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Colchicine in Ginkgo?

By Dennis V.C. Awang, PhD, FCIC, Jerry Cott, PhD, and Adriane Fugh-Berman, MD

A RECENT PROBLEMATIC STUDY CLAIMS THAT PREGNANT WOMEN who ingest herbs may endanger their babies because of colchicine accumulation in placental blood.[1] Published in the American Chemical Society's journal, *Chemical Research in Toxicology* (*CRT*), the paper reports that during an experiment to characterize natural anti-inflammatory substances, high concentrations of colchicine (49-763 ng/mL) were identified in the placental blood of women who had used herbal dietary supplements during pregnancy. The investigators then tested ginkgo and echinacea products from the Detroit area and found colchicine (26 ± 3 mcg/tablet) in an unidentified ginkgo product and in smaller quantities in an unidentified echinacea product (2.0 ± 0.5 mcg/tablet). They concluded that women who are pregnant or trying to conceive should avoid herbal products. These results, however, are highly questionable.

A naturally occurring plant alkaloid, colchicine primarily is found in *Colchicum* species, especially *C. autumnale* L. (Liliaceae), the autumn crocus or meadow saffron from the Mediterranean (quite different from common culinary saffron, *Crocus sativa* L., which is from another plant family, Iridaceae). *Colchicum* species have been used in traditional medicine since Hippocrates' time, and colchicine currently is used in conventional medicine to treat gout and familial Mediterranean fever, and as an antineoplastic agent.

Colchicine, however, does not occur in either ginkgo (*Ginkgo biloba* L. [Ginkgoaceae]) or echinacea (*Echinacea* spp. [Asteraceae]), or in any species related to either. The *CRT* publication claimed that colchicine was found in "approximately 200 species of plants across 20 genera," but this is not accurate.

The American Botanical Council, an independent non-profit research and education organization, commissioned a search of NAPRALERT, a comprehensive database of the world literature on natural products. The search, conducted by pharmacognocist Norman R. Farnsworth, PhD, revealed that "colchicine has been reported in 91 species of the Lily family (Liliaceae), comprising 28 genera. It also occurs in one species of the Araceae (*Arisaema*

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curvatum) and is reported in one species of the Asteraceae (Compositae), i.e., *Saussurea sacra*. Based on biogenetic considerations, colchicine should never be found outside of the Monocotyledoneae (e.g., Araceae, Liliaceae); thus, the report of its occurrence in *Saussurea sacra* (Asteraceae) is an anomaly that has not been duplicated by other reports on the chemistry of this species.

The only recognized sources of appreciable quantities of colchicine are *Colchicum* spp. (chiefly *C. autumnale*); the glory lily, *Gloriosa superba* L. (Liliaceae), originating in Africa and Asia (and a popular Thai medicinal plant); and an Indian medicinal plant, *Iphigenia indica* Kunth & Benth (Liliaceae).

Contamination?

If colchicine has never been reported as a normal constituent of either *Ginkgo biloba* or any *Echinacea* species, how could it be identified in these herbal products? There would seem to be no rational incentive for herbal product manufacturers to deliberately adulterate any botanical with either colchicine or colchicine-containing plant material, so contamination would be the most likely explanation.

Improper cleaning of mechanical devices used to powder and package a product containing colchicine could explain the presence of colchicine in the final products. Accidental contamination during plant harvesting is possible but seems unlikely; it would be very strange that plant materials as disparate as ginkgo leaf and echinacea root (presumably) both would be accidentally contaminated with either colchicine or colchicine-containing plant material (usually seeds or corms/rhizomes/tubers).

The possibility of cross-contamination of stored raw material would depend on whether the ginkgo raw material supplier also manufactured colchicine or *Colchicum* products, the proximity of storage of the materials, handling procedures, etc. There also is the possibility of contamination if the same storage containers were used to store all three botanicals. Identification of the manufacturer(s) of the implicated ginkgo and echinacea products would have been helpful in determining the likelihood of this scenario. Alternatively, the samples themselves could have become contaminated with colchicine in the analytical laboratory where the assays were conducted.

Other Problems with this Study

The types or quantities of commercial dietary supplements that were purchased and tested were not described in any way. It is not stated why echinacea and ginkgo were chosen (ginkgo is not commonly used during pregnancy) or how products were chosen. Neither the products tested nor the lot numbers were identified. There is no specification of whether replicate samples were analyzed, and no information on how the sampling of the herbal products was conducted. How can this work be replicated or checked? There is no way for any independent laboratory to verify the findings of this study because experimental details are not given.

Clinical details also are missing. It is stated that five of 24 samples of placental blood contained colchicine (760, 182, 106, 97, and 49 mcg/L); all five came from "women who used herbal supplements." Women who did not use herbal supplements (presumably 19, but the number is not stated) had "little or no" detectable colchicine in placental blood. "Placental blood," by the way, is a meaningless term because the placenta contains separate maternal and fetal circulatory systems. The report states that "fresh blood was collected from the human umbilical cord and placenta." Although fetal blood may be collected easily from the cord, a sample taken from the placenta would be expected to contain a mixture of maternal blood, fetal blood, and placental tissue. Drug levels may be quite different in maternal

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blood, fetal blood, and placental tissue, and mixing the three together is not useful. Also, what is the source of the "little" colchicine apparently identified in the placental blood of women who said they did not use herbs?

The herbs that were ingested by subjects are not named, and dose and duration of use are not mentioned. Had any of the women with significant colchicine blood levels actually used the ginkgo product analyzed by the authors? Although it is stated that none of the herb-using women were taking pharmaceutical colchicine, apparently they were not asked about *Colchicum*-containing herbal products. *Colchicum* is included in several multi-ingredient herbal preparations, such as the French Antigoutteux Rezall (for rheumatism and gout), and the German Colchicum-Strath (for joint disorders).

Questions must be raised about the rigor of the analytical process. The placental blood concentrations of colchicine reported appear to be inconsistent with levels of colchicine identified in products. The ginkgo product was reported to contain 26 mcg of colchicine per tablet. The therapeutic dose of colchicine is around 1 mg/d. Therapeutic serum colchicine levels are 0.3-2.4 ng/mL.[2]

Colchicine in Pregnancy

ALTHOUGH COLCHICINE IS A MITOTIC SPINDLE POISON, therapeutic colchicine is not contraindicated during pregnancy. Transplacental transfer of colchicine has been reported.[1] A woman who took 1 mg colchicine/d throughout pregnancy had plasma levels of 3.15 ng/mL at term. Umbilical cord blood contained 0.47 ng/mL.[1]

Experience with colchicine treatment of pregnant women has not suggested an increase in adverse outcomes. There is a case report from France in which a 25-year-old woman who inadvertently took colchicine during the first trimester bore an infant with vertebral malformations.[2] In contrast, several case reports described normal pregnancy outcome in women (generally with familial Mediterranean fever [FMF]) treated with colchicine with or without other drugs.[3-8] Also, an examination of the obstetric histories of 36 women with FMF on long-term colchicine treatment did not uncover significant elevations in the incidence of miscarriage rates or infertility.[9] Sixteen infants born to these mothers, who had taken colchicine during pregnancy, were all healthy and normal.[9] Another long-term study of 45 patients with FMF who had taken colchicine for many years concluded that the drug is safe to use during pregnancy at therapeutic doses.[10] The largest collection of cases described 225 pregnancies born to 116 women with FMF who used colchicine for all or part of their pregnancies. There was no increase in the frequency of adverse outcomes in these pregnancies compared to what would be anticipated in the general population.[11] ❖

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Source: Excerpted with permission from the colchicine entry in the REPROTOX® database ©2001 Reproductive Toxicology Center.

In another study, chronic dosing with 1 mg/d colchicine resulted in plasma levels of approximately 0.8-7.8 ng/mL.[3] This study reported plasma levels of greater than 700 ng/mL! How many 26 mcg ginkgo tablets would one have to consume to reach these plasma levels? A quick calculation, assuming linear kinetics, suggests approximately 10,000 tablets.

More importantly, reported concentrations were so high that, if real, serious adverse effects (including fatalities) would be inevitable.

Colchicine Poisoning

Colchicine toxicity is dose-dependent. Colchicine poisoning from plants is rare; a recent poisoning case was reported of a 44-year-old male who ingested 40 flowers of *Colchicum autumnale* L.; he reported nausea, vomiting, and abdominal pain two hours after ingestion, with diarrhea 14 hours after ingestion. Maximal colchicine levels were 4.34 ng/mL; he recovered with supportive care.[2]

Poisoning from colchicine drugs is more common; severe poisoning may cause multi-organ failure, acute respiratory distress syndrome, cardiogenic shock, and hematological toxicity, with a high mortality rate.[4] In a case series of 24 patients admitted to an ICU for acute colchicine poisoning, six of 24 (25%) died. Plasma concentrations on admission did not differ significantly between survivors (4.1 ng/mL [0.7-68.5 ng/mL]) and non-survivors (13.6 ng/mL [3.2-77.0 ng/mL]).

How could any of these mothers or infants in the Petty study have survived so many multiples of a lethal dose? Birth outcomes are not described, but since the investigators did not report any maternal or fetal deaths (or even symptoms related to colchicine toxicity), we can only assume that there were some major errors in the analyses.

Although the *CRT* article has received media attention as an example of herb-related dangers, this study is not reliable. ❖

Dr. Awang is President, MediPlant Consulting Services, White Rock, British Columbia, and serves on the editorial advisory board of Alternative Therapies in Women's Health*; Dr. Cott is Scientific Director and Chief Science Officer at Scientific Herbal Products, Inc. in College Park, MD.*

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Calcium and Pregnancy-Induced Hypertension

By Mario Merialdi, MD, and José Villar, MD

PREGNANCY-INDUCED HYPERTENSION (PIH) IS A COMMON and potentially dangerous complication of pregnancy. PIH complicates approximately 10% of pregnancies[1] and can be induced by pregnancy in normotensive women or aggravated in women with chronic hypertension.[2] PIH commonly is categorized into three progressively severe types: gestational hypertension; preeclampsia (hypertension, proteinuria, and edema); and eclampsia (preeclampsia and convulsions or coma). In addition, women with chronic hypertension also can develop preeclampsia.[2]

PIH, especially if associated with proteinuria, is associated with increased perinatal mortality and morbidity[1] and, along with infection and hemorrhage, is one of the major causes of maternal death. Despite extensive research on this disease, the etiology of PIH still is unknown and the only definitive treatment is delivery. However, early detection and appropriate management have resulted in significantly reduced maternal and perinatal mortality rates.[2] Treatment with antihypertensive drugs can prevent the development of severe PIH,[3] and treatment of eclampsia with magnesium sulfate reduces risk of further convulsions.

Nutritional interventions to prevent PIH, if successful, would have considerable clinical and public health implications, especially in developing countries where dietary deficiencies are prevalent and access to optimal obstetric care is limited. Recent epidemiological and experimental studies conducted in several countries have

Table 1

Summary of the trials in the systematic review of calcium supplementation during pregnancy[4]

Study	Location	Calcium Intake (mg)		Risk	Relative Risk
		Calcium	*Placebo*		
Levine et al[7]	USA	1,113 ± 691	1,135 ± 675	low risk	0.94 (0.77, 1.16)
Belizan et al[8]	Argentina	642 ± 448	646 ± 396	low risk	0.66 (0.35, 1.26)
Purwar et al[9]	India	336 ± 156	352 ± 142	low risk	0.17 (0.04, 0.77)
Lopez-Jaramillo et al[10]	Ecuador	628	605	high risk (teenagers)	0.21 (0.07, 0.58)
Sanchez-Ramos et al[11]	USA	630 ± 217	666 ± 226	high risk (Angiotensin II-sensitive patients)	0.31 (0.12, 0.84)
Lopez-Jaramillo et al[12]	Ecuador	low		high risk (positive roll over test)	0.09 (0.01, 1.48)
Villar and Repke[13]	USA	1,119 ± 677	1,336 ± 796	high risk (teenagers)	0.14 (0.01, 2.67)
Lopez-Jaramillo et al[14]	Ecuador	292 ± 126		low risk	0.15 (0.04, 0.66)
Villar et al[15]	Argentina, USA	1,129 ± 736	914 ± 478	low risk	0.36 (0.04, 3.24)
Crowther et al[16]	Australia	adequate		low risk	0.44 (0.21, 0.90)

Presented are mean calcium intake and standard deviations, plus relative risk for preeclampsia (95% confidence interval) associated with calcium supplementation.

shown an inverse relationship between calcium intake and preeclampsia/eclampsia. Also, maternal calcium supplementation during pregnancy may reduce the risk of PIH.[4]

If scientific evidence shows that calcium supplementation reduces the incidence of pregnancy-induced PIH, programs to provide calcium supplementation in pregnancy would be a relatively cheap and accessible intervention for reducing the worldwide burden of preeclampsia and eclampsia.

Villar and Belizan conducted a systematic review of 10 clinical trials of the effect of maternal calcium supplementation on PIH.[5] They found that baseline dietary calcium intake and the presence of risk factors for PIH were the two primary factors that were likely to modify the effect of calcium supplementation on the risk of PIH *(see Table 1)*. Six of the 10 studies reviewed examined populations with a mean dietary calcium intake of less than 900 mg/d; the remaining four studies were conducted in populations with a higher mean dietary calcium intake.

In a stratified analysis, the results of the six studies in populations with a mean dietary calcium intake of less than 900 mg/d were pooled and compared with the results obtained by the four studies conducted in populations with a mean intake of greater than 900 mg/d. The risk of developing high blood pressure was decreased more by calcium supplementation in women with low dietary calcium intakes (relative risk [RR] 0.49, 95% confidence interval [CI] 0.38, 0.62) than in women with higher intakes (RR 0.90, 95% CI 0.81, 0.99). *(See Table 2.)* Similarly, calcium supplementation reduced the risk of preeclampsia significantly among women with low calcium intake (RR 0.32, 95% CI 0.21, 0.49) but not among women with adequate intake (RR 0.86, 95% CI 0.71, 1.05). *(See Table 3.)*

Villar and Belizan then stratified clinical trials by whether they included populations at low or high risk of developing PIH. Four trials were conducted in high-risk populations and six conducted in low-risk populations. The PIH risk factors were young maternal age (teenagers), previous history of preeclampsia, increased sensitivity to angiotensin II, and pre-existing hypertension.

The analysis showed that women at high risk of developing PIH benefited more from calcium supplementation than did low-risk women. In high-risk women, calcium supplementation reduced the incidence of PIH markedly more (RR 0.35, 95% CI 0.21, 0.57) than in low-risk women (RR 0.84, 95% CI 0.76, 0.92) *(see Table 2)*. Similar results were observed in the reduction of risk of developing preeclampsia (compared to controls, in high-risk women, calcium supplementation resulted in a RR of 0.22, 95% CI 0.11, 0.43 compared to

Table 2

Subgroup analysis: Effect of calcium supplementation during pregnancy on relative risk of high blood pressure, by level of risk and dietary calcium intake[5]

Subgroup	Calcium-Supplemented Subjects (Cases/Total Subjects)	Control Subjects (Cases/Total Subjects)	Relative Risk (95% CI)
Low risk (n = 6 trials)	611/3,146	732/3,161	0.84 (0.76, 0.92)
High risk (n = 3 trials)*	15/141	54/156	0.35 (0.21, 0.57)
Adequate calcium intake (≥ 900 mg/d) (n = 4 trials)	547/2,505	614/2,517	0.90 (0.81, 0.99)
Low calcium intake (< 900 mg/d) (n = 5 trials)	79/782	172/800	0.49 (0.38, 0.62)

Presented are results pooled from nine clinical trials. One clinical trial included preeclampsia as an outcome, but did not include pregnancy-induced hypertension.

* Includes women at high risk for developing pregnancy-induced hypertension because they were teenagers, had preeclampsia previously, had pre-existing hypertension, or had increased sensitivity to angiotensin II.

a RR of 0.79, 95% CI 0.65, 0.94 in the low-risk women). *(See Table 3.)*

In conclusion, the subgroup analysis performed by Villar and Belizan showed that there is promising evidence of a protective effect of calcium supplementation on PIH, especially in women with risk factors for PIH or with low dietary calcium intake.[5] This analysis indicates that differences in baseline population characteristics may explain disparities in the results of trials studying the efficacy of similar interventions. Calcium supplementation during pregnancy is likely to be an effective strategy to reduce the incidence of PIH when provided to high-risk populations, or to populations with diets nutritionally deficient in calcium. In pregnant women with adequate calcium intake, the benefit of calcium supplementation has not been shown.[5]

Nutritional supplementation can be provided either to alleviate deficiency or, in non-deficient individuals, to obtain a pharmacological effect. Correcting calcium deficiency may be more beneficial in preventing PIH than providing this micronutrient in calcium-replete women, in whom supplementation is a pharmacological rather than a nutritional intervention.[5] A possible mechanism of calcium supplements is to prevent the rise in parathyroid hormone that occurs with low calcium intake. Increased levels of parathyroid hormone may stimulate muscular contractility, and contribute to the vasoconstriction seen in PIH.[6]

Currently, the Department of Reproductive Health and Research at the World Health Organization is implementing a large multicenter and multinational randomized clinical trial to definitively assess the effectiveness of calcium supplementation as a preventive strategy for preeclampsia in women with low calcium intake. The results of this study, expected to include 8,500 women, will inform future recommendations on calcium supplementation during pregnancy. In the meantime, the present scientific evidence suggests a beneficial effect of calcium supplementation in calcium-deficient women. Women should be encouraged to consume at least 1,200 mg of calcium per day through diet or supplementation during pregnancy. ❖

Drs. Merialdi and Villar are Medical Officers, Department of Reproductive Health and Research, World Health Organization, Geneva, Switzerland.

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Table 3

Subgroup analysis: Effect of calcium supplementation during pregnancy on relative risk of preeclampsia, by level of risk and calcium dietary intake[5]

Subgroup	Calcium-Supplemented Subjects (Cases/Total Subjects)	Control Subjects (Cases/Total Subjects)	Relative Risk (95% CI)
Low risk (n = 6 trials)	188/3,146	240/3,161	0.79 (0.65, 0.94)
High risk (n = 4 trials)*	8/266	47/291	0.22 (0.11, 0.43)
Adequate calcium intake (≥ 900 mg/d) (n = 4 trials)	169/2,505	174/2,517	0.86 (0.71, 1.05)
Low calcium intake (< 900 mg/d) (n = 6 trials)	27/907	90/935	0.32 (0.21, 0.49)

Presented are results pooled from 10 clinical trials.

* Includes women at high risk for developing pregnancy-induced hypertension because they were teenagers, had preeclampsia previously, had pre-existing hypertension, or had increased sensitivity to angiotensin II.

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Editor's Note

Red Yeast Rice Alert

An article on clinical trials of red yeast rice (*Alternative Therapies in Women's Health*, July 2001) noted that a clinical trial had been performed with Cholestin, a standardized red yeast rice extract manufactured by Pharmanex. Apparently Pharmanex has reformulated the product without changing the name; the currently marketed version of Cholestin contains not red yeast rice, but policosanol, a beeswax product. Thanks to the alert reader who pointed this out, a review of clinical trials of policosanol will appear in a future issue. ❖

CME Questions

15. Colchicine is a normal constituent of:
a. ginkgo (*Ginkgo biloba*).
b. *Echinacea* species.
c. autumn crocus (*Colchicum autumnale*).

16. Sources of contamination of herbal products include:
a. improper harvesting.
b. improper cleaning of devices used in processing or packaging.
c. improper storage.
d. All of the above

17. Calcium supplementation may reduce the risk of pregnancy-induced hypertension (PIH) in women who:
a. are at high risk of PIH.
b. have low dietary calcium intake (< 900 mg/d).
c. Both a and b are correct
d. None of the above

18. Biofeedback involves the translation of skin temperature, muscle contraction, or other physiological parameters into audio or video signals as an aid to affecting those parameters.
a. True
b. False

With Comments by Adriane Fugh-Berman, MD

Biofeedback and Raynaud's

Source: Comparison of sustained-release nifedipine and temperature biofeedback for treatment of primary Raynaud phenomenon. Results from a randomized clinical trial with 1-year follow-up. *Arch Intern Med* 2000;160: 1101-1108.

Design/Setting/Subjects: A randomized, controlled clinical trial (double-blind for drug and placebo, not blinded for biofeedback) of 313 subjects (95% white, 70% women) with primary Raynaud's phenomenon (with at least two attacks/d during the cold season).

Treatment: Subjects were divided into four groups: sustained-release nifedipine (30 mg/d titrated up to 30 mg twice a day if tolerated); placebo; temperature biofeedback; or control biofeedback (electromyographic frontalis muscle biofeedback). Those assigned to biofeedback were asked to attend 10 one-hour sessions over a five- to 10-week period during the winter and spring. Four booster sessions were scheduled in the fall for those who had not successfully learned the technique or who had missed at least half of the spring sessions. Those in the biofeedback groups were asked to utilize the technique in situations perceived as being associated with high probability of causing Raynaud's phenomenon.

Outcome Measures: The primary endpoint was the number of verified attacks during the one-year assessment. Subjects were given photographs depicting hands with different color changes. "Verified" attacks were recorded attacks with a letter code matching one of photographs depicting true Raynaud's.

Results: A total of 230 subjects (of 313 randomized) completed the trial. Compared to the placebo group, the nifedipine group experienced a 66% reduction in the number of verified attacks, and the temperature biofeedback group experienced a 32% reduction (the difference between the nifedipine group and the temperature biofeedback group did not reach statistical significance). Temperature biofeedback was not significantly different than control (EMG) biofeedback. Nifedipine-treated subjects had a significantly higher incidence of side effects including edema, flushing, and tachycardia; 15% of subjects in the nifedipine group dropped out due to adverse events.

Funding: Supported by contracts from the National Heart, Lung, and Blood Institute. Nifedipine (Procardia XL) was donated by Pfizer labs.

Comments: Although the authors conclude that temperature biofeedback "is not better than its control treatment and is inferior to sustained-release nifedipine," this is misleading. Nifedipine was clearly more effective than oral placebo, but biofeedback did not receive a fair testing in this trial. In biofeedback training, skin temperature, muscle contractions, brain waves, or other parameters are translated into audio or visual signals that a subject learns to affect using imagery, relaxation techniques, etc. Once a subject can reliably affect the parameter tested, the equipment is no longer needed. There is a great deal of individual variability in how long it takes a subject to learn the technique.

It is incredible that the authors used attendance at biofeedback sessions rather than successful learning as an endpoint for effective training. Only 35% of those in the temperature biofeedback group successfully learned the technique. Subjects were asked to attend 10 biofeedback sessions; 53 of 81 (65%) temperature biofeedback participants completed all 10 sessions (compared with 80% of those in the EMG biofeedback group). "Booster" sessions were scheduled for those who had not successfully learned the technique or who had missed half of the sessions. The researchers deemed minimum biofeedback training to be completion of at least six initial sessions or two booster sessions.

However, it is irrelevant how many sessions were attended if the subjects did not learn the technique. Assessing competence by attendance has obvious drawbacks. The researchers do note that inadequate training may have compromised the results, but acknowledgement of this obvious point is no excuse for poor trial design. The situation is comparable to a medication trial in which two-thirds of the treatment group took no medication.

The selection of EMG biofeedback as a control treatment is odd. Electromyographic frontalis muscle biofeedback is used in the treatment of tension headache, but it also is used for inducing skeletal muscle relaxation, and thus general relaxation. Raynaud's phenomenon may be triggered by stress, so EMG biofeedback should not have been considered an inactive control. In fact, a biofeedback textbook recommends the combination of frontalis muscle EMG biofeedback and temperature feedback for the treatment of Raynaud's.[1]

The question of whether biofeedback is an effective treatment for Raynaud's will have to await a better trial. ❖

Reference

1. Sedlacek K. Biofeedback treatment of primary Raynaud's disease. In Basmajian, JV, ed. *Biofeedback: Principles and Practice for Clinicians.* 3rd ed. Baltimore, MD: Williams and Wilkins; 1989:317-321.

In Future Issues:

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