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File: ■ Black Cohosh (*Actaea racemosa* syn. *Cimicifuga racemosa*)
■ Stress
■ Anxiolytic Effects

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RE: Black Cohosh Reduces Physiological and Psychological Stress Responses

Nadaoka I, Yasue M, Sami M, Kitagawa Y, Koga Y. Oral administration of *Cimicifuga racemosa* extract attenuates psychological and physiological stress responses. *Biomed Res*. June 2012;33(3):145-152.

Black cohosh (BC; *Actaea racemosa* syn. *Cimicifuga racemosa*) dietary supplements are most commonly used to reduce negative menopausal symptoms. In Native American traditional medicine, BC was used as a tonic, analgesic, and fatigue treatment, in addition to its prevalent usage in childbirth and the treatment of menstrual problems. Pharmacological studies have confirmed that BC exerts dopaminergic and serotonergic effects, rather than estrogen-like activities. In vitro, BC is an agonist of serotonin receptors, a competitive ligand and partial agonist of opiate receptors, and a positive modulator of gamma-aminobutyric acid (GABA) receptors. In vivo, BC has also been shown to attenuate the hypothalamic-pituitary-adrenal axis (HPA axis) stress response by decreasing corticosterone levels and modulating the sympathetic adrenomedullary (SAM) system stress-induced changes in dopamine (DA), serotonin (5-hydroxytryptamine [5-HT]), and norepinephrine (NE) metabolism. However, the anxiolytic effects of BC have not been evaluated in humans. This randomized, double-blind, placebo-controlled, crossover trial investigated the effects of BC on stress via the measurement of chromogranin-A (CgA; a protein used as a stress marker), cortisol, perceived stress intensity, and brainwave patterns.

This study consisted of 2 experiments with healthy adults. Twenty men (n=20) were enrolled in experiment 1, while both men (n=6) and women (n=5) were enrolled in experiment 2 (n=11). All subjects were free from a history of or current mental illness and drug use. They were instructed to continue normal sleep and other general routines, and to refrain from heavy physical exercise, tobacco use, and stimulant consumption (e.g., alcohol, caffeine, etc.) the day prior to each test. Subjects were randomized to receive either 200 mg/day of encapsulated BC extract (supplied by Nippon Funmatsu Yakuhin; Osaka, Japan) or identical placebo capsules containing 200 mg of lactose. [Note: No information on the extract preparation, concentration, or standardization was given.] Statistical significance was designated at P-values <0.05.

The first experiment consisted of 2 test sessions conducted a week apart. On the test day, baseline psychological measurements and saliva samples were collected before the subjects took the study medication. One hour following ingestion, the Uchida-Kraepelin (U-K) test, a

math-related questionnaire testing for speed and accuracy, was administered in such a way as to impede subjects' successful completion. At the end of the U-K test (time 0) and 60 minutes later, saliva and psychological parameters were again assessed. The procedure was repeated 1 week later with the subjects taking the alternate medication.

The psychological measures were a visual analog scale (VAS) of perceived stress intensity and the State-Trait Anxiety Inventory (STAI). With the BC treatment, the mean VAS score was significantly lower at time 0 compared to placebo ($P<0.01$). No significant differences in the STAI scores were observed.

The saliva samples were analyzed to determine the concentration of the physiological stress markers CgA and cortisol. CgA is an indicator of the stress response mediated by the SAM system, while cortisol is an indicator of the response mediated by the HPA axis.

The BC treatment attenuated the SAM system-mediated stress response, significantly lowering CgA concentrations midway through the U-K test ($P=0.05$), at time 0 ($P=0.01$), and 60 minutes after completing the test ($P<0.05$). No significant differences were seen in cortisol concentrations.

In experiment 2, a modified U-K test requiring oral answers was conducted 60 minutes after ingestion of the study medication. Electroencephalography (EEG) was used to measure alpha waveband brain activity prior to the U-K test (baseline), mid-test, at time 0 (end of test), and 60 minutes after the test. The test was repeated 7 days later with subjects taking the alternate treatment.

The left and right occipital EEG data was analyzed for temporal variations in the alpha waveband. A recovery trend was observed from time 0 to 60 minutes after the test but the differences were not statistically significant ($P=0.06$ and $P=0.07$, respectively).

In summary, BC significantly reduced the VAS measure of psychological stress but not the STAI. It significantly reduced the concentration of the SAM system stress response indicator, CgA, but did not affect the concentration of the HPA axis stress response indicator, cortisol. In light of the in vitro and in vivo data and the limitations of this study, the authors maintain that BC affects both the HPA axis and SAM system stress responses and they suggest that BC may be suitable for the prevention and treatment of stress-related disorders.

This study suffers from a few major problems. The results cannot be generalized to other BC extracts nor can other researchers repeat the experiments because no information regarding the BC extract preparation, concentration, or standardization is provided. Inclusion criteria are not described and exclusion criteria are limited. The testing was done in the morning, when cortisol levels are high – a flaw in the study design. In this case, the salivary CgA would have been a better indicator of psychological stress. It reflects psychological stress more rapidly and is considered more sensitive than cortisol. The sample size was also very small. Nonetheless, the balance of the evidence indicates that further studies of BC's anxiolytic mechanism of action and clinical efficacy are warranted.

—Amy C. Keller, PhD

Editorial Comment: It is interesting to note that the extant experimental and clinical evidence supports the Native American traditional use of BC as a tonic and treatment of fatigue.

Referenced article can be accessed at https://www.jstage.jst.go.jp/article/biomedres/33/3/33_145/_pdf.