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## Black cohosh acts as a mixed competitive ligand and partial agonist of the serotonin receptor.

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#### Abstract

Extracts of the rhizome of black cohosh [*Actaea racemosa* L., formerly called *Cimicifuga racemosa* (L.) Nutt.] were evaluated for potential mechanisms of action in the alleviation of menopausal hot flashes. Ovariectomized Sprague-Dawley rats were administered a 40% 2-propanol extract of black cohosh [4, 40, and 400 mg/(kg.day)] by gavage for 2 weeks with or without estradiol [50 microg/(kg.day)] to determine if black cohosh could act as an estrogen or antiestrogen on the basis of an increase in uterine weight or vaginal cellular cornification. No effects were observed on uterine weight or on vaginal cellular cornification in rats treated with black cohosh alone or in combination with 17beta-estradiol, indicating this black cohosh extract had no estrogenic or antiestrogenic properties in the ovariectomized rat model. To evaluate other potential pathways by which black cohosh might reduce menopausal hot flashes, serotonin activity was first assessed by the inhibition of radioligand binding to cell membrane preparations containing recombinant human serotonin receptor (5-HT) subtypes. A 40% 2-propanol extract of black cohosh was tested against 10 subtypes of the serotonin receptor, revealing the presence of compounds with strong binding to the 5-HT(1A), 5-HT(1D), and 5-HT(7) subtypes. Subsequent binding studies were carried out using 5-HT(1A) and 5-HT(7) receptors because of their association with the hypothalamus, which has been implicated in the generation of hot flashes. The black cohosh 40% 2-propanol extract inhibited [(3)H]lysergic acid diethylamide (LSD) binding to the human 5-HT(7) receptor (IC(50) = 2.4 +/- 0.4 microg/mL) with greater potency than binding of [(3)H]-8-hydroxy-2-(di-N-propylamino)tetralin to the rat 5-HT(1A) receptor (IC(50) = 13.9 +/- 0.6 microg/mL). Analysis of ligand binding data indicated that components of a black cohosh methanol extract functioned as a mixed competitive ligand of the 5-HT(7) receptor. In addition, a black cohosh methanol extract elevated cAMP levels in 293T-5-HT(7)-transfected HEK cells, suggesting the extract acted as a partial agonist at the receptor. The elevation in cAMP mediated by the black cohosh extract could be reversed in the presence of the antagonist methiothepin, indicating a receptor-mediated process. These data suggest that reductions in hot flashes in some women taking black cohosh may not be due to estrogenic properties. This study identifies other possible biological targets of black cohosh that could account for reported biological effects.