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FULL COMMUNICATION

Short-Term Study on the Effects of Rosemary on Cognitive Function in an Elderly Population

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ABSTRACT Rosemary (*Rosmarinus officinalis* L.) has traditional reputations that justify investigation for a potential role in reducing widespread cognitive decline in the elderly. A randomized, placebo-controlled, double-blinded, repeated-measures cross-over study was conducted to investigate possible acute effects of dried rosemary leaf powder on cognitive performance. Twenty-eight older adults (mean age, 75 years) were tested using the Cognitive Drug Research computerized assessment system 1, 2.5, 4, and 6 hours following a placebo and four different doses of rosemary. Doses were counterbalanced, and there was a 7-day washout between visits. There was a biphasic dose-dependent effect in measures of speed of memory: the lowest dose (750 mg) of rosemary had a statistically significant beneficial effect compared with placebo ($P = .01$), whereas the highest dose (6,000 mg) had a significant impairing effect ($P < .01$). There were significant deleterious effects on other measures of cognitive performance, although these were less consistent. Speed of memory is a potentially useful predictor of cognitive function during aging. The positive effect of the dose nearest normal culinary consumption points to the value of further work on effects of low doses over the longer term.

KEY WORDS: • ***acute effects*** • ***clinical trial*** • ***cognitive*** • ***memory*** • ***rosemary*** • **Rosmarinus**

INTRODUCTION

REDUCED COGNITIVE FACULTIES are a frequent consequence of aging and a major threat to quality of life. Anticholinesterase and other drug treatments are available for cognitive decline;[1] however, their potential cognitive benefits are not necessarily apparent in older subjects, and some such drugs have been shown to promote negative neurocognitive effects in this age group.[1,2]

Traditional plant-based remedies have long-standing reputations for supporting healthy aging, and recent investigations have examined the potential for cognitive enhancement of such medicines.[3–9] A recent meta-analysis of 13 randomized controlled trials into herbal interventions for dementia concluded that herbal medicines were more effective than placebo and at least equivalent to conventional therapies on common cognitive performance outcome measures.[10] Additional studies have focused on cognitive changes brought about by herbal intervention in healthy older adults (*e.g.*, for *Bacopa monnieri*,[11] *Ginkgo biloba*,[12–14] *Centella asiatica*,[15] and cranberry juice[16]). Several investigations have been conducted into members of the mint family (Lamiaceae),[17] including lemon balm (*Melissa officinalis*),[18,19] sage (*Salvia officinalis*, *Salvia lavandulaefolia*),[20–22] lavender (*Lavandula angustifolia*),[23] and rosemary (*Rosmarinus officinalis*).[23]

Rosemary (*R. officinalis* L., Family Lamiaceae) is native to the Mediterranean region, where the ancient Greeks revered it for stimulating the brain and assisting memory;[24] Dioscorides wrote of rosemary: ''the eating of its flower in a preserve comforts the brain, the heart and the stomach; sharpens understanding, restores lost memory, awakens the mind, and in sum is a healthy remedy for various cold ailments of the head and the stomach.'' Rosemary has Generally Recognized as Safe status in the United States and is widely used as a culinary herb. Extracts of rosemary and its dried leaf are also available as ''dietary supplements.''

Rosemary contains an essential oil (0.6–2%) of varying composition (three main chemotypes are found growing in Europe). The major constituents of the essential oil are 1,8-cineole, α-pinene, camphor, borneol, and carvacrol, but the exact composition can vary between individual samples and time of harvest.[25–27] Other constituents include phenolic diterpenes, flavones, the caffeic acid derivative rosmarinic acid, and the triterpene ursolic acid.[28,29]

In experimental studies, rosemary extracts were shown to possess potent radical scavenging activity.[26,30] The diterpenes carnosol and carnosic acid are thought to be the major antioxidant components,[26,27] although antioxidant properties have also been reported for several other

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constituents, including rosmarinic acid.[31–34] *In vitro* studies with rosemary extracts have demonstrated acetylcholinesterase inhibition,[8,35] butyrylcholinesterase inhibition,[36] and a protective effect on dopaminergic neurons.[37]

Using mouse models an antidepressant effect of rosemary has been identified, apparently mediated by an interaction with the monoaminergic system.[38] There are antinociceptive effects in animals[39] inhibited by naloxone pretreatment[40]—suggesting interaction with the endogenous endorphin system, as well as antispasmodic effects on tracheal smooth muscle.[41]

There are few clinical studies on the effects of rosemary. In a randomized study of 140 healthy young adults, inhalation of rosemary oil enhanced feeling of alertness and cognitive functions as evaluated using the Cognitive Drug Research (CDR) test battery used in the current study.[22] In a separate study the aroma of rosemary oil increased performance in exam students while increasing free radical scavenging activity and reducing cortisol levels.[42] However, to date there are no clinical studies on cognitive performance following ingestion of rosemary.

MATERIALS AND METHODS

The current study was a randomized, placebo-controlled, double-blinded, repeated-measures, crossover study investigating acute effects of dried rosemary (*R. officinalis* L.) leaves on cognitive performance in older adults, using a battery of tests provided by the CDR.[43] Because the acute effects of rosemary were being explored, doses higher than normally consumed in the diet were applied. Additionally, the crude rosemary powder was used in a dietary formulation rather than a pharmaceutical extract to retain the pharmacokinetic profile of ordinary culinary consumption.

Subjects

Twenty-eight subjects (eight men, 20 women) were recruited via local media and networking. They were nonsmokers between 65 and 90 years (mean, 75 years) in a stable state of health with no confounding medications and able to complete the computerized battery tests on laptop computers. Ethical approval was obtained from the Institutional Review Board of Tai Sophia Institute (Laurel, MD, USA). This study complied with current guidelines for Good Clinical Practice guidance issued by the U.S. Food and Drug Administration to protect human subjects of research and the Ethical Principles for Medical Research Involving Human Subjects adopted in the World Medical Association Declaration of Helsinki.

Treatments

The test substance consisted of 100% powdered rosemary (*R. officinalis* L.) originating from Turkey and supplied by McCormick & Co. (Hunt Valley, MD, USA). Authentication was performed by Dr. Arthur Tucker at Delaware State University (Dover, DE, USA) based on macro- and microscopic features. Seven constituents were characterized and quantified applying gas chromatographic and mass spectrometric methods modified from those of Razboršek *et al*.[44] Hydrodistillation of the rosemary sample yielded 1.4% volatile oil, consisting of 1,8-cineole (0.57%), borneol (0.14%), and α-pinene (0.13%) as the major components. In addition, key nonvolatile compounds were quantified, including rosmarinic acid (1.45% wt/wt), carnosic acid (1.73%), and ursolic acid (2.89%).

The powdered rosemary was added to a commercial tomato juice (Campbell's [Camden, NJ, USA] low sodium). Subjects on each study day received a single 16-ounce (458-mL) drink of reduced sodium tomato juice containing (in decreasing order of weight) water, tomato concentrate, potassium chloride, vitamin C (ascorbic acid), citric acid, salt, flavoring, and malic acid. Total oxygen radical absorbance capacity per serving was calculated as 10,782 μmol of Trolox equivalents, and the content of total phenolics was 299 mg of gallic acid equivalents. Each 458 mL of juice additionally contained one of the following doses of rosemary: (1) no rosemary (placebo; see below); (2) 750 mg of dried rosemary; (3) 1,500 mg of dried rosemary; (4) 3,000 mg of dried rosemary; or (5) 6,000 mg of dried rosemary. A third party prepared, codified, and delivered the treatments to participants. Masking was achieved by the use of opaque containers with black drinking straws and by chilling the drink.

Placebo consisted of the tomato juice as described above. To confound distinction further between the treated and untreated tomato juice, each dose was co-administered with colored methylcellulose-filled capsules. Subjects were informed that these capsules could be part of the treatment.

Cognitive measures

A battery of tasks from the CDR System was administered. Parallel forms of the tasks were performed at different sessions to reduce practice effect on repeated assessment. The information in all tasks was presented on the screen of a notebook computer, and with the exception of the written word recall tasks the responses were recorded via a response module containing ''NO'' and ''YES'' buttons. The battery took about 25 minutes to perform (Table 1 contains brief descriptions [see, for example, Tildesley *et al*.[20] for details]). The individual task outcomes from the battery were collapsed into five cognitive ''factors,'' as recommended by CDR following their derivation by factor analysis[43] (Fig. 1). Two of these factors concern attention: ''power of attention'' (sometimes called ''speed of attention'') reflects the ability to focus attention, whereas continuity of attention (or ''accuracy of attention') reflects the ability to sustain attention. ''Quality of working memory'' reflects the ability to successfully hold numeric and spatial information temporarily in working memory, whereas ''quality of episodic memory'' reflects the ability to store, hold, and subsequently retrieve verbal and non-verbal information in long-term (episodic) memory. ''Speed of memory'' reflects the time taken to successfully retrieve information from both working and episodic memory.

Mood measures

Mood was assessed using the Bond–Lader visual analog scales.[45] These consist of 16 100-mm lines anchored by

Table 1. Cognitive Drug Research Tests

Tests were administered in the following order:

- **Word Presentation:** A list of words is presented for the subject to remember.
- **Immediate Word Recall:** Immediately after the last word is presented, the subject is given 1 minute to write as many of the words as possible on a sheet of paper.
- **Picture Presentation:** A series of pictures for the subject to remember is presented.
- **Simple Reaction Time:** The subject is instructed to press the ''YES'' response button, as quickly as possible, every time the word ''YES'' is presented.
- **Digit Vigilance:** A target digit is pseudo-randomly selected and constantly displayed to the right of the screen. A series of digits is then presented in the center of the screen. The subject is required to press the ''YES'' button as quickly as possible every time a digit in the series matches the target digit.
- **Choice Reaction Time:** The subject is required to respond to the words ''YES'' and ''NO'' as they appear by pressing the corresponding button as quickly as possible.
- **Spatial Working Memory:** A picture of a house is presented on the screen with four of the nine windows lit. The subject is asked to memorize the position of the lit windows. For each of the subsequent presentations of the house, the subject is asked to decide whether or not the single window that is lit had been lit in the original presentation. The subject responds by pressing the corresponding ''YES'' or ''NO'' button, as appropriate, as quickly as possible.
- **Numeric Working Memory:** A series of digits is presented for the subject to hold in memory. This is followed by a series of probe digits, for each of which the subject has to decide whether it had appeared in the original series and press the corresponding ''YES'' or ''NO'' response button as quickly as possible.
- **Delayed Word Recall:** The subject is again given 1 minute to write as many of the words as possible in any order on a sheet of paper.
- **Word Recognition:** The original words from Word Presentation plus distractor words are presented, one at a time, in a randomized order. For each word, the subject is required to indicate whether he or she recognizes it from the original list of words by pressing the corresponding ''YES'' or ''NO'' button as quickly as possible.
- **Picture Recognition:** The original pictures from Picture Presentation plus distractor pictures are presented, one at a time. For each picture, the subject is required to indicate whether he or she recognizes it from the original series by pressing the corresponding ''YES'' or ''NO'' button as quickly as possible.
- **Bond-Lader Visual Analogue Scales of Mood and Alertness:** For this computerized questionnaire scale, the subject is required to rate how he or she feels ''at this moment.''[45]

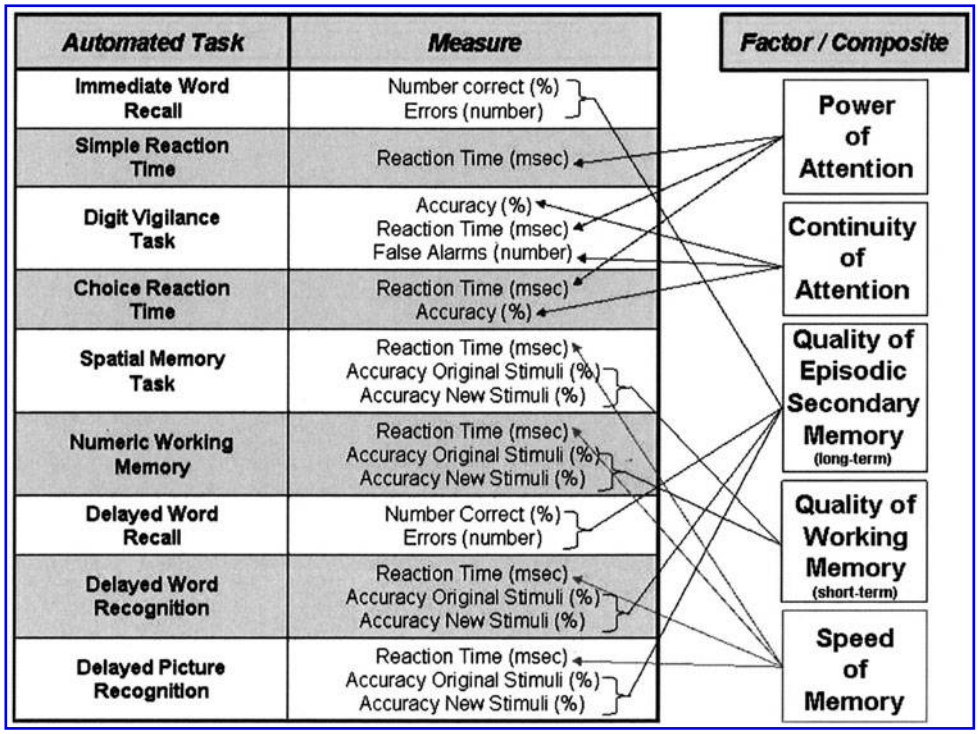

FIG. 1. Derivation of cognitive factors from the Cognitive Drug Research battery outcomes.

antonyms (*e.g.*, ''clearheaded–muzzy''), which are combined to derive three mood factors of alert, calm, and content. The Bond–Lader Visual Analogue Scales were presented by computer.

Procedure

The tests were performed under experimenter supervision on five separate 1-day treatment sessions every week for 5 weeks following a practice day. The order of intervention on the five study visits was determined by random allocation. Each study day comprised five identical testing sessions: a pre-dose testing session to establish baseline performance for that day, followed immediately by the allocated intervention and assessments at 1, 2.5, 4, and 6 hours following consumption. Subjects were asked to refrain from alcohol at least 12 hours prior to assessments on these days.

Data treatment and statistics

Changes from baseline scores for the treatments were computed for each cognitive measure, at each time point. These data were subjected to a general linear mixed-model analysis of covariance with terms fitted to the model for treatment (6,000 mg, 3,000 mg, 1,500 mg, 750 mg, 0 mg), day (Day 1, Day 2, Day 3, Day 4, and Day 5), visit (diff 1, diff 2, diff 4, diff 6), treatment × visit, and participant. A ''repeated-measures'' analysis of covariance was conducted using SAS PROC MIXED (SAS Institute, Cary, NC, USA). Using the baseline on each study day as a covariate allowed control for differences between subjects. Statistical significance was set at a value of $P < .05$, whereas $P < .01$ was set as highly significant.

RESULTS

Of the total 28 participants who began the study, one was asked to leave because of concerns about a preexisting medical condition. There were no other dropouts.

There was a main effect of treatment for ''speed of memory'' measures ($F_{4,96} = 7.19$, $P < .0001$) that was dose-specific. At 750 mg there was a significant improvement ($P = .01$), and at 6,000 mg there was a significant impairment ($P < .01$), compared with placebo. All treatments including placebo showed a significant impairment compared with baseline except the 750-mg dose, which showed negligible difference from baseline.

''Continuity of attention'' was significantly impaired at 1,500 ($P < .001$), 3,000 ($P = .04$), and 6,000 mg ($P < .001$) doses, and ''quality of working memory'' was significantly impaired at 750 ($P = .02$), 1,500 ($P = .01$), and 6,000 mg ($P = .01$), in both cases compared with placebo. However, the differences are much smaller when compared with baseline. There were no effects for the ''power of attention'' and ''quality of episodic secondary memory'' scores (Table 2 and Fig. 2).

For the self-ratings of mood and alertness, all scores including placebo were reduced from baseline as the testing day progressed. Of note was a significant improvement at 750 mg in alertness ($P = .01$) compared with placebo, whereas at 6,000 mg there was the opposite effect indicating decreased alertness compared with placebo ($P = .02$). This finding suggests a biphasic dose–response curve similar to that observed for the speed of memory factor (Table 3).

Table 2. Composite Scores for Effects of *R. officinalis* Powder on Five Cognitive Factors

Cognitive factor	*Dose*	*Composite score**	*SE*	P *value*
Power of attention (milliseconds)	750 mg	−18.493	10.650	.085
	1,500 mg	3.818	10.225	.709
	3,000 mg	6.902	10.917	.528
	6,000 mg	3.657	10.534	.729
Continuity of attention (score)	750 mg	−1.016	0.643	.117
	1,500 mg	−2.230	0.618	<.001
	3,000 mg	−1.376	0.658	.039
	6,000 mg	−2.363	0.637	<.001
Speed of memory (milliseconds)	750 mg	−231.920	91.204	.012
	1,500 mg	−96.826	87.592	.271
	3,000 mg	29.130	93.453	.755
	6,000 mg	253.830	91.390	.006
Quality of working memory (score)	750 mg	−0.157	0.065	.018
	1,500 mg	−0.167	0.063	.009
	3,000 mg	−0.098	0.067	.144
	6,000 mg	−0.169	0.065	.011
Quality of episodic memory (score)	750 mg	1.998	6.271	.750
	1,500 mg	−9.140	5.992	.131
	3,000 mg	−8.567	6.240	.174
	6,000 mg	−1.695	5.928	.775

Means averaged across time points are presented with SEs and *P* values associated with main effects of treatment.

*All scores are differences from placebo.

The mixed analysis of covariance showed there was no correlation between treatment and time in any of these findings. A further analysis was carried out to explore whether there was any global order effect. Some orders were identified, but the counterbalancing ensured they did not contribute to the study results.

There were no serious adverse events recorded in placebo or treatment groups during the study.

DISCUSSION

This study clearly demonstrates significant dose-specific effects of rosemary on ''speed of memory'' compared with placebo: positive for the lowest dose (750 mg) but negative at the highest dose tested (6,000 mg). Moreover, when compared with baseline the 750-mg dose appears to counter the impairments that occur under placebo, possibly due to fatigue. The fact that subjects at this dose subjectively reported significantly less impairment to their alertness compared with placebo strengthens the findings, particularly as there is research suggesting that mood is an underlying driver of cognitive function.[46]

Several rosemary doses produced impairment of the ''continuity of attention'' and ''quality of working memory'' factors, but none of these effects was dose specific. The mechanisms underlying these effects are not known.

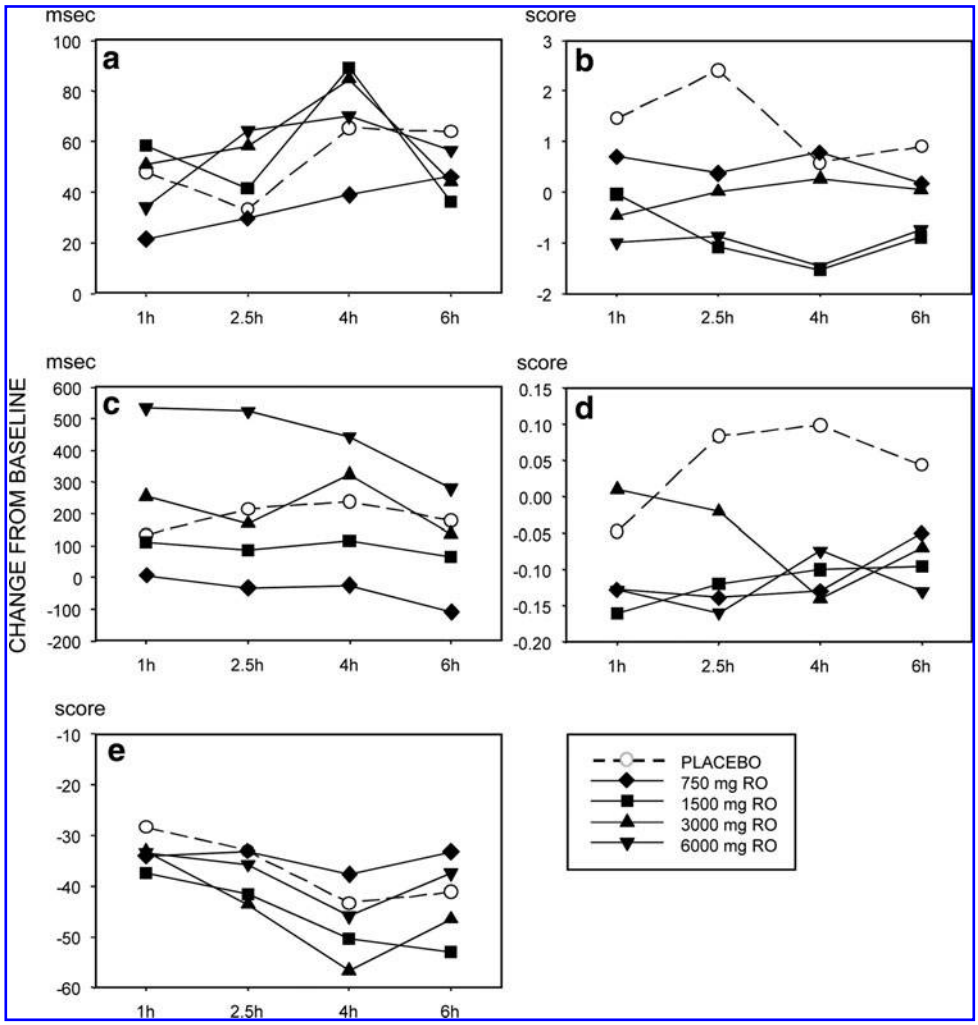

FIG. 2. Effects of *R. officinalis* (rosemary [RO]) powder (750, 1,500, 3,000, and 6,000 mg) and placebo on cognitive factors derived from Cognitive Drug Research battery scores. Mean changes from baseline are shown for (**a**) power of attention, (**b**) continuity of attention, (**c**) speed of memory, (**d**) working memory, and (**e**) secondary memory.

However, the preparation is rich in bioactive constituents, including the monoterpenoids α-pinene, 1,8-cineole, and borneol. A recently characterized extract of *S. officinalis* (sage) with both anticholinesterase and memory-enhancing properties contained these same constituents.[46] Additionally, ursolic acid, rosmarinic acid, and carnosic acid found in rosemary are bioavailable and have characterized physiological effects that may influence cognitive functioning. The presence of multiple potentially psychoactive components is also likely to underlie the complex dose–response relationships observed in the current study.[47,48]

Quality of working memory differed from speed of memory, which is interesting in light of evidence suggesting that decreased processing speed is responsible for impaired working memory and skill acquisition in older adults, possibly contributing to age-related decline in overall intelligence.[49–53] Rodríguez-Sánchez *et al.*[53] cited many reports demonstrating links between reduced speed of processing and cognitive dysfunction with impaired declarative or working memory in normal aging, traumatic brain injury, depression, and Parkinson's disease. There are two functional components of human working memory: short-term working memory and long-term working memory. Short-term working memory involves actively updating and manipulating representations, switching and dividing attention between tasks, selection of relevant information, and inhibition of irrelevant information.[54–59] Short-term working memory also encodes information so that this can be retrieved from long-term working memory. If encoding speed is not rapid enough, a person may lose information and not be able to retrieve memories from long-term working memory,[60] with a possible overall memory deficit for both short and long term and a potential decline in overall intelligence.[51,57] If decreased processing speed is responsible for impaired working memory, skill acquisition, and overall cognitive performance in older adults as is reinforced by other research,[49–51,61] then any potential to improve such processing speed warrants attention. The present study's finding for improvements in speed of memory at the 750-mg dosage merits further investigation at this and lower dosage levels.

Limitations of the study

The activity of the placebo dose is notable in all the results. The tomato juice vehicle was chosen as a means of

Table 3. Acute Cognitive Effects of *R. officinalis* Powder on Bond–Lader Mood Scale Factor Scores: "Alert," "Content," and "Calm"

Measure	*Dose*	*Score*	*SE*	P *value*
Alert	750 mg	4.061	1.619	.014
	1,500 mg	0.017	1.553	.991
	3,000 mg	−2.018	1.66	.227
	6,000 mg	−3.689	1.574	.021
Content	750 mg	1.267	1.238	.309
	1,500 mg	1.525	1.878	.202
	3,000 mg	0.546	1.269	.668
	6,000 mg	−0.294	1.204	.807
Calm	750 mg	2.779	2.207	.211
	1,500 mg	1.761	2.118	.408
	3,000 mg	2.499	2.262	.272
	6,000 mg	3.553	2.149	.105

The values represent mean change from placebo for each treatment.

delivering relatively high doses of crude rosemary powder in culinary form. However, the results suggest the combination of fluid consumption and constituents within the tomato juice were unexpectedly active. There is evidence that fluid intake may impair or improve short-term cognitive performance.[62]

The population examined was not typical of the elderly U.S. population, with education levels as well as baseline scores on the cognitive tests above the average. When coupled with the documented tendency for "participant self-selection," where volunteers in studies of this nature are likely to be healthier, more socioeconomically advantaged, and more highly motivated compared with their peers, the application of the results to broader populations is reduced.[63]

The short-term nature of the study does not address the real world impact of regular consumption of rosemary. It is not known whether regular consumption will lead to brain adaptation or cumulative benefits. Only longer-term studies will clarify whether regular consumption of rosemary enhances, diminishes, or shows no variation from the short-term effects on cognition.

Finally, several participants were able to detect taste differences. Subsequent analyses, however, showed no consistent impact of this detection, and the addition of placebo capsules to the food-based preparation may have countered this effect.

In conclusion, rosemary powder at the dose nearest normal culinary consumption demonstrated positive effects on speed of memory—a potentially useful predictor of cognitive function during aging. The result points to the value of future studies on effects of low doses of rosemary on memory and cognition over the longer term.

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AUTHOR DISCLOSURE STATEMENT

K.W. is an employee of United BioSource Corporation. A.P., J.S., S.Y.M., A.S., and L.R.B. declare no competing financial interests exist.

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