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FILE: ▪Botanical Dietary Supplements
▪Children
▪Clinical Studies

HC 050152-290

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RE: More Clinical Trials of Botanical Treatments for Children are Needed

Hrastinger A, Dietz B, Bauer R, Sagraves R, Mahady G. Is there clinical evidence supporting the use of botanical dietary supplements in children? *J Ped.* 2005;146:311–317.

A recent survey of women aged 40-60 years indicated that roughly 80% used botanical dietary supplements, comprising the largest percentage of botanical users. Another recent survey of complementary and alternative (CAM) practices suggests that the use of CAM by parents/caretakers is the single best predictor of CAM use in children. Further, a number of national and international surveys have indicated that herbal use in children is on the rise and it is estimated that up to 40% of children may be treated with herbal preparations for anxiety, asthma, attention deficit hyperactivity disorders (ADHD), insomnia and respiratory infections. The goal of this study was to "provide an overview of the medical and scientific information for the most commonly used herbal products."

The authors conducted a systematic review of the research by performing searches on four databases—PubMed, Napralert, Sci Finder, and Toxline. They limited their queries to the years 1960–2003 and searched for clinical trials in which subjects received andrographis (*Andrographis paniculata*), cranberry (*Vaccinium macrocarpon*), echinacea (*Echinacea purpurea*, *E. angustifolia*, *E. pallida*), evening primrose oil (EPO; O*enothera biennis*), garlic (*Allium sativum*), ivy leaf (*Hedera helix*), and valerian (*Valeriana officinalis*). They made their choice of herbs "based on marketing surveys," but did not define how the surveys were conducted or who conducted them. Excluded from their search were any studies that evaluated "the safety and efficacy of combination products...because of the difficulty in determining the efficacy of the individual botanical ingredients." Also excluded were the herbs such as chamomile (*Matricaria recutita*), feverfew (*Tanacetum parthenium*), ginger (*Zingiber officinale*), and ginkgo (*Ginkgo biloba*), "because of the lack of clinical studies in children."

Andrographis
Two clinical trials were identified, in which children were given a 60% ethanol extract of the aerial parts of andrographis. This standardized extract "has been used extensively in Scandinavia for the past 20 years for the treatment and prevention of the common cold." Although two studies were found, the authors only reported the results from one of them. The clinical trial they reviewed gave 200 mg of andrographis extract (standardized to 4% andrographolides) per day or placebo to 107 schoolchildren (mean age 18.4 years) for three months. No difference between the active and

placebo groups were seen for the first two months; however, after the third month those volunteers supplemented with andrographis had significantly less incidences of the common cold compared to placebo (30% vs. 62%, respectively; $P < 0.05$). [While the extract is not identified in this article, the authors are referring to Kan Jang®, manufactured by Swedish Herbal Institute, Götenborg, Sweden (HC 031008-184).]

Cranberry
Cranberry is a popular supplement for the prevention and treatment of urinary tract infections (UTIs). Although dozens of studies have been conducted with cranberry, only two studies with children were identified by the authors. These two trials evaluated the use of cranberry in children with neurogenic bladder, a bladder disorder caused by neurologic dysfunction, trauma, or disease. The trials did not show any benefit of cranberry for UTI caused by neurogenic bladder.

Echinacea
Echinacea is most frequently used to treat upper respiratory tract infections (URIs); however, the authors' did not find any randomized, placebo-controlled trials that support the herb for this use. They did not say how many trials they identified, but write, "few randomized controlled clinical trials have assessed the safety and efficacy of this plant in pediatric populations, and many studies were performed 20 to 40 years ago." They reviewed two studies, one which was not placebo-controlled and the second that tested echinacea against a placebo.

The first study tested *E. purpurea* pressed juice in 1322 children with recurrent URIs. Children 2 to 5 years old were treated with 2.5 mL 3 times a day, children 5 to 12 years old received 5 mL 2 times a day, and children >12 years old were given 5 mL 3 times a day for ten days at the onset of symptoms. URI duration was reduced by 62.2%; however, there was no placebo comparison, which limits the applicability of this study to clinical settings.

The second clinical trial, published in 2003 in the *Journal of the American Medical Association* (JAMA) was a randomized, double-blind, placebo-controlled trial of 524 healthy children, ages 2 to 11 years. Children received a syrup containing an extract of *E. purpurea* or placebo for ≤ 3 URIs during a 4-month period. Syrup was given at the onset of symptoms at a dosage of 7.5 mL/day for children 2 to 5 years old and 10 mL per day for children 6 to 11 years old. There was no statistically significant difference in duration or severity of URI in children who took the echinacea syrup compared to placebo. A transient rash developed in significantly more children receiving echinacea compared to placebo (7.1% vs. 2.7%, respectively; $P = 0.008$).

Several limitations of the JAMA study were addressed in the Comments section of the clinical trial,[1] but not discussed by the authors of this review. First, "It is thought that echinacea therapy should be initiated at the first signs of a URI to be effective...[and] it is conceivable that if the medication were started even earlier in the course of the illness, we may have found benefit." Previous trials in adults have shown efficacy when echinacea was given "when patients had a subjective feeling of a cold, rather than requiring a minimum of 2 symptoms." While this trial had an 80% power of detecting a decrease of approximately 20% in duration of URI symptoms, the authors comment, "It is possible that echinacea, as used in our study, may have had a small benefit in reducing the duration of symptoms that might have been detected with a larger sample size." Finally, although not addressed by the authors of the JAMA trial, the echinacea preparation may have contributed to the significant increase in rashes experienced by children taking the echinacea syrup. The echinacea syrup was prepared from root and aerial parts of echinacea, instead of the root alone. The aerial parts contain the flower and pollen of the plant, which may have greater allergic potential.

Evening Primrose Oil
Evening primrose oil (EPO) seeds are rich in essential fatty acids (EFAs) including γ-linolenic acid (GLA). EPO is used in the treatment of inflammatory conditions, such as atopic eczema, mastalgia (breast pain), premenstrual syndrome (PMS), psoriasis, rheumatoid arthritis, and more. The safety and efficacy of EPO in pediatric populations has been assessed in clinical trials, three of which were in children with atopic dermatitis, two in ADHD, and one in diabetes mellitus (insulin-dependent).

A double-blind, placebo-controlled clinical trial of 51 children (mean 4.2 years old) with atopic dermatitis showed "a significant improvement in the overall severity of clinical symptoms." Children were given 0.5 g/kg/day EPO, 0.5 g/kg/day of a combination of 50% EPO and 50% placebo, or placebo alone for 16 weeks. The symptoms measured were erythema (redness), scaling, crusting, edema (swelling), papules (raised areas of skin seen in dermatitis and other dermatological conditions), vesiculation (blisters), infection, lichenification (leathery, hardened areas of skin), pigmentation, and excoriation (linear break in the skin). In contrast, a second placebo-controlled trial of 58 children showed significant benefit of 2–3 g/day EPO for 16 weeks, but not significantly greater benefit than placebo. The authors comment that this might have been because the placebo given in the second trial contained sunflower oil, which has a similar spectrum of EFAs as EPO.

Garlic
"More than 26 clinical trials and three meta-analyses support the use of garlic and garlic preparations as an adjunctive therapy to dietetic management of hyperlipidemia, and for the prevention of atherosclerotic (age associated) vascular changes in adults," write the authors. One study has been conducted in children, in which 30 pediatric subjects, ages 8–18 years old with familial hyperlipidemia were given 300 mg garlic extract or placebo 3 times daily for 8 weeks. No significant reduction in total cholesterol or low-density lipoprotein (LDL) cholesterol, also called "bad cholesterol" was detected. A 10% significant increase in apopliprotein A-I (apo AI), however, did occur in volunteers receiving garlic extract compared to controls ($P = 0.03$). Apo AI is considered protective against atherosclerosis; however, the study concluded that "garlic extract therapy has no significant effect on cardiovascular risk factors in pediatric patients with familial hyperlipidemia."

Ivy Leaf
The German Commission E recommends the use of standardized extracts of ivy leaf for the treatment of URIs and coughs. One clinical trial tested a water-ethanol solution of ivy leaf extract on 24 children (4–12 years old) with bronchial asthma. Children received 35 mg of the extract per day, which was the equivalent of 210 mg of the unprocessed herb. Statistically significant improvements in airway resistance indicating reduced difficulty in breathing was experienced in the ivy leaf extract group compared to control (P value not reported).

In a second clinical trial effervescent cough tablets containing 65 mg dried ivy leaf extract (herb-to-extract ratio 5–7.5:1) were given to 1350 children ≥ 4 years old with chronic bronchitis. The children took 1-2 tablets per day depending on their age for 4 weeks. Improvement was seen in 92.2% of children for cough, 94.2% for expectoration, 83.1% for dyspnea (difficulty in breathing), and 86.9% for respiratory pain. Additionally, "in each of the four symptoms at least 38% of the initially affected patients were completely free of complaints."

Valerian
Valerian is used to decrease anxiety. One controlled clinical trial has assessed valerian extract in children. Five boys, ages 7–14 years, "with varying intellectual deficits (ID) (IQ < 70, along with conditions such as epilepsy, hyperactivity, and attention-deficit disorder) and different primary sleep problems" were included in this trial. Children received valerian extract 20 mg/kg body weight or placebo as a singly nightly dose at least one hour before bed for two weeks. Valerian resulted in a

significant decrease in sleep latency (time between going to bed and falling asleep; $P = 0.05$) and nocturnal time awake ($P = 0.02$), as well as an increase in total sleep time ($P < 0.01$) compared to placebo. Valerian and placebo both produced a significant increase in sleep quality ($P < 0.01$ and $P = 0.04$, respectively). There were no adverse events.

Conclusion

While there is a paucity of randomized controlled trials of botanicals in children, a number of which suffer from obvious methodological flaws, some studies are promising, particularly for specific pediatric disorders such as ADHD, recurrent URIs, otitis media, and sleep disorders. Further well-designed, randomized, controlled clinical trials are needed to properly establish the safety and efficacy of botanical treatments in children.

—John Neustadt, ND

References

[1]Taylor JA, Weber W, Standish L, et al. Efficacy and Safety of Echinacea in Treating Upper Respiratory Tract Infections in Children: A Randomized Controlled Trial. *JAMA.* 2003;290(21):2824-2830.

The American Botanical Council has chosen not to reprint the original article.