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Aleda M. Hess

Cedarville University, amchen@cedarville.edu

D. L. Sullivan

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Potential for toxicity with use of bitter orange extract and guarana for weight loss

Aleda M. Hess

Pharm D. Student

Ohio Northern University

Ada, Ohio 45810-9989

Donald L. Sullivan, Ph.D., R.Ph.

Associate Professor of Pharmacy Practice

Ohio Northern University

Raabe College of Pharmacy

Ada, Ohio 45810-9989

Corresponding Author:

Aleda M. Hess

3423 Mapleway Dr.

Toledo, Ohio 43614-4137

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With the recent FDA ban of the weight loss herbal supplement ephedra, manufacturers of those products are switching to other ingredients, such as bitter orange extract and guarana. Four of the five top-selling weight loss products (Metabolife®, Hydroxycut®, Dexatrim Natural®, and Xenadrine EFX®) contain either bitter orange extract, guarana, or both.¹ Are these replacements safe, or do they have the potential to cause harm?

Bitter orange extract comes from the *Citrus aurantium* plant. Its active components are: synephrine, N-methyltyramine, and furocoumarins. The amount of synephrine can vary from 1% to 30% in products. Synephrine is an alpha-adrenergic agonist believed to cause weight loss by suppressing appetite and boosting metabolism. However, it can cause vasoconstriction through stimulation of alpha-one receptors, increasing mean arterial pressure. Synephrine also causes vasoconstriction and spasms in the coronary arteries, increasing heart rate and blood pressure. N-methyltyramine, another component, can increase blood pressure by increasing norepinephrine release. The combination of synephrine and N-methyltyramine may have additive hypertensive effects and potential cardiotoxicity.² The Joint National Committee's Seventh Report even lists bitter orange as a cause of resistant hypertension. In one case report, a 55 year-old white female taking 300mg of bitter orange extract daily had an acute myocardial infarction (AMI). The patient had no history of coronary artery disease, hypertension, or hyperlipidemia but did have a 1.5 pack-per-day smoking history. Upon evaluation, the Naranjo probability scale found that bitter orange extract was the most likely source of her AMI.² One final component in bitter orange, furocoumarins, like grapefruit, are believed to be the component that inhibits the cytochrome P450 3A4 (CYP3A4) isoenzyme. Therefore, there are numerous potential drug interactions with drugs metabolized by CYP3A4 such as calcium channel blockers, antifungals, and glucocorticoids.^{2,4}

Guarana, another popular ingredient in weight-loss products, comes from the *Paullinia cupana* plant. The seed of guarana contains 2.5% to 7% caffeine (200mg/dose). In comparison, coffee only contains 1% to 2% caffeine (100mg/cup). As the dose in weight loss supplements is titrated up, the patient may be taking as much as 1800mg of caffeine a day. Caffeine acts as a central nervous system stimulant. In addition, it increases blood pressure and stimulates the release of catecholamines. Guarana in combination with drugs targeting the sympathetic nervous system, like beta-adrenergic agonists and pseudoephedrine, or with other caffeine-containing substances may have additive effects on blood pressure elevation. Guarana must be used cautiously and avoided in patients with hypertension and other cardiac conditions.² A 25 year-old female with pre-existing mitral valve prolapse drank

"Race 2005 Energy Blast with Guarana and Ginseng." She died of an intractable ventricular fibrillation due to the high caffeine content.⁵

Few studies of any kind are available on either bitter orange or guarana. However, case reports regarding their safety are emerging since the weight loss products have been reformulated. Their mechanisms of action and the case reports do not provide enough evidence about the safety of bitter orange extract and guarana. The OTC weight-loss supplements should not be recommended for use until there is conclusive data.

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