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Metals Content in Herbal Supplements

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Abstract Obesity has become an international epidemic. To evaluate the level of metals in extracts of plants prescribed as weight loss supplements, different brands containing *Camellia sinensis* (L.) Kuntze, *Citrus aurantium* L., *Cordia ecalyculata* Vell, *Ilex paraguariensis* A. St.—Hil, *Cissus quadrangularis* L., *Senna alexandrina* Mill were purchased in local market, hot acid digested, and analyzed while metal content by inductively coupled plasma optical emission spectrometry, ICP-OES. Quality assurance and quality control tests were carried out in order to monitor and control the reliability of the analytical method. For each metal evaluated, a calibration curve was prepared with certified reference material. The recovery test was performed for each batch of samples. Analyses were performed in triplicate. Quantification of aluminum, barium, cadmium, cobalt, chromium, copper, iron, lithium, manganese, molybdenum, nickel, lead, vanadium, and zinc were determined. The metals most frequently detected were manganese (15.3–329,60 mg kg^{-1}) aluminum (11.76–342.4 mg kg^{-1}), and iron (11.14–73.01 mg kg^{-1}) with higher levels in products containing *C. sinensis* China origin, *I. paraguariensis* Brazilian origin, *C. quadrangularis*, and *C. aurantium* China origin, respectively. To ensure safety consumption, an adequacy of the certification of Brazilian suppliers for herbal weight loss products is indispensable.

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Introduction

The number of diseases related to lifestyle factors as stress, obesity [1–3], excessive consumption of industrialized food containing additives, colorings, trans fats, and other ingredients [4–7], as well heavy workload [8], sedentary lifestyle, and environmental pollutants has been strongly increased [9–11].

Within these illness, obesity receives specially attention, since it has become a global epidemic disease, affecting adults and children, and has been the more significant cause of ill-death actually and is frequently associated to other diseases such as diabetes, cardiovascular problems, leading to higher morbidity [12]. According to the Brazilian Health Surveillance Secretariat of the Ministry of Health (SVS/MS), 52.5 % of the Brazilian population are overweight, the incidence higher between men 56.5 % than in women, 49.1 % [13].

Besides, many people rely on herbal medicines for weighting loss since it seems to be an easier way instead of making diet and changing lifestyle and calorie ingestion, that requires efforts [1–3, 14]. This kind of supplements is very popular and commonly used worldwide and in Brazil [15, 16] and also used as adjuvant to nutrition and physical activity, and as such, has less or no side effects when compared to traditional pharmacological treatments [17–20].

Herbs use are linked to health promotion [11, 21–23], although adverse effects have been reported. These effects are related to poor quality of the raw material, [24], erroneous identification of the species with consequent incorrect use, interactions between plants, if there is any concomitant use since they can present synergic or antagonistic effect and to impurities or contaminants as metals [23, 25].

In fact, metals present in herbal medicinal preparation as contaminant can be carcinogenic, mutagenic, teratogenic, endocrine disruptors, changes of cognitive-behavioral functions

[26], promoters of oxidative stress, which consequently initialization and promotion of cellular changes inducing to several chronic diseases as cancer with effects dependent of the type of metal and quantity/time of exposure [27].

The entrance rout of metals in herbal manufacturing process includes presence in soil, water, air; post-harvest processing, such as drying and/or elimination of liquid extractor [28].

Therefore, weight loss herbal products should be prescribed by nutritionists with recommendation of the therapy type considering the mechanism of action and administration form [29–31]. However, consumption of these products in Brazil occurred frequently without observing these rules.

The proposed of this work was to evaluate metal content in samples of dried extracts of *Ilex paraguariensis*, *Cordia ecalyculata*, *Senna alexandrina*, *Citrus aurantium*, *Cissus quadrangularis*, and *Camellia sinensis* commercially available and used as weight loss herbal supplements.

Experimental

Samples Collection

The dry extract of *Camelia sinensis* (L.) Kuntze, *Cissus aurantium* L., *Cordia ecalyculata* Vell, *Ilex paraguariensis* A. St.-Hil, *Cissus quadrangularis* L., and *Senna alexandrina* Mill was purchased in pharmacies in the metropolitan area of Vitoria, ES, Brazil. The certificate of analysis was provided for each purchased sample. The country of origin was identified from A to F, while A and B have Brazilian origin, C to F have China origin.

Processing the Samples by Acid Digestion

The samples were digested using hot acid digester equipment (Marconi MA 851) applying 1 g from each sample with addition of 3 mL of HNO_3 and 3 mL of nitric acid (HNO_3) and 2 mL of hydrogen peroxide (H_2O_2), both of analytical grade at a temperature of 120 °C (±10 °C), heated until complete digestion. The solution resulted was filtered and transferred into a 25-mL volumetric flask and the volume completed with ultrapure water. All analyses were performed in triplicates.

Inductively Coupled Plasma Optical Emission Spectrometry (ICP-OES)

Metal concentrations were estimated using ICP-OES (Thermo Scientific model iCAP 6000) equipped with pneumatic nebulizer. The system parameters were applied using the optimize source function, which automatically optimizes pump speed, nebulizer gas flow, auxiliary gas flow, coolant gas flow, and RF power for the best signal, best SBR, or best DL. In addition, the best DL parameter was chosen for the analysis.

Identification and quantification of the elements were performed in triplicate expressed in mg $kg^{-1}$of aluminum (Al), barium (Ba), cadmium (Cd), cobalt (Co), chromium (Cr), copper (Cu), iron (Fe), lithium (Li), manganese (Mn), molybdenum (Mo), nickel (Ni), lead (Pb), vanadium (V), and zinc (Zn).

Quality assurance and quality control (QA/QC) tests were carried out in order to monitor and control the reliability of the analytical method. For each metal evaluated, a calibration curve was prepared with certified reference material accepted (ISO 17025–34–35-43). The entire certificated are available as supplemental material.

The recovery test was performed for each batch of samples. Correlation coefficient (R^2) for all metals is 0.999. The blank batch validation: blank is <0.001 mg kg^{-1}; recovery measures from the batch of samples 97.78 to 113.46 %. QA: QCStd: 0.24446 to 2.7662 (Table 1).

Data Analysis

Statistical analyses were carried out using Shapiro-Kolgomorov test. Kruskal-Wallis test was used to perform non-parametric, one-way analysis for central tendency and dispersion measures of the independent samples. In addition, normality was analyzed using rejection at a significance level of 5 %. For data comparison, Mann-Whitney U test was applied.

Results and Discussion

The validation of the analytical procedure ICP-OES for quantitative determination of metals with wavelengths for selected elements, linearity; minimum, maximum values is depicted in Table 1.

Evaluation of the data by means of principal component analysis (PCA) quantified by ICP-OES, detected higher concentrations of the metals Al, Ba, Cd, Co, Cr, Cu, Fe, Li, Mn, Mo, Ni, Pb, V, and Zn in the herbs analyzed (Table 2).

The most frequently detected were Mn, Al, and Fe with Mn present in higher concentrations in the samples of *C. sinensis* (329.60 mg kg^{-1}), *I. paraguariensis* (139.16 mg kg^{-1}), and *C. quadrangularis* (39.26 mg kg^{-1}). While Al was detected in higher concentration in *C. sinensis* (342.4 mg kg^{-1}), and Fe in *S. alexandria* samples (73.01 mg.kg^{-1}) (Table 3). The median, minimum, and maximum concentration (mg kg^{-1}) of the selected metals in herbal supplements analyzed by ICP-OES is represented by Table 1. The levels detected for Mn, Al, Fe in this work are higher than the levels found for these metals in Turkish tea (Mn 277.0 ± 0.5 to 367.0 ± 0.5 μg.g^{-1}), (Al 488.0 ± 0.7 to 2164 ± 0.6 μg.g^{-1}), and (Fe 194.0 ± 0.2 to 752.0 ± 0.4 μg.g^{-1}) [32]. These differences could be explained

Table 1 Method validation, iCAP 6000 series-Duo, Thermo Scientific, pneumatic nebulization

Metals	Wavelength	Linearity (R^2)	Min Lim. (mg L^{-1})	Min Lim. (mg kg^{-1})	Max. Lim. (mg L^{-1})	Max. Lim. (mg kg^{-1})	Lecture	QC: QCStd	Rec (%)
Al	308.22	0.999737	0.01	0.25	10	250	Radial	2.7602	110.408
Ba	455.42	0.999847	0.01	0.25	1	25	Radial	0.27191	108.764
Cd	228.80	0.999919	0.001	0.025	1	25	Axial	0.27171	108.684
Co	230.70	0.9998	0.01	0.25	1	25	Axial	0.27787	111.148
Cr	205.55	0.999809	0.01	0.25	1	25	Axial	0.27909	111.636
Cu	324.75	0.999602	0.001	0.025	1	25	Axial	0.26039	104.156
Fe	259.82	0.999758	0.01	0.25	10	250	Radial	2.6969	107.876
Li	670.72	0.999973	0.01	0.25	1	25	Radial	0.28366	113.464
Mn	257.62	0.999946	0.01	0.25	1	25	Axial	0.24446	97.784
Mo	202.03	0.999894	0.01	0.25	1	25	Axial	0.26854	107.416
Ni	231.60	0.999788	0.01	0.25	1	25	Axial	0.26479	105.916
Pb	220.35	0.999822	0.01	0.25	1	25	Axial	0.27391	109.564
V	292.40	0.999858	0.01	0.25	1	25	Axial	0.28096	112.384
Zn	213.85	0.999811	0.01	0.25	1	25	Axial	0.27714	110.856

Validation data. *QC* quality control, *QCStd* quality standard control, *Rec (%)* percentage of recovery

by the tea origin, geographic and environmental condition for cultivation, and manufacture process.

Safety limits and maximum concentration of these metals are not reported for slimming botanical preparations. The metals with established limits in several publications are Cd, Cu, Hg, and Pb, including variations among these limits [33–35].

In evaluation of Nigeria herbal products, high content of Fe, Ni, Cd, Cu, Pb, Se, and Zn at levels capable of causing adverse health effects was registered [36, 37].

Regardless of dry extract, Cd was present at lower concentrations (0.00 to 0.06 mg kg^{-1}) (Table 3), and these are below all the limits proposed by WHO [38, 39] and European Pharmacopeia (EU) [35], whose maximum values are 0.3 and 0.5 mg kg^{-1}, respectively [39–41], these samples appropriated for consumption.

In addition, in the sample of *C. sinensis*, Pb was detected in low concentration (0.16 mg kg^{-1}), nickel with concentration of 5.70 mg kg^{-1} was within the limits for daily consumption (10 mg kg^{-1}) [42–44]. The content of Pb in this herbal samples was determined in the supplier G with median concentrations of 0.29 mg kg^{-1} of Brazilian origin, and those from supplier C, 0.55 mg kg^{-1} of Chinese origin been both considered save for consumption according with the limit established

Table 2 Principal component analysis (PCA) quantified by ICP-OES

Metal	*Ilex paraguariensis*	*Cordia ecalyculata*	*Senna alexandrina*	*Citrus aurantium*	*Cissus quadrangularis*	*Camellia sinensis*
Al	0	0	0	0	1	2
Ba	1	1	0	0	1	1
Cd	2	0	1	0	2	1
Co	0	0	0	1	1	2
Cr	1	1	1	3	3	4
Cu	0	0	0	3	0	2
Fe	0	0	0	3	1	2
Li	0	0	0	2	1	1
Mn	4	0	0	1	2	3
Mo	0	0	0	0	3	1
Ni	2	1	1	3	2	2
Pb	0	0	0	0	0	0
V	0	0	0	0	0	0
Zn	1	0	0	3	0	3

Table 3 Median, minimum and maximum concentration (mg kg^{-1}) of the selected metals in herbal supplements analyzed by ICP-OES

Metal	*Ilex paraguariensis* Median (min-max)	*Cordia ecalyculata* Median (min-max)	*Senna alexandrina.* Median (min-max)	*Citrus aurantium* Median (min-max)	*Cissus quadrangularis* Median (min-max)	*Camellia sinensis* Median (min-max)
Al	11.76 (9.72–1166.13)	14.76 (2.84–62.35)	37.31 (0.00–161.4)	15.14 (2.14–39.13)	35.82 (20.76–46.80)	342.4 (132.5–684.2)
Ba	3.28 (2.11–18.38)	6.30 (1.44–22.52)	14.71 (0.79–27.25)	2.13 (1.41–7.8)	4.86 (2.07–8.52)	8.61 (1.63–17.01)
Cd	0.03 (0–0.03)	0.00 (0–0.04)	0.00 (0–0.02)	0 (0–0.03)	0.02 (0.0–0.06)	0 (0–0.03)
Co	0.00 (0–1.67)	0.00 0.00	0.00 0.00	0.27 (0–0.3)	0.00 0.00	0.15 (0–0.38)
Cr	0.55 (0–3.22)	0.41 (0.22–0.49)	0.44 (0–1.5)	0.68 (0.49–8.03)	0.93 (0.45–3.7)	0.46 (0.21–0.63)
Cu	1.26 (0.68–17.03)	0.99 (0.61–3.61)	2.61 (0.39–4.9)	6.74 (3.36–10.16)	2.77 (0.97–5.09)	4.82 (0.37–8.83)
Fe	11.14 (2.51–1285.04)	16.53 (8.16–116.6)	73.01 (1.95–222.96)	49.33 (29.26–277.16)	32.17 (10.66–147.47)	59.38 (6.5–131.41)
Li	0.00 (0–0.44)	0.00 (0–0.92)	0.59 (0–1.13)	0.75 (0–3.35)	1.40 (0–2.57)	0.00 (0–1.55)
Mn	139.16 (41.65–478.46)	26.76 (3.05–206.3)	20.40 (1.81–31.25)	15.3 (8.59–29.72)	39.26 (9.51–64.38)	329.60 (13.74–588.23)
Mo	0 0	0 (0–0.43)	0.17 (0–0.44)	0 (0–0.92)	0.42 (0–0.66)	0.00 0.00
Ni	1.19 (0.47–7.60)	0.63 (0.27–0.7)	0.48 (0–0.83)	2.45 (1.95–3.58)	0.54 (0.45–2.24)	5.70 (0.26–13.33)
Pb	0 (0–0.68)	0.00 0.00	0.00 (0–0.3)	0.00 (0–0.55)	0.00 (0–0.29)	0.16 (0–0.61)
V	0.00 (0–4.04)	0.00 (0–2.1)	0.28 (0–0.37)	0.00 0.00	0.00 (0–0.38)	0.00 0.00
Zn	11.45 (3.76–33.26)	5.26 (2.08–12.43)	9.00 (1.88–16.13)	29.01 (0–119.1)	9.86 (0.9–16.23)	18.71 (4.28–34.66)

by WHO [38] of 10 and 5.0 mg kg^{-1} established by the European Pharmacopeia, respectively [38]. These data are also corroborating by Pavlova and Karadjova [45].

Ilex paraguariensis samples presented Cd values of 0.03 mg kg^{-1} while *C. quadrangularis* presented concentration of 0.02 mg kg^{-1} by the suppliers E and D, respectively. The Nigerian dried samples analyzed, Cd, exceeded by up to 1.02 % the limits established by WHO and by 5.14 % those of the US [37, 42], and the majority of the capsule preparations were strongly contaminated with Pb and Ni [42].

The presence of undeclared toxic metals in Asian products, especially natural products used in Indian Ayurveda medicine and of Chinese origin is widely reported [46–48]. Sahoo, Manchikanti, and Dey [49], pointed high frequency of the metals Fe, Pb, Hg, Cu, Cd, Zn, and As in Asian products. Liu et al. [50] demonstrated that Chinese herbal medicines contribute to the ingestion of As. Indeed, Ayurveda products as well natural products originating from Europe, Africa, and South America, including Brazil have been frequently reported with metal contamination [51].

The minerals, according to their daily requirements, are classified as trace elements or macro elements. Trace elements are those necessary in quantities lower than 100 mg day^{-1}, (cobalt, copper, chromium, iron, fluorine, iodine, manganese, molybdenum, selenium, vanadium, and zinc) while macro elements have their ingestion recommended in doses higher than 100 mg day^{-1}, (calcium, chloride, magnesium, potassium, and sodium) [52, 53].

Regarding Mn present in the samples here evaluated, concentrations were above that recommended for daily consumption [38, 39, 54] (Table 3). In comparison to the study realized by Okem et al. [51] evaluating commercial herbs in South Africa, the Mn concentrations in this present study, were higher than those reported. In the South Africa herbs, Pb concentrations achieved up to 140 % higher than the safety limits, Cd presented double concentration level limits, and essential metals as Fe, Zn, Ni, and Cr, concentrations were higher than the recommended daily intake.

For the essential metal Cu, in this study, lower median concentrations were detected compared to those described by Okem et al. [51]: 4.82 mg kg^{-1} for *C. sinensis* and 6.74 mg kg^{-1} for *C. aurantium*, compared to 14.1 and 23.3 mg kg^{-1}, respectively (Table 3). All are below recommended limits of 40 mg kg^{-1} [39].

The dried samples analyzed presented concentration of Fe and Mn of 73.01 and 329.60 mg kg^{-1}, respectively. The highest Fe medians were detected at extracts provided by suppliers C and F. These results corroborate with Tokalıoğlu [55] that registered concentrations of Fe of 98.0 and 645.0 mg kg^{-1} of Mn. Rubio et al. [53], assessed the concentration of 18 metals in teas of different species of *Mentha* L. by ICPS-OES, with identification of the following profile: Fe (406.00 mg kg^{1}) > Al (151.24 mg kg^{-1}) > Mn (55.05 mg kg^{-1}) > Zn > B > Ba > Cu > Li > Ni > Cr > Mo > Co. These data are similar the three highest concentrations identified in the dried samples currently analyzed. Although iron is an essential metal for plants and animals, elevated levels are not beneficial and considered air pollution [54], and it has been reported as accumulation metal in plants evaluated in Macedonia (515 $mg.kg^{-1}$). Considering Mn, Maharia et al. [56], registered in herbal products concentration of 601.0 mg kg^{-1}. Ting et al. [57], when assessing the contamination in botanical products of Chinese origin found Mn values of 18.54 mg L^{-1}, probably lower than the highest value found in this study, since the concentration unit differs.

Metals related to oxidative stress such as Al, Fe, Mn, Cu, and Zn are involved in neurodegenerative mechanisms [58, 59]. Al, Fe, and Cu had their level evaluated in the plasma of patients with Parkinson and higher levels identified [60]. Loef and Walach [61], in a systematic review, found that the brains of Alzheimer's patients showed high content of Fe and Cu, demonstrating the role of dietary exposure of these metals and the development of chronic, no communicable diseases, mainly related to neurotoxicity and decreased plasticity. In addition, environmental exposition to metals could lead to toxic effects or even be related to Parkinson diseases [62, 63]. The weekly intake of tolerance Al varies from 0 to 7.0 mg kg^{1}, unhealthy effects have been described when the intake is in a range of 10 to 17 mg kg^{-1} [35].

Samples of *C. aurantium*, *C. quadrangularis*, and *C. sinensis* were identified with the most content of metals and the majority of the extracts originated from China (100 % of the certificates of analysis provided for *C. quadrangularis* samples, 66.67 % of *C. aurantium*, and *C. sinensis*). All other certificates of analysis showed Brazil as the country of origin of the samples.

In fact, even when values found did not exceed the daily limits of consumption, frequent consumption and concomitant use of supplements may have a cumulative effect [64]. The extensive contamination can be explained by several critical control points that should be observed during the production process of the herbal drug (soil, air, place of cultivation, extraction processes) [15, 64–66], besides an international standardization of production should be implemented to ensure health to the final consumer.

Conclusion

Considering that metals can be accumulated causing serious damages to the liver, kidneys, or heart, it is very important to recover to a nutritionist before starting the consumption of herbal dietary supplements. On the other hand, nutritionist should consider the reliability of the compound pharmacies to ensure a health condition to the patient. Contamination of commercially available products in a localized region was evaluated in these studies and found to have potential for health risks. In addition, an adequacy of the certification of Brazilian suppliers for herbal weight loss products is necessary since this is a market is in expansion and metals contamination presence could be demonstrated representing a health risk for the population.

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