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Does Epigallocatechin Gallate Improve Mood in Heathly Adults?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not epigallocatechin gallate (EGCG) improves mood in healthy adults.

STUDY DESIGN: A review of three peer-reviewed journal articles written in the English language published between 2009 and 2012.

DATA SOURCES: Three randomized, double-blind, placebo-controlled studies comparing the effect of EGCG to placebo on mood were found using PubMed and Cochrane databases.

OUTCOMES MEASURED: Outcomes measured in the studies included change in mood. Patient ratings of mood were measured using Mood Visual Analog Scales (Mood VAS), the University of Wales Institute of Science and Technology (UWIST) mood adjective checklist, and the Bond-Lader mood scale.

RESULTS: Wightman et al.[1] showed no significant correlation between EGCG consumption and mood. Scholey et al.[2], on the other hand, found EGCG's effect on mood to be significant, increasing calmness and reducing stress with p-values of 0.04 and 0.017 respectively. Brown et al.[3] achieved similar findings with a significant increase in hedonic tone ($p = 0.048$), although decrease in tense arousal did not reach statistical significance ($p = 0.056$).

CONCLUSIONS: The summative results of these investigations indicate the need for additional studies examining the effects of EGCG on mood. The conflicting evidence provided by Wightman et al.[1], Scholey et al.[2], and Brown et al.[3] leaves the question of EGCG's efficacy in improving mood in healthy adults largely unanswered. Due to its relative safety, availability, and cost-effectiveness, further studies on efficacy of EGCG in improving mood are warranted.

KEY WORDS: epigallocatechin gallate; mood

INTRODUCTION

Mood is an omniprevalent, sustained, internally-experienced feeling tone that affects our actions and how we perceive the world. In healthy individuals, an extensive range of moods are experienced daily, varying from normal to elevated to depressed and the many shades in between. Healthy individuals feel in control of their moods. Mood disorders occur when that sense of control over mood is lost and a subjective experience of distress results. Disorders of mood manifest in a variety of ways, but almost all who suffer from mood disorders experience a disturbance in interpersonal, societal, and occupational functioning.[4] Similarly, all individuals experience anxiety and stress during their lifetime. These emotions, while often completely healthy and at times even beneficial, may become pathologic if they are uncontrolled, cause psychological distress, and interfere in other aspects of the individual's life.[5]

An exact number of health care visits per year allocated to mood remains unknown. However, a 2012 estimate indicates that 1,035,537 patients were seen for mental health related visits.[6] Depression, one of the most prevalent mood disorders, is a leading cause of morbidity and mortality, and its treatment accounts for a large portion of physician-prescribed medications. Estimates designate it the second leading cause of disability worldwide.[7] Similarly, anxiety disorders affect about 30 million people in the United States and are associated with significant morbidity.[5] Anxiety and mood disorders are extremely prevalent entities and account for a large number of mental health diagnoses.[4,5] In 2007, approximately 26.8 million adults age 18 or older reported receiving treatment for anxiety and mood disorders.[8] A total of $36.8 billion was spent on treating these conditions, half of which was on prescription medications.[8] In the same year, $1,374 per adult per year was spent by those with anxiety and mood disorder related expenses. [8]

The exact physiology of normal mood regulation as well as the pathophysiology of mood

disorders remains largely unknown. Some evidence suggests that regulation of monoamine neurotransmitters may be involved, specifically serotonin and norepinephrine.[7] Major mood disorders are thought to involve various etiologies including genetics, environmental stress, dysregulation of neurotransmission, abnormal neuroplasticity, and altered gene expression.[9] According to the Sequenced Treatment Alternatives to Relieve Depression (STAR'D) trial, current antidepressant treatments do not provide high remission rates for depression.[9] Similarly, anxiety disorders are often chronic and resistant to treatment.[5]

Current pharmacotherapy for mood and anxiety disorders includes selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), atypical antidepressants, tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and benzodiazepines. Other potential therapies include psychotherapy such as cognitive and behavioral therapy, and electroconvulsive therapy (ECT).[5,7] While the SSRIs, SNRIs, and atypical antidepressants have improved side effect profiles over the older MAOIs and TCAs, they have not shown increased efficacy in treatment of mood disorders.[9] Benzodiazepines are most commonly used for treatment of anxiety disorders. While the majority of those with anxiety disorders benefit from such pharmacotherapy initially, up to 80% of individuals relapse within a year of discontinuing the medication.[5] Currently, psychotherapy and ECT are used adjunctively or as alternatives to pharmacologic treatment. While the various psychotherapies have shown equal efficacy to that of pharmacotherapy alone, evidence remains conflicting whether there is increased benefit to combination pharmacologic and psychotherapy. Nevertheless, some studies do suggest improved outcomes with a combination of therapeutic disciplines.[4] ECT is typically only considered in resistant, severely debilitating cases.[5] Regardless of the therapeutic methods used, there remains room for improvement in treatment of anxiety and mood disorders not only

to increase therapeutic efficacy, but also to decrease side effects and reduce cost.

Tea, derived from the plant *Camellia sinensis*, remains one of the most commonly consumed beverages across the world.[3] Epigallocatechin gallate (EGCG), a natural flavonoid in green tea, has been linked to a variety of health benefits including weight management and prevention of chronic conditions such as cardiovascular disease, cancer, and neurodegenerative conditions. Some evidence suggests a significant association between green tea and decreased psychological distress.[2] In addition, green tea has been linked to anxiolytic activity and has been proposed to exhibit relaxation properties. Consumption of green tea and specifically EGCG, have therefore been hypothesized to have positive effects on individuals' self-reported mood.[3]

Disturbances in mood, whether temporary or prolonged, physiologic or pathologic, can affect all aspects of an individual's life. As a result, enhancing our understanding of mood physiology and investigating mechanisms for improving mood may serve an important role in augmenting quality of life. Finding new ways to enhance mood, even physiologic changes in mood, may be beneficial for all individuals seeking an increased quality of life. Therefore, this paper evaluates three double blind, randomized controlled trials comparing the efficacy of epigallocatechin gallate to placebo on improving mood.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not epigallocatechin gallate improves mood in healthy adults.

METHODS

Three double blind, randomized controlled trials were included in this systematic review. Studies were selected based on various criteria including population studied, interventions used, comparisons made, and outcomes measured. In all three studies, the population consisted of

healthy adults over 18 years of age. Brown et al.[3] included only male nonsmokers between 40 and 65 while Scholey et al.[2] and Wightman et al.[1] included both males and females ages 18 to 37 and 18 to 30 respectively. The intervention applied was epigallocatechin gallate (EGCG). Brown et al.[3] gave 400 mg EGCG BID in the form of Teavigo, a purified green tea extract with > 97% EGCG content. Scholey et al.[2] also gave Teavigo, but used 300 mg capsules with 94% EGCG content. Wightman et al.[1] had two treatment groups, giving either 135 or 270 mg EGCG capsules with 94% EGCG content. In all three studies, EGCG effects were compared to those of placebo. Scholey et al.[2] used flour capsules whereas Brown et al.[3] used 400 mg lactose as the control.[2,3] Selected studies were randomized, double blind, placebo-controlled trials comparing the effects of EGCG to placebo on mood and included change in mood as a measured outcome.

Articles were researched via PubMed and Cochrane databases and were selected based on relevance to the clinical question and that measured outcomes included patient oriented evidence that matters (POEMS). Key words entered in the PubMed search included “epigallocatechin gallate” and “mood.” All three of the selected studies were peer-reviewed journal articles written in the English language published between 2009 and 2012.

Studies included in this systematic review were selected based on the following inclusion criteria: all were primary research studies, randomized controlled trials, published after 1996, included POEMS, and evaluated change in mood as one of the measured outcomes. Exclusion criteria included studies involving those under 18 years of age or diagnosed with a significant medical condition including but not limited to diabetes mellitus, neurological or psychological disorder, food allergy or metabolism disorder, drug abuse, or tobacco use. Statistics reported in the three studies include the paired t-test, p-value, mean change from baseline, and ANCOVA. See Table 1 below for Demographics and Characteristics of Included Studies.

Table 1: Demographics & Characteristics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Brown, 2009[3]	Double blind RCT	100	40-65	Male, nonsmokers, 40-65 years old, BMI > 28 and < 38 kg/m^2, fasting plasma glucose < 7.0 mmol/l	Significant history of disease, current disease, or on medication	12	400 mg EGCG BID (Teavigo) vs placebo (400 mg lactose) BID
Scholey, 2011[2]	Double blind RCT	31	Mean 27.74, SD 9.28	Nonsmokers, normal weight (mean 71.4 kg, range 46-95), right-handed, English speaking	Taking illicit drugs, medications, or natural therapies, psychological (depression, anxiety) or physical conditions (food allergies, kidney, liver, and/or gastrointestinal diseases) that would affect food metabolism	2	300 mg EGCG (Teavigo) vs placebo (identical capsule containing flour)
Wightman, 2012[1]	Double blind RCT	27	18-30	Self-reported good health, free from social drugs, alcohol, prescription medication, and herbal extracts/food supplements	Patients who had suffered a head injury, neurological disorder, neurodevelopmental disorder, relevant food allergies or intolerances, smoked tobacco, drank > 600 mg/day of caffeine, or took illicit social drugs	5	135 mg EGCG vs 270 mg EGCG vs placebo

OUTCOMES MEASURED

Outcomes measured for all selected studies included patient rating of mood. Various scales were used, each with slightly different criteria. Wightman et al.[1] used the Mood Visual Analog Scale (Mood VAS) in which participants rated aspects of mood from 0-100. The Mood VAS included ratings of how relaxed, alert, jittery, tired, tense, and mentally fatigued subjects

felt in addition to an assessment of overall mood.[1] Scholey et al.[2] also required ratings of mood from 0-100, but instead used the Bond-Lader mood scale. In this trial, subjects rated level of alertness, calmness, contentedness, stress, and fatigue.[2] The final study by Brown et al.[3] assessed mood with the University of Wales Institute of Science and Technology mood adjective checklist which measured level of energetic arousal, tense arousal, hedonic tone, and general arousal.[3]

RESULTS

While all three studies were double blind, randomized controlled trials evaluating a population of healthy adults, two of the studies included both male and female participants while one included only males. Similarly, although all selected studies evaluated only adults over 18 years of age, one study utilized participants 40-65 years of age whereas the others studied those 18-30 and 18-37 years of age.[1-3] Since investigators were interested in purely healthy adults, Wightman et al.[1] included only those participants who reported themselves in good health and who did not use drugs, alcohol, prescription medications, food supplements or herbal extracts and excluded those reporting a head injury, neurologic or neurodevelopmental disorder, relevant food allergies, tobacco or illicit drug use, or consumption of over 600 mg caffeine per day. 27 healthy adults were included in the trial while an additional 5 were replaced during the trial due to nonadherence to testing procedures. All five were replaced before blinding was revealed.[1] Scholey et al.[2] included English speaking, right-handed, non-smokers of normal weight who did not take illicit drugs, medications, or natural therapies, and excluded those with psychological disorders such as depression or anxiety and physical conditions such as food allergies, kidney, liver, or gastrointestinal diseases which may have affected food metabolism.[2] Brown et al.[3] included only males self-reported as non-smokers with a BMI between 28 and 38 kg/m^2 and a fasting plasma glucose < 7.0 mmol/L. Those with significant current or past history of disease or

those on medications were excluded from the study. 100 participants were selected, matched for age and insulin resistance, and randomized into placebo and EGCG groups. Of the 50 subjects in each group, 6 of those in the placebo group did not receive the allocated intervention. In the EGCG group, all 50 received the allocated intervention, but 1 discontinued intervention during the study due to starting a new medication. For analysis, 2 members of the placebo group and 3 members of the EGCG group were excluded due to elevated 2 hour glucose values of ≥ 11.1 mmol/L resulting in n = 42 in the placebo group and n = 46 for the EGCG intervention.

Teavigo, the intervention in two of the studies has been confirmed safe for human use without any reported adverse effects.[2] Wightman et al.[1] makes no mention of their EGCG capsule safety, but no subjects were reported lost due to adverse reactions or intolerability. Similarly, neither Scholey et al.[2] nor Brown et al.[3] report discontinuation of the study due to adverse effects of EGCG intervention.

Wightman et al.[1] tested two doses of EGCG, 135 and 270 mg per day on three separate occasions. The authors were unable to determine a significant difference in outcomes in those receiving placebo compared to either dose of EGCG. Therefore, Wightman et al.[1] did not supply data analyzing effect on mood, indicating that "no significant treatment-related differences were observed."[1] Likewise, specific test statistics and statistics signifying precision of treatment effect were not reported due to lack of evidence demonstrating significant change in mood.

Scholey et al.[2] examined a 300 mg dose of EGCG per day given on two separate occasions one week apart and found a significant difference in change from baseline with treatment effect. While Scholey et al.[2] did not provide specific data for either EGCG or placebo groups when reporting stress and calmness, the p-values for both indicate that the difference between treatments was large enough to be considered statistically significant. The authors did

not provide enough data for conversion to dichotomous data. Instead, they reported t-test values comparing group change from baseline. Results of the t-test indicated an increase in self-reported calmness with EGCG compared to placebo with a t-value for EGCG of 2.17 ($p = 0.04$).[2] Results also showed a decrease in self-reported stress with an EGCG t-value of 2.52 ($p = 0.017$).[2] Results are provided in Table 2 below. Other mood measures showed no significant difference from placebo and the authors therefore did not provide associated data.[2]

Table 2: Mean Change from Baseline with EGCG Consumption

	T-Test (n = 29)	**P-Value**
Calmness	2.17	0.04
Stress	2.52	0.017

Brown et al.[3] compared treatment with 800 mg EGCG per day to 800 mg placebo for 8 weeks. The authors reported mean hedonic tone and tense arousal for both EGCG and placebo at baseline and post-intervention. The treatment effect appears relatively small given that the EGCG group's mean hedonic tone was essentially the same pre and post intervention (29.10 and 29.11 respectively).[3] The difference in EGCG and placebo post-intervention hedonic tone was considered statistically significant, however, with a p-value of 0.048.[3] Despite statistical significance, this difference appears largely due to change in placebo group between baseline and post-intervention (29.25 and 27.84 respectively), rather than to treatment effect.[3] For tense arousal, treatment appears to have had a slightly greater effect in altering the EGCG group's mean score from baseline, but post-intervention difference between placebo and EGCG did not reach statistical significance ($p = 0.056$).[3] Energetic and general arousal measures did not reach statistical significance and data was therefore not provided. The authors did not provide enough information for conversion to dichotomous data, but did report mean post-intervention and baseline scores for control and treatment groups as provided in Table 3 below. They also noted use of a mixed model repeated measures ANCOVA to analyze the relationship between self-

reported mood and treatment administered, while controlling for other variables inherent in the study's design. Covariates included alcohol intake, diet, physical activity, and body weight change and were not found to significantly impact mood results. Specific data was not provided.[3]

Table 3: Mean Values at Baseline and Post-therapy - EGCG versus Placebo

Baseline:	**Hedonic Tone**	**Tense Arousal**
EGCG	29.10 (SD 3.68)	11.29 (SD 3.06)
Placebo	29.25 (SD 3.72)	11.83 (SD 3.99)
P-Value	≤ 0.05	≤ 0.05
Post-Therapy:		
EGCG	29.11 (SE 0.44)	11.06 (SE 0.47)
Placebo	27.84 (SE 0.46)	12.33 (SE 0.45)
P-Value	0.048	0.056

DISCUSSION

Conflicting evidence in the three studies included in this review presents difficulty in determining conclusive effects of EGCG on mood. It appears that higher doses of EGCG may affect some aspects of mood, but further study is warranted before definitive conclusions can be reached. The ability of 300 mg EGCG to increase calmness while reducing stress and 800 mg to significantly increase hedonic tone offers a promising outlook on the ability of EGCG to improve mood.[2,3] Such evidence is tempered, though, by the inability of 135 and 270 mg to considerably alter mood parameters and failure of 800 mg EGCG to significantly reduce tense arousal.[1,3]

Nonetheless, green tea, with its high EGCG content, remains one of the most widely consumed beverages in the world. It has long been proposed to possess health-enhancing properties and is generally considered safe for consumption.[10] Green tea extracts are deemed safe for up to one year, and EGCG has been well tolerated at 800 mg per day for up to 4 weeks.[10, 11] Although not routine primary therapy, studies have found green tea extract useful in treatment of obesity, cancer, and high cholesterol. Currently, it is also under investigation for anxiety, stroke, diabetes, Alzheimer's and Parkinson's disease, hypertension, and osteoporosis.[10,11] Regardless of its equivocal efficacy, green tea extracts are relatively inexpensive and may provide a more cost-

effective approach to moderation of mood disorders than presently available pharmacotherapy.[11]

Currently, green tea is not recommended for infants, children, or pregnant women due to caffeine content. Caffeine also affects CYP450 metabolism and may therefore interact with SSRIs and SNRIs, both of which are commonly used to treat mood disorders. EGCG capsules, on the other hand, do not contain caffeine and have not shown significant interaction with commonly used anxiety or mood disorder medications. [10] Potential interactions do exist, however, and include increased bleeding risk with concomitant use of vitamin K antagonists, nonsteroidal anti-inflammatories, anticoagulants, salicylates, antiplatelets, or thrombolytics, depletion of folic acid levels, and increased serum concentrations of simvastatin. No adverse effects have been observed with daily green tea consumption. Its extracts, however, have been linked to hepatotoxicity, especially at high doses or if taken without food. While unproven, EGCG or its metabolites are suspected to be responsible. Other potential adverse effects include headache, dizziness, and gastrointestinal disturbances. To date, no contraindications to green tea extract exist, although caution is advised in those with hepatic failure.[11]

In this review, several factors may limit generalizability to a broader population. One such limitation is that green tea extract and EGCG are natural products. Dosing is therefore not standardized by the FDA. Depending on the manufacturer and product used, EGCG content may vary which could affect study outcomes. [10] In addition, sample sizes in all three studies were relatively small. Wightman et al.[1] included only 27 participants while Scholey et al.[2] included 31. Brown et al.[3], the largest of the three, included only 100 participants in the trial. Excepting Wightman et al.[1], studies did not restrict consumption of flavonoid-containing items other than green tea. Therefore, intake of additional substances containing EGCG or other flavonoids may have affected study outcomes. In Wightman et al.[1], several subjects lost during the trial were

replaced before blinding was revealed. This may have inadvertently altered group randomization. While Wightman et al.[1] and Scholey et al.[2] included both males and females over 18, the upper limits of their age groups did not extend past 37 years old. Alternatively, Brown et al.[3]included only males and studied those between 40 and 65, failing to include younger adults and excluding female participants. In addition, Brown et al.[3] employed subjects with some insulin resistance. Although still considered healthy adults, the presence of insulin resistance and exclusion of certain gender and age groups may limit applicability to a broader adult population. Furthermore, variation in administered EGCG dosage between the three studies and use of different, although validated, scales for mood quantification makes comparison of effects on mood difficult. [10]

CONCLUSION

Overall, evidence in this review leaves the question of EGCG's efficacy in improving mood in healthy adults largely unanswered. While Wightman et al.[1] determined EGCG did not appreciably affect mood, Scholey et al.[2] found EGCG to significantly increase calmness and reduce stress as compared to placebo. Meanwhile, Brown et al.[3] determined EGCG to somewhat alter mood, significantly increasing hedonic tone compared to placebo, and although it also decreased tense arousal, this did not reach statistical significance. Due to conflicting data between studies, a definitive conclusion on EGCG efficacy in altering mood cannot be reached.

In light of its relative safety, availability, and low cost, further study on EGCG's efficacy in improving mood is warranted. While current data remains inconclusive, further research may elicit additional evidence on EGCG's ability to alter mood. Prospective studies should focus on additional doses and standardization of EGCG content as well as assess efficacy of EGCG versus existing anxiety and mood disorder therapies. A greater number of studies with larger sample sizes, more inclusive populations, and a universal mood assessment would also prove beneficial.

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