SE=5.1; 95% CI: 3.7, 28.5; $p<0.01$). The score at 3 months follow-up for the Ginkgo Synergy® and Choline arm was significantly lower than both the OPC Synergy® and Catalyn® (mean difference=15.2; SE=5.6; 95% CI: 1.6, 28.8; $p<0.05$) and placebo (mean difference=13.4; SE=5.4; 95% CI: 0.3, 26.6; $p<0.05$) study arms. The Ginkgo Synergy® and Choline arm showed a significant improvement from 3 to 6 months follow-up (mean difference=10.4; SE=3.8; 95% CI: 1.1, 19.7; $p<0.05$). The OPC Synergy® and Catalyn® group showed non-significant decreases from baseline to 6 months follow-up, whereas the placebo group essentially stayed flat over the intervention. For social functioning, the time by randomization effect was marginally significant ($F[4,132.9]=2.3$, $p=0.06$). Post-hoc comparisons revealed that the score at 3 months follow-up for the Ginkgo Synergy® and Choline arm was significantly lower than both the OPC Synergy® and Catalyn® (mean difference=13.4; SE=5.1; 95% CI: 1.0, 25.8; $p<0.05$) and placebo (mean difference=13.0; SE=4.9; 95% CI: 1.1, 24.8; $p<0.05$) study arms. The Ginkgo Synergy® and Choline arm significantly worsened at 3 months

Variable	Category	Total Sample (n=97)	(OPC Synergy® + Catalyn®) (n=31)	(Ginkgo Synergy® + Choline) (n=33)	Placebo (n=33)	Statistic
Age	-	M = 68.8 (SD = 7.2; R = 58 , 93)	M = 68.5 (SD = 6.7; R = 59, 83)	M = 67.6 (SD = 6.3; R = 58, 82)	M = 70.3 (SD = 8.3; R= 60, 93)	F(2,96)=1.2, p=0.30
Gender	Male	27 (27.8%)	7 (22.6%)	8 (24.2%)	12 (36.4%)	$X^2(2)=1.3$, p=0.40
	Female	70 (72.2%)	24 (77.4%)	25 (75.8%)	21 (63.6%)	
Race/Ethnicity	White, non-Hispanic	80 (82.5%)	27 (87.1%)	21 (63.6%)	32 (97.0%)	$X^2(4)=14.2$, p<0.01
	Black, non-Hispanic	2 (2.1%)	1 (3.2%)	1 (3.0%)	-	
	Hispanic	15 (15.5%)	3 (9.7%)	11 (33.3%)	1 (3.0%)	
Education	Up to High School	12 (12.4%)	5 (16.1%)	5 (15.2%)	2 (6.1%)	$X^2(6)=11.4$, p=0.08
	Some Post High School Training	34 (35.1%)	11 (35.5%)	12 (36.4%)	11 (33.3%)	
	College Graduate	24 (24.7%)	7 (22.6%)	12 (36.4)	5 (15.2%)	
	Master's Degree or Higher	27 (27.8%)	8 (25.8%)	4 (12.1%)	15 (45.5%)	
Marital Status	Never Married	8 (8.2%)	-	2 (6.1%)	6 (18.2%)	$X^2(6)=9.7$, p=0.14
	Married	49 (50.5%)	16 (51.6%)	15 (45.5%)	18 (54.5%)	
	Widowed	19 (19.6%)	8 (25.8%)	7 (21.2%)	4 (12.1%)	
	Divorced/Separated	21 (21.6%)	7 (22.6%)	9 (27.3%)	5 (15.2%)	

Table 1. Sociodemographic characteristics of the sample
NOTE: M=mean; SD = standard deviation; and R = range

Medication		Category	Total Sample (n=97)	(OPC Synergy® + Catalyn®) (n=31)	(Ginkgo Synergy® + Choline) (n=33)	Placebo (n=33)	Statistic
Current Prescription	Anti-depressant	Yes	11 (11.3%)	6 (19.4%)	1 (3%)	4 (12.1%)	$X^2(2)=4.3$, p=0.12
		No	86 (88.7%)	25 (80.6%)	32 (97%)	29 (87.9%)	
	Beta blocker	Yes	7 (7.2%)	4 (12.9%)	3 (9.1%)	-	$X^2(2)=4.2$, p=0.12
		No	90 (92.8%)	27 (87.1%)	30 (90.1%)	33 (100%)	
	Anti-hypertensive	Yes	25 (25.8%)	9 (29%)	9 (27.3%)	7 (21.2%)	$X^2(2)=0.6$, p=0.75
		No	72 (74.2%)	22 (71%)	24 (72.2%)	26 (78.8%)	
	Anti-hypercholesterol	Yes	11 (11.3%)	7 (22.6%)	1 (3%)	3 (9.1%)	$X^2(2)=6.3$, p=0.04
		No	86 (88.7%)	19 (77.4%)	32 (97%)	30 (90.1%)	
	Laxative	Yes	7 (7.2%)	2 (6.5%)	3 (9.1%)	2 (6.1%)	$X^2(2)=0.3$, p=0.88
		No	90 (92.8%)	29 (93.5%)	30 (90.1%)	31 (93.9%)	
	Insomnia	Yes	10 (10.3%)	3 (9.7%)	4 (12.1%)	3 (9.1%)	$X^2(2)=0.2$, p=0.91
		No	87 (89.7%)	28 (90.3%)	29 (87.9%)	30 (90.1%)	
OTC in the prior week	Aspirin	Yes	33 (34%)	10 (32.3%)	14 (42.4%)	9 (27.3%)	$X^2(2)=1.8$, p=0.42
		No	64 (66%)	21 (67.7%)	19 (57.6%)	24 (72.2%)	
	Tylenol	Yes	34 (35.1%)	12 (38.7%)	13 (39.4%)	9 (27.3%)	$X^2(2)=1.3$, p=0.51
		No	63 (64.9%)	19 (61.3%)	20 (60.6%)	24 (72.2%)	
	Antacid	Yes	13 (13.4%)	6 (19.4%)	5 (15.2%)	2 (6.1%)	$X^2(2)=2.6$, p=0.28
		No	84 (86.6%)	25 (80.6%)	28 (84.8%)	31 (93.9%)	
	Vitamin/Mineral	Yes	67 (69.1%)	21 (67.7%)	25 (75.8%)	21 (63.6%)	$X^2(2)=1.2$, p=0.56
		No	30 (30.9%)	10 (32.3%)	8 (24.2%)	12 (36.4%)	

Table 2. Prevalence of prescription and over-the-counter medication usage

follow-up (mean difference=10.5; SE=3.2; 95% CI: 2.8, 18.3; p<0.01), but improved from 3 to 6 months follow-up (mean difference=10.9; SE=3.6; 95% CI: 2.1, 19.7; p=0.01). The OPC Synergy® and Catalyn® and placebo groups showed non-significant changes over the course of the intervention.

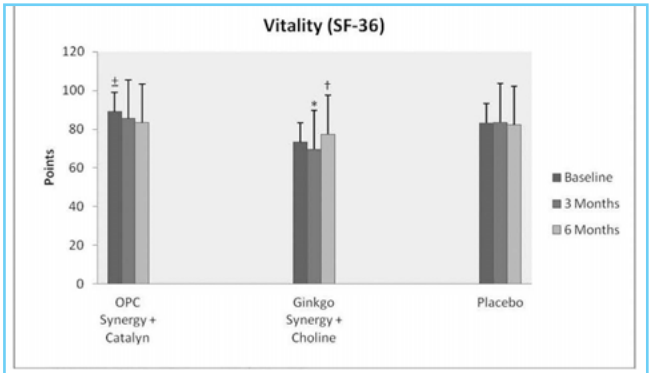


Figure 1. Vitality on the SF-36 at baseline, 3 months, and 6 months
SF-36: The Medical Outcome Study Short Form
†Significantly different from 3 Months within the same group (p=0.05)
±Significantly different from Ginkgo Synergy® + Choline at the same time point (p=0.01)
*Significantly different from OPC Synergy® + Catalyn® and Placebo at the same time point (p=0.05)

For the QWBS, the fixed effects for time, randomization, and time by randomization were non-significant.
For the BDI (see Figure 2), the time by randomization effect was significant (F[4,122.8]=3.6, p<0.01). Post-hoc comparisons revealed that the baseline score for the Ginkgo Synergy® and Choline study arm was significantly higher than the OPC Synergy® and Catalyn® (mean difference=4.6; SE=1.3; 95% CI: 1.5, 7.7; p=0.001) and placebo (mean difference=4.5; SE=1.2; 95% CI: 1.5, 7.5; p=0.001) arms. The score at 3 months follow-up for the Ginkgo Synergy® and Choline arm was significantly higher than the OPC Synergy® and Catalyn® (mean difference=5.1; SE=1.3; 95% CI: 1.9, 8.2; p=0.001) and placebo (mean difference=3.6; SE=1.3; 95% CI: 0.6, 6.7; p<0.05) arms. The Ginkgo Synergy® and Choline arm showed a significant improvement in depressive symptoms from baseline to 6 months follow-up (mean difference=2.2; SE=0.9; 95% CI: 0.1, 4.3; p<0.05) and 3 to 6 months follow-up (mean difference=2.7; SE=0.9; 95% CI: 0.6, 4.7; p<0.01). The OPC Synergy® and Catalyn® and placebo groups showed non-significant increases over the intervention.
For the BAI, the fixed effects for time (F[2,111.5]=4.0, p<0.05) and randomization (F[2,107.0]=4.0, p<0.05) were significant, but the effect for time by randomization was non-significant.

DISCUSSION

In the current study, overall health-related QOL and SF-36 subscales related to mental health, pain, and physical functioning were not impacted by either

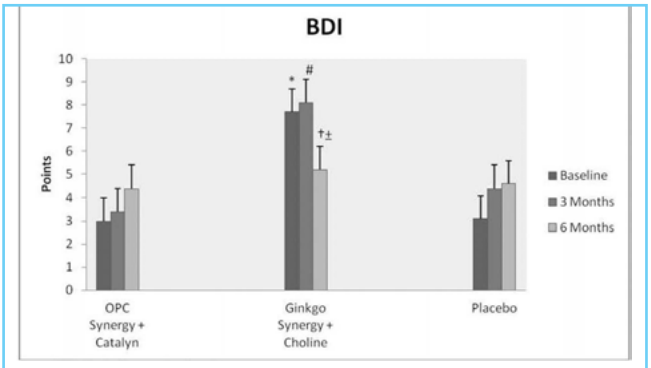


Figure 2. BDI at baseline, 3 months, and 6 months
BDI: Beck Depression Inventory
†Significantly different from Baseline within the same group (p=0.05)
±Significantly different from 3 Months within the same group (p=0.01)
*Significantly different from OPC Synergy® + Catalyn® and Placebo at the same time point (p=0.001)
#Significantly different from OPC Synergy® + Catalyn® and Placebo at the same time point (p=0.001 and p=0.05)

dietary supplement regimen. The Ginkgo Synergy® and Choline arm did show a 10% improvement on the SF-36 vitality scale from 3 to 6 months follow-up, however this was not significantly different from the placebo group at 6 months. Our findings are in agreement with recent studies examining the direct effects of dietary supplementation on QOL. A study examining the effect of a green tea extract in postmenopausal women with osteopenia found no significant changes in any QOL domain after 24 weeks of supplementation (24). Another study found that vitamin D supplementation among oncology patients with bone metastasis did not impact QOL, vitality, physical functioning, or mental health (25).

The Ginkgo Synergy® and Choline group showed a 32% improvement in depressive symptoms, as measured by the BDI from baseline to 6 months follow-up after a non-significant worsening at 3 months. Despite this decrease, depressive symptoms for both the Ginkgo Synergy® and Choline and the OPC Synergy® and Catalyn® groups were not significantly different from the placebo group at 6 months. Our findings are inconsistent with other studies demonstrating improvements in depression and anxiety. A recent study found that 240 mg of ginkgo biloba taken once per day for 24 weeks was beneficial on scores of neuropsychiatric impairment, including apathy and depression/dysphoria, compared to placebo in a sample of adults with mild to moderate dementia (26). In a review of commonly used herbal therapies, ginkgo biloba supplementation was found to improve cognitive function in dementia and Alzheimer's disease (27). Another study showed improvement in ratings of depression and cognition after taking 240 mg of ginkgo biloba for 22 weeks in a sample of adults who met criteria for probable Alzheimer's disease (28). The improvements among individuals in the ginkgo biloba only group were similar to Donepezil mono-therapy or combined ginkgo biloba plus Donepezil. More importantly, in this study both ginkgo biloba intervention arms resulted in fewer side effects compared to Donepezil alone. Thus, the authors concluded that consumers may prefer the combination of alternative approaches with standard care because of fewer side effects (28).

Limitations

Several limitations should be noted in the current investigation. We enrolled a predominantly white, non-Hispanic, well-educated sample, so our results may not be generalizable to persons of different racial/ethnic backgrounds and/or with limited education. Furthermore, our findings may be restricted by the length of the intervention, given that QOL and mental health changes may take longer than 6 months to occur. With the elevated baseline scores in QOL, we may also have enrolled a "very healthy" sample that was less sensitive to changes in dietary supplementation. Our subjects were instructed not to take dietary supplements with the same nutrients contained in the intervention formulae during the 6 months of the study. However, 70% of our subjects were taking dietary supplements, which may have interfered with our results. Inconsistencies in the findings of our study versus others, particularly for ginkgo biloba, could be due to dose, plant form, extract strength, and other associated production and quality factors. Finally, the findings of our study are also potentially limited by a small sample size in each study arm.

CONCLUSIONS

The formulae used in the current study were well-tolerated among all subjects, as is typically reported in the literature. The Ginkgo Synergy® and Choline group displayed an improvement in depressive symptoms as measured by the BDI, however the OPC Synergy® and Catalyn® study group (containing antioxidants and B vitamins) was less effective. A high-quality, concentrated dietary supplement formula (gingko biloba and choline) may offer an opportunity for healthy older adults to improve depressive symptoms; however additional research is needed in a larger, more diverse population.

ACKNOWLEDGEMENTS

We are thankful to all of the volunteers who participated in this study. JEL, ABM, ET, LC, SL, MH, JD, JMW, JK, DB, and EP contributed to the design of the study. JEL, ABM, ET, LC, SL, MH, JD, JMW, and JK contributed to the collection and analysis of the data. JEL, SC, ET, SA, JL, LC, JK, DB, and EP contributed to the writing of the article. JEL had primary responsibility for final content. All authors read and approved the final manuscript.

JK has received income as a distributor of Standard Process products. JEL, SC, ABM, ET, SA, JL, LC, SL, MH, JD, and JMW have no conflicts of interest to report. DB and EP were employees of Standard Process at the time of study execution.

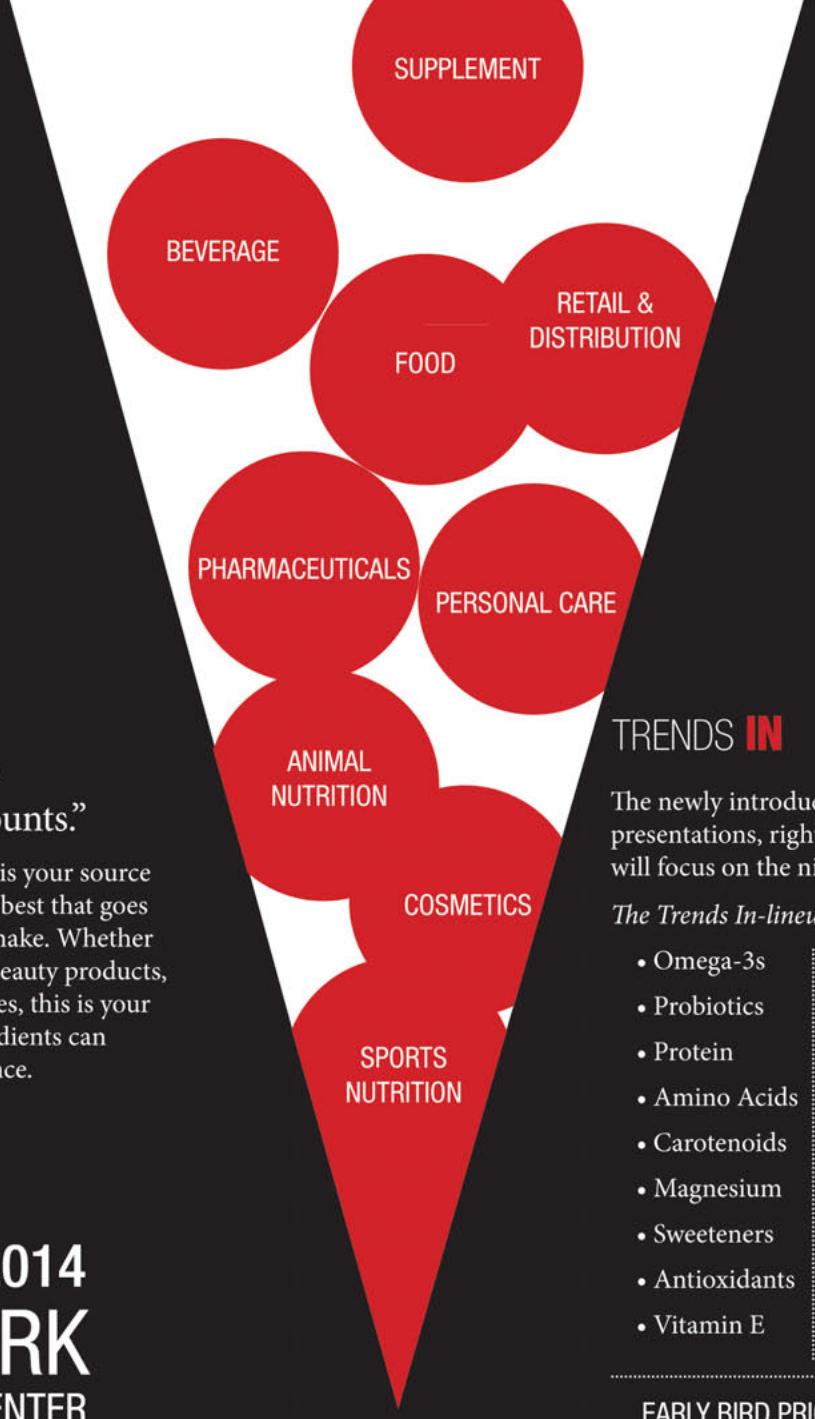
Sources of support: This work was funded by a grant from Standard Process, Inc.

Clinicaltrials.gov ID: NCT01672359

REFERENCES

1. Federal Interagency Forum on Aging-Related Statistics, *Older Americans 2004: Key indicators of well-being,* U.S. Government Printing Office, Washington, DC, (2004).
2. Williams A., *Measuring the quality of life of the elderly,* in *Public economics and the quality of life*, Edited by Evans, A., Wingo, L., Eds.; Johns Hopkins University Press, Baltimore, pp 282-297.(1977).
3. World Health Organization, *World Health Organization Quality of Life-100,* World Health Organization, Division of Mental Health, Geneva, (1995).
4. Nutrition Business Journal, *Nutrition Business Journal Supplement Business Report 2010,* Pendon Media, Inc., Cleveland, OH, (2010).
5. Centers for Disease Control and Prevention: http://www.cdc.gov/nchs/data/nhanes/databriefs/dietary.pdf National health and nutrition examination survey III: Use of dietary supplements. (last checked on April 17 2012).
6. Cieza A., Maier P., Poppel E., Effects of Ginkgo biloba on mental functioning in healthy volunteers, *Arch Med Res,* **34(5)**, 373-381 (2003).
7. Carlson J. J., Farquhar J. W., DiNucci E., Ausserer L., Zehnder J., Miller D., Berra K., Hagerty L., Haskell W. L., Safety and efficacy of a ginkgo biloba-containing dietary supplement on cognitive function, quality of life, and platelet function in healthy, cognitively intact older adults, *J Am Diet Assoc,* **107(3)**, 422-432 (2007).
8. Stewart A. L., Hays R. D., Ware J. E., Jr., The MOS short-form general health survey. Reliability and validity in a patient population, *Med Care,* **26(7)**, 724-735 (1988).
9. Sakakibara H., Ishida K., Grundmann O., Nakajima J., Seo S., Butterweck V., Minami Y., Saito S., Kawai Y., Nakaya Y., Terao

J., Antidepressant effect of extracts from Ginkgo biloba leaves in behavioral models, *Biol Pharm Bull,* **29(8)**, 1767-1770 (2006).
10. Rojas P., Serrano-Garcia N., Medina-Campos O. N., Pedraza-Chaverri J., Ogren S. O., Rojas C., Antidepressant-like effect of a Ginkgo biloba extract (EGb761) in the mouse forced swimming test: role of oxidative stress, *Neurochem Int,* **59(5)**, 628-636 (2011).
11. Kar P., Laight D., Rooprai H. K., Shaw K. M., Cummings M., Effects of grape seed extract in Type 2 diabetic subjects at high cardiovascular risk: a double blind randomized placebo controlled trial examining metabolic markers, vascular tone, inflammation, oxidative stress and insulin sensitivity, *Diabet Med,* **26(5)**, 526-531 (2009).
12. Feringa H. H., Laskey D. A., Dickson J. E., Coleman C. I., The effect of grape seed extract on cardiovascular risk markers: a meta-analysis of randomized controlled trials, *J Am Diet Assoc,* **111(8)**, 1173-1181 (2011).
13. Li G., Mbuagbaw L., Samaan Z., Zhang S., Adachi J. D., Papaioannou A., Thabane L., Efficacy of vitamin D supplementation in depression in adults: a systematic review protocol, *Syst Rev,* **2**, 64 (2013).
14. Pludowski P., Holick M. F., Pilz S., Wagner C. L., Hollis B. W., Grant W. B., Shoenfeld Y., Lerchbaum E., Llewellyn D. J., Kienreich K., Soni M., Vitamin D effects on musculoskeletal health, immunity, autoimmunity, cardiovascular disease, cancer, fertility, pregnancy, dementia and mortality-a review of recent evidence, *Autoimmun Rev,* **12(10)**, 976-989 (2013).
15. Huang W., Shah S., Long Q., Crankshaw A. K., Tangpricha V., Improvement of pain, sleep, and quality of life in chronic pain patients with vitamin D supplementation, *Clin J Pain,* **29(4)**, 341-347 (2013).
16. Folstein M. F., Folstein S. E., McHugh P. R., "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician, *J Psychiatr Res,* **12(3)**, 189-198 (1975).
17. Derogatis L. R., Melisaratos N., The brief symptom inventory: An introductory report, *Psychological Medicine,* **13**, 595-605 (1983).
18. Beck A. T., Steer R. A., Brown G. K., *Manual for Beck depression inventory-II,* Psychological Corporation, San Antonio, Texas, (1996).
19. Pfeiffer R. I., A short portable mental status questionnaire for the assessment of organic brain deficit in elderly patients, *Journal of American Geriatrics Society,* **23**, 433-441 (1975).
20. Wechsler D., *The Wechsler memory scale-revised,* The Psychological Corporation, NY, (1987).
21. Ware J. E., Jr., Sherbourne C. D., The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection, *Med Care,* **30(6)**, 473-483 (1992).
22. Kaplan R. M., An outcomes-based model for directing decisions in women's health care, *Clin Obstet Gynecol,* **37(1)**, 192-206 (1994).
23. Beck A. T., Steer R. A., *Beck anxiety inventory manual,* Harcourt Brace and Company, San Antonio, (1993).
24. Shen C. L., Chyu M. C., Pence B. C., Yeh J. K., Zhang Y., Felton C. K., Doctolero S., Wang J. S., Green tea polyphenols supplementation and Tai Chi exercise for postmenopausal osteopenic women: safety and quality of life report, *BMC Complement Altern Med,* **10**, 76 (2010).
25. Segal E., Felder S., Haim N., Yoffe-Sheinman H., Peer A., Wollner M., Shen-Or Z., Ish-Shalom S., Vitamin D deficiency in oncology patients--an ignored condition: impact on hypocalcemia and quality of life, *Isr Med Assoc J,* **14(10)**, 607-612 (2012).
26. Bachinskaya N., Hoerr R., Ihl R., Alleviating neuropsychiatric symptoms in dementia: the effects of Ginkgo biloba extract EGb 761. Findings from a randomized controlled trial, *Neuropsychiatr Dis Treat,* **7**, 209-215 (2011).
27. Ernst E., The risk-benefit profile of commonly used herbal therapies: Ginkgo, St. John's Wort, Ginseng, Echinacea, Saw Palmetto, and Kava, *Ann Intern Med,* **136(1)**, 42-53 (2002).
28. Yancheva S., Ihl R., Nikolova G., Panayotov P., Schlaefke S., Hoerr R., Ginkgo biloba extract EGb 761(R), donepezil or both combined in the treatment of Alzheimer's disease with neuropsychiatric features: a randomised, double-blind, exploratory trial, *Aging Ment Health,* **13(2)**, 183-190 (2009).



As the saying goes,
"it's what's on the inside that counts."

Ingredient Marketplace is your source to learn more about the best that goes into whatever it is you make. Whether it's pharmaceuticals or beauty products, supplements or beverages, this is your chance to see why ingredients can make a world of difference.

Get an inside look at Ingredient Marketplace. Register today!

JUNE 2-3, 2014
NEW YORK
JACOB JAVITS CENTER

TRENDS IN

The newly introduced **Trends In** presentations, right on the expo hall floor, will focus on the nine hottest ingredients.

The Trends In-lineup includes:

- Omega-3s
- Probiotics
- Protein
- Amino Acids
- Carotenoids
- Magnesium
- Sweeteners
- Antioxidants
- Vitamin E

$99 *good thru 4/25/2014*

The Marketplace Pass is now an all-inclusive package that includes: 2- day expo hall access, Trends In, featured speaker address, Drinks on Us reception and Ingredient IQ.

EARLY BIRD PRICING ENDS APRIL 25

iM™
INGREDIENTMARKETPLACE
a SupplySide Event

What's Inside Matters

supplysideshow.com