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Potential risks of dietary supplements for weight loss containing synephrine and caffeine available in Portugal

Riscos dos suplementos alimentares para emagrecer contendo sinefrina e cafeína disponíveis em Portugal

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ABSTRACT

Objective
Caffeine and synephrine are normally included in weight loss products due to their claimed thermogenic effects. We aimed to determine the amount of caffeine and synephrine in dietary supplements available on websites that could ship to Portugal. We also aimed to check if levels comply with those recommended by health and food authorities.

Methods
This observational study conducted a search on platforms selling dietary supplements and examined their labeling. The inclusion criteria were supplements containing both synephrine and caffeine, regardless of quantity or use. The exclusion criteria were products in which only one of the components was present or in which the formula and ingredient amounts were not fully described on the label.

Results
Within the established inclusion and exclusion criteria, 20 dietary supplements were found. Supplements contained synephrine in the form of bitter orange extract (*Citrus aurantium*). A median of 153 mg (95% CI: 40-334) was found for the extract. The estimated synephrine levels for those extracts were a median of 11 mg (95% CI: 6-20). Regarding caffeine, the median for content was 200 mg (95% CI: 176-250), though the real value is higher, given the presence of several vegetable sources of caffeine. Moreover, 65% of supplements exceed the limits recommended by the German Federal Institute for Risk Assessment for synephrine levels, and 30% exceed 200mg of caffeine.

Conclusion
It was possible to conclude that 65% and 30% of dietary supplements exceed the levels recommended by food security agencies for synephrine and caffeine, respectively, which might carry potential health risks for the consumer.

Keywords: Caffeine. *Citrus aurantium*. Dietary supplements. Synephrine. Toxicity. Weight Loss.

RESUMO

Objetivo

Cafeína e sinefrina são normalmente incluídas em produtos para perda de peso devido aos alegados efeitos termogénicos. Neste estudo foi avaliada a quantidade de cafeína e sinefrina encontrada em suplementos alimentares disponíveis em sítios da internet que enviam para Portugal. Além disso, investigou-se se essas quantidades estão de acordo com as recomendações das autoridades de saúde e alimentares.

Métodos

Este estudo observacional realizou uma busca em sítios da internet que vendem suplementos desportivos, nos quais foram analisados os rótulos. Os critérios de inclusão foram suplementos que continham sinefrina e cafeína, independentemente da quantidade e do uso. Os critérios de exclusão foram suplementos que continham apenas um dos componentes e aqueles cujas quantidades dos ingredientes não estavam discriminadas no rótulo.

Resultados

Foram encontrados 20 suplementos alimentares, os quais possuíam sinefrina na forma de extrato de laranja amarga (Citrus aurantium). Foi encontrada uma mediana de 153 mg (IC 95%: 40-334) para o extrato. Os níveis medianos estimados de sinefrina foram 11 mg (IC 95%: 6-20). Relativamente à cafeína, a mediana foi de 200 mg (IC 95%: 176-250), embora o valor possa ser mais elevado dada a presença de várias fontes vegetais de cafeína. Além disso, 65% dos suplementos excedem os limites recomendados pelo Instituto Federal Alemão de Avaliação dos Riscos para a sinefrina e 30% apresentam mais de 200 mg de cafeína.

Conclusão

Dessa forma, foi possível concluir que 65% e 30% dos suplementos alimentares excedem as quantidades recomendadas pelas autoridades de segurança alimentar de sinefrina e cafeína, respetivamente, o que poderá colocar em risco a saúde do consumidor.

Palavras-chave: *Cafeína. Citrus aurantium. Suplementos nutricionais. Sinefrina. Toxicidade. Perda de peso.*

INTRODUCTION

Caffeine and synephrine are substances normally included in weight loss products due to claims that they promote a thermogenic effect, that is, to stimulate the metabolism and increase caloric expenditure [1-4].

Caffeine is an alkaloid found in varying amounts in the grains, leaves, and fruits of more than 60 plants, and coffee is the world's leading source of caffeine in the diet [5,6]. This substance contributes to positive effects on sports performance, as it increases attention and alertness, delays the feeling of tiredness, increases time-trial performance, can increase performance in anaerobic exercises, increases the rate of glycogen synthesis, and has no impact on hydration status [3]. This substance is effective in trained athletes when consumed in low to moderate doses (~3-6 mg/kg) because when consumed in higher doses, it does not result in an ergogenic effect (>9 mg/kg) [3]. Given these effects, caffeine is often used in dietary supplements for weight loss.

Synephrine is a derivative of phenylethylamine and a sympathomimetic agent that can be used to stimulate specific adrenergic receptors (β_3, but not β_1, β_2, or α_1), which stimulate fat metabolism without any side effects typically associated with other compounds that boost adrenergic receptors [7]. Its wider interest became relevant when companies started substituting *Citrus aurantium* for ephedra in their formulations, as the US Food and Drug Administration had banned the use of ephedrine in dietary supplements [8]. Synephrine is naturally present in bitter orange (*Citrus aurantium*) and other citrus species [9]. *Citrus aurantium* is a known fruit that is commonly used as a herbal medicine to treat digestive problems in Asia, and as a mild stimulant, it contributes to appetite suppression and increased metabolic rate and lipolysis [8]. It has been shown in clinical trials that the ingestion of p-synephrine raises fat oxidation during exercise [7,10].

This component is identified as being responsible for action in weight loss products containing bitter orange or *Citrus aurantium*.

Synephrine is widely used in combination with caffeine and other ingredients in products designed to support weight management [2,6,11]. Given their use in Dietary Supplements (DS), several health and food authorities have issued recommendations on the levels deemed safe for human use. Table 1 summarizes several reference values for synephrine and caffeine consumption.

The legislation for dietary supplements varies among countries, but within the European Union, harmonization across member states ensures less disparity. The European Union legislation

Table 1 – Safety authorities' recommendations for synephrine and caffeine consumption.

Reference	Institut	Document	Synephrine	Caffeine	Synfrine + Caffeine
[18]	France/ANSES	Dietary supplements for weight loss containing p-synephrine	- The Agency considers that intake levels of p-synephrine through food supplements must remain below 20 mg/day. - Do not take p-synephrine-based weight-loss supplements along with caffeine, and strongly discourage taking such products during physical exercise, as well as their use by sensitive groups, including individuals following medical treatments, pregnant or breastfeeding women, children, and adolescents.	N.A.	N.A.
[28]	New Zealand Medicines and Medical Devices Safety Authority (MedSafe)	Committees "Minutes of the 30th meeting of the Medicines Classification Committee - 26 November 2003"	- Recommended maximum dose of 30 mg / day of synephrine.	N.A.	N.A.
[16]	Health Canada	"Guidelines for the use of Synephrine in Natural Health Products"	- Maximum dose of 30 mg/day. - Caffeine is not allowed in products that contain synephrine.	Healthy adults: No more than 400 mg of caffeine per day. - For women of childbearing age, the recommendation is a maximum daily caffeine intake of no more than 300 mg	N.A.
[17]	Health Canada	"Synephrine, Octopamine and Caffeine, Health Risk Assessment (HRA) Report"	- Maximum doses of 50 mg / day of p-synephrine when not combined.	N.A.	- Maximum dose of 40 mg of p-synephrine in combination with a maximum dose of 320 mg /day of caffeine in healthy adults
[15]	German Federal Institute of Risk Assessment (BfR)	Opinion "Health assessment of sports and weight loss products containing synephrine and caffeine"	- Maximum of 6.7 mg / day in food supplements, ensuring that in conjunction with ingestion of foods containing synephrine, it does not exceed 25.7 mg / day (95th percentile of regular consumers of foods containing synephrine).	N.A.	N.A.
[6]	Europe / European Food Safety Authority (EFSA)	EFSA explains risk assessment	N.A.	- Intakes up to 400mg per day (about 5.7mg / kg bw per day) consumed throughout the day do not raise safety concerns for healthy adults in the general population, except pregnant women (no more than 200 mg/day).	N.A.

Note: N.A.: Not Available.

was transposed to Portuguese legislation, and the manufacturer or person responsible for placing food supplements on the market must notify the Directorate General for Food and Veterinary (Portuguese DGAV) when starting to market a food supplement [12]. The labels must include all the ingredients and state that the product is a dietary supplement. Moreover, that organization is responsible for recording and following up on adverse reactions [12]. In the past few years, the problems associated with overweight and obesity have been getting worse, and the market for DS for weight loss has been increasing and is expected to continue increasing, which means more users are exposed to the risks associated with DS intake [13]. This paper aimed to report the amount of caffeine and synephrine found in dietary supplements available on websites that are commonly used by Portuguese consumers and that could be shipped to Portugal.

METHODS

In this observational study, dietary supplements were searched on internet platforms selling sports supplements. The product labels' description of the ingredients was the only basis for the supplement analysis. For the selection of DS within this research, inclusion and exclusion criteria were established. For the inclusion criteria, only dietary supplements that contained both active ingredients, synephrine (either pure or in the form of Citrus aurantium extract) and caffeine, regardless of quantity and use, were included. As for the exclusion criteria, dietary supplements were not included if only one of the components was on the label, or if the formula and ingredient amounts were not fully described. The search for dietary supplements was conducted by the first author, and inclusion and exclusion criteria were evaluated by the last author. This type of study and methodology was previously described by our group in an earlier publication [14].

The information contained on the labels of DS was taken from the websites of the company's Prozis (www.prozis.pt), Eunutrition (eunutrition.com), Myprotein (pt.myprotein.com/), NutriTienda websites (www.nutritienda.com/en), Amazon (www.amazon.com), Fitnis (www.fitnis.pt) and PlanetaHuerto (www.planetahuerto.pt). These websites were chosen because they are major players in selling supplements to the Portuguese market and could be shipped to Portugal. The ingredients disclosed on the label were thoroughly analyzed and grouped. The search for supplements was conducted between October 2020 and November 2020. After the investigation, twenty supplements were found that met the inclusion criteria. Statistical analysis and graphics were performed using GraphPad Prism 10 software (CA, USA).

In a later stage, the databases PubMed, Science Direct, and Google Scholar were used to search scientific articles for bibliographic support, with the keywords "Caffeine and synephrine, toxicology", "Citrus aurantium and caffeine, adverse cardiovascular"; "dietary supplements, body weight".

RESULTS

The ingredients and respective quantities mentioned on the label, prepared by the producers and/or distributors of 20 DSs containing synephrine and caffeine, are described in Table 2. The table describes different groups: synephrine or bitter orange extract (*Citrus aurantium*), caffeine, vegetable extracts with caffeine, other plant extracts, amino acids, micronutrients, and finally, others. It's important to mention that the amounts referred to are for the recommended daily dose. The energy and macronutrient value of these supplements is not available as they do not provide relevant calories, thus, the caloric value is not listed on the label.

Table 2 – Comparison of dietary supplements for weight loss containing synephrine and caffeine available on websites regarding all ingredients present. The amounts referred are for the recommended daily dose mentioned by the producer on the label.

Nº	Supplements (company)	Daily recommended dose	Synephrine or bitter orange extract (*citrus aurantium*)	Caffeine	Vegetable extracts with caffeine	Other plant extracts	Amino acids	Micronutrients	Others
1	Lipo 6 Black Ultra Concentrate 72 caps (nutrex)	2 capsules	120 mg - Bitter orange extract	360 mg	180 mg – guarana (containing 22% caffeine)	5 mg – piper nigrum. 5 mg – cayenne pepper	L-tyrosine - 220 mg	Chromium - 200 mg	-
2	ThermoCore™ 90 caps (amix)	2 capsules	10 mg - Bitter orange extract (95% synephrine)	160 mg	200 mg - guarana; 250 mg – green tea extract	*Coleus forskohlii* (10% Forskohlii) - 250mg; White Willow extract - 200 mg; Black pepper extract - 5 mg;	-	-	-
3	Thermo Speed Extreme (Mega Capsules) (olimp nutrition)	2 capsules	334 mg of *Citrus aurantium* (of which 20 mg synephrine)	160 mg	182 mg - guarana extract (22%); 500 mg – green tea extract	Black pepper extract - 5 mg; Pioerin (95%) - 5 mg	L-tyrosine: 1000 mg	-	-
4	Grenade Thermo Detonator (Grenade)	4 capsules	840 mg bitter orange extract	450 mg	1000 mg – green tea; 20 mg – green coffee	-	Cayenne - 400 mg; Phenylalanine - 50 mg	-	-
5	Crank (ESN)	1 spoon = 19 g	100 mg bitter orange extract (of which 6 mg synephrine)	300 mg	250 mg – green tea extract	Grape seed extract - 250 mg; Schizandra extract - 200 mg; Ginseng root extract - 100 mg; Rhodiola rosea extract - 100 mg; Pepper extract - 4.07 mg; including piperine 4 mg	Citrulline malate - 6000 mg; Arginine alpha-ketoglutarate - 4000 mg; L-tyrosine - 1000 mg; L-glycine - 1000 mg; Taurine - 1000 mg; Glucuronolactone - 500 mg	-	-
6	Termogénico Completo (BULK)	3 capsules	450 mg Citrus aurantium	300 mg	300 mg – green tea extract	Bioperine black pepper extract - 5 mg; French ketones - 150 mg; Cayenne pepper - 150 mg	L-tyrosine - 200 mg; L-thianine - 150 mg	Chromium picolinate - 1 mg	-
7	Citrolinea Max – 40 Comprimidos (ESI)	2 pills	500 mg - bitter orange extract (of which 30 mg synephrine)	10% caffeine - 100 mg	Guarana (Paullilia cupana K.) caffeine - 400 mg; green tea (Camelia sinensis) - 300 mg; kola nut (Cola Nitida Schott); caffeine - 300 mg	20% polyphenols -60 mg	L-carnitine - 200 mg	-	-
8	Thermopure Boost (Myprotein)	4 capsules	125 mg Citrus aurantium	175.5 mg	450 mg – green tea extract	Siberian ginseng - 150 mg; 225 mg of extract equivalent to 900 mg of white beans; Thermogenic mixture (caffeine, black ketones, powdered cayenne pepper, chocamine) - 825 mg	-	Chromium - 118.8 µg; Vitamin B6 - 4.6 mg; Vitamin B12 - 24 µg	-

Table 2 – Comparison of dietary supplements for weight loss containing synephrine and caffeine available on websites regarding all ingredients present. The amounts referred are for the recommended daily dose mentioned by the producer on the label.

Nº	Supplements (company)	Daily recommended dose	Synephrine or bitter orange extract (*citrus aurantium*)	Caffeine	Vegetable extracts with caffeine	Other plant extracts	Amino acids	Micronutrients	Others
9	Pwd Redhell Essence 90 capsules (PWD Nutrition)	3 capsules	180 mg - Bitter orange extract	100 mg	300 mg - guarana; Kola nut (2,5% de caffeine) - 240 mg	Grass mate - 135 mg, Fucus - 100 mg, Resveratrol 45 mg	Acetyl-L-Tyrosine 300 mg, 300 mg acetylcarnitine	Anti-caking agent (magnesium stearate)	Bulking agent (maltodextrin); 27 mg of anti-caking agent (silicon dioxide); Capsule (gelatin and coloring (E171 and E172)
10	Thermo Shape 2.0 (Activlab)	3 capsules	300 mg - Bitter orange extract	200 mg	200 mg – green tea extract	EGCG (epigallocatechin gallate) - 90 mg; Cambodia garcinia extract - 150 mg; HCA - hydroxycitric acid: 90 mg; Cayenne pepper extract - 100 mg; Capsaicin - 0.3 mg; Black pepper extract - 5 mg; Piperine - 4.7 mg	L-carnitine - 300 mg; L-tyrosine - 100 mg	Chromium – 40 µg	-
11	Thermonex 120 capsules (BSN)	3 capsules	20 mg - Bitter orange extract (*Citrus aurantium* 10% synephrine)	250 mg	375 mg – green tea extract	Green mate – 20 mg	Octopamine HCL - 200 mg; Evodiamine - 40 mg; L-Tyrosine - 300 mg; Naringin - 50 mg; Diiodotyrosine - 100 mcg	-	Iodotyrosine - 100mcg
12	Lipo 6 Black Hers - 120 capsules (nutrex)	3 capsules	40 mg - *Citrus aurantium*	200 mg	-	Cocoa Theobroma (grain) - 208.5 mg; *Coleus forskohlii* (Root) (containing Forskolin) - 25 mg; Teacrina (as TeaCrine®) - 50 mg	-	Iodine - 75 mcg; Vitamin D - 100 IU; Folic acid - 100 mcg; Vitamin B12 - 1.25 mcg; Chromium - 20 mcg	Glycerin, water, hypromellose (vegetable capsule), titanium, dye: Allura Red (E129), Bright blue FCF (E133), Yellow (E110)
13	Lipo Tone up Évolution (EU nutrition)	3 capsules	100 mg - Bitter Orange extract (Citrus aurantium 6% synephrine)	200 mg	100 mg - guarana; 200 mg – green tea extract; dry extract of kola nut - 300 mg	Black pepper extract - 9 mg; White Willow Bark Extract - 150 mg; dry extract Evodia - 100 mg; Powdered melon - 100 mg; Dry extract of bauhinia - 21 mg; Dry extract of garcinia (garcinia cambogia) - 40 mg, Dry extract pillosina cnidium - 21 mg	L-tyrosine - 100 mg	Chromium picolinate - 200 mg	-

Table 2 – Comparison of dietary supplements for weight loss containing synephrine and caffeine available on websites regarding all ingredients present. The amounts referred are for the recommended daily dose mentioned by the producer on the label.

Nº	Supplements (company)	Daily recommended dose	Synephrine or bitter orange extract (*citrus aurantium*)	Caffeine	Vegetable extracts with caffeine	Other plant extracts	Amino acids	Micronutrients	Others
14	Machine Man Burner 120 caps (Activlab)	4 capsules	335 mg bitter orange extract	156 mg	200 mg – guarana; 223 mg – green tea extract	5.30 mg black pepper extract; 100 mg cayenne peppe; 300 mg of Dandelion (*Taraxacum officinale*), 300 mg of Horsetail Extract (*Equisetum arvense*) (whole plant), 300 mg of *Fucus vesiculosus* (extract) (with 300 µg of Iodine)	1000 mg L-Carnitine, 1000 mg Taurine, 400 mg L-Tyrosine, 300 mg of L-Tryptophan, 200 mg of L-Phenylalanine	32 mg of Vitamin B3 (Niacin), 12 mg of Vitamin B5 (Pantothenic Acid), 2.80 mg of Vitamin B2 (Riboflavin), 2.80 mg Vitamin B6 (Pyridoxine), 2.20 mg of Vitamin B1 (Thiamine), 400 µg of Vitamin B9 (Folic Acid), 100 µg of Vitamin B7 (Biotin), 5 µg of Vitamin B12 (Cyanocobalamin), 400 µg chromium	400 mg of FOS (Fructooligo-saccharides), 400 mg of Inulin, 400 mg of Chitosan, 200 mg of Alpha Lipoic Acid (ALA), 100 mg of Inositol
15	Stack Fire Plus (+WATT)	2 capsules	200 mg bitter orange extract (of which 12 mg synephrine)	200 mg	100 mg green tea	84 mg (garcinia cambogia); 100 mg cayenne); 184 mg of cocoa extract (Theobroma cacao) (seed), 60 mg of Fucus vesiculosus (with 0.2% Iodine), 40 mg of *Coleus forskohlii* (root) (with forskolin)	L-carnitine 100 mg	80 mg Vitamin C; 12 mg Vitamin E	100 mg alpha lipoic acid (ALA)
16	Thermo Shape Man 120 caps (activlab)	3 capsules	300 mg bitter orange extract	200 mg	-	-	500 mg L-Tyrosine	4.2 mg Vitamin B6; 15 µg Vitamin D; Pantothenic acid (vitamin B5) 18 mg 300%; Zinc 30 mg 300%	Sodium D-aspartate 1500 mg; D-aspartic acid 1150 mg
17	Lipolean 90 Caps (Amix)	2 capsules	10 mg - *Citrus aurantium* (Standardized by 6% Synephrine)	200 mg	4 mg guarana extraxt; 8 mg green tea extract	5 mg Black pepper; 60 mg Capsicum Extract, 20 mg White Willow Extract (*Salix alba L.*) (bark) (with 15% Salicin), 6 mg Ginger Extract (*Zingiber officinale*) (root) (with 20% gingeroles)	54 mg L-Carnitine; 10 mg L-Tryptophan; 50 Taurine	2.8 Vitamin B6	530 mg of conjugated linoleic acid (CLA)
18	Lipolean Man Cut Packs (Amix)	1 pack	10 mg *Citrus aurantium* (6% of synephrine)	200 mg	4 mg Guarana; 8 mg green tea extract	250 mg Garcinia cambogia; 60 mg Capsicum Extract, 20 mg White Willow Extract (*Salix Alba l.*) (With 15% Salicin), 6mg Ginger Extract (*Zingiber officinale*) (with 20% gingeroles)	604 mg L-Carnitine, 550 mg Taurine, 100 mg L-Methionine, 10 mg L-Tryptophan	4.3 mg of Vitamin B6 (Pyridoxine)	550 mg Choline Bitartrate, 550 mg Inositol, 250 mg Betaine HCL

Table 2 – Comparison of dietary supplements for weight loss containing synephrine and caffeine available on websites regarding all ingredients present. The amounts referred are for the recommended daily dose mentioned by the producer on the label.

Nº	Supplements (company)	Daily recommended dose	Synephrine or bitter orange extract (*citrus aurantium*)	Caffeine	Vegetable extracts with caffeine	Other plant extracts	Amino acids	Micronutrients	Others
19	Lipo Tone up Super woman (EU Nutrition)	3 capsules	400 mg bitter orange extract	200 mg	60 mg guarana; 100 mg green tea extract	6mg Cayenne; 6 mg black pepper; 100 mg of cocoa Extract (*Theobroma cacao*), 100 mg of Maca Extract (Lepidium meyenii walpers), 60 mg of Giseng Extract (Panax giseng camey), 51 mg of Dandelion (*Taraxacum officinale*) (extract), 21 mg of Cinnamon (*Cinnamomum verum J. Presl*) (powder)	400 mg Acetyl L-Carnitine, 100 mg L-Arginine	100 mg of Vitamin B1 (Thiamine), 21 mg of Vitamin C, 0.9 mg of Vitamin B6 (Pyridoxine); 200 µg chromium	100 mg collagen, 45 mg coenzyme Q10
20	Ripped Freak (PharmaFreak)	2 capsules	30 mg bitter orange (*Citrus aurantium*)	350 mg	Green tea: 200 mg (leaf) + 140 mg GTC + 90 mg EGCG	200 mg Cayenne; 60 mg of Olea europaea (leaf)	-	80 mg of Vitamin C, 1.40 mg of Vitamin B6 (Pyridoxine), 5.0 µg of Vitamin D	-

Of the 20 supplements containing caffeine and synephrine or *Citrus aurantium*, none of the supplements contained pure synephrine in their composition, but rather in the form of bitter orange extract (*Citrus aurantium*). Supplements contain standardized extracts of *Citrus aurantium* for their synephrine content, which is normally standardized at 6%. Regarding the amount of bitter orange extract and considering the daily recommended dose, the minimum value found was 10 mg, corresponding to supplements number 2 and 18, and the maximum value was 840 mg, corresponding to number 4. Therefore, 6 supplements provide less than 100 mg, 6 provide between 100 mg and 200 mg, and 8 supplements provide more than 200 mg of *Citrus aurantium* per daily dose.

Regarding the amount of caffeine and considering the daily recommended dose, the minimum value found was 100 mg, which corresponds to DS number 7 and 9, while the maximum value found was 450 mg, corresponding to number 4. Also, 6 DS have more than 200 mg of caffeine. In addition to caffeine, about 95% of supplements contained other combinations of plant extracts that contained caffeine, namely green tea, green tea extract, guarana extract, and kola nut. This addition makes it impossible to estimate the exact amount of caffeine present in those DS.

With a total of 20 DS found, the median was calculated, as well as the 95% confidence interval for caffeine, bitter orange extract, and the estimated value of synephrine, and those values are depicted in Figure 1. The synephrine levels were estimated considering that bitter orange extracts are normally standardized at 6%, except in some formulations that mention other percentages (10% or even 95%). For synephrine, the median is 11 mg with a 95% confidence interval of 6 – 20 mg. Thus, the median for caffeine is 200 mg with a 95% confidence interval of 176 – 250 mg. We calculated the caffeine amount based on the amount of caffeine anhydrous reported on the label and could not estimate the amount provided by plant sources. As for the bitter orange extract, the is median is 153 mg with a 95% confidence interval of 40 – 334 mg (Figure 1).

Apart from the primary constituents, several other plant extract constituents have been disclosed, such as polyphenols, cayenne, cocoa, and black pepper extracts. Moreover, DS contain amino acids, micronutrients, and others that can be considered vestigial. Furthermore, the nutritional information on the label or the description on the websites sometimes included the following

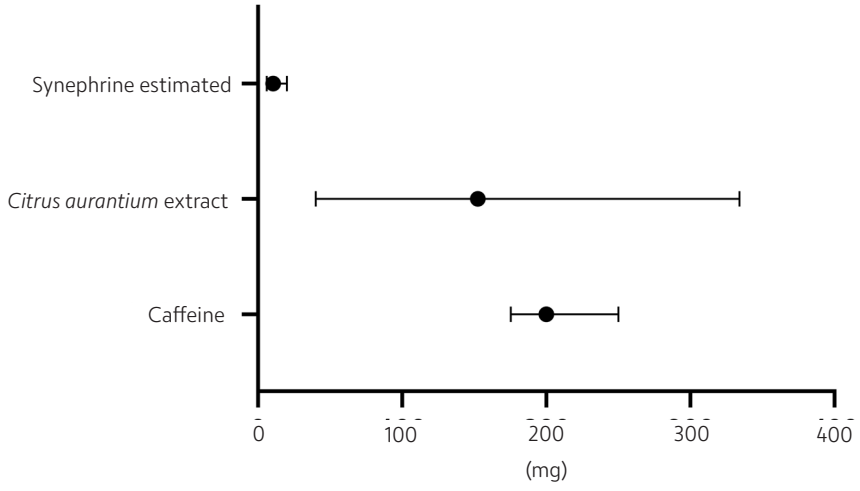

Figure 1 – Graph plotting the median and confidence interval of caffeine, bitter orange extract, and estimated values of synephrine in the twenty supplements analyzed. Values are calculated according to the daily doses recommended by the manufacturer.

warnings: "Food supplements should not be used as a substitute for a varied and balanced diet, as well as a healthy lifestyle", "Keep out of the reach of children", "Do not exceed the recommended daily dose", "This product is not intended to diagnose, treat, cure or prevent any disease", "The consumption of this product is contraindicated for people with physical or mental problems, those taking any medication, under the age of 18, pregnant women and those under medical supervision", "Avoid this product if you are allergic to aspirin or have high blood pressure, arrhythmia, glaucoma, seizures, ulcers, difficulty urinating, an enlarged prostate, diabetes, thyroid or eating disorders".

DISCUSSION

Several international safety authorities in different European Union (EU) Member States have carried out risk assessments or issued warnings for synephrine intended for weight loss and sports performance improvement, such as its combination with caffeine [6]. Of the organizations analyzed, it is worth noting that they present very different daily limits. For instance, the German Federal Institute for Risk Assessment (BfR) deemed a safe maximum daily dose of 6,7 mg of synephrine in food supplements [15]. In this study, only seven supplements respected this recommendation, while approximately 65% of supplements exceeded the limits imposed by this organization and may endanger the health of those who consume these products, according to that organization. Based on the Medsafe organization in New Zealand, the recommended dose is 30 mg. Of the analyzed supplements, 95% fell within the recommended dose except one, number 4. In 2010, Health Canada established a maximum limit of 30 mg/day of synephrine, reasoning that supplements containing both components, synephrine and caffeine, were not allowed [16]. However, in 2011, the same safety authority, Health Canada, mentioned that a maximum dose of 50 mg was recommended when synephrine is taken alone. Still, when combined with caffeine, the maximum amount allowed was 40 mg of synephrine or less in combination with a maximum of 320 mg of caffeine in healthy adults [17]. For the recommendation of 2011 by Health Canada, all supplements comply, not exceeding the maximum of 50 mg of synephrine, however, when the two ingredients are combined one supplement recommends taking 450 mg of caffeine and 50mg of synephrine (number 4). Of note, the real caffeine amount in several supplements is certainly higher, as several contain plant extracts that also contain caffeine. This addition may increase the total amount of caffeine intake, rendering it impossible for the consumer to know the exact amount of caffeine included in the supplement. Regarding caffeine consumption, the European Food Safety Authority (EFSA) recommends a maximum intake of up to 400 mg for healthy adults but only up to 200 mg for pregnant and breastfeeding women [6].

In 2014, the institution ANSES concluded that the effects of p-synephrine alone are observed from around 20 mg, as with 50 mg there is an evident effect on heart rate and systolic and diastolic blood pressure, and that caffeine can potentiate the cardiovascular effects of synephrine [18]. Thus, ANSES recommends avoiding the combination of p-synephrine with caffeine [18]. This agency also recognizes that using mixtures containing p-synephrine during physical exercise may modify blood pressure tolerance and increase acute cardiovascular risk [18]. It is worth mentioning that four supplements had p-synephrine levels higher than 20 mg. Considering the high amount of p-synephrine and its combination with caffeine in these four products without the need for a prescription, they can have consequences for patients with cardiovascular problems.

Several clinical trials were designed to assess the potential adverse effects and toxicity of synephrine and caffeine in supplements. A recent randomized, double-blind, and placebo-controlled trial was conducted involving 12 male adults (mean age 21 years) [19]. *Citrus aurantium* (600 mg,

p-synephrine at 30% concentration [180 mg]) or placebo (600 mg of starch) was ingested 90 min before the evaluation of several cardiovascular parameters. No differences from placebo were found in diastolic blood pressure, pulse pressure, mean arterial pressure, and heart rate, leading the authors to conclude that p-synephrine has a safe cardiovascular profile under these conditions [19]. A review analyzed published case reports concerning adverse effects related to multi-ingredient dietary supplements (DS) containing bitter orange extract [20]. More than 30 clinical studies involving bitter orange extract and p-synephrine have been published, and despite many cardiovascular or other significant adverse effects associated with the consumption of bitter orange extract and p-synephrine, the authors ruled that at daily and individual doses as high as 104 mg p-synephrine there is no demonstration of adverse events [20]. Still, the authors mention that "in some cases products were not being consumed as recommended, and it was not always clear whether the subjects were using other unreported DS and/or drugs" [20, p.3]. Finally, the authors stress that the studies "do not demonstrate a direct relationship between bitter orange extract (p-synephrine) and the observed effect" [20, p.7]. More recently, a new review of reports on cases of adverse events related to synephrine intake was performed, and the authors concluded that DS containing synephrine might lead to serious adverse health events [21]. This study contradicts the earlier findings of Stohs and Ray, who in their review of case reports, argued for the safety of synephrine [20]. De Jong and co-authors reviewed 30 case reports describing a total of 35 patients who reported adverse events following the use of synephrine-containing supplements [21]. Patients presented chest pain, palpitations, syncope, and dizziness, but of more concern were the diagnoses of ischemic heart disease, cardiac arrhythmias, and cerebrovascular disease. The authors concluded that there was "an association between the use of pre-workout supplements containing synephrine and adverse events, mainly related to the cardiovascular system" [21, p. 1]. They also noticed that several patients diagnosed with diseases of the circulatory system used a supplement containing synephrine and caffeine, which might indicate that when combined the adverse effects might be higher than when used alone.

Several studies in humans assessed the safety of the combination of synephrine and caffeine [22-24]. In a double-blind clinical trial 16 subjects (13 male and 3 female, with a mean age of 20 years) were given several treatments, including either 325 mg of caffeine or 337 mg of caffeine plus 46 mg of p-synephrine [23]. After 2 hours of being quietly seated, these treatments significantly increased mean systolic blood pressure [23]. Ten physically active males (mean age 25 years) were included in a double-blind trial and tested the metabolic and cardiovascular effects of a complex containing 100 mg of Citrus Aurantium + 100 mg of Caffeine [22]. This dose was sufficient to promote glucose sparing at rest and modest increases in SNS activity, though the role of each component was not disclosed [22]. Haller and collaborators conducted a three-arm randomized placebo-controlled crossover clinical trial involving 10 healthy men and women aged between 18-45 years [24]. Subjects ingested one dose of DS with 21 mg synephrine and 304 mg caffeine under resting conditions and 1 hour before moderately intense exercise, with a placebo exercise control [24]. Blood pressure and plasma glucose increased post-exercise after supplementation use, which might be problematic for patients with cardiovascular problems and diabetes [24]. Overall, the studies above emphasize the need for more quality-controlled and randomized trials, as well as double-blind and placebo-controlled studies, regarding the safety of DS that contain caffeine and p-synephrine.

This study has several limitations. First, our analysis is based on the information described on the labels provided by the producers, which might not be fully accurate. A recent study conducted in the United States found that 40% of the 57 sports supplements analyzed didn't even have detectable quantities of ingredients that were listed on their labels [25]. In this report, dietary supplements were reconstituted in methanol and analyzed by liquid chromatography quadrupole time-of-flight

mass spectrometry. Moreover, 89% of these products had labels that inaccurately indicated the amounts of those ingredients, and 12% contained at least one ingredient prohibited by the U.S. Food and Drug Administration (FDA) [25]. It should also be noted that dietary supplements can be contaminated or artificially fortified with doping agents, leading to athletes failing a doping test, despite inadvertent administration of doping agents that were not included in the label [26]. Another study in Italy analyzed weight loss supplements by Liquid Chromatography-tandem Mass Spectrometry (LC–MS/MS) to detect and quantify simultaneously different categories of active molecules [27]. The amount of caffeine reported on the label by the producer did not always correspond to what was detected (about ±30% variation) [27]. The same was found for synephrine, and there was even one product that contained synephrine that was not declared on the label [27]. These previous studies highlight that fraud can be frequent in the supplements market. We estimated the content of synephrine contained in the supplements based on the information contained in the labels, and we did not perform any analytical measurements. Importantly, it is impossible to estimate based solely on the label the full amount of caffeine provided by some DS that are made of mixtures of several botanical sources of caffeine, rendering the quantity of caffeine in these supplements higher than estimated. Also, the 20 DS described herein do not reflect consumer preferences, and the dose administered by the user might not correspond to the one recommended by the product, leading to lower or higher amounts of substances to which consumers are being exposed to daily.

CONCLUSION

Several supplements have amounts of synephrine and caffeine that exceed those recommended by health safety agencies, which can put consumers' health at risk. In addition, not only can the combination of p-synephrine and caffeine components cause adverse cardiovascular effects, but other compounds can potentiate these problems or even other medications taken at the same time for a disease. Also, individuals with known cardiovascular diseases who consume this type of supplement and do not have this information may be at greater health risk. Unfortunately, there is a lack of literature and studies on this topic, as well as a lack of scientific evidence regarding adverse effects.

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