Attenuation of Laboratory-Induced Stress in Humans After Acute Administration of *Melissa officinalis* (Lemon Balm)

David O. Kennedy, Bsc, PhD, Wendy Little, Bsc, and Andrew B. Scholey, Bsc, PhD

Objective: *Melissa officinalis* (lemon balm) is contemporaneously used as a mild sedative and/or calming agent. Although recent research has demonstrated modulation of mood in keeping with these roles, no studies to date have directly investigated the effects of this herbal medication on laboratory-induced psychological stress. **Methods:** In this double-blind, placebo-controlled, randomized, balanced crossover experiment, 18 healthy volunteers received two separate single doses of a standardized *M. officinalis* extract (300 mg, 600 mg) and a placebo, on separate days separated by a 7-day washout period. Modulation of mood was assessed during predose and 1-hour postdose completions of a 20-minute version of the Defined Intensity Stressor Simulation (DISS) battery. Cognitive performance on the four concurrent tasks of the battery was also assessed. **Results:** The results showed that the 600-mg dose of Melissa ameliorated the negative mood effects of the DISS, with significantly increased self-ratings of calmness and reduced self-ratings of alertness. In addition, a significant increase in the speed of mathematical processing, with no reduction in accuracy, was observed after ingestion of the 300-mg dose. **Conclusion:** These results suggest that the potential for *M. officinalis* to mitigate the effects of stress deserves further investigation. **Key words:** acute effects, *Melissa officinalis*, lemon balm, stress, mood.

DISS = Defined Intensity Stressor Simulation.

INTRODUCTION

The perennial lemon scented herb *Melissa officinalis* (lemon balm) has been in use as a pancultural medicinal treatment for more than 2 millennia. Its traditional indications have included administration for its general beneficial effects on the brain, as a treatment for memory disorders (1), and for "all complaints supposed to proceed from a disordered state of the nervous system'' (2). Contemporary reports emphasize the sedative, spasmolytic, and antibacterial effects of *M. officinalis*, with indications encompassing nervous disorders, gastrointestinal disorders, and sleep disturbance (3–5).

Melissa is most commonly sold over the counter in combination with other herbs, most notably *Valeriana officinalis* (valerian) (6,7). This combination has been shown to improve the sleep quality of healthy normal sleepers (8), and to have an effect on sleep parameters in poor sleepers similar to that of 0.125 mg of triazolam (9). Several studies in rodents have also suggested a mildly sedative effect of *M. officinalis* alone, with observations of a reduction in spontaneous movement in mice after administration of both the volatile oil of *M. officinalis* as well as the isolated terpenes (10) and a reduction in behavioral parameters in mice after the administration of a hydroalcoholic extract of *M. officinalis* (11). A single, double-blind, placebo-controlled study also assessed the behavioral effects of *M. officinalis* aromatherapy in a group of patients suffering from severe dementia. In comparison to placebo a significant reduction in agitation and social withdrawal, and an increase in constructive activities resulted from the 4-week treatment with essential oil (12).

Although the mechanisms of action of Melissa are poorly understood, it has been suggested that the active components of extracts made from the leaves include monoterpenoid aldehydes, flavonoids, polyphenolic compounds including rosmarinic acid (13), and monoterpene glycosides (14). These components may well underlie a number of effects seen in vitro, which include potent antioxidant properties (15,16) and an affinity for binding to both nicotinic and muscarinic receptors in human brain cortex tissue (17). The latter mechanism is of specific interest as modulation of the cholinergic system may well be beneficial to cognitive function, most particularly in conditions, such as Alzheimer's disease, that feature cholinergic dysregulation.

Given the potential for extracts of *M. officinalis* to interact with the cholinergic system, two recent studies from our own laboratories have assessed both cholinergic receptor binding and the cognitive and mood effects of single doses of *M. officinalis* in healthy humans. In the first of these double-blind, placebo-controlled, balanced-crossover studies (18), three separate single doses of a concentrated commercial *M. officinalis* extract (300 mg, 600 mg, 900 mg; Pharmaton S.A., Lugano, Switzerland) plus a placebo were administered in a counterbalanced manner to 20 participants, with a 7-day washout period between testing days. The most notable result of this experiment was a striking dose-dependent impairment in accuracy across a number of timed, computerized memory tasks. Mood was also modulated, with participants' self-ratings of calmness, as assessed with Bond-Lader mood scales, increasing for the lowest dose (300 mg), whereas "alertness" was decreased for the highest, and cognitively most deleterious, dose (900 mg). Although this pattern of results is broadly in line with the contemporary role of *M. officinalis* as a mild sedative, it is not in keeping with beneficial modulation of cholinergic activity. Indeed, the subsequent in vitro analysis of the extract showed that it did not exhibit the expected cholinergic receptor binding properties, with negligible displacement of [^{3}H]-(*N*)-nicotine from nicotinic receptors, and comparatively low displacement of [^{3}H]-(*N*)-scopolamine from muscarinic receptors in human brain tissue. The second investigation (19), therefore, extended this line of research by initially screening a number of dried leaf samples for cholinergic binding, with a dried leaf with both substantial nicotinic and muscarinic binding properties being taken forward into

From the Human Cognitive Neuroscience Unit, Division of Psychology, University of Northumbria, Newcastle upon Tyne, NE1 8ST UK.

Address correspondence and reprint requests to David O. Kennedy, Human Cognitive Neuroscience Unit, Division of Psychology, University of Northumbria, Newcastle upon Tyne NE1 8ST, UK. E-mail: david.kennedy@unn.ac.uk

Received for publication November 6, 2003; revision received February 2, 2004.

DOI: 10.1097/01.psy.0000132877.72833.71

0033-3174/04/6604-0607

the behavioral assessment. In this instance, decrements were seen on the same memory tasks as the previous experiment, but these reduced with increasing dose of dried leaf. The highest dose (1,600 mg) was overwhelmingly beneficial, with improved accuracy seen on immediate and delayed word recall tasks. Both the highest and middle (1,000 mg) doses also again led to significantly increased self-ratings of calmness. Although cognitive (and particularly memory) improvement was restricted to the *M. officinalis* with cholinergic receptor binding properties, both the methanolic extract (18) and the dried leaf (19) led to increased calmness. This suggests that this robust modulation reflects the working of another, as yet unidentified, mechanism.

In this preliminary, double-blind, placebo-controlled, balanced-crossover study, the calming properties of *M. officinalis* were examined further with an assessment of its ability to modulate performance and mood during mild, laboratory-induced, psychological stress at 1 hour after treatment (mood effects were detected at this time point in both of the previous investigations). The effects of single doses (300 mg and 600 mg) of the previously utilized (18) noncholinergic, methanolic *M. officinalis* extract on mood and cognitive performance were assessed while participants completed the Defined Intensity Stressor Simulation (DISS) computerized battery. The DISS has previously been shown to increase negative ratings of mood and engender physiological responses concomitant with increased stress (20,21).

MATERIALS AND METHODS

Participants

Ten males and eight females (mean age = 29.11 years, SD = 6.81) took part in the study, which was approved by the Ethics Committee of the Psychology Division of Northumbria University and was carried out in accordance with the Declaration of Helsinki. Participants comprised an unpaid opportunity sample of undergraduates from the University of Northumbria. Before taking part in the study, participants signed an informed consent form and completed a medical health questionnaire. All participants reported that they were in good health, were not taking any recreational or prescription drugs, with the exception of oral contraceptive pills, and were nonsmokers. Participants refrained from consuming any caffeine-containing products for a minimum of 2 hours, and alcohol for a minimum of 12 hours before each testing session. Participants were tested individually in laboratory conditions.

Before the experiment, a power analysis (22) suggested that, for the intended within-subjects analysis and alpha level of 0.05, the sample size of 18 would have an 80% chance of detecting an effect size (0.6) similar to that seen in the previous investigations of the mood effects of *M. officinalis* (18,19).

Treatments

An encapsulated, standardized, commercial extract of *M. officinalis* prepared by Pharmaton SA (Lugano, Switzerland) was utilized in the current study. The production method involves dried leaves of *M. officinalis* being reduced to fragments and extracted up to exhaustion in a 30:70 methanol–water mixture. The resultant liquid extract is evaporated and homogenized to yield a soft extract, to which inert processing agents (dried glucose syrup and colloidal anhydrous silicon dioxide to 7% and 3% of the final dried weight respectively) are added. This mixture is homogenized and taken to dryness, ground, mixed, and sieved.

On each study day, participants received four capsules of identical appearance, each containing either an inert placebo or 150 mg of *M. officinalis* extract. Depending on the condition to which they were allocated on that particular day the combination corresponded to a dose of either 0 mg (placebo), 300 mg, or 600 mg of *M. officinalis* extract. Blinding of the treatments for the study was undertaken by a disinterested third party. After completion of each testing session participants were asked whether they had formed any opinion as to the nature of the day's treatment.

Materials

The Defined Intensity Stressor Simulation (DISS) Computerized Battery

The DISS computerized battery (Stress-Sim Ltd, The Coach House, Plymouth, www.stress-sim.co.uk) comprises a set of four concurrent cognitive and psychomotor tasks presented via a split screen. This newly developed instrument was chosen for several reasons. It has the advantage over other laboratory stressors of being both automated (thus essentially eliminating experimenter effects) and drawing on random stimuli for each test, allowing for multiple testing sessions of the same participant. All responses are made with an external mouse. In this instance, a 20-minute version of the DISS was employed. The modules selected were the mathematical processing, visual monitoring, auditory monitoring, and memory search tasks. Participants were instructed via on screen standard instructions to attend simultaneously to all four tasks, while monitoring the central counter displaying their accumulated aggregate score. Accuracy and speed of response dictate the score, with failure to respond resulting in negative scoring. Previous research has shown that simultaneous performance of these four tasks engenders increases in subjective stress and frustration and stress-related physiological responses, including an increase in salivary IgA (20,21).

In the current study, all four tasks were set at a medium difficulty/intensity level and were performed for 20 minutes. The on-screen layout of the battery is shown in Figure 1. The four tasks are described below.

Mathematical Processing Task

A series of calculations are presented. The participant adds two numbers, entering the three-figure answer via an onscreen number pad. On completion of each calculation, the participant clicks on the "done" button, which cues the next calculation. Ten points are awarded for each correct answer and 10 points are deducted from the running total for each incorrect answer.

Auditory Monitoring Task

One of two tones of different pitches is sounded approximately every 5 seconds throughout the session in a random order. Participants are instructed to click on the box labeled "incoming mail" every time they hear the higher pitched of the two tones. Ten points are awarded for correctly identifying the higher pitched tone and 10 points are deducted for an incorrect response or for no response.

Visual Monitoring Task

A small dot drifts outwards from the center of a target comprising five concentric circles. The participant is instructed to allow the dot to travel as far out of the center as possible, without letting it hit the edge of the target, before clicking on the "reset" button. Two points are added to the running total for every circle that the dot passes through (with a maximum of 10 points), with a penalty of 10 points for every half second that passes between the dot hitting the outer edge and the participant clicking on the "reset" button.

Memory Search Task

Four letters appear for the participants to remember. After 4 seconds, the letters disappear but can be viewed again by clicking on "retrieve list" button. Approximately every 10 seconds, a single target letter appears. Participants are instructed to indicate whether the target letter had appeared in the original list of four letters by clicking on the "yes" or "no" buttons. Ten points are awarded for a correct answer, 10 points deducted for an incorrect answer or no response, and 5 points are deducted every time the list was retrieved.

Bond-Lader Visual Analogue Mood Scales (23)

Mood was assessed before and after each completion of the DISS battery using the visual analogue scales of Bond and Lader (23). These scales were

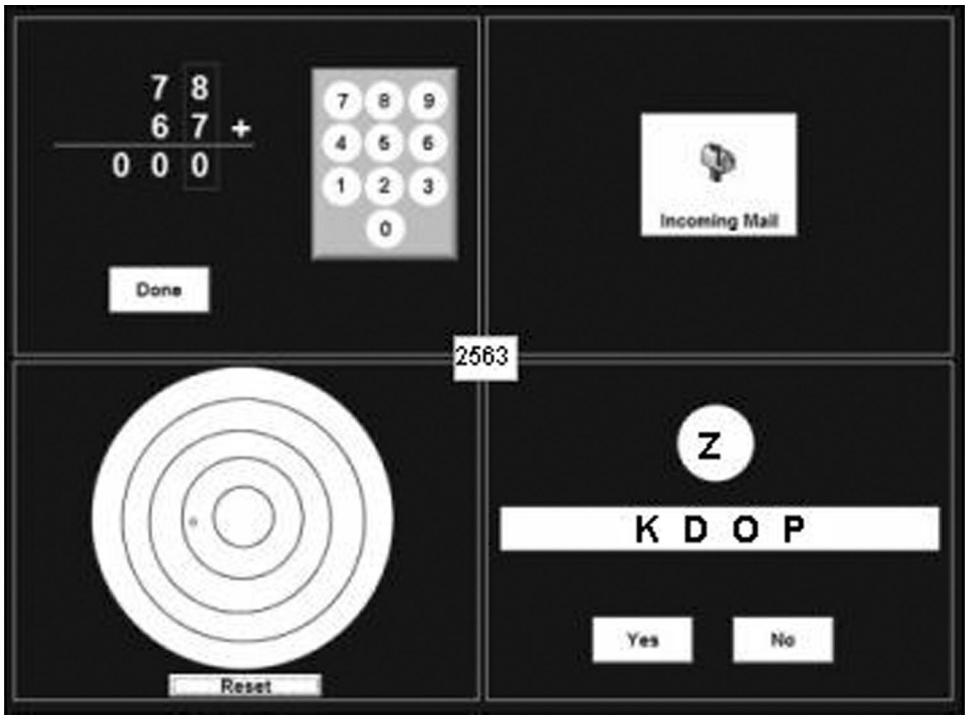

Figure 1. The on-screen layout of the Defined Intensity Stressor Simulation battery. The concurrent tasks comprise (clockwise from top left) "mathematical processing," "auditory monitoring," "memory search," and "visual monitoring." The participant's aggregate score for the four tasks is shown at the center of the display. All responses are made via a standard computer mouse.

originally designed for assessing the mood effects of anxiolytics (23) and have been subsequently utilized in numerous pharmacological, psychopharmacological, and medical trials. As with other mood visual analogue scales, high reliability and validity have been demonstrated (24).

The Bond and Lader scales comprise a total of 16 100-mm lines anchored at either end by antonyms. Participants mark their current subjective state between the antonyms on the line. Each line is scored as millimeters to the mark from the negative antonym. From the resultant scores, three measures derived by factor analysis can be isolated (23). These have been described by Bond and Lader as representing the following: "alertness" (represented by lines anchored by alert–drowsy, attentive–dreamy, lethargic–energetic, muzzy–clearheaded, well-coordinated–clumsy, mentally slow–quick witted, strong–feeble, interested–bored, incompetent–proficient); "calmness" (calm–excited, tense–relaxed); and "contentedness" (contented–discontented, troubled–tranquil, happy–sad, antagonistic–friendly, withdrawn–sociable). Scores for each factor represent the unweighted average number of millimeters (maximum 100 mm) from the negative antonym for the individual scales contributing to the factor.

In the current study, raw scores (pre- and post-DISS, at both pre- and posttreatment) were analyzed in the initial three-way analysis of variance (ANOVA) (see below) to assess the main effect of the stressor battery and interactions with treatment. For the primary statistical analysis (planned comparisons), for each completion of the DISS, mood scores before completion were subtracted from mood scores after completion. This provided a single score representing the change in each mood factor engendered by the stressor battery. This score for the predose completion of the battery was then subtracted from the same score 1 hour postdose to generate a single "change from baseline" score representing the differential effects of treatment on the two battery completions.

Procedure

Before the first study day, a third party, using random number tables, allocated participants to a treatment regimen dictated by a Latin square, which counterbalanced the order of treatments across the 3 days of the study. Each of the 3 days was separated by a 7-day "washout" period, with testing taking place in dedicated laboratory facilities at the same time on each day.

Immediately before and after each completion of the DISS battery, participants filled out Bond-Lader mood scales.

Each day of the study comprised an initial predose completion of the 20-minute DISS battery (plus mood scales before and after), followed by ingestion of the day's treatment. One hour postdose, participants completed the DISS battery (plus mood scales before and after).

The running order of each testing session (plus mean scores at each mood scale completion) is represented in Figure 2.

Statistics

Initial Analysis

Before the primary analysis of mood and performance data (planned comparisons; see below) an initial three-way repeated measures ANOVA (pre/post DISS mood scores × pretreatment/posttreatment × condition) was carried out on the raw Bond-Lader mood scores (alertness, contentedness, calmness) to establish the following: the main effects of the DISS battery on mood; any main effects of treatment group or interaction between treatment and pre/posttreatment; and any interaction between treatment group and the change in mood scores (pre/post DISS) pre and posttreatment.

Only planned comparisons of those mood measures that reached significance on the initial ANOVA are reported below. Significant results from the initial analyses are reported with the relevant measure below.

Mood Effects of DISS

In the case of mood measures generating a significant main effect on the initial three-way ANOVA a further confirmatory analysis assessed the mood effects of the DISS in the absence of treatment. This was accomplished by submitting pre- and post-DISS data from all three baseline completions (ie, data from the mood assessments before and after the DISS before all three condition treatments) to a two-way repeated-measures ANOVA (Condition X mood scores before and after predose DISS) with planned comparisons

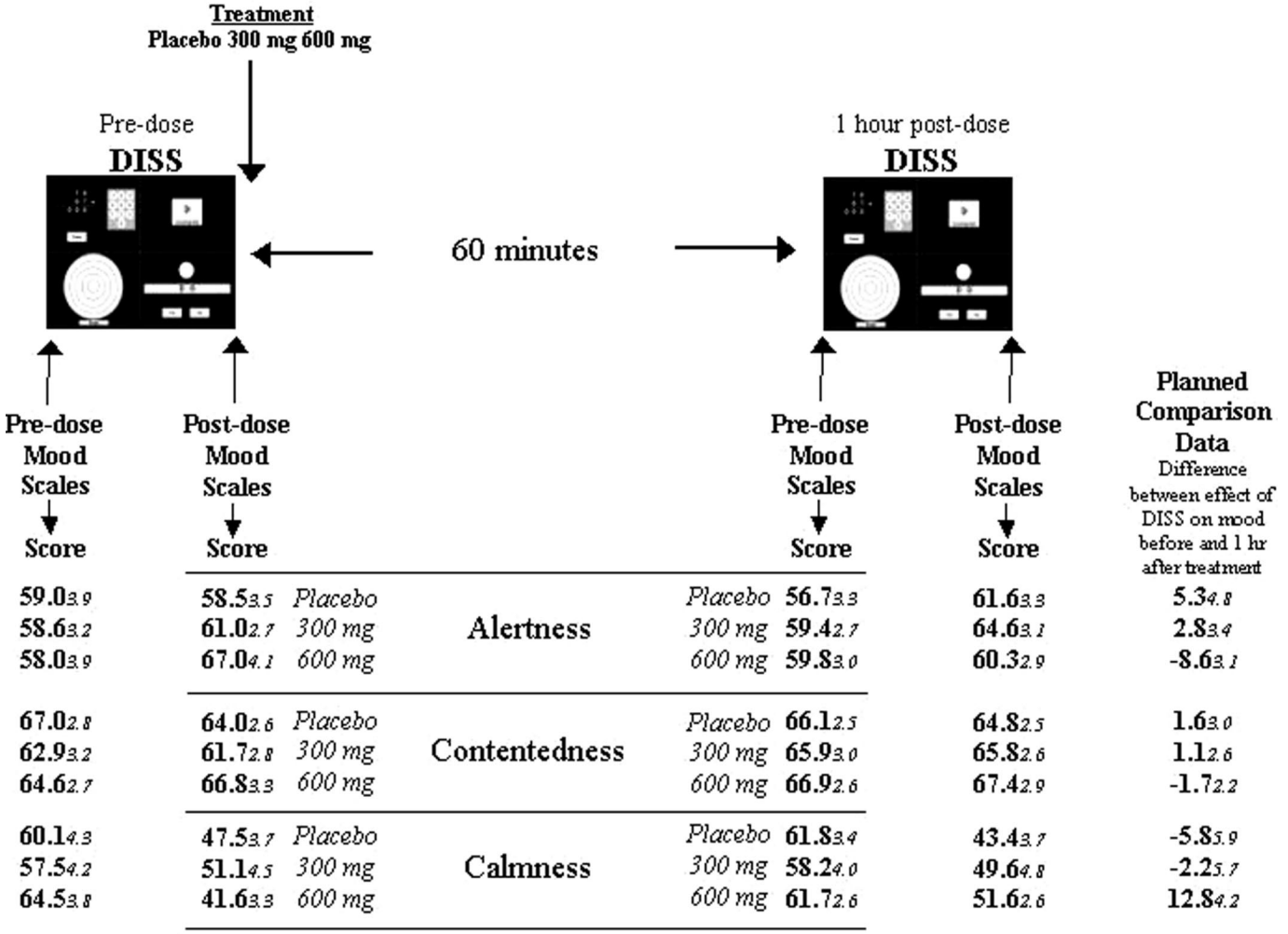

Figure 2. Schematic representation of the running order of the experiment, with mean scores (with standard errors) for each of the mood assessments, and "change from baseline" data (change in mood score during predose Defined Intensity Stressor Simulation (DISS) *minus* change in mood scores during 1 hour posttreatment DISS).

(utilizing MSError) of pre- vs. post data for "alertness," "contentedness," and "calmness" as described below.

Primary Analysis of Treatment Effects on Mood and DISS Performance

Scores for treatment-related changes in the participants' "alertness," "contentedness," and "calmness" mood factor scores during pre- and posttreatment DISS completion were analyzed as "change from baseline." To accomplish this, the change in mood score during the DISS before treatment was subtracted from the change in mood score during the DISS 1 hour after treatment.

An initial, one-way, repeated-measures ANOVA was then carried out to establish MSError for each measure. The primary statistical analysis of the "change from baseline" data followed the recommendations of Keppel (25) and was undertaken using a priori planned comparisons, utilizing *t* tests with the MSError from the one-way ANOVA as an error term, with the resulting *t* score evaluated on the degrees of freedom for MSError. For each measure, data from the placebo condition were compared with that for each of the two doses of *M. officinalis* (300 mg, and 600 mg).

To ensure the overall Type I error protection level, only those planned comparisons associated with measures that generated a significant main effect or interaction effect, or a trend toward the same, on the initial ANOVA are reported. Furthermore, all testing was two-tailed, comparisons were strictly planned before the study and were restricted to the number of conditions − 1 (25).

RESULTS

No adverse side effects were reported for any of the treatments, and all the participants completed the study.

Mood Effects of DISS

The initial three-way ANOVAs showed that there was a significant main effect ($F(1,17) = 4.92$, $p = .04$) of DISS completion on "alert" scores from the Bond-Lader visual analogue scales with scores rising from 58.6 (average millimeters) pre- DISS to 62.2 mm post-DISS. Similarly "calm" was significantly reduced ($F(1,17) = 39.27$, $p < .001$) with average ratings reducing from 60.6 mm to 47.5 mm.

Confirmatory planned comparisons of the pretreatment baseline data (for all three conditions; see Statistics) showed that completion of the DISS in the absence of treatment led to a significant reduction in subjective ratings of "calmness" (60.7 mm reducing to 46.7 mm) on the Bond-Lader visual analogue scales ($t(34) = 3.86$, $p < .001$). However, battery completion in the absence of treatment narrowly failed to have a significant effect on ratings of "alertness" ($t(34) = 1.97$, $p =$

.06) with scores rising from 58.5 mm to 62.2 mm. There was no effect detected by either analysis on contentedness.

Effects of Treatment on Mood Change During the DISS

Calmness

The initial three-way ANOVA showed a significant ($F(2,34) = 3.42$, $p = .04$) three-way interaction for calmness (pre/post DISS mood scores × pretreatment/posttreatment × condition, ie, the difference between how participants' mood was affected by completing the pre- and posttreatment DISSs was modulated by the treatment). Planned comparisons of the Bond-Lader factor "change from baseline" scores revealed that, in comparison to placebo, the 600-mg dose of *M. officinalis* led to significantly increased self-ratings of calmness after completion of the DISS battery ($t(34) = 2.47$, $p = .02$).

Alertness

The initial three-way ANOVA revealed a similar three-way interaction for the alertness factor ($F(2,34) = 4.97$, $p = .01$). Planned comparisons showed that the same 600-mg dose also led to a significant reduction in alertness ($t(34) = 2.96$, $p = .006$) during the posttreatment DISS.

The lower (300-mg) dose did not lead to any significant modulation of mood. Contentedness was also not significantly affected. Change from baseline scores for the mood factors are shown in Figure 3.

Effects of Treatment on Cognitive Measures During the DISS

Planned comparisons revealed that, in comparison to placebo, the 300-mg dose of *M. officinalis* led to a marginally significant increase in the number of calculations completed on the mathematical processing task ($t(34) = 2.03$, $p = .05$). The same dose also led to a significantly greater number of correctly answered calculations ($t(34) = 2.07$, $p = .04$). No significant effects of treatment were revealed either for the higher dose of *M. officinalis* or on the performance of the memory search task or the visual/auditory monitoring tasks. Treatment effects on performance outcomes are presented in Figure 4.

With regard to identification of the days' treatments, on questioning, too few participants had formed an opinion as to the nature of the respective days treatments to allow any meaningful statistical analysis. Reference to the data from those who believed that they could identify the respective treatments suggested that their ability to detect the treatment was at the level of chance.

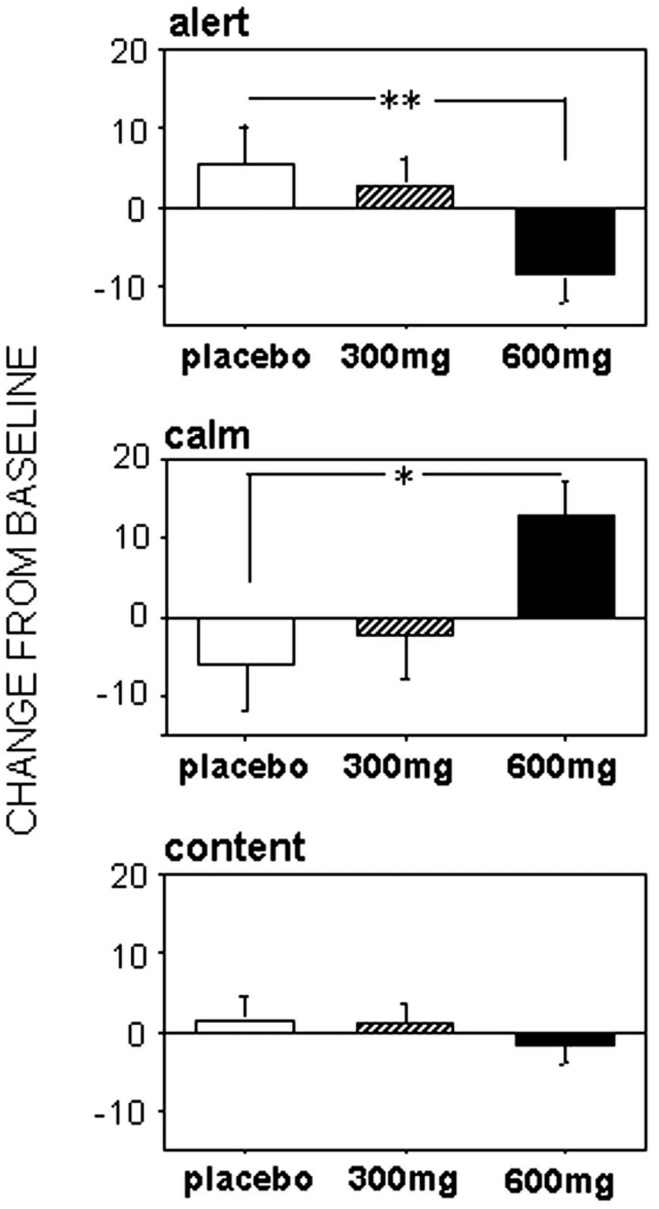

Figure 3. Effects of treatment (300 mg, 600 mg *Melissa officinalis*) on modulation of mood during the Defined Intensity Stressor Simulation battery (*$p < .05$; **$p < .001$ from planned comparisons).

DISCUSSION

The results of the current study confirm that acute administration of *M. officinalis* can ameliorate the negative change in mood associated with a 20-minute psychological stressor battery. While the completion of the DISS battery led to significant reductions in calmness, and a trend toward increased alertness, the 600-mg dose of *M. officinalis* directly ameliorated these mood effects. This dose was associated both with significantly improved calmness and significantly decreased alertness in comparison to placebo during the postdose completion of the DISS. This direct improvement in mood was seen in the absence of any detrimental effects on performance of the DISS tasks. Although no modulation of the mood effects of the stressor battery were seen after the 300-mg dose, this dose was associated with increased speed and accuracy of mathematical processing. The initial analysis of variance suggested that there was no significant effect on mood predose and 1 hour postdose in the absence of the stressor.

The mood effects associated with the 600-mg dose of *M. officinalis* in the present study are consistent with this herb's

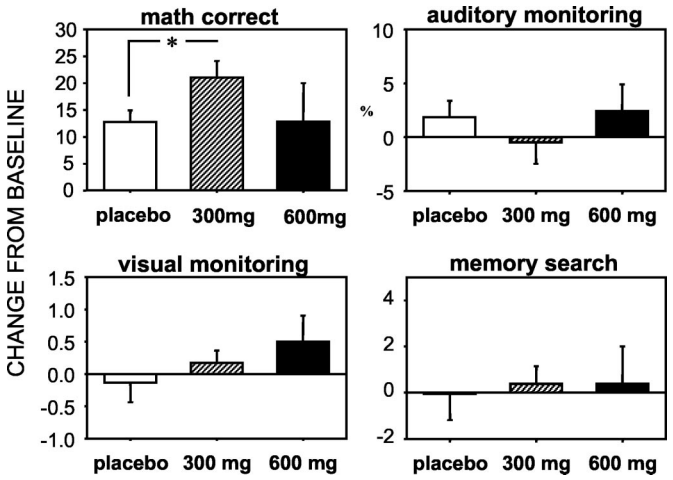

Figure 4. Effects of treatment (300 mg, 600 mg *Melissa officinalis*) on performance accuracy of the four concurrent tasks making up the Defined Intensity Stressor Simulation battery. Scores are change in number of correct answers for "math correct" and percentage change for the other three tasks (*$p < .05$ from planned comparisons).

traditional reputation as a calming agent and mild sedative (4). They also support contemporary reports of sedative effects in mice (10,11), reduced agitation in severe dementia patients after chronic consumption (12), and modulated self-ratings of mood after acute administration to healthy young volunteers (18,19).

The current study utilized single doses of the same standardized extract of *M. officinalis* as a previous study (18) that reported both significantly increased calmness, most notably after the lowest dose (300 mg), and significantly reduced alertness after the highest dose (900 mg). In contrast to the present study, no changes in mood were reported after administration of the 600-mg dose. Although the reason for this inconsistency is unclear, it is notable that in the previous study the mood scale data were collected on each occasion before completion of a 25 minute computerized cognitive battery, and therefore reflected "resting" mood rather than that after a potential psychological stressor. Alternatively, the discrepancy in dose–response may more parsimoniously be simply seen as reflecting the differences between the two experimental situations.

In both of the previous single-dose studies (18,19), cognitive decrements in terms of either reduced accuracy or reduced speed were evident on several tasks. In the current study, no cognitive decrements were evident, and the lowest dose led to improved mathematical processing. In the previous studies, the decrements were specific to the most difficult tasks (ie, those with the longest response latencies), with no effect seen on the performance of easier tasks. It is possible that the tasks utilized in the multitasking battery here would individually fall into the "easier" category. It may also be relevant that cognitive improvements evinced in the current study were restricted to the mathematical processing task, which was the only self-paced task within the DISS. All other tasks provoked responses continuously throughout the session.

The mechanism by which Melissa increased subjective ratings of calmness, reduced alertness, and improved some aspects of performance is currently unknown. Previous investigations have demonstrated negligible nicotinic and low muscarinic binding properties for this particular extract (18). The effects seen here are therefore unlikely to be attributable to direct interactions within the cholinergic system. It seems plausible to suggest that interactions may take place with other neurotransmitters. Given the pattern of mood modulation, the GABAergic system would seem to be an obvious potential target, with the sedative properties of *M. officinalis* potentially being elicited through the inhibitory action of GABA within the central nervous system. In this respect, it is particularly noteworthy that the pattern of mood modulation evinced here is identical to that previously seen after administration of benzodiazepines (ie, decreased alertness, increased calmness, no effect on contentedness) utilizing Bond-Lader mood scales (26). It is also possible, given the wide range of potentially active components, that the effects of *M. officinalis* are mediated through a combination of mechanisms, with potential interactions with a number of neurotransmitter systems. The potential for receptor binding across neurotransmitter systems by this species deserves further attention.

Because *M. officinalis* is rarely sold by itself, the effects of herbal combinations might usefully be investigated utilizing the same paradigm. Of particular interest here, *Valeriana officinalis* (valerian) is known for its sedative effects and anxiolytic properties (27) and is the most common herb to be sold commercially in combination with *M. officinalis* (see the German pharmaceutical industry's current "Rote Liste" for details). Although research into the effects of valerian on stress is limited, a recent study suggested that its ingestion could ameliorate participants' subjective ratings of "pressure" and reduce systolic blood pressure during laboratory induced stress (28).

Although the present study only investigated the effects of single doses of *M. officinalis*, the results suggest that, taken at a moderate dose, extracts from this plant may be beneficial in moderating subjective feelings of stress, without impairing cognitive performance. Because this was intended as a preliminary study in healthy humans, it will be necessary to confirm the clinical significance of the stress reducing effects of this herb both in pathologically stressed groups and in volunteers suffering natural "day to day" stress. Furthermore, it is important that future studies incorporate physiological measurements of stress indicators. The results here, together with those from previous studies of this herb in humans (12,18,19), certainly suggest a robust effect on mood. Nevertheless, it has to be acknowledged that the sample size here was relatively small ($n = 18$, repeated measures), and the treatment was administered immediately after an acute stressor.

In conclusion, the results of the current study suggest that extracts of *M. officinalis* can attenuate the subjective effects of laboratory-induced stress. Because the ingestion of *M. officinalis* appears to be well tolerated (8) with no reported side effects (29), and has now been shown to have robust effects on

mood (12,18,19), further research might well be directed to the question of whether either acute or chronic regimens of *M. officinalis* (or combinations including *V. officinalis*) might provide a safer alternative to prescribed drugs such as benzodiazepines in the mitigation of the effects of mild psychological stress.

REFERENCES

1. Perry EK, Pickering AT, Wang WW, Houghton PJ, Perry NSL. Medicinal plants and Alzheimer's disease: from ethnobotany to phytotherapy. J Pharm Pharmacol 1999;51:527–34.
2. Grieve M. A modern herbal. London: Johnathan Cape; 1931.
3. Bartram T. Encyclopaedia of herbal medicine. London: Grace Publishers; 1995.
4. Bisset NG, Wichtl M. Herbal drugs. Stuttgart: Medpharm; 1994.
5. Kommission E. Monograph. Melissenbla'tter, Bundesanzeiger, 1984; 05.12.
6. Weiss RF. Herbal medicine. Sweden: Arcanum; 1988.
7. Rote liste CMDI/Boehringer Ingelheim. 2001.
8. Cerny A, Schmid K. Tolerability and efficacy of valerian/lemon balm in healthy volunteers: a double-blind, placebo-controlled, multicentre study. Fitoterapia 1999;70:221–8.
9. Dressing H, Riemann D, Low H, Schredl M, Reh C, Laux P, Muller WE. Insomnia: are valerian/balm combination of equal value to benzodiazepine? Therapiewoche 1992;42:726–36.
10. Wagner H, Sprinkmeyer L. Uber die pharmakologische Wirkung von Melissengeist. Dtsch Apoth Ztg 1973;113:1159–66.
11. Souliman R, Fleurentin J, Mortier F, Misslin R, Derrieu G, Pelt JM. Neurotropic action of the hydroalcoholic extract of Melissa officinalis in the mouse. Planta Medica 1991;57:105–9.
12. Ballard C, O'Brien J, Reichelt K, Perry E. Aromatherapy as a safe and effective treatment for the management of agitation in severe dementia: the results of a double blind, placebo controlled trial. J Clin Psychiatry 2002;63:553–8.
13. Carnat AP, Carnat A, Fraisse D, Lamaison JL. The aromatic and polyphenolic composition of lemon balm (Melissa officinalis L. subsp. officinalis) tea. Pharm Acta Helv 1998;72:301–5.
14. Mulkens A, Stephanou E, Kapetenadis I. Heterosides a genines volatiles dans les feuilles de Melissa officinalis L. (lamiaceae). Pharm Acta Helv 1985;60:276–8.
15. Mantle D, Eddeb F, Pickering AT. Comparison of relative antioxidant activities of British medicinal plant species in vitro. J Ethnopharmacol 2000;72:47–51.
16. Hohmann J, Zupko I, Redei D, Csanyi M, Falkay G, Manthe I, Janicsak G. Protective effects of the aerial parts of Salvia officinalis, Melissa officinalis and Lavandula angustifolia and their constituents against enzyme-dependent and enzyme independent lipid peroxidation. Planta Med 1999;65:576–8.
17. Wake G, Court J, Pickering A, Lewis R, Wilkins R, Perry E. CNS acetylcholine receptor activity in European medicinal plants traditionally used to improve failing memory. J Ethnopharmacol 2000;69:105–14.
18. Kennedy DO, Scholey AB, Tildesley NTJ, Perry EK, Wesnes KA. Modulation of mood and cognitive performance following acute administration of Melissa officinalis (lemon balm). Pharmacol Biochem Behav 2002;72:953–64.
19. Kennedy DO, Wake G, Savelev S, Tildesley NTJ, Perry EK, Wake G, Wesnes KA, Scholey AB. Modulation of mood and cognitive performance following administration of single doses of Melissa officinalis (Lemon balm) with human CNS nicotinic and muscarinic receptor binding properties. Neuropsychopharmacology 2003;28:1871–81.
20. Wetherell MA, Sidgreaves MC. The Defined Intensity Stressor Simulation (DISS): the effects of increasing intensity on S-IgA reactivity and perceptions of workload, stress and arousal. Proc Br Psychol Soc 12:74.
21. Wetherell MA, Hyland ME, Harris JE. Secretory immunoglobulin A reactivity to acute and cumulative acute multi-tasking stress: relationships between reactivity and perceived workload. Biol Psychol 2004;66: 257–70.
22. Faul F, Erdfelder E. A priori, post-hoc and compromise power analyses for MS-DOS (computer programme) Bonn, FRG, University of Bonn. Dept of Psychology. 1992.
23. Bond A, Lader M. The use of analogue scales in rating subjective feelings. Br J Psychol 1974;47:211–8.
24. Ahearn EP. The use of visual analog scales in mood-disorders: a critical review. J Psychiatr Res 1997;31:569–79.
25. Kepple G. Design and analysis. Englewood Cliffs, NJ: Prentice Hall; 1991.
26. Thompson JM, Neave N, Moss MC, Scholey AB, Wesnes K, Girdler NM. Cognitive properties of sedation agents: comparison of the effects of nitrous oxide and midazolam on memory and mood. Br Dent J 1999;187: 557–62.
27. Kohnen R, Oswald WD. The effects of valerian, propranolol, and their combination on activation, performance and mood of healthy volunteers under social stress conditions. Pharmacopsychiatry 1988;21:447–8.
28. Cropley M, Cave Z, Ellis J, Middleton RW. Effects of kava and valerian on human physiological and psychological responses to mental stress assessed under laboratory conditions. Phytother Res 2002;16:23–7.
29. Wong AHC, Smith M, Boon HS. Herbal remedies in psychiatric practice. Arch Gen Psychiatry 1998;55:1033–44.