

ORIGINAL RESEARCH

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# A Randomized, Double-blind, Placebo Controlled Study Examining the Effects of a Combination Nutraceutical Formula on Cognitive Functioning and Mood

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## ABSTRACT

The combination nutraceutical formula consisting of Huperzine A, Vinpocetine and Acetyl-L-Carnitine was examined in a 30-day double blind, placebo controlled clinical trial assessing a range of cognitive and mood variables. Seventy-four healthy participants, 43 in the combination nutraceutical formula group and 31 in the placebo group, with a mean age of 48 years, completed the study. Statistically significant improvements in several variables relative to placebo could be attributed to the 30 days administration of the combination nutraceutical formula, including working memory accuracy ( $p < .03$ ), long term memory consolidation ( $p < .02$ ) and mood ( $p < .02$ ), suggesting an improvement in complex cognitive processes. The cognitive processes assess both the initial stages of holding information in conscious awareness as well as the encoding and retrieval of recently learned material. The mood measures

assessed levels of anger and depression. Interestingly, improvements in speed of memory retrieval suggest functioning equivalent to age cohorts of approximately 10 or more years younger. A range of more simple measures of information processing speed, such as reaction time and other indices of mood, were not improved. The results suggest the promise of special nutraceutical formulations for improving cognition. There were also no side effects or adverse reactions reported by the participants.

## INTRODUCTION

With increasing life expectancies and the maturation of the “baby boom” generation, adapting to the challenges posed by the ageing population has been identified as one of the major issues facing contemporary western societies. Human ageing has significant societal, economic, health and personal costs. Increasing age is associated with a cluster of illnesses involving oxidative stress, including cardiovascular and respiratory disease, as well as neurological conditions such as Parkinson’s disease (PD) and Alzheimer’s disease (AD).

A time-honored and much empirically supported method of promoting optimal health throughout the lifespan has been through the adoption and maintenance of an appropriate, healthy diet. Recent research suggests that this

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principle not only applies to protection from “physical ailments” such as cardiovascular problems, but may also extend to ameliorating the effects of cognitive decline associated with increased age. The maintenance of brain health underpinning intact cognition is a key factor to maintaining a positive, engaged and productive lifestyle. In light of this fact, the role of diet, including supplementation with nutritional and even pharmacological interventions capable of ameliorating the declining neurocognitive changes that occur with age, constitute vital areas of research. Accordingly, there is considerable interest in whether natural supplements or nutraceuticals can improve cognition.

The combination nutraceutical formula has been developed to improve cognitive functioning, particularly in an age group showing normal age related cognitive decline. The combination nutraceutical formula is a compound of Huperzine A, Vinpocetine and Acetyl-L-Carnitine ingredients, which individually have been extensively studied in experimental animal and human clinical trials. We provide a brief summary of these studies below. Additionally, a recent review in *JANA*<sup>1</sup> has outlined the evidence for their mode of action on the human brain with a particular focus on improving cognition and memory.

#### **Huperzine A (HupA)**

Huperzine A (HupA), isolated from the Chinese herb *Huperzia serrata*, has been suggested to be a promising compound to treat Alzheimer’s disease.<sup>2</sup> Consistent with this view are the results of studies revealing that HupA functions as a reversible inhibitor of acetylcholinesterase,<sup>3</sup> which increases the amount of synaptic acetylcholine available for neurotransmission. Additionally, based on observations in the rat cerebral cortex,<sup>4</sup> studies have proposed that HupA functions as a non-competitive antagonist of NMDA receptors. HupA has been found to reverse or attenuate cognitive deficits in a broad range of animal models.<sup>5</sup> Numerous clinical trials have demonstrated that Hup A is effective in relieving memory deficits associated with college students,<sup>6</sup> the elderly and Alzheimer’s disease without any serious adverse side effects,<sup>5</sup> and is considered to be a safe supplement.<sup>7</sup>

#### **Vinpocetine (VIN)**

Vinpocetine (VIN), derived from the Periwinkle plant (*Vinca minor*)<sup>8</sup> is widely used as a neuroprotective agent.<sup>9, 10, 11, 12</sup> The primary action of VIN is to enhance cerebral vascular blood flow, brain energy metabolism<sup>12, 13, 14, 15</sup> and increase the neuronal uptake of glucose and oxygen.<sup>12, 16, 17</sup> Due to these beneficial actions, VIN has been used in the prevention and treatment of conditions and diseases associated with compromised cognitive function.<sup>12, 20</sup> VIN has been shown to improve the speed of memory learning and recall in cognitively healthy subjects<sup>18, 19</sup> and in cognitively compromised subjects.<sup>8</sup>

#### **Acetyl-L-Carnitine (ALC)**

Acetyl-L-Carnitine (ALC) is naturally synthesized in

the human brain, liver and kidney<sup>21</sup> and may have beneficial properties in treating age related disorders such as Alzheimer’s dementia.<sup>22, 23, 24</sup> Further, studies have shown that ALC may be beneficial in the treatment of depression,<sup>25, 26</sup> attention deficit disorders<sup>27, 28</sup> and cognitive impairment induced by alcohol.<sup>29</sup> ALC plays an essential role in energy production by facilitating the uptake of Acetyl CoA into the mitochondria during fatty acid oxidation<sup>30, 31</sup> and increases ATP energy production.<sup>32</sup> ALC also enhances acetylcholine synthesis<sup>33, 34</sup> and cerebral vascular blood flow,<sup>35, 36</sup> which are implicated in age related normal and abnormal states of cognitive decline, such as Alzheimer’s disease.

We hypothesized that the combination nutraceutical formula compound would have a strong effect on improving cognitive functioning, attention, energy levels, stress adaptation and mood states. We tested this hypothesis by conducting a randomized double blind placebo controlled human trial with 90 participants.

## **METHOD AND MATERIALS**

### **Participants**

Ninety participants (45 in each of the two groups) were initially enrolled into the 30 day chronic study. Seventy-four (74) participants completed the 30 days and were tested at both baseline and at 30 days (43 in the combination nutraceutical formula group and 31 in the control group). The mean age of the combination nutraceutical formula group was 49.5 years (SD = 1.6 22-66 years) and the mean age of the placebo group was 47.1 years (SD = 1.9 24-62) years. There was no significant difference in the number of males or females who participated in the study.

### **Inclusion/Exclusion criteria**

Each participant underwent an individual screening appointment with a registered nurse. Screening incorporated a medical history and cognitive assessment. Participants were eligible if they were aged between 22 and 66 years of age. Exclusion criteria included the following: not currently taking prescription drugs affecting the brain or nervous system (e.g., Modafinil, acetylcholinesterase inhibitors, anticholinergics, stimulants, L-dopa, MAO inhibitors, NMDA receptor antagonists, methylphenidate, amphetamine, pseudo-ephedrine, SSRIs and other anti-depressant medication); not currently taking OTC medications affecting the brain (e.g., ephedra based diet pills); those who have not used any supplements within the past 30 days that have an effect on cognitive function, memory, anxiety, depression (e.g. Ginseng, Gingko, Vinpocetine, 5HTP, Tryptophan, St. John’s Wort, ephedrine (ephedra), alpha GPC, Citicoline, phosphatidylserine, acetyl-l-carnitine, Focus Factor™); not active smokers; not taking the following: anti-coagulant drugs (Warfarin, Heparin, Plavix); anti-cholinergics or acetylcholinesterase inhibitors (bethanechol, Ureholine),

donepezil (Aricept), rivastigmine (Exelon), galantamine (Reminyl), edrophonium (Enoln, Reversol, Tensilon), neostigmine (Prostigmin); do not have any of the following health conditions: AIDS, HIV, chronic fatigue syndrome, Epstein-Barr, fibromyalgia, lupus, multiple sclerosis, thyroiditis, ulcerative colitis, Crohn's disease, irritable bowel syndrome, dementia including Alzheimer's and Parkinson's disease, Type 1 or 2 diabetes, insomnia or sleep apnea, narcolepsy; no history of head trauma; no neurological deficits; not pregnant or lactating; not anticipating any planned changes in lifestyle (e.g. exercise regimen) for the duration of the study; and no known allergies to nuts.

### Study Design

The study was a randomized double blind placebo-controlled design in which participants were allocated either a daily dose of the combination nutraceutical formula or placebo for 30 days. The dose was 1,515 mg per day and each participant was instructed to take 3 pills per day. The combination nutraceutical formula, known as ProceraAVH, was provided by 20/20 Brain Power Partners, LLC (Founders of Brain Research Labs), Laguna Beach, California.

### Measures

Several cognitive and psychological measures were assessed at baseline and at 30 days.

### Cognitive Testing

The CDR® program is an automated computerized cognitive assessment system, which has been used in more than 250 published clinical drug studies. The CDR system comprises a battery of cognitive tests that are sensitive to the effects of psychopharmacological substances.<sup>37</sup> The CDR system profiles and assesses a range of cognitive functions, including attention, information processing, sub-loops of working memory, reasoning, secondary memory and skilled coordination. All tasks in the battery are computer controlled, with information being presented on high-resolution monitors, and the responses recorded via a response module containing two buttons, one marked 'YES,' the other marked 'NO.' The versions of the tests specified for elderly participants were employed. The selected battery took the participants around 30 minutes to complete and parallel forms of the tasks were presented at subsequent testing sessions. The cognitive tests used from the battery are presented in Table 1.

The Profile of Mood States (POMS) is a self-report designed to measure six dimensions of mood: tension/anxiety; depression/dejection; anger/hostility; vigor/activity; fatigue/inertia; and confusion/bewilderment.<sup>38</sup>

**Table 1.** The CDR (Cognitive Drug Research) Computerized Cognitive Assessment System (Areas of Cognition Measured)

<b>Level I: Attention</b>	
<i>The ability to select, evaluate and respond to appropriate environmental information</i>	
Task	Cognitive States and Processes Assessed
Simple Reaction Time	Alertness, power of concentration Primary stage of information processing
Choice Reaction Time	As above, plus stimulus discrimination; response organization
Digit Vigilance	Intensive vigilance; sustained attention; ability to ignore distraction
<b>Level II: Short Term or Working Memory</b>	
<i>The ability to temporarily store the information relevant to ongoing tasks</i>	
Task	Cognitive States and Processes Assessed
Numeric Working Memory	Sub-vocal rehearsal of digit sequences Articulatory loop sub-system of working memory
Spatial Working Memory	Ability to temporarily retain spatial information Visuo-Spatial sub-loop of working memory
<b>Level III: Long Term or Episodic Secondary Memory</b>	
<i>The ability to register, store and retrieve information over any period required</i>	
Task	Cognitive States and Processes Assessed
Word Recall*	Ability to store and recall verbal information; capacity for un-cued retrieval of words; episodic secondary verbal recall
Word Recognition	Ability (speed and sensitivity) to discriminate novel from previously presented words; episodic secondary recognition
Picture Recognition	Ability to discriminate novel from previously presented pictorial information; episodic secondary non-verbal visual recognition
Face Recognition*	Ability to discriminate novel from previously presented faces; episodic secondary face recognition

\* Face recognition task and word recall task were not administered in this study.

## Procedure

At baseline each participant completed a general health assessment, which included blood pressure, height and weight, and were then randomly allocated into one of the two treatment groups. They then completed a CDR practice session, which is required in order to become familiar with the tests. After completing the practice session, they were administered the cognitive and psychological tests. Thirty days after their first visit, they completed cognitive and psychological testing again.

## RESULTS

A series of repeated measures (ANOVAs) were calculated to examine the changes between baseline and 30 days administration of the combination nutraceutical formula and placebo on the cognitive and psychological measures. As this was the first clinical trial combining the three components in the combination nutraceutical formula, we report the statisti-

cally significant analyses ( $p < .05$ ) as well as the analyses approaching statistical significance ( $p > .05 \leq .10$ ), which will help the design of future studies assessing this compound.

### (1) COGNITION

Non-significant changes in simple reaction time, digit vigilance and choice reaction time, spatial working memory and picture recognition, (long term memory consolidation of objects), were observed over the 30 days administration of the trial. However, 30 days administration of the combination nutraceutical formula (compared to placebo) improved a range of cognitive processes. Means and SDs for these variables are reported in Table 2.

#### Numeric Working Memory

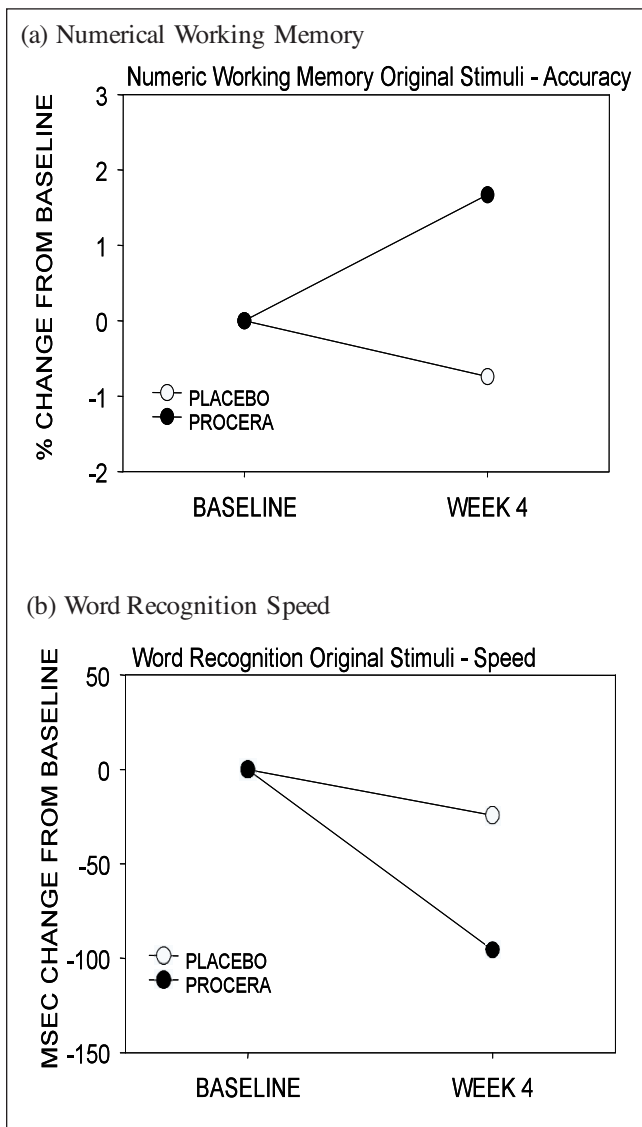
Participants on the combination nutraceutical formula treatment showed statistically significant improvement ( $p < .03$ ) in numeric working memory accuracy compared to placebo participants. A statistically significant improvement in holding numbers in working memory (immediate

**Table 2:** Means and SDs for significant outcome variables at baseline and again at 30 days for the combination nutraceutical formula (ProceraAVH) and placebo groups.

	Condition	Mean	Std. Deviation	P
Numeric Working Memory Original Stimuli - Accuracy - baseline	Procera AVH	93.76	5.14	P < .03
	Placebo	95.77	5.26	
Numeric Working Memory Original Stimuli - Accuracy - week 4	Procera AVH	95.43	3.39	P < .03
	Placebo	95.03	3.94	
Word Recognition Original Stimuli - Speed: Mean - baseline	Procera AVH	853.12	184.99	P < .02
	Placebo	774.99	122.44	
Word Recognition Original Stimuli - Speed: Mean - week 4	Procera AVH	757.52	138.40	P < .02
	Placebo	750.54	7.03	
Depression/Dejection baseline (POMS)	Procera AVH	8.00	9.42	P < .06
	Placebo	5.19	8.54	
Depression/Dejection - week 4 (POMS)	Procera AVH	4.32	5.12	P < .06
	Placebo	4.35	6.57	
Anger/Hostility baseline (POMS)	Procera AVH	7.83	7.56	P < .03
	Placebo	4.48	5.80	
Anger/Hostility - week 4 (POMS)	Procera AVH	4.16	4.30	P < .03
	Placebo	3.80	6.12	
Total Mood Disturbance score BL (POMS)	Procera AVH	65.93	30.50	P < .02
	Placebo	52.90	23.86	
Total Mood Disturbance score - week 4 (POMS)	Procera AVH	47.55	17.16	P < .02
	Placebo	46.51	21.42	

memory) was shown from baseline to day 30 due to the combination nutraceutical formula treatment (see Figure 1).

**Figure 1:** Changes in Numeric Working Memory Accuracy Changes and Word Recognition Speed (long term memory) for placebo and the combination nutraceutical formula (ProceraAVH).



### Spatial Working Memory

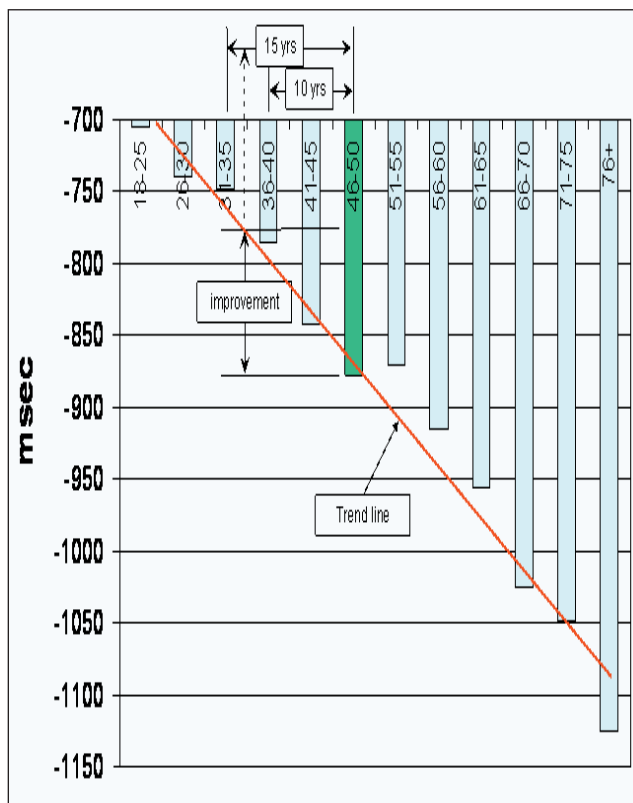
There was also a trend towards statistical significance ( $p < .09$ ) for the number of outliers during the spatial working memory task. Outliers indicate lapses in concentration over the duration of the task. Participants in the combination nutraceutical formula treatment group showed less mean number of such lapses during the task and were therefore better able to focus and concentrate/process during the spatial working memory task, which is a complex cognitive task.

### Word Recognition

The speed of performance during the word recognition

task was significantly improved ( $p < .02$ ) for participants on the combination nutraceutical formula treatment compared to the placebo treatment over the 30 days of administration (Table 1). This indicated that the combination nutraceutical formula significantly improved memory consolidation processes and in particular, the speed at which a participant was able to consolidate and access new memories into long term storage (Figure 1). As extensive age related normative data are available for the speed of recognition task from the CDR battery, it was possible to calculate the approximate improvement in relative age related functioning due to the combination nutraceutical formula treatment. An improvement in RT of approximately 100 msec was seen in the Procera group compared to approximately 20 msec in the placebo group. Given that the mean age of the group was 48 years, a net improvement of approximately 80 msec on this task (measuring speed of long term memory retrieval) equates to approximately the functioning of age bands some 10-15 years younger (Figure 2).

**Figure 2:** Age related improvements in speed of memory retrieval with the combination nutraceutical formula (ProceraAVH). Improvements in RT due to 30 days administration of the combination nutraceutical formula, (compared to placebo), equate to between 10 and 15 years of normal age-related decline in speed of memory retrieval (80 msec), given the mean age of the sample (48 years). Graph adapted with the kind permission of Cognitive Drug Research (CDR UK).



## (2) MOOD

### Depression

The combination nutraceutical formula group showed a decrease in depression scores relative to the placebo group ( $p < .06$ ). This suggests that the combination nutraceutical formula may improve depressive mood conditions.

### Anger/Hostility

The combination nutraceutical formula group showed a statistically significant ( $p < .03$ ) decrease in anger/hostility over the 30 days trial relative to the placebo group. This indicates that 30 days of treatment with the combination nutraceutical formula significantly improves feelings of anger and hostility. This result is supportive of the decrease in depression scores.

### Confusion

Participants in the combination nutraceutical formula group also showed a decrease in confusion over the 30 days trial ( $p < .06$ ), which was greater than in the placebo participants. Again, this result is consistent with the decrease in depression and anger/hostility shown by the combination nutraceutical formula participants over the 30 days trial. A decrease in confusion may be best understood in terms of improving mental clarity.

### Vigor

A non-significant change in vigor scores were observed across the 30 days of the trial ( $P < .10$ ). An improvement in vigor may be best understood in terms of increased mental energy.

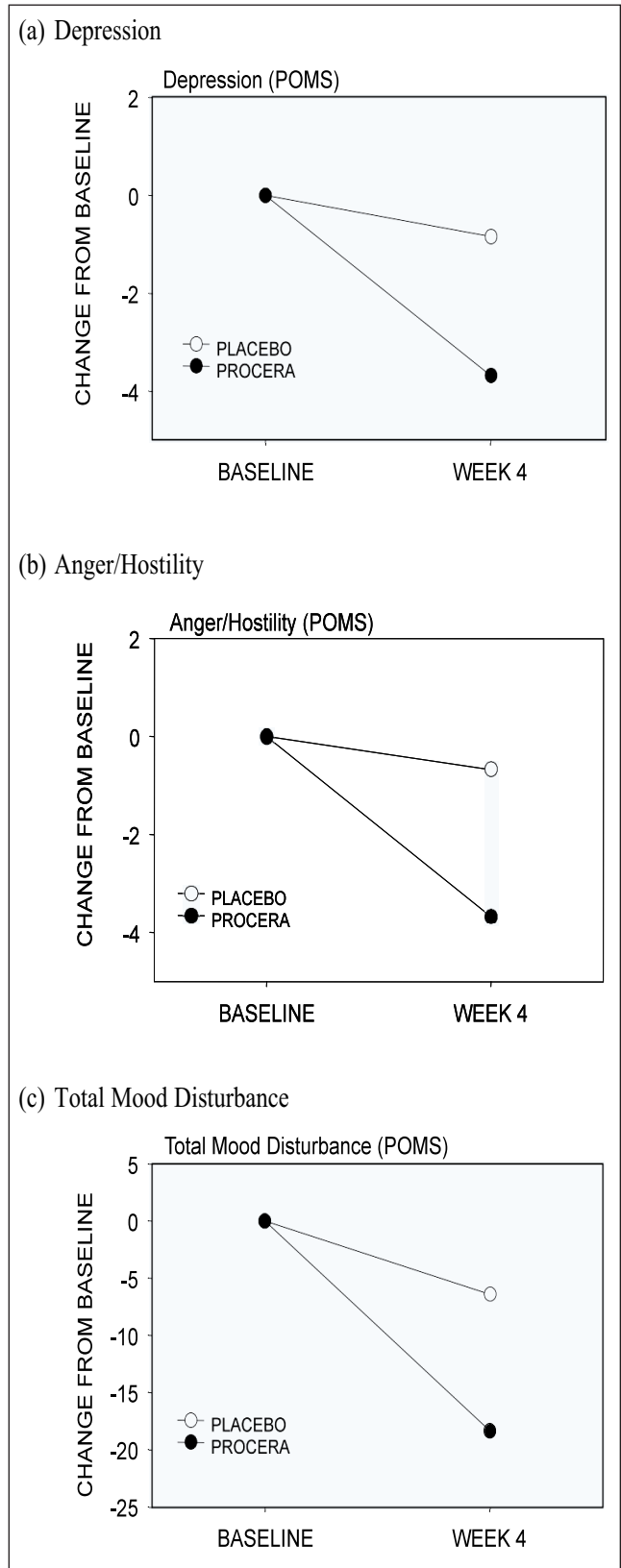
### Total Mood Disturbance

The main factor score relating to negative moods on the POMS is total mood disturbance. This factor may be regarded as a highly reliable indicator of changes in negative emotions or moods over the 30 days of supplementation. There was a highly significant change in the total mood disturbance over the 30 days in favor of the combination nutraceutical formula group compared to the placebo group ( $p < .02$ ). This improvement in mood due to the combination nutraceutical formula is consistent with the observed changes in depression, anger/hostility, confusion and vigor. The result also suggests that changes in mood due to the combination nutraceutical formula are highly noticeable in the participants. Figure 2 displays the changes from baseline over the 30 days treatment for the combination nutraceutical formula and placebo groups.

### (3) Safety

There were no statistically significant differences in side-effects between the two conditions after 30 days of administration.

**Figure 3:** Changes in mood variables for placebo and the combination nutraceutical (ProceraAVH) formula conditions relative to baseline scores.<sup>7</sup>



## DISCUSSION

This was the first double blind placebo controlled study to examine the effect of 30 days administration of the combination nutraceutical formula, called ProceraAVH, on cognitive and mood variables. The data from this trial provide evidence that this compound improves a range of cognitive and mood variables in healthy adults. The cognitive changes were observable using a highly standardized and reliable battery of cognitive tasks, and the mood changes were readily observed and reported by the participants.

In terms of the cognitive variables, there is evidence that the unique ProceraAVH nutraceutical formula mainly improves functioning during complex cognitive tasks that assess memory (working and long term, or consolidation) rather than in simple discrimination tasks such as choice reaction time. Interestingly, the cognitive processes that appear to be improved relate to the middle (working memory; consolidation) and late stages of memory functioning (memory retrieval of newly learned material). This may suggest a specific focus of effect on the human brain, incorporating frontal and temporal circuits that underpin working memory and long term memory consolidation.

In terms of mood, the combination nutraceutical formula appears to improve mental clarity and mental energy, and to help repair mood disturbances. Mood disturbances are commonly experienced from time to time by all adults, together with confusion and low level depressive symptoms. The combination nutraceutical formula appears to improve these moods, which may be important in improving cognitive processes. Memory in particular is very sensitive to disturbances in mood such as anxiety and other negative emotions that fall under the umbrella of terms such as depression.

Overall, the results suggest that the combination nutraceutical formula, ProceraAVH, exerts beneficial effects on both cognition and mood. The results of the present study confirm the results and conclusions of the extensive literature examining Vinpocetine, Huperzine A and Acetyl-L-Carnitine singly on cognition and mood in animals and humans. Future larger scale trials on this formulation should be undertaken as a matter of priority in order to explore additional possible areas and conditions of impact. Of particular merit is the question of whether the combination nutraceutical formula may have the greatest effect on the elderly, in whom cognition is most challenged.

## ACKNOWLEDGEMENT

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