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Integrative Medicine

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Vol. 18, Issue 4, April 2015
www.ahcmedia.com

HYPERTENSION

ABSTRACT & COMMENTARY

Blueberry Consumption Improves Blood Pressure and Arterial Stiffness in Postmenopausal Women with Hypertension

By Traci Pantuso ND, MS

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Dr. Pantuso reports no financial relationships relevant to this field of study.

SYNOPSIS: This randomized, double-blind, placebo-controlled study demonstrated that consumption of freeze-dried blueberry powder twice daily for 8 weeks improved blood pressure and measurements of arterial stiffness in postmenopausal women with pre- or stage 1 hypertension.

SOURCE: Johnson SA, et al. Daily blueberry consumption improves blood pressure and arterial stiffness in postmenopausal women with pre- and stage 1-hypertension: A randomized, double-blind, placebo-controlled clinical trial. *J Acad Nutr Diet* 2015; in press.

A randomized, double-blind, placebo-controlled clinical trial design was used to investigate the effects of freeze-dried blueberries on blood pressure and arterial stiffness in postmenopausal women with pre- or stage 1 hypertension (HTN) (≥ 125/85 mmHg and ≤ 160/90 mmHg). Eighty-one postmenopausal women between the ages of 45-65 years with pre- or stage 1-HTN were recruited in the greater Tallahassee, FL, area.

Women were excluded from the study if they were diagnosed with uncontrolled HTN (> 160/100 mmHg) or cardiovascular disease; were heavy smokers (> 20 cigarettes/day); were diagnosed with asthma, glaucoma, thyroid, kidney, liver, or pancreatic disease; had active cancer; or were receiving hormone replacement therapy or insulin. Forty-eight women who met the inclusion criteria

Financial Disclosure: *Integrative Medicine Alert*'s executive editor David Kiefer, MD, peer reviewer J. Adam Rindfleisch, MD, MPhil, AHC Media executive editor Leslie Coplin, and managing editor Leslie Hamlin report no financial relationships relevant to this field of study.

Integrative Medicine [ALERT]

Integrative Medicine Alert,
Integrative Medicine Alert (ISSN 1096-942X) is published monthly by AHC Media LLC, One Atlanta Plaza, 950 East Paces Ferry Road NE, Suite 2850, Atlanta, GA 30326.

Periodicals Postage Paid at Atlanta, GA, and at additional mailing offices.

GST Registration Number: R128870672.
POSTMASTER: Send address changes to *Integrative Medicine Alert*, P.O. Box 550669, Atlanta, GA 30355.

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were enrolled in the study and were instructed to not change their diet or physical activity pattern throughout the study.

The women were instructed to mix 11 grams of freeze-dried blueberry powder in water twice daily (the equivalent of 1 cup of fresh blueberries per day). The freeze-dried blueberry powder contained a 50/50 mix of *Vaccinium virgatum* and *Vaccinium corymbosum* high brush berries. The authors also instructed the women to mix in Splenda or vanilla for extra flavoring if required. The placebo powder contained artificial and natural blueberry flavoring, maltodextrin, fructose, artificial purple and red color, and citric acid and silica dioxide. The nutritional composition of both the freeze-dried blueberry powder and placebo powder were measured; however, the authors did not comment on whether a taste comparison was performed between the powders (*see Table 1*).

Blood pressure, height, weight, body mass index (BMI), and waist circumference were measured at baseline, 4-, and 8-week time points. Arterial stiffness was also measured as an outcome using a carotid-femoral pulse wave velocity and brachial ankle pulse wave velocity performed at baseline, 4, and 8 weeks. Pulse wave velocity is used to assess arterial stiffness and also may be used to predict future cardiovascular events. Nitric oxide (NO), superoxide dismutase (SOD), and C- reactive protein (CRP) were measured from blood samples taken at baseline, 4, and 8 weeks. Statistical analysis was performed using analysis of variance (ANOVA) models to detect statistical analysis between groups and over time, and P values < 0.05 were considered statistically significant.

Forty women completed the study, and 17% (20% for the treatment group and 13% for the control group) of women dropped out of the study due to noncompliance, medical, and health-related issues such as gastrointestinal complaints and personal reasons. The authors looked at differences between groups at the 0, 4-, and 8-week timepoints and analyzed with ANOVA.

No significant differences were detected in age, height, weight, BMI, or waist circumference between groups throughout study. No significant differences were detected at baseline for systolic blood pressure (SBP), diastolic blood pressure (DBP), and arterial stiffness measurements between groups.

SBP and DBP were significantly reduced by 5.1% (7 mmHg; $P < 0.05$) and 6.4% (5 mmHg; $P < 0.01$), respectively, in the

Table 1: Different Blueberry Preparations and Their Nutrient Compositions

	Placebo powder (22 g)	Freeze-dried blueberry powder (22 g)	Fresh blueberry (1 cup)
Anthocyanins (mg/g)	0	4.69	Not measured
Phenolics (mg/g)	0	8.45	Not measured
Oxygen Radical Absorbance (µmol TEC/g)	0	80.52	Not measured
Potassium (mg)	0	103.18	112
Calcium (mg)	0	7.50	9.00
Vitamin C (mg)	0	2.27	14.10
Protein (g)	0.17	0.59	1.08
Fiber (g)	0	4.73	3.50
Total Carb (g)	20.82	20.57	21.02
kCal	86	87	83

Adapted from: Johnson SA, et al. Daily blueberry consumption improves blood pressure and arterial stiffness in postmenopausal women with pre- and Stage 1- hypertension: A randomized, double-blind, placebo-controlled clinical trial. *J Acad Nutr Diet* 2015; in press.

Summary Points

- In postmenopausal women diagnosed with pre- or stage 1-hypertension, 22 grams of freeze-dried blueberry powder significantly improved both systolic and diastolic blood pressure after 8 weeks compared to baseline.
- In addition, blueberry powder significantly improved arterial stiffness, which may be modulated through the significant increase in nitric oxide measured at 8 weeks, compared to baseline in the blueberry group.

blueberry group at 8 weeks compared to baseline (*see Table 2*).

No significant decrease in either SBP or DBP was noted in the control group (*see Table 2*). There was a significant decrease in the brachial ankle-pulse wave velocity at 8 weeks compared to baseline in the blueberry group ($P < 0.01$) (*see Table 2*). No change in the brachial-ankle pulse wave velocity was noted in the control group (*see Table 2*). There were no significant changes in CRP levels noted in either group during the study. SOD and NO levels were significantly increased at 8 weeks compared to baseline in the blueberry group (*see Table 2*). SOD levels in the control group were significantly changed at both 4 and 8 weeks, while no significant changes in NO levels were detected in the control group (*see Table 2*).

Table 2: Differences Between Blueberry and Control Groups

	Blueberry	Control
Baseline	SBP: 138 ± 14 DBP: 80 ± 7 baPWV: 1498 ± 179 SOD: 0.21 ± 0.06 NO: 9.11 ± 7.95	SBP: 138 ± 15 DBP: 78 ± 8 baPWV: 1470 ± 194 SOD: 0.23 ± 0.05 NO: 9.81 ± 7.20
4 weeks	SBP: 136 ± 15 DBP: 77 ± 10 baPWV: 1466 ± 203 SOD: 0.36 ± 0.11** NO: 13.86 ± 11.45	SBP: 136 ± 15 DBP: 78 ± 11 baPWV: 1464 ± 174 SOD: 0.40 ± 0.06** NO: 9.20 ± 5.95
8 weeks	SBP: 131 ± 17* DBP: 75 ± 9** baPWV: 1401 ± 122** SOD: 0.50 ± 0.22** NO: 15.35 ± 11.16*	SBP: 139 ± 15 DBP: 80 ± 15 baPWV: 1,477 ± 175 SOD: 0.49 ± 0.15** NO: 10.73 ± 5.63

Systolic blood pressure (SBP; mmHg), diastolic blood pressure (DBP; mm Hg), brachial-ankle pulse wave velocity (baPWV; cm/sec), superoxide dismutase (SOD; U/mL) and nitric oxide (NO; µM) levels.

*$P < 0.05$ for within group differences in comparison to baseline

**$P < 0.01$ for within group differences in comparison to baseline

Adapted from: Johnson SA, et al. Daily blueberry consumption improves blood pressure and arterial stiffness in postmenopausal women with pre- and Stage 1- hypertension: A randomized, double-blind, placebo-controlled clinical trial. *J Acad Nutr Diet* 2015; in press.

Eight women dropped out of the study due to personal reasons, gastrointestinal issues, and non-compliance. The authors do not mention the number of women that discontinued the study for each particular reason.

■ COMMENTARY

This study demonstrated improvements in blood pressure and arterial stiffness in postmenopausal women with pre- or stage 1-HTN with consumption of 22 grams of freeze-dried blueberry powder (equivalent to 1 cup of blueberries per day) after 8 weeks compared to baseline. The BP findings may have been significant, with a 7/5 mmHg reduction in SBP/DBP, but it is important to compare to other clinically significant dietary lifestyle modifications that have been shown to reduce blood pressure. The DASH diet with sodium restriction has been shown to reduce BP 12/6 mmHg (SBP/DBP) in hypertensive adults, and the DASH diet without sodium restriction reduced BP 6/2 mmHg (SBP/DBP) in hypertensive adults over 14 weeks.[1] Weight loss of 4.4-8.8 lbs (2-4 kg) has also been shown to decrease SBP in the range of 3-8 mmHg.[2]

NO is an important chemical mediator that is known to relax blood vessels and was increased in the blueberry group at 8 weeks compared to baseline.[3] SOD levels were also significantly higher at 8 weeks compared to baseline in both the control and blueberry groups, making the validity of this finding questionable.

There are a number of limitations to this study, including the number of participants and the relatively short trial period. The number of participants was low, but comparable to many herbal studies and the authors discuss that because of this, the study may have been underpowered.

Eight women did not complete the study due to noncompliance, medical, and health-related issues such as gastrointestinal complaints, taste fatigue as the participants mixed the blueberry and placebo powder into their beverages, and personal reasons. The authors did not provide further detail; however, gastrointestinal complaints and taste fatigue as a result of the powder are important factors when recommending a freeze-dried powder for clinical use. This study did not control for physical activity, diet, or smoking, which are all HTN risk factors.[4] In a previous 3-week study, blueberry consumption

did not appear to have the same effect on lowering blood pressure in adult smokers.[5] The women in this study were not excluded for smoking fewer than 20 cigarettes per day, which may have impacted the results of this study. The study was also funded by the U.S. Highbush Blueberry Council/U.S. Department of Agriculture, which provided the freeze-dried blueberry and placebo powders. Because the study population was postmenopausal women with pre- and stage 1-HTN, it is difficult to extrapolate the results of this study to other populations. However, a previous study investigating blueberry powder consumption in men and women with metabolic syndrome who were of middle age and obese demonstrated a reduction in SBP and DBP after 8 weeks of supplementation.[6]

The participants in this study consumed freeze-dried blueberry powder.; other studies have demonstrated high intakes of flavonoids, such as the anthocyanins found in blueberries, have been associated with a decreased risk of HTN and myocardial infarction incidence or prevalence.[6,7] It is difficult to equivocate the effects that fresh blueberries would have compared to the freeze-dried powder from the results of this study. However, the authors note that freeze-drying blueberries has been shown to "cause the least loss of key nutrients." The freeze-dried blueberry powder used in this study was made from 50/50 mix of *V. virgatum* and *V. corymbosum* high brush berries; which may or may not have the same bioflavanoid profile as blueberries that are easily obtained from the grocery store. Another factor to consider when recommending blueberry consumption is to specify that the berries should be organic, as they are ranked number 14 on the Environmental Working Group's list of Fruits and Vegetables With Pesticide Residue Data.[8]

In summary, 1 cup of organic blueberries per day, fresh or frozen, combined with a dietary pattern such as the Mediterranean or DASH diet and adequate physical activity to maintain a healthy weight may improve hypertension and other cardiovascular risk factors.[2-9] These recommendations should be considered as part of a preventive or treatment strategy for both healthy and hypertensive patients. ■

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GASTROINTESTINAL DISEASE

ABSTRACT & COMMENTARY

Managing IBS with Semi-permanent Embedded Fibers at Acupuncture Sites

By William C. Haas, III, MD, MPH

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Dr. Haas reports no financial relationships relative to this field of study.

SYNOPSIS: Catgut-embedded acupuncture, which involves embedding fibers of animal intestines into the skin at acupuncture points, improved abdominal pain, constipation, and bloating as well as symptoms of depression among patients with irritable bowel syndrome compared to both sham acupuncture and conventional drug therapy.

SOURCE: R Rafiei, et al. A new acupuncture method for management of irritable bowel syndrome: A randomized double-blind clinical trial. *J Res Med Sci* 2014;19:913-917.

Irritable bowel syndrome (IBS) is a disorder characterized by chronic abdominal pain, bloating, and alteration of bowel habits. The precise etiology of the syndrome is unknown, with many factors, such as dietary, immunologic, and psychosocial factors, hypothesized to contribute to the disorder. By and

Summary Points

- Despite some methodological flaws, the present study found that catgut acupuncture potentially reduces the symptoms of constipation-dominate irritable bowel syndrome (IBS).
- Four weeks after treatment, catgut acupuncture may decrease IBS pain by approximately 60%.

large, IBS treatments target symptom relief and vary from conventional pharmacotherapy to integrative approaches such as acupuncture. The use of traditional acupuncture for IBS is somewhat controversial, as previous studies have yielded mixed results.[1]

The present study applies a different method of acupuncture, catgut embedding, in an attempt to decrease the symptom severity and/or pain associated with IBS. The technique of catgut acupuncture involves embedding fibers of sheep or goat intestines into designated acupuncture points and provides continuous stimulation until the fibers are absorbed. A form of this technique has been used in traditional Chinese medicine for thousands of years, but only more recently has it been shown to be effective in conditions such as perimenopausal syndrome, chronic urticarial, and insomnia.[2-4] The method is generally regarded as safe, with only one case report referencing complications of tender subcutaneous nodules erupting at embedding sites approximately 1 month after treatment.[5]

The researchers designed a randomized, double-blind, sham-control trial to assess the efficacy of catgut acupuncture among patients meeting Rome III criteria for IBS. Sixty patients were enrolled from two academic medical centers and one private gastrointestinal clinic. Inclusion criteria were limited to Rome III symptom severity — recurrent abdominal pain or discomfort for ≥ 3 days per month over a 3-month period associated with, but not limited to, relief with defecation, change in stool frequency or form, and or abdominal bloating.[6] Exclusion criteria included pregnancy, diabetes mellitus, scleroderma, inflammatory bowel disease, prior small intestinal surgery, or recent gastrointestinal infections.

Prior to randomization, patients were observed during a 2-week washout period and given 135 mg of Colofac (mebeverine) daily, an accepted drug regimen for IBS. After the washout period, patients were randomly assigned to one of three treatment groups: 1) catgut embedding acupuncture, 2) sham acupuncture, or 3) Colofac 135 mg. Details regarding sham treatments were not provided. Moreover, the number of acupuncture sessions was not clearly specified; however, sessions presumably occurred once, given that semi-permanent fibers were embedded in the catgut group. All acupuncture treatments were performed by the same trained professional. Acupuncture sites differed between the sham group and the catgut group, with the inclusion of sites for weight-loss in the catgut group. Acupuncture sites within the two treatment groups, however, were standardized according to the following designation: 1) sham group (GB26, SP8, 1 inch ST25, UB22, Ren5) and 2) catgut group (UB17, 23, 25. DU3, SP9, 15, ST25, 36, Ren12, and 4. Kid15).

Outcomes measured included frequency of IBS symptoms (diarrhea, constipation, and bloating) as well as mean gastrointestinal pain scores. Additionally, both depression and anxiety were assessed using the Beck inventory questionnaire. Baseline surveys were administered after the 2-week washout period and again 4 weeks after the treatment intervention.

There were no significant differences between groups among basic demographic characteristics (age, sex, or weight) at baseline. With regard to IBS symptoms, frequency of constipation and bloating declined in both the catgut and sham groups, with the catgut group experiencing a greater reduction in frequency. The drug-only group did not differ significantly from baseline with regard to constipation or bloating. No mention was made regarding changes in diarrhea frequency, but according to the corresponding figure, there did not appear to be a significant decline among or between the groups. Unfortunately, neither standard deviations nor the significance values were presented in the figure or accompanying text reviewing the changes in IBS symptoms. With regard to severity of gastrointestinal pain, the catgut group experienced an approximate 60% reduction in pain scores ($P < 0.05$), while the sham and drug groups experienced only a 33% and 19% reduction, respectively ($P < 0.05$). Depression scores were significantly lower among all groups, with the largest difference noted between the catgut and drug group ($P = 0.002$). Anxiety scores also trended toward improvement among all groups, but decreases were not noted to be significant ($P = 0.077$). Unfortunately, baseline scores for both depression and anxiety were not reported and relative changes could not be calculated accordingly. Finally, a 2 kg (± 0.88) weight loss was noted in the catgut group ($P < 0.05$), with no significant weight loss reported in the sham or drug group.

■ COMMENTARY

Based on these results, catgut-embedded therapy appears to be superior to both traditional acupuncture

and Colofac therapy in the management of IBS, especially with regard to abdominal pain and colonic symptoms of constipation and bloating. Traditional acupuncture is hypothesized to influence the serotonergic, cholinergic, and glutaminergic pathways of the brain-gut axis,[7] thereby altering the perception of gastrointestinal pain and discomfort among patients suffering from IBS. Catgut acupuncture is likely to act via the same mechanism, with the benefit of providing more constant activation to the acupuncture sites, which may account for improved outcomes in the present study. Several issues, however, should be considered before clinicians can feel confident recommending catgut acupuncture to patients suffering from IBS.

["Although the results of this study are intriguing and provide a positive association between catgut acupuncture and IBS, health care providers should heed caution in recommending this modality..."]

The researchers made a concerted effort to eliminate selection bias through the design of a randomized, double-blind, sham-control study. Unfortunately, eliminating internal sources of bias was not as easily achieved. Blinding the acupuncture practitioner was not feasible, as the technique of catgut embedding is significantly different from sham acupuncture. The acupuncture practitioner, therefore, may have inadvertently introduced an important source of performance bias, as he/she was aware of which patients were in the treatment group.

Given their focus on evaluating the efficacy of a new acupuncture method for IBS, the researchers could have opted for greater standardization with regard to the acupuncture protocol, especially between the catgut and sham groups. Although different acupuncture sites may be used to treat the same condition according to principles of traditional Chinese medicine, the researchers reportedly selected acupuncture sites that differed between the groups, with the inclusion of sites hypothesized to target weight-loss in the catgut group.[5] Therefore, the results of the study should not be solely attributed to the method of embedding semi-absorbable filaments, but perhaps due to the effects of the acupuncture sites chosen as well.

Interestingly, researchers opted to report on weight loss associated with the catgut acupuncture. Caution should be advised when interpreting these results, as the study was not designed to assess weight loss, which was a secondary variable. Several other unaccounted variables could have affected weight loss or gain, such as self-imposed differences in diet or exercise between treatment groups. Furthermore, the catgut group included acupuncture sites for weight loss as mentioned above.

Aside from the potential shortcomings in the methods, there were also several places where interpreting the results was challenging. Neither standard deviations nor significance values were reported in the figure displaying IBS symptoms. The corresponding text also inconsistently reported significance values. Additionally, baseline depression and anxiety scores were not reported; hence, the relative change in depression and anxiety could not be assessed. In the end, a more detailed presentation of the results would have provided a clearer understanding regarding the effect of catgut acupuncture on IBS.

Although the results of the present study are intriguing and provide a positive association between catgut acupuncture and IBS, health care providers should heed caution in recommending this modality until the results are replicated and the methodology improved. Furthermore, while the present study did not report any adverse events, the introduction of semi-permanent fibers into the skin could serve as a nidus for infection or an inflammatory response if proper technique is not used. Finally, the identification of practitioners with excellent technique may prove difficult, as this form of acupuncture is not widely available in the United States. ■

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ABSTRACT & COMMENTARY

Aromatherapy: A Replacement for Antidepressants?

By Ingrid Martin, MD

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Dr. Martin reports no financial relationships relevant to this field of study.

SYNOPSIS: This randomized, double-blind, placebo-controlled study of an oral preparation of the essential oil of lavender showed that it is more effective for the treatment of generalized anxiety disorder than either placebo or an SSRI.

SOURCE: Kasper S, et al. Lavender oil preparation Silexan is effective in generalized anxiety disorder — a randomized, double-blind comparison to placebo and paroxetine. *Int J Neuropsychopharmacol* 2014;17:859-869.

The purpose of this study was to investigate the anxiolytic efficacy of Silexan, which is an oral herbal medication prepared from the fresh flowering tops of *Lavandula angustifolia* by steam distillation, with standardization of the main constituents of linalool and linalyl acetate. The study was designed as a randomized, double-blind, multicenter trial, in a two-stage design. A total of 616 patients were recruited and 536 of these were treated. All participants were male and female outpatients, between 18 and 65 years old, from 57 psychiatric and general practices in Germany. They all met the DSM-IV criteria for moderate to severe generalized anxiety disorder (GAD), with specific criteria measured by the Hamilton Anxiety Rating scale (HAMA) and Covi anxiety scale, and they had been suffering from GAD for an average of about 2.5 years. The main exclusion criteria were the presence of another DSM-IV-TR Axis I diagnosis (including major depression) in the 6 months before the study, patients with predominant and/or severe depressive symptoms, risk of suicide, substance abuse, and schizophrenia. The four treatment groups (described below) were comparable at baseline.

There was an initial treatment-free screening and washout period of 3-7 days duration. Participants meeting the selection criteria were then randomized into four groups receiving 10 weeks treatment with either 80 mg of Silexan, 160 mg of Silexan, 20 mg of paroxetine, or placebo, with efficacy and safety assessments performed after 2, 4, 6, 8, and 10 weeks. Other than the paroxetine, psychiatric medications were not allowed during the study or for 30 days prior to screening. The treatment phase was followed by a 1-week weaning phase to document possible withdrawal effects. Patients taking paroxetine took the active drug every other day, while patients taking Silexan took a placebo for this week. Although this was initially designed as a two-stage study, it was terminated without a second part, as the anxiolytic efficacy of Silexan was already considered to be demonstrated in the interim analysis after the first part of the study.

Summary Points

- A randomized, double-blind, placebo-controlled trial of lavender oil found it to be more effective for generalized anxiety disorder than placebo or SSRIs.
- Although the results of the study were positive, it is important to note that the study was funded by the Schwabe company, which manufactures the product studied in this trial.
- Since alternatives to SSRIs and benzodiazepines are needed for anxiety, independently funded study of this preparation should be conducted.

The study used the HAMA scale to assess participants at the 2-week follow-up visits, and all study groups showed a decrease in total score during treatment. The HAMA is a rating scale to assess the severity of anxiety, with a possible score of 0-56. A score of 18-24 indicates mild-to-moderate anxiety severity, with scores 25-30 indicating moderate-to-severe anxiety.

Improvements in HAMA were significantly greater for both Silexan groups than for the placebo or paroxetine groups, with decreases as follows: Silexan 160 mg/d (14.1 ± 9.3), Silexan 80 mg/d (12.8 ± 8.7), paroxetine

(11.3 ± 8.0), and placebo (9.5 ± 9.0). Responders were classified as having a decrease in HAMA total score by at least 50% from their baseline, and those in remission classified as having a HAMA total score of < 10 points by the end of treatment. The percentage of patients who responded to treatment according to this pre-specified HAMA criteria were as follows: 60.3% of the Silexan 160 mg/d group were classified as responders and 46.3% were in remission, compared to 51.9% and 33.3% for Silexan 80 mg/d; 43.2% and 34.1% for paroxetine; and 37.8% and 29.6% in the placebo group ($P = 0.01$).

Gastrointestinal disorders, infections, and nervous system disorders were the most common adverse events across all study groups. The severity of these were not discussed, but it is mentioned that a total of 5 "serious adverse events" were reported during and up to 1 month after randomized treatment (Silexan 160 mg/d 2; 80 mg/d 2; paroxetine 1). The percentage of adverse effects were similar in the placebo group (30.9%) and both the Silexan groups (25.0% for the 160 mg/d group, and 34.8% for the 80 mg/d group), while the paroxetine group had a higher rate of adverse events (40.9%). The only class of adverse events that was significantly (> 3%) higher in the Silexan groups over placebo was gastrointestinal disorders. Intention-to-treat analysis included dropouts and those who did not adhere to protocol, although subsets that excluded these groups were also analyzed.

The authors concluded that Silexan showed convincing anxiolytic efficacy as well as a favorable safety profile. Silexan at daily doses of 160 mg or 80 mg given for 10 weeks is at least as efficacious as paroxetine in reducing the primary symptoms of anxiety in patients suffering from GAD. The dosages were safe and, unlike paroxetine, adverse event rates with Silexan did not exceed those of placebo. They added that the preparation had a profound beneficial effect on comorbid depression.

■ COMMENTARY

Essential oils of aromatic plants have been extensively studied and used for their psychological effects, especially their effects on depression and anxiety. Most of these studies have utilized aromatics either topically or inhaled — in massages, baths, and various diffusion modalities. The results have generally been favorable, with many studies showing at least a slight improvement in anxiety and depression, whatever the modality employed.[1] However, the use of essential oils internally has generally been frowned on in the United States due to safety concerns, such as hepatotoxicity and central nervous system effects. This is not the case in Europe, where essential oils in capsules are sold over the counter in many pharmacies for the treatment of viral respiratory infections, gastrointestinal disorders, insomnia, mood disturbances, and so on. The German Commission E has approved for internal use specific essential oils, including fennel, anise, caraway, cinnamon bark, eucalyptus, and lavender (*L. angustifolia*).[2] The amount of essential oil found in a capsule of Silexan is 80 mg, which is about four drops, a tiny amount considering that the LD50 for *L. angustifolia* is > 5g/kg.[3] Silexan is just one of the brands of encapsulated essential oil available in Europe, and any form of lavender (*L. angustifolia*) diluted in vegetable oil and put into a capsule may well be just as effective for anxiety. However, consumers who are considering making their own would need to be knowledgeable about proper dilution methods and be aware that other species of lavender, such as spike lavender (*Lavandula spica*) or lavandin, (*Lavandula latifolia*) have significantly higher camphor content, which can cause epileptiform convulsions if taken internally.

This interesting study compares lavender taken internally with paroxetine, one of the recommended first-line treatments for GAD, with the effects of lavender at 6 weeks appearing to be more favorable in both efficacy and safety than the SSRI. The HAMA scale has limitations, given the fact that it is clinically scored, and, therefore, is somewhat subjective. However, it is widely used to document the results of pharmacotherapy and psychotherapy. An increase or decrease of 12 or 14 points, such as seen in this study, is of definite clinical and not just statistical significance. Previous studies on the benefits of paroxetine for anxiety have shown, as in this particular trial, that it has only a modest advantage over placebo for the treatment of anxiety or depression.[4] However, given the side effects of selective serotonin reuptake inhibitors (SSRIs) — which commonly include sexual dysfunction, insomnia, drowsiness, weight gain, and headaches, and rarely include increased suicidal ideation in children and serotonin syndrome — the benefit may not be substantial enough to justify using paroxetine, or SSRIs in general, as first-line treatment for anxiety if another treatment is available.

Certainly the benefits of this oral preparation of lavender appear to be consistently positive: Other studies have found similarly high rates of response to Silexan for anxiety. A randomized, double-blind, placebo-controlled study of Silexan for subsyndromal anxiety in 2010 concluded, "Silexan was superior to placebo regarding the percentage of responders (76.9 vs 49.1%, $P < 0.001$) and remitters (60.6 vs 42.6%, $P = 0.009$)," with HAMA and PSQI scores used to measure outcomes.[4] Studies have also shown consistently low safety concerns about Silexan.[5,6] This particular study is well designed, with double-blinding

(almost impossible to perform in topical aromatherapy trials, and achieved here by use of tiny amounts of lavender oil in the paroxetine and placebo capsules to give them a similar fragrance to the Silexan), effective number of randomized participants, full reporting of data, including patients who did not finish the trial or who had serious protocol violations, and total and subgroup analyses.

However, there are limitations to this study. The authors acknowledge that the results may have been influenced by a larger number of premature withdrawals from the paroxetine group and the fact that only 20 mg/d of paroxetine was used (with 20-50 mg/d being the usual therapeutic dose). Other limitations include the fact that 75% of participants were female, although this could be justified by the fact that women are twice as likely to suffer from anxiety disorders as men;[7] subgroup analysis in the study showed no substantial differences in response between males and females. Another issue is that only two of the participants were not Caucasian, although other ethnic groups were not excluded according to the authors.

Perhaps the most serious drawback is that Silexan is manufactured by Dr Willmar Schwabe GmbH & Co. (it is sold in Germany as "Lasea," and in the United States as "Calm Aid" by Nature's Way, a Schwabe subsidiary). The study was completely funded by the Schwabe company, and five of the seven authors have received grant support from, or are members of advisory boards for, Schwabe. The remaining two authors are both employees of Schwabe. However, positive the results, this fact must surely weigh heavily against them, with numerous studies showing the negative effects of what is known as "funding bias."[8] Since alternatives to SSRIs and benzodiazepines are greatly needed for anxiety, the next step should be an independently funded study of this apparently useful preparation. ■

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METABOLIC SYNDROME

ABSTRACT & COMMENTARY

Curcuminoids for Inflammation and Oxidative Stress Levels in Individuals with Metabolic Syndrome

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Dr. Decker reports no financial relationships relevant to this field of study.

SYNOPSIS: Bioavailable cucuminoids were found to reduce oxidative stress and inflammation in individuals diagnosed with metabolic syndrome. Superoxide dismutase activity, malondialdehyde, and C-reactive protein (CRP) concentration were each significantly improved after short-term (8 weeks) of supplementation with curcuminoids. Meta-analysis of eight other studies investigating the impact of curcuminoids on various health parameters, including serum CRP concentration, also found a significant reduction of CRP with curcuminoid supplementation.

SOURCE: Panahi Y, et al. Antioxidant and anti-inflammatory effects of curcuminoid-piperine combination in subjects with metabolic syndrome: A randomized controlled trial and an updated meta-analysis. *Clin Nutr* 2015; Jan 7 [Epub ahead of print].

Summary Points

- The study investigated the effect of curcuminoid (and piperine) supplementation on inflammation and oxidative stress parameters in individuals with metabolic syndrome.
- A significant reduction from baseline was observed in C-reactive protein (CRP), malondialdehyde (MDA), fasting blood glucose, and hemoglobin A1C in individuals supplemented with curcuminoids, and a significant increase in superoxide dismutase (SOD) activity was seen.
- Serum CRP and MDA concentrations were significantly decreased while SOD activity was significantly improved in the curcuminoid group compared to the control.
- Meta-analysis of eight additional randomized placebo-controlled trials found a significant reduction in serum CRP concentration after supplementation with curcuminoids.

Curcuminoids, the bioactive constituents of *Curcuma longa* (commonly known as turmeric), have been researched extensively for the treatment of a variety of conditions including autoimmune disease, cancer prevention, liver disease, atherosclerosis, and diabetes.[1] Multiple anti-oxidative and anti-inflammatory actions of curcuminoids have been demonstrated, including the inhibition and scavenging of free radicals,[2] as well as the reduction of pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor-α.[3]

In this Phase 3, randomized, double-blind, placebo-controlled trial, 117 individuals diagnosed with metabolic syndrome and not receiving lipid-lowering therapy were randomized to receive a bioavailable curcuminoid preparation or a placebo daily for a period of 8 weeks. A bioavailable curcuminoid preparation containing 500 mg of mixed curcuminoids (curcumin, demethoxycurcumin, and bisdemethoxycurcumin) with 5 mg of piperine was administered twice daily. Bioavailability of curcumin is known to be enhanced when taken in combination with piperine.[4] Diagnosis of metabolic syndrome was made according to the criteria of the National Cholesterol Education Program Adult Treatment Panel III. Individuals were excluded from the study if they were pregnant or breastfeeding, had a known malignancy, had a known sensitivity to turmeric, or were not compliant with protocols for at least 1week.

Parameters assessed in this study included:

- serum highly-specific C-reactive protein (hs-CRP) concentration
- serum malondialdehyde (MDA) concentration (a marker of lipid peroxidation)
- serum superoxide dismutase (SOD) activity
- fasting blood glucose (FBG)
- hemoglobin A1c (HbA1c)

At baseline, the intervention group was found to have significantly higher BMI, FBG, and HbA1c levels and a lower SOD activity. Results were subsequently assessed for the possible effect of the different baseline body mass index (BMI) and FBG using a univariate analysis of covariance assessment.

Upon completion of the 8-week intervention period, significant reduction from baseline was observed in CRP ($P < 0.001$), MDA ($P < 0.001$), FBG ($P < 0.001$), and HbA1c ($P = 0.048$) in the individuals supplemented with curcuminoids, and a significant increase in SOD activity ($P < 0.001$) was seen. The placebo group experienced a significant increase in serum SOD activity ($P = 0.001$) and FBG ($P = 0.011$) and no significant change in CRP, MDA, or HbA1C levels. In comparison to the placebo group, a significant reduction in serum CRP ($P < 0.001$) and MDA ($P < 0.001$) concentrations and increased SOD ($P < 0.001$) activity were seen in the curcuminoid group. No significant adverse effects were reported, and dropouts were comparable between the two groups (nine and eight subjects from the curcuminoid group and placebo group, respectively).

Although multiple parameters (BMI, FBG, HbA1c, and SOD) were significantly different in the intervention group from the control at baseline, when the effect of confounders was assessed, the impact of curcuminoid supplementation on SOD, MDA, and CRP remained statistically significant ($P < 0.001$).

Additionally, a meta-analysis was performed by the authors of this study to investigate the impact of curcumin supplementation on serum CRP. Eight studies met the inclusion criteria for this meta-analysis, and all but one were a placebo-controlled, double-blind studies. Curcumin dosage ranged from 80 mg to 6 g per day, and the intervention period ranged from 2-12 weeks. Curcuminoid supplementation was found to be associated with a significant reduction in serum CRP of -2.20 mg/L ($P = 0.01$; 95% confidence interval [CI] -3.96 to -0.44). Meta-regression did not find an association between administered dose of curcuminoids and change in CRP; however, in two of the studies utilizing higher doses of curcumin, the form was not optimized for bioavailability.

■ COMMENTARY

Turmeric is a popular supplement for conditions involving inflammation and oxidative damage. Non-medically educated consumers often self-select products that include curcumin as well as other popular botanicals such as ginger (*Zingiber officinale*) and *Boswellia serrata* (also known as Indian frankincense) for inflammation.[5] Clinical studies have been performed investigating the use of curcuminoids for the treatment of more than 35 common and less common medical conditions as diverse as renal transplant, ß-Thalassemia, peptic ulcer, and *Helicobacter pylori*, to the more common issues of autoimmunity, diabetes, Alzheimer's disease, and cancer therapies.[1] Curcumin has been found to reduce inflammation in a multitude of other conditions and pathology associated with an inflammatory state.[6] A multitude of mechanisms by which curcuminoids may act therapeutically has been shown. These often relate back to oxidative stress and inflammation, but they also encompass other antimicrobial[7] and anticancer[8] actions.

Metabolic syndrome is associated with multiple negative health effects, including increased cardiovascular, diabetes, and cancer risk. Inflammation[9] and oxidative stress[10] are associated with the development of further pathology, and both tend to be increased in individuals with metabolic syndrome. Means by which to address this syndrome with nutritional and botanical agents is of interest, as the primary agents that are used for treatment of this condition only include hypoglycemic and lipid-altering agents.

One of the primary drawbacks of this study was that there were significant differences between the intervention and control groups at baseline. Although the results were assessed for the possible impact of a higher baseline BMI and FBG, the baseline difference of HbA1c and SOD activity was not accounted for. One might anticipate that if SOD activity is lower at baseline, it would be easier to improve upon this parameter. It also may be that there were some individuals who had baseline data significantly outside of a standard deviation of the remainder of the group. A significant deviation from the mean possibly should have been exclusion criteria for the study, as it may indicate other physiologic or unknown disease processes that may have an effect on the study outcomes. Finally, an intention-to-treat analysis was not performed, as the individuals who dropped out were lost to follow-up.

There are many reasons to consider the selection of curcumin as an agent for the treatment of metabolic syndrome. Curcuminoids have been shown to improve lipid profiles, reducing serum triglycerides, total cholesterol, non-high density lipoprotein cholesterol, and lipoprotein(a) levels. Curcumin also has been shown to have anti-hyperglycemic and insulin sensitizer effects.[12] CRP levels are commonly elevated in individuals with abdominal adiposity characteristic of metabolic syndrome,[13] and they are associated with the development of cardiovascular pathology.[14] Therefore, findings that curcuminoids also serve to improve this parameter (including the meta-analysis data) further support the use of curcuminoids to support the overall health of individuals with metabolic syndrome.

The bioavailability of curcumin, as addressed by this study and mentioned pertaining to the meta-analysis as well, is something that must not be neglected. Studies have shown that curcumin and its metabolites are not detectable in serum or plasma at doses of curcuminoids < 3.6-4.0 grams per day when taken without special preparation for improved bioavailability.[16,17] Selection of curcumin preparations with piperine[4] or in a phospholipid-complexed form have been shown to have increased bioavailability over curcumin taken without these agents. Additional formulations may be available with improved bioavailability, but until this has been verified with clinical studies, curcumin in a preparation with piperine or phospholipids should be selected.

Turmeric, from which curcuminoids are extracted, contains between 2-9% curcumin.[18] Since 1 teaspoon of turmeric is approximately 1.5 grams (a maximum of 0.135 g of curcuminoids), to achieve a dosage of 4 grams of curcuminoids a person would have to consume a minimum of 30 teaspoons. It is likely that the dietary consumption of turmeric may not impact physiological parameters in a demonstrable manner, as this is a dosage far greater than most individuals would ever consume. Since curcuminoids are fat-soluble, in theory, there may be improved absorption when turmeric is taken with other fats or black pepper (source of piperine); however, there have not been studies to support this hypothesis.

Given the wide array of data supporting the use of curcumin for the reduction of an inflammatory state, supplementation with curcumin should be considered for individuals with metabolic syndrome particularly if there are other concomitant inflammation-mediated conditions such as autoimmune disease. ■

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CME QUESTIONS

1. **In postmenopausal women diagnosed with pre- or stage 1-HTN, the addition of 22 grams of freeze-dried blueberry powder (the equivalent of 1 cup of fresh blueberries) demonstrated which of the following?**
   a. Increased SBP, decreased DBP
   b. Decreased SBP, decreased DBP
   c. Increased SBP, increased arterial stiffness
   d. Decreased SBP, increased DBP
2. **Which of the following statements is true regarding catgut acupuncture?**
   a. Catgut acupuncture is a proven method for weight loss.
   b. Catgut acupuncture involves embedding cat intestines within the designate acupuncture site.
   c. Catgut acupuncture confers better outcomes for anxiety over depression.
   d. Catgut acupuncture reduces gastrointestinal pain scores to a greater degree than sham acupuncture.
3. **In individuals with metabolic syndrome, a bioavailable curcumin preparation containing 500 mg of curcuminoids taken twice daily was found to:**
   a. reduce markers of inflammation but did not improve superoxide dismutase activity compared to placebo.
   b. reduce markers of inflammation and improve superoxide dismutase activity compared to placebo.
   c. improve superoxide dismutase activity but did not reduce markers of inflammation compared to placebo.
   d. not have a significant effect on inflammation or oxidative stress as compared to placebo.

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- present evidence-based clinical analyses of commonly used alternative therapies;
- make informed, evidence-based recommendations to clinicians about whether to consider using such therapies in practice; and;
- describe and critique the objectives, methods, results and conclusions of useful, current, peer-reviewed clinical studies in alternative medicine as published in the scientific literature.

[IN FUTURE ISSUES]

Generic dietrary supplements

Probiotics and rheumatoid arthritis

Glycemic index and cardiovascular disease

Updates in integrative therapies for fibromyalgia