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The Efficacy of Dietary Supplementation with Cocoa to Improve Cognitive Function in Adults

Alex Kaplun
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Abstract
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Methods: An exhaustive search of available literature was conducted using the MEDLINE-Ovid, Google Scholar and CINAHL databases. Keywords searched included cocoa and cognition. Articles that assessed effects of cocoa flavanols on cognition were included. The quality of relevant articles was evaluated using the GRADE Working Group guidelines.

Results: This review summarizes the accumulated evidence of research of cognitive effects of cocoa flavanols not covered by Scholey et al and Sokolov et al. Three randomized controlled studies met eligibility criteria and were included in this systematic review. One study of 37 adults found a statistically significant improvement in performance of cognitive tests in patients using cocoa flavanols supplementation. A second study of 90 adults showed acute improvements in performance of fatigability tests. In the third study 37 adults patients showed improvements in activation of dentate gyrus of the hippocampus as well as some memory tests. All studies had low quality of evidence based on the GRADE guidelines.

Conclusion: Cocoa-derived flavanols need further investigation to understand their effect on cognition and memory but preliminary results are promising.

Keywords: Cocoa and cognition.

Degree Type
Capstone Project

Degree Name
Master of Science in Physician Assistant Studies

First Advisor
Annjanette Sommers, PA-C, M.S. |

Keywords
Cocoa, cognition

Subject Categories
Medicine and Health Sciences

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NOTICE TO READERS

The Efficacy of Dietary Supplementation with Cocoa to Improve Cognitive Function in Adults

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A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

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For the Masters of Science Degree, 2016

Faculty Advisor: Mark Pedemonte, MD

Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS

Biography

Alex Kaplun lives in Fort Collins, CO with his wife and two children. Medicine is his second career. He holds a masters degree in electrical engineering with focus on integrated circuit design and has ten years of experience with IBM.

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To *Pacific PA program faculty and staff :*Thank you for making this possible.

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BVRT………. Benton Visual Retention Test
CBV……….. Cerebral Blood Volume
CDB………... Cognitive Demand Battery
CFs…………. cocoa flavanols
DG…………. Dentate Gyrus
HF………….. high flavanols
IF…………... intermediate flavanols
LF…………... low flavanols
MMSE…....... Mini-Mental State Examination
ModBent…… Modified-Benton
RVIP……….. Rapid Visual Information Processing
SUCCAB…... Swinburne University Computerized Cognitive Assessment Battery
TMT………... Trail Making Test
VFT………... Verbal Fluency Test

The Efficacy of Dietary Supplementation with Cocoa to Improve Cognitive Function in Adults

BACKGROUND

Cocoa is a product of processing the cocoa bean, aka cacao bean. The initial product of roasting and grinding of the cocoa bean is a paste. It is then further separated into cocoa powder (aka cocoa) and cocoa butter. Cocoa, cocoa butter and sugar are further processed and mixed to produce chocolate, a product popular in Western society. Cocoa powder in its unprocessed form is bitter and not sweet. It was respected for its medicinal properties in Mesoamerican culture.

Cocoa is rich in flavanols, a subgroup of flavonoids, a common compound in plants.[1] Cocoa flavanols (CFs) pharmacodynamics have been well researched in the past. It is accepted that peak blood levels are reached at 2-3 hours after digestion and it has been demonstrated that CFs cross the blood-brain barrier. Prior research has shown that CFs have positive effects on the cardiovascular system.[2] Cognitive effects of these compounds have been investigated, but not proved to be of significance in the past.[1,2] Small pilot studies continue to be supported by large cocoa consumers like Mars, Inc.

CFs are available on the market as dietary supplements in a variety of forms. They are inexpensive and there is no known harm associated with their use.

Two systematic review were published in 2013 by Scholey et al. and Sokolov et. al. This review summarizes the accumulated evidence of research of cognitive effects of cocoa flavanols published since 2013.

METHODS

An exhaustive search of available literature was conducted in using the MEDLINE-Ovid, Google Scholar and CINAHL databases. Keywords searched included cocoa and cognition. Only publications that assessed effects of cocoa flavanols on cognition were included. Additionally, only studies conducted after 2013, performed on human subjects and in the English language were considered . The quality of relevant articles was evaluated using the GRADE scale.[3]

RESULTS

An initial search of Medline-OVID using the aforementioned keywords revealed 36 articles. Four articles[1,2,4,5] met eligibility criteria. Google Scholar search indicated one more important study.[6] Review of CINAHL search results did not add to the search. The two latest review studies[1,2] indicated lack of solid evidence of effects of cocoa on cognition. They were both published in 2013 and included complementary sets of sources. The three latest studies by Massee et al[6], Mastroiacovo et al[4] and Brickman[5] et al were included in the current review. See Table 1 for details.

Massee et al (2015)

In May 2015 an Australian-based team centered at the Swinburne University of Technology published results of a clinical randomized, placebo-controlled, double-blind study[6] with 40 initial participants. All subjects were young individuals in their mid-twenties in good health. The population was heavily skewed towards well-educated females.[6]

Study design cover both acute and subchronic (30 day post initial dose) effects of CFs. Participants were screened for mental and physiological fitness as well as intake of dietary supplements and prescription medications.[6]

Supplementation as well as placebo were provided in identical tablet form. Tablets with active ingredients contained 350 mg polyphenols (including flavanol) and 5.56 mg caffeine. Study subjects were randomly placed to a placebo group or to a group given active ingredients. Both groups were instructed to take one tablet daily for 4 weeks, with the last tablet taken a day before final testing. There were 38 participants who returned to complete testing after 4 weeks, 19 in each group.[6]

Primary outcomes included several cognitive test sets. Swinburne University Computerized Cognitive Assessment Battery (SUCCAB) was intended as a main cognitive assessment. SUCCAB was primarily focused on visual processing and memory. Cognitive Demand Battery (CDB) was performed over thirty minutes and was intended to check for changes in fatigability. CDB included Serial 7s and 3s, Rapid Visual Information Processing (RVIP) task and self-reported mental fatigue scale.[6]

Secondary outcomes were blood pressure and blood flow through common carotid artery using doppler US.[6]

Only CDB tests included significant findings. Serial 7 in cycle 1 of testing on day 1 was the most notable. Subjective fatigue scale in acute testing on day 1 showed less fatigue in CFs group, but then it also showed less fatigue in the placebo group on subacute testing at 1 week. Authors admitted to not being able to explain this discrepancy.[6]

Authors felt the need to emphasize importance of findings by estimating the necessary sample size based on the statistical analysis of the results. Their calculations showed a minimum required number of participants in each group to be 13, noticeably less than the 20 used.[6]

No significant findings were available in SUCCAB testing results or any of the secondary outcome measures. Authors deny any conflict of interests.[6]

The study was significantly limited due to use of the supplement with low flavanol content. The problem was acknowledged by authors.[6]

Mastroiacovo et al (2015)

This well-balanced small study[4] is notable for thoroughly addressing potential confounders. The mechanism of CFs effect on human cognition is not established, but it is speculated to be related to antioxidative properties of CFs. Dietary flavonols are present in foods other than cocoa. Antioxidants come from various food sources, dietary supplements and medications. Cognition is influenced by mental and physical health. This study used strict screening methods to eliminate participants with depression, smoking, BMI >30, recent significant weight changes, cognitive impairment determined by MMSE < 27, know history of cardiovascular disease or cerebrovascular events, as well as users of relevant medications such as benzodiazepines, antidepressants and antioxidants (e.g., vitamins C and E , statins, and glitazones). Dietary flavonols intake was normalized by detailed analysis of participants diets and then closely monitored over a 1-week initiation period.[4]

The study is a randomized controlled double-blind parallel-arm study involving 90 elderly individuals ages 62-85. Participants were separated into three groups: high flavanol (HF) intake of 993 mg per day, intermediate flavanol (IF) intake of 520 mg per day and low flavanol (LF) intake of 48 mg per day. CFs were provided in form of a drink, provided by Mars, Inc. LF drink included only cocoa , HF and IF were supplemented with CFs extracts. There was a reasonable drop-out rate with four participants leaving the study. Three groups at completion had

29 (HF), 29 (IF), 28 (LF) participants. See Table 2. The three groups were taking supplements for 8 weeks. Testing was done at the beginning before the first dose and at 8 weeks. The second set of tests was administered about 24 hours after consumption to eliminate any acute effects of CFs.[4]

Changes in cognitive function after 8 weeks of CFs intervention were measured using standard cognitive tests: Mini-Mental State Examination (MMSE), Trail Making Test (TMT) A and B, Verbal Fluency Test (VFT). They were considered as primary outcomes. Secondary outcomes were physiological measurements that included blood pressure, fasting insulin and glucose plasma levels and plasma 8-iso-prostaglandin F2a levels as a measure of oxidative stress.[4]

Significant primary outcomes are summarized in the Table 2. TMT A and B showed significant improvement in time to completion in HF and IF groups. VFT scores improved across all groups. The most remarkable finding in this study was the dose-response gradient that was observed in TMT and VFT results. Similar improvements were found consistently in secondary outcomes.[4]

Authors speculate about the correlation of secondary outcomes and cognitive findings. The study invites further research in identifying the mechanism by which CFs influences cognitive function.[4]

Brickman et al (2014)

A New York City based team published a study covering several aspects of research in neurophysiology of learning and memory formation. They developed a methodology of testing of the brain activity specific to dentate gyrus (DG) of hippocampus. DG is speculated to be central to learning and memory.[5] Custom testing methodology included two unique components.

They developed a software to quantify and evaluate cerebral blood volume (CBV) using fMRI images from the data combined from several subjects. The other custom piece was a version of Benton Visual Retention Test (BVRT), named Modified-Benton (ModBent). It was a set of custom visual patterns designed to focus on DG function. Above mentioned methods were validated in a calibration study that demonstrated a decline in CBV of DG with age.[5]

The effect of CFs on cognition was measured in a randomized controlled, double-masked, 3-month dietary intervention study among 50-69 year olds. Thirty seven subjects that completed the study belonged to one of four groups (see Table 2): High Flavanol (HF) and Low Flavanol (LF) each with and without additional exercise regiment. The selection mechanism is described in details in the paper, but no dropout details were given. Groups were small, under 20 participants, heavily skewed towards an educated female population.[5]

Primary outcomes of the study were quantified CBV-fMRI results and the ModBent response time. Secondary outcomes were delayed retention task and aerobic capacity (VO2 max). Aerobic capacity was measured in expectation to see the influence of aerobic exercise.[5]

Significant improvement (P=0.038) in ModBent times was noted in HF group.[5] Exercise did not have an effect on outcomes. Delayed retention task did not show any difference between groups. ModBent correlated with CBV-fMRI findings.[5]

There was a significant conflict of interest in the study design. Authors acknowledged funding from Mars, Inc. as well as the fact that one of the authors was employed at the same company.[5] Regardless, the results of this study established a clear relationship between CFs intake and increase in CBV of DG. There were no questionable or unexplained results.[5]

DISCUSSION

The three studies[4,5,6] discussed in this paper show a low quality of research of the effects of CFs on human cognition. All three share a significant number of tests that did not show any response to dietary intervention. This is likely due to the lack of understanding of CFs mechanism of action as well as lack of precise testing techniques. However, to date no study or anecdotal finding has shown harm from CFs's use. This may indicate a lack of toxicity of CFs compounds. It may also indicate that the doses used in research to date are too low and lack of observed effect is due to inadequate dosing.

Brickman et al[5] is the only study trying to address both issues with focus on DG function and custom designed ModBent tests. But authors failed to demonstrate that CFs central effects are limited to DG. Despite the high potential for bias, this study[5] has encouraging results and calls for larger scale research with less potential for bias.

Both Massee et al[6] and Mastroiacovo et al[4] make an attempt to evaluate acute and subchronic effects of CFs. They both use a sophisticated approach in isolation of potential confounders. The Mastroiacovo et al study[4] presents a most reliable finding verifying CFs's influence on cognition with the gradient response to the supplement. This alone, once independently confirmed on a larger scale, can lead to clinical applications.

Results of Massee et al study[6] add additional data points in support of acute effects of CFs on cognitive performance. Unfortunately, the successful reduction in speed of Serial 7s test is not useful without an explanation of lack of findings in the Serial 3s. The study points to the need of further research of higher CFs content interventions and more sophisticated tests.

All studies reviewed are small pilot studies and invite more research to verify findings. Clinicians should hope for more studies in the near future that would address larger more diverse populations, CFs's mechanism of action and dosing.

CONCLUSION

CFs have shown a potential for improvement of cognition in human subjects. The mechanism of action, appropriate dosing and if there are any safety issues are still not clear. No adverse effects of CFs were found to date and there are no reasons to discourage use of CFs supplements available on the market at this time. Future research is expected to bring new light to the health improvement potentials of this widely available product.

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Table 1. Characteristics of Reviewed Studies

Table 1. GRADE Assessment: Characteristics of Reviewed Studies								
Design	Included Outcomes	Downgrade Criteria					Upgrade	Quality
		Limitations	Indirectness	Imprecision	Inconsistency	Publication bias likely		
Massee et al (2015)[6]								
RCT	CDB	not serious	very serious[a]	serious[b]	not serious	not likely	none	**Low**
Mastroiacovo et al (2015)[4]								
RCT	TMT A+B VFT	not serious	serious[c]	serious[b]	not serious	likely[d]	Dose-response gradient	**Very low**
Brickman et al (2014)[5]								
RCT	ModBent	not serious	not serious	serious[b]	not serious	likely[d]	none	**Low**

a Use of polyphenols with low flavanol content
b Small sample sizes
c Lacked placebo group
d Funding by Mars,Inc.

Table 2. Summary of Findings

Brickman et al (2014)[5]						
outcome	HF(N=19) 900 mg CFs + 138 mg epicatechin per dose	LF(N=18) 10 mg CFs + <2 mg epicatechin per dose	t	P		
ModBent, ms	1,997	2,627	2.17	0.038		
Mastroiacovo et al (2015)[4]						
outcome	HF 993 mg flavanols/serving N=30	IF 520 mg flavanols/serving N=30	LF 48 mg flavanols/serving) N=30	P		
	Δ(week 0 - week 8)	Δ(week 0 - week 8)	Δ(week 0 - week 8)			
TMT A, s	8.57 ± 0.38	6.67 ± 0.45	0.77 ± 1.57	<0.0001		
TMT B, s	16.50 ± 0.8	14.20 ± 0.49	1.10 ± 0.68	<0.0001		
VFT words/60 s	7.70 ± 1.09	3.57 ± 1.23	1.33 ± 0.45	<0.0001		
Massee et al (2015)[6]						
	250 mg catechin polyphenols + 5.56 mg caffeine N=19		placebo N=19			
	M	SD	M	SD	F	p
serial 7's, acute, cycle 1, correct numbers	21.55	11.20	15.39	9.22	5.98	0.02