

## Presence of *p*-synephrine in teas commercialized in Porto Alegre (RS/Brazil)

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*Citrus aurantium* (bitter orange) is characterized by the presence of *p*-synephrine, an amine structurally and pharmacologically related to ephedrine. Besides the same adverse effects as ephedrine, nowadays it is believed that altered levels of *p*-synephrine can be associated to the occurrence of migraine and cluster headaches. Leaves and fruits of this species are highly commercialized in form of teas and herbal preparations, but without taking into account the risks associated with its use. This work describes a survey of teas and herbal preparations containing *C. aurantium*, commercialized in Porto Alegre (RS/Brazil), in order to verify the presence of *p*-synephrine. Comparing with the mean amount available in the supermarkets, around 20% of the teas and 10% of the herbal preparations declared the presence of *C. aurantium* in their labels. In a sampling of 15 teas and 2 herbal preparations selected for the analysis, the presence of *p*-synephrine was characterized in all samples, with levels between 0.0040 to 0.2308%, leading to a caution that even being natural products, they are not free of adverse effects.

**Uniterms:** *Citrus aurantium*. *P*-synephrine/adverse effects. Bitter orange. Teas/analysis.

*Citrus aurantium* (laranjeira-azedada) é caracterizada pela presença de *p*-sinefrina, amina estrutural e farmacologicamente similar à efedrina. Além de poder causar efeitos adversos similares aos da efedrina, atualmente acredita-se que níveis endógenos alterados de *p*-sinefrina possam estar associados à causa da enxaqueca. Folhas e frutos desta espécie são largamente comercializados na forma de chá e em preparados de erva-mate, sem que sejam considerados os riscos associados ao seu uso. Neste sentido, este trabalho descreve uma pesquisa em chás e preparados de erva-mate comercializados em Porto Alegre, para verificar a presença de *C. aurantium* e *p*-sinefrina. Comparando com a quantidade média disponível nas prateleiras dos supermercados, cerca de 20% dos chás e 10% dos preparados de erva-mate declaravam nos rótulos conter *C. aurantium*. De uma amostragem de 15 chás e 2 preparados de erva-mate selecionados para análise, em todos foi caracterizada a presença de *p*-sinefrina com níveis variando de 0,0040 a 0,2308%, levando ao alerta de que mesmo sendo naturais, estes produtos podem não ser destituídos de reações adversas.

**Unitermos:** *Citrus aurantium*. *p*-Sinefrina/efeito adversos. Laranja-amarga. Chás/análise.

### INTRODUCTION

*Citrus aurantium* L. (Rutaceae), a plant known as bitter orange, *laranjeira-amarga* or *laranjeira-cavalo* (Carvalho-Freitas, Costa, 2002; Kuster, Rocha, 2003), is chemically characterized by the presence of volatile oils,

flavonoids, furanocoumarins and amines, especially *p*-synephrine (Fugh-Berman, Myers, 2004). Popularly, it is used as digestive, sedative, anxiolytic (Carvalho-Freitas, Costa, 2002; Pultrini, Galindo, Costa, 2006), gastrointestinal stimulating, general tonic (Bouchard *et al.*, 2005), as seasoning in culinary (Fugh-Berman, Myers, 2004), aromatizing and in perfumery (Rogers, 1981). Some of these uses, as sedative and anxiolytic, present scientific support (Rogers, 1981; Carvalho-Freitas, Costa, 2002; Pultrini, Galindo, Costa, 2006).

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Currently, the use of *C. aurantium* is very diffused in stimulant, slimmer and thermogenic preparations (Linck, Thiesen, Leal, 2006), and in products commercialized as “dietary supplements” (Calapai *et al.*, 1999; Bouchard *et al.*, 2005; Firenzuoli, Gori, Calapai, 2005), due to presence of *p*-synephrine, an adrenergic amine structurally and pharmacologically similar to ephedrine. This use dissemination was stimulated by the Food and Drug Administration (FDA) prohibition of ephedrine containing products commercialization, occurred the in 2004 April (Bent, Padula, Neuhaus, 2004; Bouchard *et al.*, 2005) as a consequence of the clinical association between its use and hypertension, ischemia, cardiac and psychiatric problems (Fugh-Berman, Myers, 2004; Bouchard *et al.*, 2005). Thus, appeared the “*ephedra-free*” products, whose formula do not contain ephedrine anymore, but extracts of *C. aurantium*, standardized as *p*-synephrine.

The substitution of ephedrine for *p*-synephrine was based on the hypothesis of specific stimulation of  $\beta_3$ -adrenergic receptors. As a matter of fact, when stimulated, these receptors cause increase in metabolic rate, leading to lipolysis stimulation and burning of calories (Kalman *et al.*, 2000). However, there is no scientific proof that *p*-synephrine, or extracts of *C. aurantium*, effectively promote body weight decrease in humans (Bent, Padula, Neuhaus, 2004).

Despite the information respecting the utilization of *C. aurantium* as thermogenic agent being quite limited, it is well established in the literature that, just as ephedrine, the *p*-synephrine acts as on  $\beta$ -adrenergic, as on  $\alpha$  receptors (Fugh-Berman, Myers, 2004; Arbo *et al.*, 2008), and could cause similar adverse effects, which could be pronounced when associated to caffeine and salicin (Dulloo, Miller, 1987; Daly, Krieger, Dulloo, 1993; Bray, Ryan, 1997; Haller, Jacob, Benowitz, 2004; Bouchard *et al.*, 2005), substances generally present in commercial preparations.

The association of citric species containing *p*-synephrine with mate or yerba maté is a worrying fact, because it is known that the association of *p*-synephrine with a stimulant, such as the caffeine present in yerba maté, could bring more pronounced adverse effects (Bouchard *et al.*, 2005). In human, effects such as tachycardia, cardiac arrhythmia, acute myocardial infarction, syncope and cerebral ischemia were reported after use of dietary supplements containing *p*-synephrine and, in one of the ischemia cases, there was association with caffeine (Bouchard *et al.*, 2005; Firenzuoli, Gori, Calapai, 2005).

The *p*-synephrine and its biogenetic precursors, tyramine and octopamine, are called trace amines due to their low endogenous quantity (D’Andrea *et al.*, 2004b). Currently, it is believed that metabolism disorders of these

amines are associated with migraine and cluster headaches (D’Andrea *et al.*, 2004a, b). Therefore, the consumption of food rich in these amines, such as cheese, wine, chocolate, *in natura* citric fruits, juices and teas, could accentuate the picture of people suffering cephalaea. Studies demonstrate also that altered basal levels of trace amines are related with neurological and psychiatric pathologies, such as schizophrenia, depression, attention deficit, epilepsy, chemical dependence, phenylketonuria and in the neurodegenerative diseases of Parkinson and Alzheimer (Branchek, Blackburn, 2003; D’Andrea *et al.*, 2003; D’Andrea *et al.*, 2004a, b; Aridon *et al.*, 2004; Berry, 2004; Shimazu, Miklya, 2004; Lewin, 2006).

In this context, and based on the commercialization of teas and yerba maté as food and soft drinks, the objective of this work was to bring a lifting of teas and yerba maté preparations containing citric species in their compositions, available in supermarkets of Porto Alegre/RS, and verify the presence of *p*-synephrine in selected samples.

## MATERIAL AND METHODS

### Samples and standards

Samples of 15 teas and 2 preparations of yerba maté (*Ilex paraguariensis*) were selected for analysis and purchased in a supermarkets network, in the city of Porto Alegre (RS, Brazil). The selection criteria took into account the trademark (it was attempted to acquire, at least, a representative of every trademark), the indication (stimulants) and the fact to be a tea said ‘citric’ (some aromatic teas of non-citric flavors, even containing *C. aurantium*, did not participate in the sampling). A *p*-synephrine standard (99% of purity) was acquired from Sigma Chemical Co. (St. Louis, USA).

### Extraction

Approximately 4 g of vegetal material were weighed into a conic test tube of 15 mL (Falcon type) and 2 extractions were developed with 4 mL of methanol every one, by stirring during 20 minutes, followed by centrifugation of 15 minutes at 3000 rpm. The supernatants were assembled, and the extract were lead to dryness in double boiler within a glass capsule, and the residue resuspended in small amount of methanol. For the verification of *p*-synephrine presence, the extracts were initially submitted to thin layer chromatography (TLC) and them to a high performance liquid chromatography with ultraviolet detection (HPLC/UV)

**Thin layer chromatography (TLC)**

The samples were applied in a silica gel GF<sub>254</sub> plate, together with standard of *p*-synephrine, utilizing as eluent

butanol:acetic acid:water (4:1:2.2; v:v:v - R<sub>f</sub> 0.62-0.65) and ninhydrin:butanol:acetic acid (30:10:0.3; m/v/v), as chromogenic agent, followed by warming at 100 °C for 10 minutes.

**TABLE I** – Listing of samples of teas containing *Citrus aurantium*, commercialized in supermarkets of Porto Alegre and analyzed respecting to presence of *p*-synephrine (*p*-SIN)

| <b>Professed composition in the product label</b>  | <b><i>p</i>-SIN (%)</b> |
|--|-------------------------|
| 1. Scrubbed leaves of orange tree ( <i>C. aurantium</i> ).   | 0.0961                  |
| 2. Leaves of orange tree ( <i>C. aurantium</i> ).  | 0.0046                  |
| 3. Leaves of sweet lime tree ( <i>C. aurantium</i> ).  | 0.0132                  |
| 4. Flowers of dog rose ( <i>R. canina</i> ), fruits of dehydrated apple tree ( <i>P. malus</i> ), peel of fruits from orange tree ( <i>C. aurantium</i> ), peel of fruits from lime tree ( <i>C. limonum</i> ) and natural flavor of tangerine.  | 0.0052                  |
| 5. Flowers and fruits of dog rose ( <i>R. canina</i> ), flowers of hibiscus ( <i>H. sabdariffa</i> ) peels of fruits from apple tree ( <i>P. malus</i> ), peel of fruits from orange tree ( <i>C. aurantium</i> ), fruits of raspberry ( <i>R. idaeus</i> ) and natural flavor of orange.  | 0.0040                  |
| 6. Fruits from apple tree ( <i>P. malus</i> ), fruits of dog rose ( <i>R. canina</i> ), peel of fruits from orange tree ( <i>C. aurantium</i> ), leaves of lemon grass ( <i>C. citratus</i> ), flowers of hibiscus ( <i>H. sabdariffa</i> ), root of chicory ( <i>C. intybus</i> ), acidulating citric acid and flavoring.   | 0.0063                  |
| 7. Flowers of dog rose ( <i>R. canina</i> ), apple ( <i>P. malus</i> ), flowers of hibiscus ( <i>H. sabdariffa</i> ), leaves of lemon grass ( <i>C. citratus</i> ), peels of fruits from orange tree ( <i>C. aurantium</i> ), peels of lemon ( <i>C. limonum</i> ), flavor identical to natural lemon and acidulating citric acid (INS 330).   | 0.0112                  |
| 8. Pup of apple ( <i>P. malus</i> ), flowers of hibiscus ( <i>H. sabdariffa</i> ), leaves of barbed wire grass ( <i>C. citratus</i> ), peels of sweet orange ( <i>C. aurantium</i> ), leaves and other parts of spearmint ( <i>M. arvensis</i> ). Lemon, orange and pineapple taste natural flavor.  | 0.0042                  |
| 9. Fruits from apple tree ( <i>P. malus</i> ), fruits from strawberry ( <i>F. vesca</i> ), fruits from orange tree ( <i>C. aurantium</i> ), flowers of hibiscus ( <i>H. sabdariffa</i> ), leaves of lemon grass ( <i>C. citratus</i> ) and apple flavor.   | 0.0135                  |
| 10. Dehydrated fruits from orange tree ( <i>C. aurantium</i> ), leaves of lemon grass ( <i>C. citratus</i> ), roots of chicory ( <i>C. intybus</i> ), peel of fruits from lemon tree ( <i>C. limonum</i> ), flowers of hibiscus ( <i>H. sabdariffa</i> ) and leaves of yerba maté ( <i>I. paraguayensis</i> ).   | 0.0277                  |
| 11. Leaves of spearmint ( <i>M. piperita</i> ), leaves of lemon grass ( <i>C. citratus</i> ), fruits from apple tree ( <i>P. malus</i> ), flowers and fruits of dog rose ( <i>R. canina</i> ), lemon peel ( <i>C. limonum</i> ), rhizome from ginger ( <i>Z. officinalis</i> ), orange peel ( <i>C. aurantium</i> ), flowers of hibiscus ( <i>H. sabdariffa</i> ), ascorbic acid (Vit. C), root of chicory ( <i>C. intybus</i> ), acidulating citric acid and aromatizing. | 0.0076                  |
| 12. Fruits of national anise ( <i>F. vulgare</i> ), leaves of boldu ( <i>P. boldo</i> ), orange peel ( <i>C. aurantium</i> ), flowers of hibiscus ( <i>H. sabdariffa</i> ), leaves and twigs of mint ( <i>M. piperita</i> ), leaves of lemon grass ( <i>C. citratus</i> ), acidulating citric acid and aromatizing identical to natural flavor of pineapple and banana.  | 0.0156                  |
| 13. Fruits of apple tree ( <i>P. malus</i> ), flowers of hibiscus ( <i>H. sabdariffa</i> ), leaves of gorse ( <i>B. genistelloides</i> ), fruits of national anise ( <i>F. vulgare</i> ), leaves of boldu ( <i>P. boldus</i> ), orange peel ( <i>C. aurantium</i> ), fruits of silvester rose ( <i>R. canina</i> ) and aromatizing.  | 0.0092                  |
| 14. Fruits of apple tree ( <i>P. malus</i> ), fruits of silvester rose ( <i>R. canina</i> ), leaves of black tea ( <i>C. sinensis</i> ), peel of cinnamon ( <i>C. zeylanicum</i> ), peel of sweet orange ( <i>C. aurantium</i> ) flowers of hibiscus ( <i>H. sabdariffa</i> ), root of chicory ( <i>C. intybus</i> ), leaves of lemon grass ( <i>C. citratus</i> ), flowers of carnation ( <i>S. aromaticum</i> ), acidulating citric acid and aromatizing.                | 0.0136                  |
| 15. Fruits of fennel ( <i>F. vulgare</i> ), yerba maté ( <i>I. paraguayensis</i> ), peel of fruits from sweet orange ( <i>C. aurantium</i> ), peel of fruits and flowers from lemon ( <i>C. limonum</i> ) and peel of cinnamon ( <i>C. zeylanicum</i> ).   | 0.0088                  |
| 16. Leaves of lemon grass ( <i>C. citratus</i> ), leaves of boldu ( <i>P. boldus</i> ), leaves and twigs of mint ( <i>M. arvensis</i> ), orange peels ( <i>C. aurantium</i> ).   | 0.0178                  |
| 17. Yerba maté ( <i>I. paraguayensis</i> ), orange peels ( <i>C. aurantium</i> ), leaves and other parts of mint twigs ( <i>M. piperita</i> ), flowers of camomile ( <i>M. recutita</i> ) and leaves of lemon grass ( <i>C. citratus</i> ).  | 0.2308                  |

## Ultraviolet high performance liquid chromatography (HPLC/UV)

The samples were diluted in the proportion 1:12 in water, filtered through a membrane with pores sized 0.45 µm (Millipore, Bedford, USA) and injected into a high performance liquid chromatograph (Knauer, Berlin, Germany) equipped with a pump model K 1001, online degasser model K 5004, manual injector with loop of 20 µl, besides a detector UV/VIS model K 2501 with EUROCHROM 2000 SOFTWARE<sup>®</sup>, 2.05 for Windows (Knauer, Berlin, Germany). The chromatographic separation was developed utilizing a reverse phase column C18 Eurospher-100<sup>®</sup>, 150 x 4 mm with pore sized 5 µm of particle diameter ( $p_d$ ), with pre-column Eurospher-100<sup>®</sup>, 5 x 4 mm, 5 µm of particle diameter. The peaks were detected at 220 nm. As mobile phase, mixings of acetonitrile:water:trifluoroacetic acid (TFA) in the proportion 5:95:0.01, as phase A; and acetonitrile:TFA (100:0.01) as phase B were utilized, in flow of 0.6 mL/min. The program of linear gradient employed was of 100 – 59% of A (8 minutes); 100% of B (9 minutes), and then the system remained in isocratic mode 100% of A during 3 minutes, with total analysis time of 12 minutes. The volume of injection was of 20 µL. The chromatographic separation was developed at room temperature. The peak of interest was identified by comparison to *p*-synephrine standard retention time (4 minutes). The method was previously validated in our laboratory (Arbo *et al.*, 2008).

## RESULTS AND DISCUSSIONS

This study was based on the fact that for long time, plants have been indiscriminately used by population, associated to the fake idea that everything that is natural, could not harm the health (Simões, 2004). Within this context are the teas utilized not only for medicinal purposes, but also as hot and cool beverages, and the preparations of yerba maté that are very appreciated by *gaucho* people, whom use *chimarrão* (infusion based on yerba maté - *Ilex paraguariensis* St. Hill.) as part of their culture.

Great quantity of products containing citric species (21 teas and 2 yerba maté preparations) was found, the majority named “orange” and having no specification about the citric species, being all of them classified as *C. aurantium*. The products containing *C. aurantium* totalized about 20% of teas and 10% of yerba maté preparations available at supermarkets counters.

From this lifting, 15 teas and 2 yerba maté preparations (n=17) were selected for analysis respecting the presence of *p*-synephrine, and forwarded for selection by

TLC and further confirmation by HPLC/UV, being evidenced the presence of *p*-synephrine in all analyzed samples, with amounts varying from 0.0040 up to 0.2308% (Table I), similar to already reported concentrations for species of *Citrus* occurring in Southern Brazil (Arbo *et al.*, 2008).

In the developed lifting, it was observed that some teas (included in the sampling) are indicated as stimulants, being suggested to be ingested at morning “to help to wake up”; or as metabolism accelerator in order “to help to slim”, and even associated to vitamin C (ascorbic acid) “to help to fight against the somnolence caused by influenza and cold”. However, the teas are not considered medications by legislation, but food; not existing so a specific raw material control as it does exist for phytotherapeutic medications (Brasil, 2004).

## CONCLUSION

Face to these data, it is evidenced the presence of *p*-synephrine in citric teas and yerba maté preparations containing *C. aurantium*, commercialized in Porto Alegre (RS) and analyzed in this study. Therefore, it is necessary to adopt some caution when consuming products containing great amounts of *p*-synephrine, as there are adverse event reports associated to its use and lack of scientific proof for their supposed therapeutic effects.

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