The Effects of Cocoa Flavanol Consumption on Cognitive Function

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The Effects of Cocoa Flavanol Consumption on Cognitive Function

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

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In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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Abstract

**Objective:** The objective of this selective EBM review is to determine the effect of cocoa flavanol consumption on cognitive behavior.


**Data sources:** Three double blind randomized controlled trials comparing cognitive function after consumption of drinks with high cocoa flavanol level were found using PedMed and Ovid.

**Outcomes measured:** Cognitive function was measured by various tests: a Cognitive Demand Battery composed of two serial subtraction tasks, a Rapid Visual Information processing task, a mental fatigue scale over 1 hour, the Mini Mental Status Examination, Trail Making Test, a verbal fluency test, and a visual spatial working memory for location task.

**Results:** The RCT conducted by Desideri et al found the groups who consumed cocoa flavanol had a significantly reduced time to complete the Trail Making test and significantly improved verbal fluency test scores compared with the control. The study did not find significant change in the Mini Mental State examination after cocoa flavanol ingestion. The Scholey et al study found there were variable changes in the Cognitive Battery Demand testing. With Serial Three subtractions there were statistically significant effects of cocoa flavanol with a greater number correct and fewer errors compared with the control. With the Serial Sevens task and Rapid Visual Information processing tasks there were not any significant differences between the control and the group who consumed cocoa flavanol. The Field et al study showed participants who consumed cocoa flavanol had a statistically significant improvement on visual spatial tasks and a faster reaction time than the control.

**Conclusions:** The evidence is inconclusive whether there is an effect of cocoa flavanols on cognitive function. Future studies collecting data on the effect of habitual consumption of cocoa flavanol on cognitive performance could prove most relevant for preventing age related cognitive changes. Two of the studies sampled young adults; compiling more trials with adult participants would be beneficial to assessing whether cocoa flavanols can prevent or improve age related cognitive function decline.

**Key words:** Cocoa flavanol, cognitive function
Introduction:

Cognition is defined as conscious mental activities: the activities of thinking, understanding, learning, and remembering. Cognitive impairment is the state of individuals who are memory impaired but well-functioning and without evidence of dementia. Cocoa flavanol ingestion is associated with increased cerebral blood flow and brain activation and have been proposed to be effective in reversing age related declines in neurocognitive function by increasing the number and strength of the connections between neurons, reducing neuronal loss, and through their ability to interact with the molecular architecture of the brain responsible for memory. This paper evaluates three double blind, randomized, controlled trials comparing cognitive function after the ingestion of cocoa flavanols.

This topic is relevant to PA practice because the US population continues to live longer with each generation; therefore, maintaining and enhancing cognitive function is of importance as there are commonly age related cognitive declines in attention and short term memory. A population based study found 16% of individuals aged 70-89 without dementia to have mild cognitive impairment. Mild cognitive impairment puts individuals at increased risk of developing dementia and Alzheimer’s disease. In 2013, Alzheimer’s disease is expected to cost the US $203 billion in health care costs. Increasing cognitive ability is of relevance to all age groups and is beneficial in daily activities and occupational tasks. Screening for cognitive function changes is part of the criteria for Medicare’s yearly wellness exam.

There remains to be much that is unknown in regard to cognitive function impairment as it is difficult to predict and is highly variable between individuals. There is no current effective prevention or treatment. Flavonoids, found in many plant based foods, may be associated with a decreased risk of incident dementia and with lower prevalence of cognitive impairment, a better
cognitive evolution over a 10 year period, and better dose dependent performance of several cognitive abilities in elderly subjects.¹

While there is not yet a standard cure or treatment of cognitive impairment there are dozens of dietary supplements marketed as enhancing cognitive function such as gingko biloba, phosphatidylcholine, and ginseng.⁴ Currently, there are no effective preventive strategies for cognitive decline. Most research points to modifiable lifestyle factors, such as poor diet and physical and cognitive inactivity, as being associated with the risk of dementia. Therefore, prevention of cognitive decline is aimed at treating heart disease risk factors such as elevated cholesterol, obesity, diabetes, and hypertension.⁵

Research has not yielded a cure for cognitive function decline but many natural products have been proposed as able to enhance cognition. Cocoa flavanol ingestion is associated with increased cerebral blood flow and brain activation so cocoa flavanols may be a safe and natural way to increase attention, short term memory, and cognitive function.⁶

Objective:

The objective of this selective EBM review is to determine the effect of cocoa flavanol consumption on cognitive behavior.

Methods:

The three studies utilized were randomized, double blind, controlled clinical trials. The populations ranged from 18-30 years old for two of the studies, and alternatively an elderly population with mild cognitive impairment was observed in one study. The interventions studied in all three RCTs were the consumption of drinks with a high cocoa flavanol level, in comparison to groups that consume a drink with a low level of cocoa flavanol. The main
outcome measured was cognitive function and secondary outcomes included changes in blood pressure and changes in mood.

To find data sources I searched PubMed and Ovid with the key words “cocoa flavanol” and “cognitive function.” All articles were published in peer-reviewed journals in the English language. Articles were selected based on relevance to clinical topic of interest, dates in which they were published, and whether they represented patient-oriented evidence that matters. To be considered as adequate studies to be reviewed, experimentation was required to involve randomized, controlled and double blind clinical trials published after 1996. Exclusion criteria included patients diagnosed with dementia. The summary of statistics reported include: p-values and F (ANOVA).

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th># Pts</th>
<th>Age (yrs)</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>W/D</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desideri (2012)</td>
<td>Double-blind randomized parallel arm study</td>
<td>90</td>
<td>“elderly”</td>
<td>Participants were recruited among patients referred to the Alzheimer unit of the University of L’Aquila Geriatric Division for mild cognitive impairment (MCI), as diagnosed according to the revised Peterson criteria.</td>
<td>The selection criteria for the population included that none of the participants was obese (BMI &gt;30 kg/m2), a current smoker, or on statin treatment.</td>
<td>3</td>
<td>Consumption of a drink containing a high level (~990 mg per serving) of cocoa flavanols once daily for 8 weeks or consumption of a drink containing an intermediate (~520 mg per serving) or low (~45 mg per serving) level of cocoa flavanols once daily for 8 weeks</td>
</tr>
</tbody>
</table>
### Outcomes measured:

The main outcome measured was cognitive function in all three RCTs. In the Desideri et al study, cognitive function after consumption of cocoa flavanol in individuals with mild cognitive impairment was measured by the Mini Mental Status Examination, Trail Making Test, and a verbal fluency test. Desideri et al measured blood pressure and various metabolic parameters as secondary outcomes. Scholey et al assessed cognitive function with a Cognitive Demand Battery composed of two serial subtraction tasks, and used the Spielberger state anxiety questionnaire to assess anxiety symptoms. Field et al tested each participant at a high and low cocoa flavanol level on separate occasions to assess cognitive function. Field et al assessed
cognitive function with various tests including a visual spatial working memory task and a choice reaction time test designed to engage processes of sustained attention and inhibition.

Results:

The RCT conducted by Desideri et al assessed the impact of regular (once daily) cocoa flavanol consumption on cognitive function in individuals with mild cognitive impairment in an 8 week study. Participants were recruited among those referred to the Alzheimer unit of the University of L’Aquila Geriatric Division for mild cognitive impairment, and selection criteria included that none of the participants were obese, a current smoker, or under statin treatment. The participants were divided into a high, intermediate, and low level of cocoa flavanol ingestion. The groups were comparable in terms of sex, age, cardiovascular risk factors, and pharmacological treatments. The main measurement was cognitive function as assessed by the Mini Mental State Examination, Trail Making Test, and a verbal fluency test. Two participants in the intermediate group discontinued the study after 4 weeks because of personal reasons and one participant in the low ingestion group discontinued after 2 weeks because of reported gastric discomfort. All 3 were followed up during the entire study period and data was included according to intention to treat procedure. Overall compliance was 99.4% at week 8 and adherence to protocol was evaluated at each visit by a questionnaire checklist. The Mini Mental State Examination score did not change significantly between the 3 groups during the study (p=0.13). The time to complete the Trail Making test significantly reduced in the groups who consumed high and intermediate levels of cocoa flavanol but did not change in the low cocoa flavanol level group (Table 2). Verbal fluency test scores significantly improved in the groups with high and intermediate cocoa flavanol ingestion (Table 3). Systolic and diastolic blood pressures significantly changed during the study period with significant reduction in the high and
intermediate level flavanol groups. Blood pressure did not change in the group who consumed a low level of flavanol (p<0.0001).

Table 2: Change in time to complete Trail Making Test from week 1 to week 8 (calculated as week 8 time minus week 1 time) among groups ingesting high, intermediate, or low cocoa flavanol amounts.

<table>
<thead>
<tr>
<th>Amount of cocoa flavanol consumed</th>
<th>Change in time (seconds)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (990mg)</td>
<td>-14.3±4.2</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Intermediate (520mg)</td>
<td>-8.8±3.4</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Low (45mg)</td>
<td>+1.1±13</td>
<td>0.65</td>
</tr>
</tbody>
</table>

Table 3: Verbal fluency score among groups ingesting high, intermediate, or low cocoa flavanol amounts.

<table>
<thead>
<tr>
<th>Amount of cocoa flavanol consumed</th>
<th>Verbal fluency (words/60 seconds)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (990mg)</td>
<td>8.0±5.3</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Intermediate (520mg)</td>
<td>5.1±3.1</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Low (45mg)</td>
<td>1.2±2.7</td>
<td>0.014</td>
</tr>
</tbody>
</table>

Table 4: Blood pressure change from week 1 to week 8 among groups ingesting high, intermediate, or low cocoa flavanol amounts.

<table>
<thead>
<tr>
<th>Amount of cocoa flavanol consumed</th>
<th>Systolic BP change (mm Hg)</th>
<th>P value</th>
<th>Diastolic BP (mm Hg)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (990mg)</td>
<td>-10.1±9.2</td>
<td>&lt;.0001</td>
<td>-4.8±5.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Intermediate (520mg)</td>
<td>-8.2±8.5</td>
<td>&lt;.0001</td>
<td>-3.4±7.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Low (45mg)</td>
<td>-1.4±9.4</td>
<td>0.16</td>
<td>-0.9±6.8</td>
<td>0.14</td>
</tr>
</tbody>
</table>

The RCT conducted by Scholey et al compared consumption of a drink containing 520mg and 994mg cocoa flavanol and a control drink. The study used healthy undergraduate students aged 18-35 years old as subjects and conducting the study on four separate occasions at least three days apart for each subject. To assess compliance, salivary caffeine levels were measured in order to confirm adherence to caffeine abstinence instructions. To test for baseline differences between the groups which may have skewed change from baseline scores, prior to
the primary statistical analysis, all pre-dose baseline measures were subjected to one way repeated measures ANOVAs. There was not a significant effect of cocoa flavanol consumption with the Spielberger state anxiety questionnaire (F<1 in all cases), and there were variable changes in the Cognitive Battery Demand testing. With Serial Three subtractions there were statistically significant effects of drink consumption on the number of Serial Threes correct and the number of errors with a greater number correct (F=18.6, p <.001) and fewer errors (F=4.67, p=0.01) at 20 minutes following 994mg of cocoa flavanol compared with the control. With the Serial Sevens task there were not any significant differences between the control and consumption of cocoa flavanol (F<1, p>0.1). With the Rapid Visual Information processing tasks (RVIP) there were no significant treatment effects on accuracy (F=1.13, p>0.1) but participants were significantly faster (F=0.66, p=0.03) at the task. Excluded from the study were patients who used illicit drugs or prescription or over the counter medications so as to avoid results that were skewed by interactions with medications or illicit drugs.

The RCT by Field et al was conducted in the School of Psychology and Clinical Language Sciences at the University of Reading and included 30 participants between 18-25 years old who were recruited from the Undergraduate Research Panel and received course credit for their participation. The study compared participants visual spatial working memory with and without cocoa flavanol supplementation and found a significant difference between the two conditions (F=3.41, p=0.05). Results showed that with high cocoa flavanol ingestion the groups had a greater percent correct on visual spatial tasks (Table 5). In the reaction time assessment the participants to consume a high cocoa flavanol drink had a faster reaction time (Table 5) than the control. The study excluded participants who reported having medically restricted diet or any kind of ongoing illness, and all participants had normal visual acuity or acuity corrected to
normal by glasses. For 24 hours prior to study days and during the 2 hour interval between consumption and testing participants were asked to avoid consuming a list of foods and drinks containing flavonoids, as well as alcohol and caffeine. To increase compliance researchers told participants that a cheek swab would be collected and analyzed to check conformity to restrictions, however the swab was collected and not analyzed.

Table 5: Visual spatial and reaction time tasks comparing high cocoa flavanol ingestion and control groups.

<table>
<thead>
<tr>
<th>Amount of cocoa flavanol consumed</th>
<th>High CF</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual spatial (% correct)</td>
<td>87.13±9.32</td>
<td>83.51±11.16</td>
</tr>
<tr>
<td>Reaction time (ms)</td>
<td>538±149</td>
<td>557±85</td>
</tr>
</tbody>
</table>

In regards to safety, all three studies did not find evidence of any relevant adverse effects. The studies did not quantify adverse effects as there were not any consistent adverse findings to be evaluated. A participant in one study, Desideri et al, reported nonspecific gastric discomfort.

Discussion:

The data from Desideri et al found cognitive performance was improved with cocoa flavanol consumption and blood pressure, both systolic and diastolic, was decreased. The study was a 2 month intervention so the extent and duration of cognitive benefits, and their impact on mild cognitive impairment are not known. It is also unclear whether the observed benefits in neurocognition are a result of the cocoa flavanols themselves or a “secondary effect related to general improvements in cardiovascular function or health.” A limitation was that the study population included subjects without known cardiovascular disease and therefore was not representative of all subjects with mild cognitive impairment. Overall the results provide
evidence that flavanol containing foods could be an effective dietary approach for improving aspects of cognitive dysfunction.

The results of Scholey et al demonstrate that the acute consumption of cocoa flavanol can improve cognitive performance during cognitive processing in healthy young participants. Compared with the nutrient matched, low flavanol control drink, some improvements in cognition were found after consumption of both the 520mg and 994 mg cocoa flavanol drinks, and interestingly the 520mg drink was most beneficial. The data suggests that the Serial Threes task draws on different neurocognitive substrates than the Serial Sevens. It is unclear why the 520mg drink led to better cognitive function with a lower level of cocoa flavanol than the 994mg drink. The study was limited by the population’s small age range, between 18 and 35 years old, and small sample size of 30 individuals.

The results of Field et al demonstrate that performance on tests of visual system function in healthy young adults can be improved by acute consumption of cocoa flavanol. A reduction in time required to integrate visual motion could be beneficial in everyday tasks like driving. There are reasons to predict that the chronic effects of cocoa flavanol supplementation on visual function will be larger than the acute effects discussed in the research by Field et al. Dietary flavonoids are neuroprotective, enhance the endothelial function, and suppress inflammatory processes, all of which would likely be beneficial for the retina and visual cortex. Rat models suggest that epigallocatechin gallate, a flavonoid from green tea, has a protective effect on the neural layer of the retina and accelerates recovery from various insults to the retina. The findings from Field et al are limited by their basis on visual function in young adults and their findings could be extended to investigate the effects of cocoa flavanol on vision in older adults since decline in visual processing is associated with aging.
Research has previously shown that flavanol rich chocolate and cocoa products may have a small but statistically significant effect in lowering blood pressure by 2-3 mm Hg in the short term.\textsuperscript{8} Yet, the literature notes that long-term trials are needed to determine whether or not blood pressure is reduced on a chronic basis by daily ingestion of cocoa. Research is also needed to determine the effect of cocoa flavanol on cardiovascular events and to assess potential adverse effects associated with chronic ingestion of cocoa products.\textsuperscript{8}

\textbf{Conclusion:}

The evidence is inconclusive whether there is an effect of cocoa flavanols on cognitive function. It would be of great interest to explore the chronic effects of cocoa flavanol ingestion and comparing them to those elicited acutely as in the discussed studies. Future studies collecting data on cocoa flavanol’s effect on cognitive performance with habitual consumption could prove most relevant for preventing age related cognitive changes. Two of the studies sampled young adults between 18 and 35 years old but compiling more trials with adult participants would be beneficial to assessing whether cocoa flavanols can prevent or improve age related cognitive function decline. It would also be interesting to compare caffeine ingestion to cocoa flavanol ingestion in future trials to rule the possibility that the caffeine ingredient in cocoa is contributing to its positive effects.
References: