National Alzheimer's Project Act (NAPA)

The information that follows was included as an attachment to an email submitted by the public.

For more information about NAPA, visit the NAPA website at:

http://aspe.hhs.gov/national-alzheimers-project-act

dose and at 1 hour, 2.5 hours, 4 hours and 6 hours post-dose. The most notable result of this experiment was a striking dose-dependent impairment on a 'Quality of Memory' measure derived by factor analysis from the Cognitive Drug Research (CDR) computerised assessment battery. More specifically, decrements were most pronounced, and increased with dose, on two timed memory tasks (delayed word recognition and a spatial memory task). The overall pattern of results also showed that the lowest dose (300 mg) engendered increased 'calmness' at the first two post-dose testing sessions (1 hour and 2.5 hours), and the middle dose (600 mg) led to improved performance on attention tasks. The highest dose, however, was not associated with any benefits, and led to the most pronounced decrements on the memory tasks along with reduced 'alertness' at all post-dose testing sessions. Whilst this pattern of results is broadly in line with the contemporary role of *M. officinalis* as a calming agent and mild sedative, it is not in keeping with beneficial modulation of cholinergic activity. Indeed, the *in vitro* analysis of the extract (completed after the behavioural experiment) showed that the extract in question showed 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.

As this left open the question of the cognitive and mood effects of a cholinergically 'active' *M. officinalis* the second experiment [58] was conducted in two distinct phases. In the first phase an initial *in vitro* investigation of the cholinesterase inhibitory and cholinergic receptor binding properties of eight acquisitions of organically grown *M. officinalis* of known provenance was undertaken. Whilst none of the samples of dried leaf led to measurable inhibition of cholinesterase, all eight samples showed a substantial affinity for muscarinic receptors. The sample chosen for the behavioural experiment was one of a number of samples that also exhibited a substantial affinity for nicotinic receptors (IC^{50} concentrations of 0.18 mg ml-1 and 3.47 mg ml-1 respectively for the displacement of [^{3}H]-(N)-nicotine and [^{3}H]-(N)- scopolamine). The second phase of the experiment utilised a similar methodology to the previous study, with participants receiving three single doses of the dried M. officinalis leaf (600mg, 1000mg, 1600mg) and a placebo, counterbalanced, at seven day intervals. Testing took place pre-dose and at 1, 3 and 6 hours post-dose using the CDR battery, in this case augmented with a 5 minute 'cholinergically sensitive' rapid visual information processing task (RVIP). The results showed that whilst the lowest dose was associated with decrements on both the RVIP and the same timed memory tasks as had been disrupted in the previous study, these effects attenuated with increasing dose. The highest (1600 mg) dose of dried leaf led not only to increased 'calmness' (as measured by Bond-Lader mood scales) at all post-dose time points, but also significantly improved performance on the 'Quality of Memory' factor at the 3 and 6 hours post-dose testing sessions.

The pattern of results from the two studies was speculatively interpreted as reflecting the workings of more than one mechanism [58]. It seems likely that the decrements on the more difficult timed tasks - which were seen to decrease with increasing doses of dried leaf, and increase with dose following ingestion of the more highly concentrated manufactured extract - reflect the working of a single mechanism. Furthermore, given that the manufactured extract had little cholinergic activity, it would seem that one or more different mechanisms were responsible for both these effects and the improved calmness seen following the most beneficial dose of each treatment. The remaining memory improvements seen for the highest dose of the 'cholinergic' *M. officinalis* leaf could certainly be accommodated within the expected pattern of 'cholinergic' effects.

In partial support of this interpretation (at least with respect to mood effects), a further study examined the effects of the methanolic *M. officinalis* extract on laboratory induced acute psychological stress [65]. This double-blind, placebo-controlled, counterbalanced cross-over study assessed the mood and performance effects of two separate doses (300 mg, 600 mg) of the methanolic commercial extract of *M. officinalis* during the performance of the 'Defined Intensity Stress Simulator' (DISS) laboratory stressor battery by 18 healthy young participants. Whilst completion of the battery itself led to increased subjective ratings of alertness and reduced ratings of calmness, the 600 mg dose of *M. officinalis* extract led to a direct significant attenuation of these negative mood effects.

Chronic Administration in Alzheimer's Disease

Two recent double-blind, placebo-controlled studies have also assessed the effects of M. officinalis in sufferers from dementia. Ballard *et al.* [66] examined the effect of *M. officinalis* essential oil aromatherapy (in comparison to vegetable oil) on ratings of agitation and quality of life of 71 patients suffering from severe dementia. Following 4 weeks treatment patients in the active treatment group were rated, in comparison to the placebo group, as being less agitated, less socially withdrawn, and as engaging in more time spent in constructive activities.

Utilising a similar methodology as their study into the effects of *S. officinalis* (see above), Akhondzadeh *et al.* [67] also assessed the effects of 60 drops/day of a tincture of *M. officinalis* in the 35 sufferers from mild to moderate dementia (20 verum, 15 placebo) that completed their 16 week trial. At the study end-point the results showed a clear cognitive advantage (ADAS-cog and Clinical Dementia Rating) and reduced agitation for the *M. officinalis* group. Once again, however, the profile of the declines for the placebo group (+5.6 points on the ADAS-cog) and the improvements for the *M. officinalis* group (-6.4 points) would not have been anticipated from the results of larger trials assessing the effects of other anti-dementia treatments.

ROSEMARINUS OFFICINALIS

Historical Perspective

Rosemary has a long and eminent history as a sacred herb, associated particularly with the remembrance of love and death. This history originates with the ancient Egyptians' use of the herb in the mummification process, and spans the cultures of ancient Greece and the Romans. In these latter societies one of its other, more curious uses was as a memory enhancer [68]. Greek students wore sprigs or garlands of rosemary at times of educational demand, and Roman stu-