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In vivo assessment of botanical supplementation on human cytochrome P450 phenotypes: Citrus aurantium, Echinacea purpurea, milk thistle, and saw palmetto*

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Objectives: Phytochemical-mediated modulation of cytochrome P450 (CYP) activity may underlie many herb-drug interactions. Single–time point phenotypic metabolic ratios were used to determine whether long-term supplementation of Citrus aurantium, Echinacea purpurea, milk thistle (Silybum marianum), or saw palmetto (Serenoa repens) extracts affected CYP1A2, CYP2D6, CYP2E1, or CYP3A4 activity.

Methods: Twelve healthy volunteers (6 women, 6 men) were randomly assigned to receive C aurantium, E purpurea, milk thistle, or saw palmetto for 28 days. For each subject, a 30-day washout period was interposed between each supplementation phase. Probe drug cocktails of midazolam and caffeine, followed 24 hours later by chlorzoxazone and debrisoquin (INN, debrisoquine), were administered before (baseline) and at the end of supplementation. Presupplementation and postsupplementation phenotypic trait measurements were determined for CYP3A4, CYP1A2, CYP2E1, and CYP2D6 by use of 1-hydroxymidazolam/midazolam serum ratios (1-hour sample), paraxanthine/caffeine serum ratios (6-hour sample), 6-hydroxychlorzoxazone/chlorzoxazone serum ratios (2-hour sample), and debrisoquin urinary recovery ratios (8-hour collection), respectively. The content of purported "active" phytochemicals was determined for each supplement.

Results: Comparisons of presupplementation and postsupplementation phenotypic ratios suggested that these particular supplements had no significant effect on CYP1A2, CYP2D6, CYP2E1, or CYP3A4 activity. Phytochemical profiles indicated that C aurantium was devoid of the CYP3A4 inhibitor 6',7'-dihydroxybergamottin. Quantities of fatty acids, flavonolignans, and cichoric acid were consistent with label claims for saw palmetto, milk thistle, and E purpurea, respectively.

Conclusions: Botanical supplements containing C aurantium, milk thistle, or saw palmetto extracts appear to pose a minimal risk for CYP-mediated herb-drug interactions in humans. Although the effects of E purpurea on CYP activity were minor, further study into the interaction potential of this botanical is merited

Citrus aurantium, an Ingredient of Dietary Supplements Marketed for Weight Loss: Current Status of Clinical and Basic Research

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Abstract
Seville orange (Citrus aurantium) extracts are being marketed as a safe alternative to ephedra in herbal weight-loss products, but C. aurantium may also have the potential to cause adverse health effects. C. aurantium contains synephrine (oxedrine), which is structurally similar to epinephrine. Although no adverse events have been associated with ingestion of C. aurantium products thus far, synephrine increases blood pressure in humans and other species, and has the potential to increase cardiovascular events. Additionally, C. aurantium contains 6′,7′-dihydroxybergamottin and bergapten, both of which inhibit cytochrome P450-3A, and would be expected to increase serum levels of many drugs. There is little evidence that products containing C. aurantium are an effective aid to weight loss. Synephrine has lipolytic effects in human fat cells only at high doses, and octopamine does not have lipolytic effects in human adipocytes.

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Exactly which synephrine alkaloids does Citrus aurantium (bitter orange) contain?
Editors' Note: The article below is a technical report of the constituents of bitter orange, a commonly used over-the-counter (OTC) preparation for weight loss. The US Food and Drug Administration has called for the scientific community to assess existing and future OTC weight loss preparations to determine if they contain constituents that might produce adverse events in susceptible individuals. Allison and colleagues have determined that one such preparation of bitter orange contains both p-synephrine and m-synephrine. Their report confirms that it is not possible to rely on ingredient labels of OTC weight reduction preparations, and additional studies should be performed to determine if ingredients that may cause harm are present.
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Abstract
Following the withdrawal of ephedrine from the dietary supplement marketplace sales of products containing Citrus aurantium (CA) (bitter orange) for weight loss are believed to have increased dramatically. CA contains a number of constituents speculated to lead to weight loss, of which the most frequently cited constituent is synephrine. Concerns have been raised about the safety of products containing synephrine. To develop an adequate basis for clinical and public health recommendations, it is necessary to understand the nature of the synephrine alkaloids in CA. There

are six possible isomers of synephrine (para, meta, ortho; and for each a d or l form). Some authors have stated that CA contains only p-synephrine, whereas other authors have stated that CA contains m-synephrine. This is an important distinction because the two molecules have different pharmacologic properties, which may differentially affect safety and efficacy. We are unable to identify published data that explicitly show whether CA contains p-synephrine, m-synephrine, or both. In this brief report, we show that at least one product purportedly containing synephrine alkaloids from CA contains both p-synephrine and m-synephrine. We believe this justifies further investigation into which synephrine alkaloids are present in CA and products purportedly containing synephrine alkaloids from CA and the relative quantities of each of the different isomers.

Citrus aurantium and synephrine alkaloids in the treatment of overweight and obesity: an update

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Summary
Obesity is a major health problem facing the developed and developing world. Efforts by individuals, health professionals, educators, and policy makers to combat the escalating trend of growing obesity prevalence have been multifaceted and mixed in outcome. Various dietary supplements have been marketed to reduce obesity. These products have been suggested to accomplish this by decreasing energy intake and energy absorption, and/or increasing metabolic rate. Ephedra, one such supplement, was banned from sale in the US market because of concerns about adverse events. Another substance, Citrus aurantium, which contains several compounds including synephrine alkaloids, has been suggested as a safe alternative. This review examines the evidence for safety and efficacy of C. aurantium and synephrine alkaloids as examined in animal studies, clinical weight loss trials, acute physiologic studies and case reports. Although at least three reviews of C. aurantium have been published, our review expands upon these by: (i) distinguishing and evaluating the efficacy of C. aurantium and related compounds; (ii) including results from previously unreviewed research; (iii) incorporating recent case reports that serve to highlight, in an anecdotal way, potential adverse events related to the use of C. aurantium and related compounds; and (iv) offering recommendations to guide the design of future trials to evaluate the safety and efficacy of C. aurantium. While some evidence is promising, we conclude that larger and more rigorous clinical trials are necessary to draw adequate conclusions regarding the safety and efficacy of C. aurantium and synephrine alkaloids for promoting weight loss.

Uses and Properties of Citrus Flavonoids

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Section:
Pharmacology

Abstract

Flavonoids are a widely distributed group of polyphenolic compounds with health-related properties, which are based in their antioxidant activity. These properties have been found to include anticancer, antiviral, antiinflammatory activities, effects on capillary fragility, and an ability to inhibit human platelet aggregation. The antioxidant capacity of any flavonoid will be determined by a combination of the O-dihydroxy structure in the B-ring, the 2,3-double bond in conjugation with a 4-oxo function and the presence of both hydroxyl groups in positions 3 and 5. Flavanones, flavones, and flavonols are the flavonoids present in Citrus, and although flavones and flavonols have been found in low concentrations in Citrus tissues, in relationship to flavanones, these types of compounds have been show to be powerful antioxidants and free radical scavengers. Some Citrus flavonoids can be used directly as repellents or toxins or be used in plant improvement programs to obtain more resistant crops. In addition, some Citrus flavonoids and their derivates, in the field of food technology, are principally known for their ability to provide a bitter or sweet taste and as bitterness inhibitor.
Related Compounds: Amines and Proteins
Fast CE analysis of adrenergic amines in different parts of Citrus aurantium fruit and dietary supplements
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Teria Trerè,
Francesca Bugamelli,
Anna Ferranti,
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Journal of Separation Science
Special Issue: Analysis of Amino Acids and Peptides
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Abstract
A CE method has been developed for the simultaneous analysis of the adrenergic amines synephrine, octopamine and tyramine in Citrus aurantium (bitter orange) fruit extracts and in dietary supplements. The analytes were separated on a fused silica capillary (50 μm id, 40.0 cm effective length, 48.5 cm total length) using a BGE composed of phosphate buffer (pH 2.5, 50 mM) and applying a 30 kV potential. The samples were injected hydrodynamically at 50 mbar for 25 s. The use of photodiode array detection (λ=195 nm) allowed the quantification of the analytes and the control of peak purity. The method has been fully validated, obtaining satisfactory values of precision and extraction yield. The analytes are extracted with water from the dried whole fruits or fruit parts (endocarp, mesocarp and exocarp) or from the commercial formulations and directly injected into the CE apparatus. The results obtained were satisfactory in terms of precision (RSD < 5.7%) and accuracy (recovery > 89%). Thus, the method has demonstrated to be suitable for the qualitative and quantitative determination of synephrine, octopamine and tyramine in C. aurantium extracts, for dietary supplement quality control and for food adulteration identification.

Screening for Inhibitory Activity of Citrus Fruit Extracts against Platelet Cyclooxygenase and Lipoxygenase

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J. Agric. Food Chem., 1996, 44 (3), pp 725–729
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Publication Date (Web): March 19, 1996

Abstract

Inhibitory activities of the albedo extracts of 42 species and cultivars of the genus Citrus and those of two Fortunella and one Poncirus species against rat platelet cyclooxygenase and lipoxygenase were screened. Among the species investigated, the extract of Lumie (Citrus lumia) was shown to possess the highest inhibitory activity against cyclooxygenase (IC50 = 24 μg/mL), and that of Shuto (Citrus aurantium) was the highest against lipoxygenase (IC50 = 56 μg/mL). The albedo extracts of citrus from the same taxonomic group appeared to have similar inhibitory tendencies toward these enzymes. The flavedo extract of ripe lumie inhibited cyclooxygenase to the same degree as the albedo, more than the pulp extract. The flavedo, pulp, and juice extracts of ripe Ponkan (C. reticulata) also inhibited lipoxygenase in addition to the albedo extract. Both the flavedo and albedo tissues were shown to be effective sources of inhibitory compounds against cyclooxygenase and lipoxygenase.