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**Are High-Dose Cocoa Polyphenols Effective In Improving
Emotional States In Healthy Individuals Ages 18-65 Years Old For
Long-Term Treatment?**

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

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 whether or not high-dose cocoa polyphenols are effective in improving emotional states in healthy individuals ages 18-65 years old for long-term treatment.

STUDY DESIGN: Systematic review of two randomized controlled trials (RCTs) and one randomized parallel open-label clinical trial, all published between 2008 and 2013, all English language.

DATA SOURCES: These three studies that evaluate the effectiveness of cocoa polyphenols in emotional state improvement were found using the PubMed database based on their relevance to the clinical question and their inclusion of patient-oriented outcomes.

OUTCOMES MEASURED: These three articles compared changes in mood and emotional states after ingestion of cocoa polyphenols with follow-up self-reported questionnaires and Bond and Lader Visual Analogue Scales (VAS).

RESULTS: Two of the three studies found no significant improvement in mood post-consumption of cocoa polyphenols. Martin et al. demonstrated that consumption of milk chocolate or dark chocolate did not improve mood on subjective questionnaires analyzed by F-scores ($p=0.147$).¹¹ The Crews et al. study revealed no clinically significant difference ($p= .392$) in mood between the dark chocolate plus cocoa group and placebo group reported on questionnaires for the duration of six weeks.¹² In contrast, the Pase et al. study demonstrated a significant improvement in contentment versus the placebo with consumption of cocoa polyphenols ($p<0.05$) utilizing comparison of mean values on visual analogue scales (VAS).⁵

CONCLUSION: There is conflicting data regarding the relationship of cocoa polyphenols and emotional/mood states. The results of two of these studies showed no significant effect comparing mood states before and after consumption of chocolate sources containing cocoa polyphenols for short durations of time under 6 weeks. However, the results of the third study showed that ingestion of cocoa polyphenols for a least 30 days improved contentment. Therefore, it may be possible to improve emotional/mood states in individuals ages 18-65 with cocoa polyphenols when utilized for a longer duration. Consequently, more randomized controlled clinical trials need to be performed to explore this relationship.

KEYWORDS: cocoa polyphenols, dark chocolate, mood, effects

INTRODUCTION

Polyphenols are natural micronutrients found in various types of foods that have become the topic of discussion in nutritional health research. Due to their antioxidant and antiradical properties, polyphenols such as resveratrol in red wine, curcumin in turmeric and epigallocatechin-3-gallate in green tea, have proven beneficial to people who suffer from cancer, metabolic and cardiovascular disease.¹ Although known as a delectable food item, another noteworthy polyphenol that has a history of medicinal use is cocoa. Cocoa polyphenols (proanthocyanidins, flavanols, procyanidins) are considered bioactive compounds with antioxidant, antiradical and antiplatelet effects, also deeming a positive role in the treatment of metabolic and heart disease.^{1,2}

The delicate balance of therapy and psychopharmacological treatment is a nationwide concern for mental healthcare providers. However, 56% of American adults with mental illness still do not receive treatment due to accessibility of care.³ Lack of access to care can be mitigated with the use of alternative options for treatment, reducing transportation issues and financial burden which inhibit continuity of care. In addition, healthcare was once unattainable for many people due to its high costs and lack of insurance coverage. Now the goal is to provide the highest quality of care at the lowest cost, which can be achieved by providing alternative natural care to conditions historically treated with medication. Many people today are looking for natural and organic ways to treat conditions, including management of emotional states. For example, moderate to severe depression, considered a negative emotional state, has been treated chemically, but these treatments are too harsh for mild depression or decreased emotional states.⁴ Cocoa polyphenols may serve as an organic supplement and alternative treatment for improving emotional states and may benefit individuals psychologically.⁵ This paper evaluates three

randomized controlled trials comparing the effect of cocoa polyphenols as a method for improving emotional/mood states in healthy individuals ages 18 to 65 years old.

The incidence and prevalence of improved mood is unknown. However, negative mood states such as depression, affects 300 million people of all ages worldwide.⁴ It is very common, up to 30% of primary care patients have depressive symptoms.⁶ And with these many primary care visits, healthcare cost to treat increases. Total healthcare cost for overall mood is not available, but compared to medications and specialist visits, the addition of cocoa polyphenols can be very cost effective. Cocoa polyphenol extract 500mg to 700mg capsules (30-120 capsules supply) costs range from \$7.99-\$19.13 per bottle. Conversely, depression in America costs \$210 billion per year, and costs per patient can range from \$30-\$200 per month.⁷ Most recent data shows that in 2014, 78.4% visits to primary care specialists were preventive care. Mental and mood disorders accounted for 7.4% of healthcare visits, and there were 41,498 psychiatry visits in the U.S.⁸

The interplay of multiple factors causes emotional states: activation of different areas of the brain, the release of neurotransmitters and hormones, and the autonomic nervous system response.⁹ Copious amounts of research are available regarding negative emotional states and treatment. Positive emotional states are understood through the application of information from negative emotional state research. Due to its complexity, emotional/mood states, especially depressed mood states, are treated in a multidisciplinary way. Primarily, depressed mood states are treated with lifestyle changes involving exercise, nutrition, sleep hygiene, social support, and stress reduction. Psychotherapy is utilized in conjunction with lifestyle changes to help people manage their mood states in a cognitive behavioral way. If more support is needed in addition to lifestyle changes and psychotherapy, conventional medical therapies such as TCAs, SSRIs,

SNRIs, MAOIs, and stimulants are used to improved mood states, chronic or acute. Alternative treatments to medications and other lifestyle changes include relaxation techniques and acupuncture.¹⁰ Naturopathic methods involve vitamin and supplements therapy, for example St. John's Wort and cocoa polyphenols. Many people choose to eat foods high in fat and sugar when feeling stressed or have negative emotions and believe it makes them feel better. Only recently has research started to focus on this belief and the possible scientific association between cocoa polyphenols and emotional states.⁵

OBJECTIVE

The objective of this selective EBM review is to determine “Are high-dose cocoa polyphenols effective in improving emotional states in healthy individuals ages 18-65 years old for long-term treatment?”

METHODS

This review looks at two randomized, double-blind, placebo-controlled clinical trials and one randomized parallel open-label clinical trial. Each study included healthy female and male participants, ages 18-65 years old, amongst intervention and control groups.^{5,11,12} All studies examined patient-oriented outcomes by evaluating changes in mood from baseline in response to ingestion of cocoa polyphenols. The interventions in all three studies were cocoa polyphenols, distributed to participants in a variety of chocolate products with various total amounts of polyphenols, and over durations ranging from 2 weeks to 6 weeks. Participants were assigned to these intervention groups or similarly matched placebo groups. One study compared two types of chocolate to a non-chocolate snack instead of similarly matched placebo. Individuals in each intervention group were matched demographically to placebo and non-chocolate groups. Two studies used different self-reported questionnaires and one study used a visual scale to assess

changes in mood pre- and post-consumption for results comparison. Improvement in mood through perception of change was ultimately the outcome measured in each study.

This systematic review included searches in the PubMed database and Cochrane Systematic Reviews to ensure that no systematic review was conducted on this topic. All three studies were published in peer-reviewed journals in the English language between the years 2008 and 2013, although one study was conducted in Australia³, and another was conducted in Switzerland¹. Key words used to find these articles were “cocoa polyphenols”, “dark chocolate”, “effects” and “mood”. These articles were chosen based on their relevance to the clinical question and their inclusion of patient-oriented outcomes. Similar inclusion and exclusion criteria with some differences specific to each study was used for all three studies as outlined below (see Table 1). The inclusion criteria included randomized controlled trials (RCT) performed within the past 10 years and published in peer-reviewed journals that involved adults aged 18 to 77 years old who were considered healthy and cognitively intact. This review attempted to exclude studies conducted over ten years ago, with participants who were children or had comorbidities that could interfere with cocoa polyphenol metabolism and perception of mood.

Table 1: Demographics and Characteristics of included studies

Study	Type	#Pt	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Intervention
Pase ⁵ (2013)	Double blind RCT	87	40-65 yrs old	-Ages 40-65 -healthy (free of age-related disease such as dementia and cardiovascular disease)	Diagnosed heart disease or HTN, anxiety, depression, psychiatric disorders, epilepsy, food metabolism disorders (kidney, liver, GI disease), pregnant or breastfeeding, taking vitamin supplements,	16	20g dark chocolate drink with 500mg or 250mg of cocoa polyphenols once daily

					herbal extracts, illicit drugs or smoking		
Crews ¹³ (2008)	Double blind RCT	101	>60 yrs old	-Ages >60 yrs old -healthy, cognitive intact -total score of greater than or equal to 24 out of 30 on MMSE	H/o dementia, significant neurocognitive impairment, active or significant cardiovascular, pulmonary, neurological, endocrine, renal, urological, hepatic, hematological or GI disorders; Uncontrolled HTN, significant head injuries, hypoxia/anoxia, cholesterol, learning disabilities, color blindness, psychiatric/substance abuse disorders, antihypertensive/hypolipidemic/NSAIDs/anticoagulants/psychotropic medication use	11	Dark chocolate 37g bar plus 80u cocoa product with ~400mg cocoa polyphenols PO once daily
Martin ¹² (2012)	Open-label RCT	90	18-35 yrs old	-Ages 18-35 yrs old -BMI 18-25kg/m ² -varied anxiety levels on State-Trait Anxiety Inventory	Psychiatric or GI disorders, smoking, appetite-controlling medications or diets, medications that affect sensory function	0	Milk chocolate or dark chocolate snack 100g BID

Participants for all three studies were selected on a volunteer basis and considered healthy and cognitively intact, meaning without age-related disorders such as dementia or any disorders that may cause mood dysregulation.^{5,11,12} Statistical analysis in all studies utilized p-values to determine significance of mean changes in mood from baseline. The Crews et. al study utilized the Pearson chi-square test to determine subjective perceptions of changes from pre-

treatment baseline to the end-of-treatment phase in mood with treatment group self-reports data (for baseline data to determine postintervention comparison).¹² Martin et. al reported an analysis of variance F-score to assess food condition effects on anxiety trait groups and perceived emotional states in the short-term and with repeated exposure.¹¹ An analysis of co-variance was utilized in the Pase et. al study to compare the effects of each treatment condition (placebo, low cocoa polyphenol and high cocoa polyphenol groups) at different intervals of time (1, 2.5, 4 hr post dose, and day 30) to baseline measurements of content, a mood variable, followed by paired t-tests to examine differences between low-dose and high-dose cocoa polyphenols.⁵

OUTCOMES MEASURED

All three studies examined the effect of cocoa polyphenol supplementation via chocolate sources on mood states in healthy individuals. Martin et. al examined the effects of three different food conditions (milk chocolate, dark chocolate, and cheese and crackers) on postprandial anxiety and emotional states by questionnaires administered during time intervals before and after consumption of the food conditions, in which participants utilized a 4-point scale from extremely negative to extremely positive emotions, rating their emotional state for a duration of two weeks; These time intervals were 0 minutes (pre-prandial), 10 minutes and 60 minutes (post-prandial).¹¹ Pase et. al utilized Bond and Lader Visual Analogue Scales to assess self-reported mood states and provide outcome scores for contentedness over the course of thirty days; self-reports were collected on Day 1 and Day 30, at 1 hour, 2.5 hours, and 4 hours post dose on both days.⁵ A single follow-up self-report questionnaire to measure changes in mood perception at the end of six weeks of dark chocolate and cocoa consumption or a placebo was used in the Crews et. al study.¹² This follow-up self-report questionnaire was compared to similar reports of mood perception in a MMSE used at baseline.

RESULTS

Two of the three studies found similar results about the effects of cocoa polyphenols on mood/emotional states. In the randomized controlled trial by Crews et. al, a statistically significant change was not seen in mood states with supplementation of dark chocolate plus a cocoa beverage.¹² As reported by both the dark chocolate plus cocoa group and the low polyphenol placebo group in the follow-up self-report questionnaires, there was no difference found in subjective perceptions of change from pre-treatment baseline to the end-of-treatment phase in mood ($\chi^2 = 2.995, P = 0.392$).¹² There were 101 individuals randomly assigned to intervention groups in the beginning of the study, but only 90 individuals remained throughout the entire study; therefore, approximately 11% were lost to follow-up.¹² Tabulations of the total amounts of dark chocolate plus cocoa beverage and placebo products were used to assess treatment adherence until the completion of the study; deviation of 20% or more from the optimum treatment regimen was considered nonadherence, in which only one individual of the placebo group was considered such and excluded from study analysis.¹²

The Martin et. al study also found no statistically significant improvement in emotion with the consumption of milk chocolate and dark chocolate observed in a duration of two weeks in both the low and high anxiety groups.¹¹ Subjective reports to questionnaires completed by both anxiety groups for milk chocolate and dark chocolate showed no difference on perceived emotional state after repeated consumption of products ($P = 0.147$); the amount of change on each test day was similar.¹¹ An ANOVA F-score of 1.71 for variance among the groups and within each group was reported, meaning the emotional change with milk chocolate, dark chocolate, and cheese and crackers snacks in fact was very small determining no significance seen.¹¹ Ninety individuals participated in the study with no reports of individuals lost to follow-

up, therefore all individuals were accounted for in the study analysis. Participants were asked to report deviations from assigned consumption products and dietary restrictions.¹¹

The Pase et. al study did show a statistically significant improvement in contentment with the high-dose cocoa polyphenols dark chocolate drink versus the low-dose cocoa polyphenol and placebo groups following thirty days of treatment.⁵ Visual analogue scale scores indicated a significant effect of treatment was found following 30 days of treatment in the ‘content’ measurement ($F(2,68)=3.66, p<0.05$); only mean values for the high-dose polyphenol group after 30 days of treatment increased from baseline (mean values 71.78 and 65.75, respectively; see Table 2).⁵ Further paired t-tests were performed to compare high-dose polyphenol group and low-dose polyphenol group, showing a significant increase in content for the high-polyphenol group only (see Table 3).⁵ However, there were no significant changes found for contentedness after each timed interval administration of both high-dose and low-dose polyphenols and the placebo group (see Table 4).⁵ This study began with 78 participants and concluded with 72 participants, resulting in an approximated 8% lost to follow-up, and one individual was excluded from analysis due to low compliance.⁵

Table 2: ANCOVA results comparison for measure ‘Content’ of each treatment group after 30 days of supplementation

Treatment	Baseline		Day 30		ANOVA		
	M	(SD)	M	(SD)	N	$F(2,68)$	p -value
Placebo	67.61	(12.91)	66.86	(14.11)	22	3.66	0.03
250mg	66.73	(12.21)	63.72	(13.64)	25		
500mg	65.75	(14.20)	71.78	(13.99)	24		

Table 3: Follow-up paired t-test comparison for measure ‘Content’ of each treatment group after 30 days of supplementation

Treatment	t -test	p -value
Placebo	0.03	1.02

Low-dose polyphenol (250mg)	1.02	0.32
High-dose polyphenol (500mg)	-2.54	<0.05

Table 4: ANCOVA results comparison for measure ‘Content’ of each treatment group at 1, 2.5, and 4h post dose

Treatment	Baseline		1h		2.5h		4h		ANOVA		
	M	(SD)	M	(SD)	M	(SD)	M	(SD)	n	F	<i>p-value</i>
Placebo	66.00	(12.45)	62.53	(14.19)	62.18	(16.92)	60.78	(18.59)	25	1.32	0.27
250mg	67.33	(13.77)	68.55	(14.35)	63.35	(15.71)	61.69	(19.89)	26		
500mg	65.33	(14.06)	67/85	(14.48)	63.38	(12.83)	62.20	(15.73)	25		

Adverse side effects varied among the three studies. Only one adverse effect was reported in the Pase et. al study; a participant developed mouth ulcers, but was not excluded from the study analysis.⁵ The most adverse effects were reported in the Crews et. al study, with a total of 13 adverse events in the dark chocolate and cocoa group, and 10 adverse events reported in the placebo group.¹² However, no causal relationship between each adverse event to the interventions was found.¹² Adverse side effects were not mentioned in the Martin et. al study.¹¹

DISCUSSION

Cocoa polyphenols have received much attention in recent years for showing potential positive effects in vasodilation and antioxidant properties. Its potential role of improving emotional/mood states deems valuable for individuals who are searching for a safe, naturopathic, and cost-effective remedy for long-term treatment. The cost of prescription medication for treatment of altered mood states can be exponentially high, but the cost of this natural nutrient is much more cost effective with an almost non-existent side-effect profile.¹ Cocoa polyphenols are readily available and sold over the counter, making it an effortless way to obtain treatment. Cocoa polyphenols represent an avenue of 21st century medicine in which consumers are seeking more preventative and naturopathic remedies for their medical problems, including emotional

states. Its role in neurocognitive parameters has also been identified, and this factor can be very valuable to those who suffer from altered mood states.²

Along with the contradicting results in these studies, there are many limitations that may have affected the outcomes. All studies were volunteer-based, which may have led to a risk of bias with participants having presumptive predilection to chocolate and chocolate flavor which could have skewed reporting mood/emotional states. There was no specific regulation of participants' diets throughout the studies to account for polyphenol consumption outside of the study intervention and therefore control for possible confounding factors; the only study that included participants' food diaries to oversee outside polyphenol consumption with division into high versus low polyphenol food groups to maintain difference in high-dose and low-dose intervention group was done by Pase et al.⁵ The other two studies were simply by request to avoid consumption of polyphenols but no official attempt to regulate was made. Furthermore, each study had a small sample size which could have affected the statistical significance of the data obtained.

The experimental designs of all studies also had some limitations. Overall, these studies each had different age groups as participants with no overlap. In consideration of the only study that had a significant finding, this result can only be applied to individuals ages 40-65, which cannot be said for the age groups tested in the other two studies. All study designs had varied amounts of cocoa polyphenols classified as high-dose versus low-dose; therefore, the application of the results cannot specify an exact amount that will be beneficial for the general population.

One major limitation, non-blinding of participants, was performed in the Martin et. al study.¹¹ All participants were exposed to the interventions, which could have enhanced or

degraded the mood perception before consumption of the food conditions, greatly affecting the validity of the results.

Despite extensive exclusion criteria to increase validity in all three studies, all questionnaires and ratings used to evaluate participants' responses were different, with the content of the questionnaires in these studies not mentioned. This affects not only validity but also reliability of the testing results. Furthermore, all durations of treatment were different across all studies, increasing subjectivity of the results and decreasing the reliability of the study design.

CONCLUSION

Besides promising research of its vasodilatory and antioxidant properties, present psychiatric data in determining whether or not cocoa polyphenols is an effective means to improve mood is inconclusive. These three research studies attempted to determine a relationship between cocoa polyphenols and mood, but the conflicting findings warrant further investigation. To explore the possible significant findings in one study further, there needs to be more double-blind randomized controlled trials to be performed to reduce bias. These future studies should have larger sample sizes, longer durations of treatment, and standardized testing protocols used to assess mood/emotional states. Until more studies are performed, the effects of long-term cocoa polyphenol use on emotional states cannot be determined.

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