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Salvia lavandulaefolia (Spanish Sage) enhances memory in healthy young volunteers

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Abstract

Sage (*Salvia*) has a longstanding reputation in British herbal encyclopaedias as an agent that enhances memory, although there is little evidence regarding the efficacy of sage from systematized trials. Based on known pharmacokinetic and binding properties, it was hypothesised that acute administration of sage would enhance memory in young adult volunteers. Two experiments utilised a placebo-controlled, double-blind, balanced, crossover methodology. In Trial 1, 20 participants received 50, 100 and 150 μl of a standardised essential oil extract of *Salvia lavandulaefolia* and placebo. In Trial 2, 24 participants received 25 and 50 μl of a standardised essential oil extract of *S. lavandulaefolia* and placebo. Doses were separated by a 7-day washout period with treatment order determined by Latin squares. Assessment was undertaken using the Cognitive Drug Research computerised test battery prior to treatment and 1, 2.5, 4 and 6 h thereafter. The primary outcome measures were immediate and delayed word recall.

The 50 μl dose of *Salvia* essential oil significantly improved immediate word recall in both studies. These results represent the first systematic evidence that *Salvia* is capable of acute modulation of cognition in healthy young adults.

Keywords: *Salvia*; Sage; Acute effects; Cholinergic; Memory

1. Introduction

Phytochemicals have been widely used in Chinese and Ayurvedic cultures for many years to restore declining cognitive functions (Mantle et al., 2000). More recently, the efficacy of active compounds derived from European and Oriental medicinal plants is being explored as possible treatments for dementia, particularly Alzheimer's disease (AD) (Perry et al., 1999; Wake et al., 2000; Mantle et al., 2000). These include *Ginkgo biloba* (ginkolides) (Le Bars et al., 1997), *Panax ginseng* (ginsenosides) (D'Angelo et al., 1986; Caso Marasco et al., 1996), nicotine as derived from *Nicotiana tobaccum* (White and Levin, 1999), *Huperzia serrata* (huperzine) (Zangara, this issue) and *Galanthus nivalis* (galanthamine) (Raskind et al., 2000).

Historically, several European herbs have been used for memory enhancement or "strengthening the brain" (Gerard, 1597, in Jackson, 1876). Although most have not been researched pharmacologically, many prescriptions used in Chinese herbal medicines include *Salvia* species for the treatment of disorders such as depression, epilepsy and age-related memory loss (Cho et al., 1994; Chung et al., 1994; Dhawan, 1994; Okugawa et al., 1996; Su et al., 1994).

Acetylcholine has a functional role in key cognitive functions including learning and memory, arousal and attentional processes (Rusted et al., 2000). The anticholinesterase activity of essential oils and extracts of *Salvia officinalis* and *S. lavandulaefolia* has been previously demonstrated in vivo (Perry et al., 1997, 2002) and in human postmortem brain tissue (Perry et al., 1996). Oral adminis-

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tration of the essential oil of *S. lavandulaefolia* to young rats has been shown to result in AChE inhibition in selected brain areas. Compared to the control group, there was a significant decrease in AChE activity in the striatum but not the hippocampus at the lower dose. At the higher dose, there was a significant decrease in AChE activity in both the striatum and the hippocampus (Perry et al., 1997, 2002). The ability of *S. lavandulaefolia* to inhibit the activity of AChE in the hippocampus is consistent with the reported memory-enhancing properties of sage. It is also of potential significance in improving cognitive function in AD as this area plays a major role in memory processing and is severely affected in the disorder.

Salvia is also reported as having antioxidant (Mantle et al., 2000), oestrogenic (Tyler, 1993; Duke, 1985; Planchon and Bretin, 1946; Reynolds, 1996; Birge, 1997; Silva et al., 2001) and anti-inflammatory properties (Tyler, 1993), and these actions are also considered to be of potential value in AD therapy.

Improvements on cognition following single doses of cholinesterase inhibitors have also been demonstrated (Almkvist et al., 2001). Patients with mild AD received either 40 mg of tacrine or placebo and were assessed for visuospatial ability, episodic memory and attention. Significant improvements were found for measures of attention for those receiving tacrine compared to placebo. It follows that a starting point for demonstrating efficacy of cognitive enhancing agents is in normal human subjects. In our laboratory, a series of such studies have been conducted into the potential cognitive enhancing properties of *G. biloba*, *P. ginseng*, a gingko/ginseng combination, and *Melissa officinalis* (Kennedy et al., 2000, 2001a,b, 2002a,b, in press; Scholey and Kennedy, 2002). The cognitive effects of sage in a controlled study of normal individuals have not previously been reported. The aim of this study was to investigate the acute cognitive effects of *Salvia* in a cohort of healthy young volunteers.

S. lavandulaefolia and *S. officinalis* have similar compositions with the exception of the thujone content. *S. officinalis* has a much higher concentration of thujone which is toxic in large doses (Leung and Foster, 1996), so it has been suggested that *S. lavandulaefolia* may be a more suitable treatment (Mantle et al., 2000). Following the in vitro and in vivo work reported above, the essential oil of *S. lavandulaefolia* was selected for this study.

2. Materials and methods

This investigation formed part of a comprehensive assessment of the acute cognitive effects of *S. lavandulaefolia*. Placebo-controlled, double-blind methodology was used involving multi-dose, multiple-testing time regimes with a 7-day washout between doses. This design is similar to that used in the Kennedy series (Kennedy et al., 2000, 2001a,b, 2002a,b; Scholey and Kennedy, 2002).

The study involved two consecutive trials involving different, overlapping dose ranges and was approved by the Joint Ethics Committee of Newcastle and North Tyneside Health Authority. Prior to participation, each volunteer signed an informed consent form and completed a medical health questionnaire. This included questions regarding high blood pressure and the possibility of pregnancy, since there is some evidence that sage is contraindicated for both of these conditions (Bartram, 1998; Pages et al., 1992; Fournier et al., 1993). All participants self-reported that they were in good health and were taking no medication with the exception, for some female volunteers, of the contraceptive pill. Heavy smokers (>10 cigarettes/day) were excluded from the study. Of the 44 participants, only 7 were light social smokers and they agreed to abstain from smoking before and during testing sessions. All participants abstained from caffeine-containing products and alcohol throughout each study day. They were allowed a light breakfast and lunch in order to maintain ecological validity and to minimise any deprivation effects.

2.1. Participants

2.1.1. Trial 1

Eighteen female and two male undergraduate volunteers (mean age, 19.7 years; range, 18–31) were recruited through opportunity sampling at Northumbria University.

2.1.2. Trial 2

Sixteen female and eight male undergraduate volunteers (mean age, 23.21 years; range, 18–37), recruited as in Trial 1, took part in Trial 2.

2.2. Cognitive measures

Simple word recall was the core cognitive measure utilised. This is one of the most readily identifiable aspects of cognitive function which has implications for everyday functions and is severely impaired in AD. This assessment forms part of the Cognitive Drug Research computerised assessment battery. The instrument has been used in over 500 European and North American drug trials and has been shown to be sensitive to cognitive improvements (Moss et al., 1998; Scholey et al., 1999) and to changes in cognition with a wide variety of drug treatments (e.g., Ebert et al., 1998; O'Neill et al., 1995).

A tailored version of the battery, similar to that which has previously been found to be sensitive to improved cognitive function as a consequence of ingestion of both *G. biloba* (Wesnes et al., 1987; Kennedy et al., 2000) and a ginkgo/ginseng combination (Wesnes et al., 1997; Kennedy et al., 2001a,b), was used. Computer-controlled word presentation was administered with parallel forms of the tests being presented at each testing session. Presentation was via VGA colour monitors and all responses were recorded via pencil and paper. This paper focuses on word recall from the

two trials; results from other outcomes are reported elsewhere (Tildesley et al., under review).

Tests were administered in the following order:

Word presentation: Fifteen common English words were presented in sequence on the monitor for the participant to remember. The words were matched for linguistic frequency and concreteness. Stimulus duration was 1 s, as was the interstimulus interval.

Immediate word recall: The participant was allowed 60 s to write down as many of the words as possible. The task was scored as number correct, errors, and intrusions and the resulting score was converted into a percentage.

Delayed word recall: Twenty minutes after the word presentation, the participant was again given 60 s to write down as many of the words as possible. The percentage score was computed as for immediate word recall.

2.3. Treatments

2.3.1. Capsules

Capsules containing *S. lavandulaefolia* essential oil combined with sunflower oil or sunflower oil alone were prepared by Powerhealth (10 Central Avenue, Pocklington, York) using standardised essential oil purchased in June 2000 from Baldwins (171–173 Walworth Rd, London).

GCMS was performed by the Scottish Agricultural Council, Auchincruive, Scotland, and the terpene constituents were as follows (%): α-pinene, 6.5; camphene, 6.3; β-pinene, 5.4; myrlene, 1.9; limonene, 1.2; 1,8-cineole, 25.8; camphor, 24.4; caryophyllene, 1.2; terpinen-4-OL, 2.0; borneol, 3.3; α-terpineol, 2.8.

In addition, inhibition of acetylcholinesterase was determined using bovine enzyme and a modified version of the Ellman method using a 96-well microplate (Perry et al., 2000a,b). The IC_{50} for *S. lavandulaefolia* essential oil was 0.07 mg/ml (Fig. 1).

2.3.2. Trial 1

On each study day participants received four capsules of identical appearance, each containing either an inert placebo (100 μl of sunflower oil) or 50 μl of *S. lavandulaefolia* essential oil (+50 μl sunflower oil). The double-blind pseudorandomisation design of this study corresponded to each participant receiving a dose of either 0 (placebo), 50 μl, 100 μl, or 150 μl of *S. lavandulaefolia* essential oil on each visit.

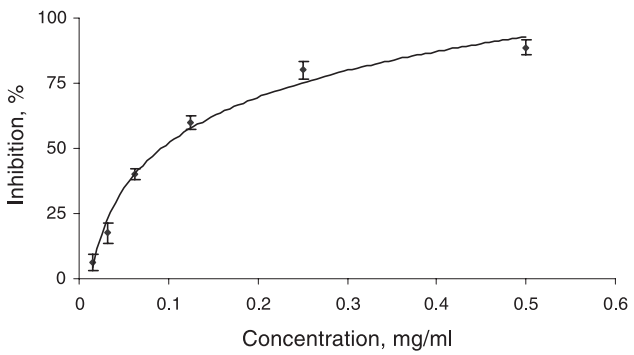

Fig. 1. Inhibition of bovine acetylcholinesterase by *S. lavandulaefolia* essential oil.

2.3.3. Trial 2

This followed similar methodology to Trial 1 except that the treatments were placebo or active doses of 25 and 50 μl of *S. lavandulaefolia* essential oil.

2.4. Procedure

Each participant was required to attend a total of five (Trial 1) or four (Trial 2) study days. Testing days were conducted 7 days apart to ensure a sufficient washout between conditions. The half-life of *S. lavandulaefolia* essential oil and its constituents is not known so this interval was chosen to err on the side of caution. Additionally, the counterbalanced nature of the design would essentially negate any carry-over effects. Testing took place in a suite of laboratories with participants visually isolated from each other.

On arrival at their first session, participants were randomly allocated to a treatment regime using a Latin square design that counterbalanced the order of treatments across the four active days of Trial 1 or the three visits of Trial 2. The first day was identical to the following four, except that no treatment (active or placebo) was administered to allow familiarisation with the test battery and procedure. Data from the five sessions of this practice day were not included in any analysis.

Each study day comprised five identical testing sessions. The first was a pre-dose testing session that established baseline performance for that day and was immediately followed by the day's treatment on Visits 2 to 5. Further testing sessions began at 1, 2.5, 4 and 6 h following consumption of the day's treatment. Each testing session included completion of the immediate and delayed word recall tasks.

2.5. Statistics

Immediate word recall and delayed word recall scores were analysed as "change from baseline" using the Minitab statistical package. The initial analysis was made using repeated-measures analysis of variance. Following the recommendations of Keppel (1991), the omnibus F test was eschewed in favour of planned comparisons being made between the placebo and the different doses of *Salvia* at each time point utilising t tests with the mean squares for "Dose × Time × Subjects" as an error term. To ensure the overall protection level, all testing was two tailed and only probabilities associated with preplanned comparisons were calculated (Keppel, 1991).

3. Results

3.1. Trial 1: S. lavandulaefolia (50, 100 and 150 μl)

One participant dropped out of the study (for reasons unrelated to any aspect of the study), and data from this subject were not analysed. There were a number of significant time- and dose-specific changes following two of the active doses of *Salvia*. Planned comparisons of the change from baseline data revealed that administration of the 50 and 100 μl doses of *Salvia* resulted in increases in the percentage of words recalled on the immediate word recall in comparison to placebo (Table 1a). This effect was significant following 50 μl at 1 h [$t(162) = 2.02$, $P < .05$], 2.5 h [$t(162) = 3.75$, $P < .0005$] and 100 μl at 2.5 h [$t(162) = 2.43$, $P < .05$]. There was no significant effect of the 150 μl dose on immediate word recall.

For the delayed word recall, a significant increase in the number of words recalled compared to placebo was evident for the 50 μl dose at 1 h [$t(162) = 2.32$, $P < .05$] and 2.5 h time points [$t(162) = 4.16$, $P < .0001$]. A significant increase in the percentage number of words recalled was also found for the 100 μl dose at the 2.5 h session [$t(162) = 2.92$, $P < .01$]. Again there was no significant effect on delayed word recall following administration of the 150 μl dose.

3.2. Trial 2: S. lavandulaefolia (25 and 50 μl)

There were a number of significant time- and dose-specific changes following the active doses of *Salvia*. Planned comparisons of the change from baseline data revealed that administration of the 50 μl dose of *Salvia* resulted in a significant increase in the percentage number of words recalled during the immediate word recall task (Table 1b). This effect was evident following 50 μl [$t(138) = 2.05$, $P < .05$] at 1 and 4 h [$t(138) = 2.00$, $P < .05$] post-dose. No significant effect was evident for the 25 μl dose, although there was a trend for improved immediate recall 1 h post-dose [$t(138)$ 1.96, $P = .051$]. For the delayed word recall, no significant changes compared to placebo were found for either of the active doses of *Salvia*, although there was a trend towards improved delayed recall following the 25 μl dose at 1 h [$t(138) = 1.82$, $P = .072$] and for the 50 μl dose at 4 h post-dose [$(132) = 1.94$, $P = .053$].

4. Discussion

The results of the current study indicate that ingestion of single doses of *S. lavandulaefolia* can enhance memory in a dose-dependent manner in healthy young adults. The most striking effect was on immediate word recall. In Trial 1, memory performance was enhanced for the 50 μl dose at 1 and 2.5 h time points. The effect was also apparent following administration of the 100 μl dose at 2.5 h post-dose sessions. A dose-specific enhancement on delayed word recall was also observed for the 50 μl dose at 1 and 2.5 h post-dose. In Trial 2, the immediate word recall effect at 1 h was maintained, and this was coupled with improved memory performance at 4 h post-dose testing session for the same dose. No significant enhancement on either immediate or delayed word recall was found for either the lowest

Table 1
Effects of *S. lavandulaefolia* essential oil (25, 50, 100 and 150 μl) and placebo on immediate and delayed word recall in (a) Trial 1 and (b) Trial 2

	Treatment	Pre-dose baseline	Post-dose change from baseline			
			1 h	2.5 h	4 h	6 h
(a) Trial 1						
Immediate word recall	Placebo	56.14 (3.73)	− 7.37 (3.40)	− 9.47 (3.56)	− 7.72 (4.69)	− 7.19 (3.74)
(% correct)	50 μl	50.18 (2.19)	**0.35 (2.06)** *	**3.51 (3.31)** * * *	− 2.81 (2.13)	− 5.26 (3.06)
	100 μl	53.16 (3.45)	− 3.68 (3.66)	**− 1.05 (3.76)** *	− 7.37 (3.05)	− 8.59 (4.44)
	150 μl	52.81 (2.62)	− 3.16 (3.96)	− 10.00 (3.62)	− 3.51 (3.30)	− 4.91 (4.83)
Delayed word recall	Placebo	42.63 (3.90)	11.23 (2.35)	− 16.32 (2.91)	− 14.21 (3.36)	− 17.02 (2.69)
(% correct)	50 μl	34.21 (3.12)	**− 2.81 (2.46)** *	**− 1.58 (3.12)** * * * *	− 8.25 (3.65)	− 11.75 (4.39)
	100 μl	37.37 (3.57)	− 11.05 (3.10)	**− 5.97 (3.41)** * *	− 12.46 (3.46)	− 17.89 (3.74)
	150 μl	38.95 (3.10)	− 12.98 (5.66)	− 10.88 (3.20)	− 7.54 (3.09)	− 13.33 (4.31)
(b) Trial 2						
Immediate word recall	Placebo	51.53 (3.73)	− 9.86 (3.31)	− 5.28 (3.37)	− 10.83 (4.19)	− 4.72 (2.05)
(% correct)	25 μl	50.00 (3.80)	− 3.06 (2.07)	− 8.06 (2.78)	− 5.83 (3.30)	− 9.58 (3.32)
	50 μl	48.55 (3.22)	**− 2.08 (3.26)** *	− 1.67 (3.09)	**− 3.89 (2.40)** *	− 5.14 (2.76)
Delayed word recall	Placebo	37.36 (3.71)	− 12.08 (3.05)	− 8.47 (3.12)	− 14.86 (3.98)	− 11.25 (2.56)
(% correct)	25 μl	34.72 (4.01)	− 6.39 (3.51)	− 10.28 (3.54)	− 11.39 (3.83)	− 12.92 (3.57)
	50 μl	35.83 (3.43)	− 8.47 (2.86)	− 12.64 (3.11)	− 8.75 (4.00)	− 12.22 (4.02)

Mean percentage recall scores are depicted for baseline and change from baseline with standard errors in parentheses. Significant changes are rendered in boldface.

* $P < .05$, compared with the corresponding placebo score.

** $P < .01$, compared with the corresponding placebo score.

*** $P < .001$, compared with the corresponding placebo score.

**** $P < .0001$, compared with the corresponding placebo score.

(25 μl) or the highest (150 μl) doses of *Salvia*. Given that drug enhancement of cognitive function is often fragile, we regard these data as providing fairly consistent evidence that *Salvia* has memory-enhancing potential. In keeping with the long history of safe usage, there were no adverse reactions reported here. This increases the potential of *Salvia* as a treatment for dementia given the side effects of current prescription cholinesterase inhibitors.

The two studies reported here used placebo-controlled, double-blind, crossover methodology, which we consider to be the most effective design for addressing the potential for plant extracts to modulate mood and cognitive function. Nevertheless, there exists a remote possibility that participants may have been able to detect *Salvia* in the active treatments and modify their behaviour accordingly. No participant commented on any aspect of flavour or odour, but systematic data were not recorded regarding this aspect of the study. However, this possibility seems extremely unlikely given the fact that the most effective dose was 50 μl in both studies. This was the highest dose in Trial 2 and the lowest dose in Trial 1, meaning that participants would have been able to modifying their behaviour based on nonpharmacological properties of the capsules in a dose-specific manner. The memory-enhancing dose is highly (though not completely) consistent between the two trials. In Trial 1, the pattern of memory enhancement follows the classic ''inverted U''-shaped dose–response curve characteristic of many psychopharmacological agents. In the case of the extract employed here, this may be the result of increasing doses of one, several or many agents having complex additive, negating or synergistic effects upon the neural substrates underlying memory performance.

It is worth noting that the baseline scores for the 50 μl treatment were the lowest of all treatments (although not significantly so). It is possible that this dose was most effective due to chance poorer performance on the days in which participants received this optimum dose. The balanced nature of the design makes this doubtful. However, further research might usefully address the intriguing possibility that *Salvia* might be most effective in enhancing cognition in situations where baseline performance is low.

In conclusion, these findings thus provide support for the reputation of *Salvia* as a memory enhancer (Gerard, 1597, in Jackson, 1876; Hill, 1755). The demonstration of anticholinesterase inhibition here (Fig. 1) is consistent with previous reports. Evidence of such activity of essential oil of *S. lavandulaefolia* in human brain tissue has been demonstrated both in vitro and in vivo (Perry et al., 1996, 1997). In vivo oral administration of oil of *Salvia* inhibits AChE in selected brain areas in rats (Perry et al., 1997). As acetylcholine is vital to cognitive functions including learning and memory, it is possible that the memory enhancement evident from the results of this study is due to the anticholinesterase properties of *Salvia*, although given the rich pharmacology of *Salvia* that includes many other mechanisms of potential value, further mechanistic studies are needed.

The primary symptom of AD is a loss of memory. The encouraging memory-enhancing properties of *Salvia* in this acute administration paradigm and the favourable pharmacological profile suggest that *Salvia* is potentially a novel therapeutic treatment for AD. Placebo-controlled trials in this patient population are indicated as are trials in non-demented elderly and those with mild cognitive impairment. There is also the potential to compare different extracts, e.g. essential oil, as in the present study with whole leaf extracts and alternative species other than *S. lavandulaefolia* need to be explored.

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