P.O. Box 144345 Austin, TX 78714-4345 ▪ 512.926.4900 ▪ Fax: 512.926.2345 ▪ www.herbalgram.org

HerbClip™

FILE: ▪Echinacea (*Echinacea* spp.)
▪Endocannabinoid System
▪Alkamides

HC 100254-306

Date: June 15, 2006

RE: Study Examines Echinacea's Alkamides

Woelkart K, Xu W, Pei Y, Makriyannis A, Picone R, Bauer R. The endocannabinoid system as a target for alkamides from *Echinacea angustifolia* roots. *Planta Med.* 2005;71:701–705.

Echinacea angustifolia is one of three echinacea species widely used medicinally, the other two being *E. purpurea* and *E. pallida*. These plants have a long history of medicinal use by Native Americans, and are indigenous to the central and southwestern United States. Traditionally, roots of these plants were used to treat insect and snake bites. Today echinacea is commonly used to treat upper respiratory disorders and other conditions where cell-mediated immune stimulation (defending against bacteria and viruses) is desired. Long-chained fatty acid alkamides found in high concentrations in the aerial parts of all echinacea species and in the roots of *E. angustifolia* and *E. purpurea* and are believed to be responsible at least in part for echinacea's immune-modulating features. Some of the pharmacokinetic properties (absorption, distribution, and elimination) of echinacea alkamides were recently defined by Woelkart K et al.[1] and others.[2]

The current in vitro study adds to the growing body of research defining the bioactivity of echinacea by characterizing the effects of alkamides on two cell receptors (molecules embedded in cell membranes that translate extracellular signals into intracellular activity), namely, cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2). This study used rat-isolated CB1 and mouse-isolated CB2 receptors. CB1 is most highly concentrated in the brain, "where it is responsible for the characteristic effects of cannabis, including catalepsy [rigidity of limbs], depression of motor activity, analgesia and feelings of relaxation and well being." The CB2 receptor is found in immune cells in the periphery (not in the brain). These receptors, as well as two other cannabinoid molecules—fatty acid amidohydrolase (FAAH) and anandamide—"are current targets for the development of novel medications for pain, immunosuppression, peripheral vascular disease, appetite enhancement or suppression, and mental illness."

Alkamides were isolated from two-year old *E. angustifolia* roots (Heilfpflanzen Sandfort GmbH & Co KG, Olfen, Germany) using supercritical carbon dioxide (CO_2) extracted by Finzelberg, Andernach, Germany. This extraction method provided a drug (77:1 extract ratio in 1.30% yield). Alkamides were then isolated from this extract and characterized as: (1) tetradeca-2*E*-ene-10,12-diynoic acid isobutylamide, (2) undeca-2*E/Z*,4*Z/E*-diene-8,10-diynoic acid isobutylamides, (3) undeca-2*E/Z*-ene-8,10-diynoic acid isobutylamides, (4) dodeca-2*E*,4*Z*-diene-8,10-diynoic acid isobutylamide, (5) dodeca-2*E*-ene-8,10-diynoic acid isobutylamide, (6) dodeca-2*E*,4*Z*-diene-8,10-diynoic acid isobutylamide, (7) dodeca-2*E*,4*Z*,10*Z*-triene-8-ynoic acid isobutylamide, (8) dodeca-2*E*,4*E*,8*Z*,10*E/Z*-tetraenoic acid isobutylamides, (9) pentadeca-2*E*,9*Z*-diene-12,14-diynoic acid 2-methylbutylamide, (10) dodeca-2*E*-ene-8,10-diynoic acid 2-methylbutylamide, (11) dodeca-2*E*,4*E*,8*Z*-trienoic acid isobutylamide, and (12) dodeca-2*E*,4*E*-dienoic acid isobutylamide.

Echinacea alkamides showed a binding affinity (Ki value, which is the concentration of a substance required to inhibit by 50% the activity of a second substance) for CB1 and CB2 receptors. Alkamide 9 showed the greatest binding affinity for CB1, at a concentration of 2.035 (1.6–2.7) µM (micromoles), followed by alkamide 10 (4.116 [2.8–6.1] µM), and alkamide 12 (6.147 [4.8–7.8] µM). On the other hand, alkamide 1 was most selective for CB2, at a concentration of 1.867 (1.0–3.4) µM, followed by alkamide 11 at 4.569 (3.3–6.3) µM, and alkamide 8 at 5.499 (3.7–8.2) µM.

In a second experiment, the researchers tested the ability of echinacea alkamides to inhibit the activity of FAAH, which would prolong the activity on CB1 and CB2. FAAH activity was inhibited by 23% by alkamide 1, 14.4% by alkamide 11, and 11.7% by alkamide 12. Interestingly, alkamide 1 showed the highest affinity and selectivity for CB2 and the greatest FAAH inhibition.

The characterization of the active alkamides in echinacea root is an important step towards an understanding of echinacea's bioactive compounds and immune system effects. These results need to be confirmed in human cell lines. Future research could standardize the alkamides and test them in human clinical trials. However, the greatest safety and efficacy of echinacea in humans may be when a broadly complex mixture of alkamides and other compounds is administered rather than narrowly fractionated preparations.

—John Neustadt, ND

References

[1] Woelkart K, Koidl C, Grisold A, et al. Bioavailability and pharmacokinetics of alkamides from the roots of Echinacea angustifolia in humans. *J Clin Pharmacol.* Jun 2005;45(6):683-689.

[2]Dietz B, Heilmann J, Bauer R. Absorption of dodeca-2E,4E,8Z,10E/Z-tetraenoic acid isobutylamides after oral application of Echinacea purpurea tincture. *Planta Med.* Dec 2001;67(9):863-864.

Enclosure: Referenced article reprinted with permission from Georg Thieme Verlag.