Multielement Determination in Medicinal Plants and Herbal Medicines Containing *Cynara scolymus* L., *Harpagophytum procumbens* D.C., and *Maytenus ilifolia* (Mart.) ex Reiss from Brazil Using ICP OES

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Abstract

Worldwide, medicinal plants and herbal medicines are widely consumed. The aim of this study was to determine macro- (Ca, K, Mg, Na, and P) and microelements (Al, As, Ba, Cd, Co, Cr, Cu, Fe, Mn, Mo, Ni, Pb, Sb, Se, Si, Sn, Sr, V, and Zn) in medicinal plants and herbal medicines: "globe artichoke" - *Cynara scolymus* L., "devil's claw" - *Harpagophytum procumbens* D.C., and "espinheira santa" - *Maytenus ilifolia* (Mart) ex Reiss. Concentrations of 24 (essential and toxic potentially) elements in samples from Brazil were determined using a sequential optical emission spectrometer with inductively coupled plasma optical emission spectrometry (ICP OES) after acid digestion, assisted by microwave radiation. Principal component analysis (PCA) and hierarchical cluster analysis (HCA) were used to carry out an exploratory analysis of samples. The elements were quantified (in μg/g): Al (20.24–1261.64), Ba (18.90–63.18), Ca (2877.6–19,957.40), Cr (0.28–1.38), Cu (4.16–21.99), Fe (8.54–627.49), K (1786.12–32,297.19), Mg (505.82–6174.52), Mn (0.40–205.64), Na (1717.23–18,596.45), Ni (< LoQ–0.99), P (35.12–2899.91), Se (1.52–3.71), Sn (1.53–12.43), Sr (52.33–84.31), V (< LoQ–0.24), and Zn (2.60–30.56). As, Cd, Co, Mo, Pb, and Sb, in all the investigated samples, were found to be below the limit of detection (LoD) and quantification (LoQ) values of ICP OES. These medicinal plants and herbal medicines can be sources of Ca, K, Mg, Na, P, Cu, Fe, Mn, Se, and Zn. All samples showed considerable levels of Al. PCA and HCA showed that the samples separated into two large groups.

Introduction

The use of plants for treatment of diseases is related to human evolution itself, in all periods and social strata. The phytotherapy and the use of medicinal plants are traditionally part of popular medicine, based on the knowledge of different populations, users, and professionals. Plants and herbal medicines have contributed to the development of new therapeutic strategies, through the isolation and identification of secondary metabolites and macro- and microelements, which act directly or indirectly through various molecular and cellular mechanisms [1, 2].

Worldwide, even with the advancement of the pharmaceutical industry, the use of plants for medicinal purposes is very recurrent and can be influenced by several factors. Among these factors, especially in developing countries, the following stand out: wide biodiversity, socioeconomic and cultural issues, high cost of medicines, and the difficulty of accessing the Health System, especially for individuals living in rural areas. Therefore, the easy access to plants and herbal medicines, associated with the current trend to use natural resources as an alternative to synthetic medicines, strengthens

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consumption [3, 4]. In Brazil, among the herbal medicines offered to the population by the Unified Health System (UHS), its highlight is the "globe artichoke" (*Cynara scolymus* L.), "devil's claw" (*Harpagophytum procumbens* DC.) and "espinheira santa" (*Maytenus ilifolia* Mart ex Reiss), used in treatment of hepatic/biliar diseases, gastrointestinal disorders, and inflammatory processes (osteoarthritis and arthritic diseases), respectively [5–7].

About 80% of the world's population depends on traditional medicine for basic health needs. And, almost 85% of this practice involves the use of medicinal plants, extracts, and active ingredients [8]. Between 1981 and 2010, of the 1073 New Chemical Entities (NCE) approved as medicines by the Food and Drug Administration (FDA), only 36% were classified as truly synthetic, with 64% being natural molecules, derived, or synthesized based on natural compounds [9]. Despite the interest in molecular modeling, combinatorial chemistry and other chemical synthesis techniques, the natural products, still constitute an important basis for new therapeutic agents (antimicrobials, antioxidants, antitumor, antilipidemic, immunomodulatory, among others) and supplementary sources of vitamins and minerals [10, 11].

The essential elements (macro- and micronutrients), in adequate concentrations, are important for the normal functioning of vital organs and metabolic and cellular processes. However, in concentrations above sufficient, several of these essential metals are injurious to living organisms [12]. Elements considered potentially toxic, such as Cd, Ni, and Pb, are harmful and must be monitored, in biological samples and drugs, especially those of plant origin (herbal medicines) [13]. Medicinal plants originate and are harvested mainly from wild habitats, and often, its origins, botanical identity, purity, safety, and effectiveness are not evaluated. A fundamental question regarding the use of medicinal plants and herbal medicines should be the quality control, safety, and benefit of plant products directly related to raw materials [14].

In multielement analysis of biological samples, digestion techniques are required and, wet decomposition procedures by assisted microwave radiation are efficient [10, 15]. For multi-element determination, several spectrometric techniques of atomic absorption and emission are available. Among these, inductively coupled plasma optical emission spectrometry (ICP OES) is used for the determination of trace metals in biological samples, due to high sensitivity, multielement capability, lower limits of detection and quantifications, ruggedness, and speed of analysis [16–24]. Multivariate designs and mathematical-statistical techniques to establish optimal conditions of the analytical methods for multielement analysis by ICP OES were relevant [25]. Principal component analysis (PCA) and hierarchical cluster analysis (HCA) allow analyzing similarities or differences between samples in a given data set, such as homogeneity or heterogeneity, grouping the samples according to the degree of similarity.

Thus, the aim of this study was to determine, by axial view ICP OES, macro- (Ca, K, Mg, Na, and P) and microelements (Al, As, Ba, Cd, Co, Cr, Cu, Fe, Mn, Mo, Ni, Pb, Sb, Se, Si, Sn, V, and Zn), after digestion procedure assisted by microwave radiation, in plants and herbal medicines containing "globe artichoke" - *Cynara scolymus* L., "devil's claw" - *Harpagophytum procumbens* D.C., and "espinheira santa" - *Maytenus ilifolia* (Mart.) ex Reiss.

Material and Methods

Sampling

Herbal medicines used in the analyses were selected due to its meaningfulness for UHS and the Brazilian population and were donated by the industry responsible for production of these products, with the following presentations: global artichoke (300 mg capsules), espinheira santa (380 mg capsules), and coated tablets (450 mg) of dry extract of devil's claw. It is noteworthy that these herbal medicines are widely distributed for all regions of Brazil, as well as marketed in other countries in South America and Africa. All samples were originally stored in the primary packaging and closed plastic containers until analysis. The contents of the capsules and tablets (pool) were mixed with the aid of a mortar and pestle. Samples of the medicinal plants "globe artichoke" - *Cynara scolymus* L., "devil's claw" - *Harpagophytum procumbens* D.C., and "espinheira santa" - *Maytenus ilifolia* (Mart.) ex Reiss were acquired in a commercial establishment, in the city of Salvador, Bahia, Brazil. All samples were stored in a dark and dry place until analyses.

Reagents, Reference Materials, and Standard Solutions

The reagents were of the highest commercially available degrees of purity. Suprapur grade 65% (m/m) HNO_3 (Merck®, Darmstadt, DA, Germany) and 30% (m/m) H_2O_2 (Vetec®, São Paulo, SP, Brazil) were used for sample digestion. Monoelement solutions SpecSol® (São José dos Campos, São Paulo, Brazil) containing 10,000 mg/L Na; 4000 mg/L of Ca, K, Mg, Na, and P; and 1000 mg/L of Al, As, Ba, Cd, Co, Cr, Cu, Fe, Mn, Mo, Ni, Pb, Sb, Se, Si, Sn, Sr, V, and Zn were acquired for preparation of multielementary solutions for macro- and microelements. Dissolved organic carbon content (%DOC) was assessed in the digested samples, using a reference solution of 20,000 mg/L SpecSol® (São José dos Campos, São Paulo, Brazil). Organic carbon was digested using citric acid J.T. Baker®, Upper Saucon Township (Pennsylvania, USA). For evaluation of accuracy of the analytical procedure, spinach leaves Certified Reference Material 1570a (CRM 1570a) obtained from the National Institute of

Standards and Technology (Gaithersburg, MD, USA) was used. Argon gas, with a minimum purity of 99.999% (White Martins, São Paulo, Brazil), was used to purge the optical system and to generate plasma.

Multielementary solutions for macro- (with a concentration of 500 mg/L) and microelements (with a concentration of 20 mg/L) in 0.5% nitric acid (v/v) were used. Analytical curves were prepared in 2.0 mol/L HNO_3, for macro- (Ca, K, Mg, Na, and P) and microelemnts (Al, As, Ba, Cd, Co, Cr, Cu, Fe, Mn, Mo, Ni, Pb, Sb, Se, Si, Sn, Sr, V, and Zn) in the concentration ranges of 0–300.0 and 0–7.0 mg/L, respectively.

The solutions used were of high purity water, with specific resistivity of 18.2 MΩ cm^{-1} obtained by the Milli-Q® water purification system (Millipore, Bedford, MA, USA). All materials (glasswares, polypropylene tubes, and miscellaneous materials) used in the laboratory were decontaminated with 10% HNO_3 (v/v), bathed for 24 h (overnight), and washed abundantly with ultrapure water. Then, all the materials were dried in clean air conditions in the temperature-controlled room with air conditioning.

Instrumentation

An analytical balance (ALC/210.4, Sartorius, Goettingen, Germany) was used. For the total acid digestion of samples (medicinal plants and herbal medicines), a commercial high-pressure laboratory microwave oven (Milestone Ethos 1600 Microwave Labstation, Sorisole, Italy) was used at a frequency of 2450 Hz and energy output of 900 W. This microwave digestion system was equipped with ten 100-mL tetrafluoromethoxy vessels and a ceramic vessel jacket. The maximum operating temperature and pressure were 180 °C, 1000 W, and 100 bar, respectively, in 30 min.

The multielement determinations were conducted in a Vista simultaneous inductively coupled plasma optical emission spectrometer (Varian, Mulgrave, Australia), with axial viewing and a Charge Coupled Device (CCD) solid-state detector that allows measurements from 167 to 785 nm. The sample introduction system was performed using a One-Neb nebulizer and a single-step cyclonic nebulizer chamber. The instrumental conditions of ICP OES were RF generator of 40 MHz, power of 1.3 kW, plasma gas flow rate of 15 L/min, auxiliary gas flow rate of 1.5 L/min, nebulizer gas flow rate of 0.7 L/min, and sample uptake rate of 0.8 L/min. The wavelengths of the analytical lines were selected according to previous interference studies, considering the most prominent line, and alternatively, secondary lines were used to prevent possible interferences.

Microwave Procedure, Residual Acidity, and Digested Dissolved Organic Carbon

Approximately, 300 mg of each sample (herbal medicines and medicinal plants) was directly inserted into a microwave closed vessel, and 1 mL of 30% (v/v) H_2O_2 + 7.0 mL of 65% (v/v) HNO_3 solutions were added [10]. The heating program was implemented in four successive steps, maintained at constant pressure (35 bar): step (1) 6 min, 750 W, and 90 °C; step (2) 4 min, 750 W, and 90 °C; step (3) 8 min, 1000 W, and 180 °C; and step (4) 15 min, 1000 W, and 180 °C. Afterwards, ventilation was used (20 min) for cooling.

After the digestion procedure and subsequent cooling, the digested samples were diluted with deionized water to a final volume of 25.0 mL (micro) and 50.0 mL (macroelements). Blanks were prepared in each batch sample. All experiments were performed in triplicate. The resulted solutions were analyzed using ICP OES. Digestion efficiency was evaluated by the determination of the dissolved organic carbon (DOC) on ICP OES at 193.027 nm [22]. Residual acidity of the digested samples was evaluated by acid-base titration with a standard solution of sodium hydroxide (0.09987 mol/L) and phenolphthalein (1.0% m/v, in ethanol).

Analytical Validation Parameters

The method was validated through the analysis of linearity, stability, precision, and accuracy, in accordance to the protocols suggested by the International Conference on Harmonisation (ICH) guidelines [26]. Background equivalent concentration (BEC) and limits of detection (LOD) and quantification (LOQ) were obtained according to International Union of Pure and Applied Chemistry (IUPAC) recommendations [27]. Linearity was determined by the correlation coefficients of the analytical curves generated by the injections (triplicate) of the working solutions at five concentration levels. The stabilities of the multielement solution and samples were evaluated by checking possible changes in the analytical signal after the analysis by ICP OES. These solutions were evaluated for 24 h, at room temperature and kept at 37 °C (for 2 h), at 0.05 and 0.5 mol/L HNO_3. Triplicate averages with a standard deviation (RSD) lower than 10% were considered satisfactory for evaluation of the precision. For evaluation of accuracy, spinach leaves (CRM 1570a) obtained from NIST were used for most elements. In order to expand the accuracy studies, for all the elements, tests of addition and recovery of analytes were carried out (10 μg of Ca, K, Mg, Na, and P and 5 μg for other analytes). Recoveries (> 80%) were considered satisfactory for assessing the accuracy of the proposed method.

Multivariate Analysis

PCA and HCA were used to carry out an exploratory analysis of medicinal plants and herbal medicines samples. An analysis of the principal components was performed from a data matrix composed of 18 variables and 14 variables (18 × 14) and, the data was autoscaled as a form of pre-processing. HCA was

created by the Euclidean distance and Ward's method, and the results were displayed through the dendogram. All data were analyzed using Statistica® version 7.0 (StatSoft, Tulsa, USA).

Results and Discussion

Analytical Performance and Validation

The quality assurance of medicines requires reliability of the experimental data, and therefore, the validation of analytical methods is one of the continuous stages of methodological development, from a chemical, managerial, and certification point of view. The acid digestion method, assisted by microwaves, proved to be linear, over the entire concentration range studied ($R^2 > 0.99$). All solutions used were stable for a period longer than 24 h, with the maintenance of the analytical signal after analysis by ICP OES.

Precision was examined under repeatability and reproducibility conditions, and values lower than 10% indicated a significant precision of this method. For checking the accuracy of the method, spinach leaves (CRM 1570a) were used for most elements, and data suggest a variation range between 90 and 110%. Tests of addition and recovery of analytes were carried out showed that the results are in significant agreement with the reference values obtained with the same is true with the spiked samples and recovery testing (> 80%). At a 95% confidence level, the paired t test revealed that there was no significant difference between the values obtained with the proposed protocol when applied to herbal medicines or certified samples, respectively ($p > 0.05$). LoD and LoQ were obtained for macro- and microelements and determined using ICP OES

(Tables 1 and 2), using the BEC and the standard deviation of the measurements of the blank solutions and the slope of the calibration curves. LoD and LoQ were similar or inferior to those found for some methods reported in the literature [10] to determine minerals in plant and herbal drugs.

Microwave-assisted digestion has some advantages, such as minimizing the risk of contamination, increasing the efficiency of the decomposition process, less residual acidity, and less time required for digestion. The efficiency of sample digestion is the critical step that affects analytical results for multielement determinations by ICP OES techniques [22]. The residual carbon contents were $2.5 \pm 0.2\%$ ($n = 3$) and residual acidities of digest samples were 2.0 ± 0.5 mol L^{-1}, confirming the good digestion efficiency of the proposed method.

Determination of Macro- and Microelements in Medicinal Plants and Herbal Medicines

Using the ICP OES technique, the content (in µg/g) of five macro- (Ca, K, Mg, Na, and P), ten essential microelements (Ba, Co, Cu, Fe, Mn, Mo, Se, Sr, V, and Zn) and eight potentially toxic elements (Al, As, Cd, Cr, Ni, Pb, Sb, and Sn), in medicinal plants and herbal medicines varied between samples, according to each plant species (Tables 1 and 2).

The determinations of inorganic components in plants (medicinal or not) and derivatives are of great interest to public health, since these elements can influence in the pharmacological action, due to the role that certain elements play in human and animal health. On the other hand, the concentrations of macro- and microelements in plants depend not only on the inherent nature of the plant but also on the

Table 1 Concentration (µg/g) of macroelements in medicinal plants and herbal medicines (mean ± standard deviation, $n = 3$, 95% confidence level)

Samples/analytes and spectral lines (nm)	Ca 422.673	K 766.491	Mg 285.213	Na 588.995	P 220.353
EFT	2,877.6 ± 95.44	1786.12 ± 63.94	505.82 ± 14.61	1,717.23 ± 35.68	221.79 ± 5.73
AFT	8,286.51 ± 219.74	26,132.69 ± 353.61	2,454.42 ± 60.37	2,222.18 ± 20.20	1,926.67 ± 60.61
GFT	1,593.32 ± 185.55	1,939.31 ± 10.30	1,666.56 ± 153.39	3,719.29 ± 148.62	35.12 ± 3.49
EDV	14,388.37 ± 193.93	14,136.61 ± 214.18	3,746.63 ± 15.69	8,586.20 ± 10.10	1,592.00 ± 3.87
ADV	19,957.40 ± 1794,63	32,297.19 ± 3,271.71	6,170.52 ± 380.21	3,577.58 ± 580.93	2,899.91 ± 93.16
GDV	10,919.55 ± 132.90	9,696.55 ± 189.13	4,505.29 ± 130.38	18,596.45 ± 48.74	742.81 ± 22.35
LoD	1.653	0.514	0.224	5.445	1.542
LoQ	4.958	1.541	0.673	16.337	4.625
a	55583.7	61956.5	14461.6	373706.4	1340.5
b	737058.9	263689.3	74720.9	756769.8	84.8
R^2	0.993	0.999	0.9985	0.9963	0.9997

EFT, "espinheira santa" (herbal medicine); *AFT*, global artichoke (herbal medicine); *GFT*, devil's claw (herbal medicine); *EDV*, "espinheira santa" (medicinal plant); *ADV*, global artichoke (medicinal plant); *GDV*, devil's claw (medicinal plant); *ND*, not determined; *a*, angular coefficient; *b*, linear coefficient; *R^2*, determination coefficient; *LoD*, limit of detection; *LoQ*, limit of quantification

Table 2 Concentration (μg/g) of microelements in medicinal plants and herbal medicines (mean ± standard deviation, $n = 3$, 95% confidence level)

Samples/ analytes and spectral lines (nm)	Al 396.152	As 193.696	Ba 455.403	Cd 226.502	Co 228.615	Cr 205.560	Cu 324.754	Fe 238.204	Mn 257.610
EFT	25.45 ± 1.36	<LoQ	<LoQ	<LoQ	<LoQ	<LoQ	5.45 ± 0.93	8.57 ± 0.93	1.30 ± 0.19
AFT	20.24 ± 2.30	<LoQ	<LoQ	<LoQ	<LoQ	<LoQ	5.07 ± 0.35	31.74 ± 4.54	26.69 ± 0.25
GFT	1261.64 ± 47.32	<LoQ	<LoQ	<LoQ	<LoQ	<LoQ	4.16 ± 1.52	55.04 ± 9.10	0.40 ± 0.02
EDV	111.26 ± 2.16	<LoQ	63.18 ± 0.72	<LoQ	<LoQ	1.38 ± 0.08	15.21 ± 1.44	126.36 ± 4.87	205.64 ± 2.05
ADV	414.72 ± 57.90	<LoQ	18.90 ± 1.54	<LoQ	<LoQ	0.28 ± 0.04	11.32 ± 2.15	280.21 ± 25.20	173.45 ± 56.20
GDV	1238.94 ± 49.92	<LoQ	56.39 ± 2.11	<LoQ	<LoQ	15.99 ± 1.36	21.99 ± 1.11	627.49 ± 15.58	60.92 ± 1.83
LoD	0.290	0.056	0.006	0.019	0.067	0.051	0.296	0.257	0.033
LoQ	0.870	0.169	0.019	0.059	0.202	0.153	0.887	0.770	0.101
a	43589.6	695.9	1484829.7	48417.1	11447.4	6964.1	34304.6	26419.2	271162
b	4337.1	46.1	159748.6	1908.6	349.2	291.3	981.2	992.21	10116.2
R^2	0.9991	0.999	0.999	0.9998	0.9994	0.9997	0.9994	0.9996	0.9994

Samples/ analytes	Mo 202.032	Ni 216.555	Pb 220.353	Sb 206.834	Se 196.026	Sn 283.998	Sr 407.771	V 311.837	Zn 213.857
EFT	<LoQ	<LoQ	<LoQ	<LoQ	2.43 ± 0.32	<LoQ	<LoQ	<LoQ	2.60 ± 0.36
AFT	<LoQ	<LoQ	<LoQ	<LoQ	3.71 ± 0.27	<LoQ	<LoQ	<LoQ	13.83 ± 1.28
GFT	<LoQ	<LoQ	<LoQ	<LoQ	<LoQ	<LoQ	<LoQ	<LoQ	6.94 ± 1.48
EDV	<LoQ	0.99 ± 0.01	<LoQ	<LoQ	3.36 ± 0.23	7.72 ± 2.43	84.31 ± 0.32	<LoQ	17.69 ± 0.56
ADV	<LoQ	<LoQ	<LoQ	<LoQ	1.81 ± 0.31	1.53 ± 0.04	52.33 ± 2.02	<LoQ	30.56 ± 4.95
GDV	<LoQ	<LoQ	<LoQ	<LoQ	1.52 ± 0.08	12.43 ± 1.33	76.15 ± 1.63	0.24 ± 0.09	18.73 ± 1.05
LoD	0.273	0.118	0.375	1.171	1.166	0.348	0.011	0.009	0.167
LoQ	0.819	0.355	1.125	3.511	3.498	1.043	0.034	0.027	0.502
a	5196.5	8285.3	1682.3	1482.8	504.9	2116.9	3481765.8	59331.2	30835.9
b	214	372.7	135.8	65.9	35.05	147.2	423640.4	1559.6	242.8
R^2	0.9998	0.9996	0.9997	0.9996	0.9986	0.9997	0.9991	0.9997	0.9989

EFT, "espinheira santa" (herbal medicine); *AFT*, global artichoke (herbal medicine); *GFT*, devil's claw (herbal medicine); *EDV*, "espinheira santa" (medicinal plant); *ADV*, global artichoke (medicinal plant); *GDV* devil's claw (medicinal plant); *ND*, not determined; *a*, angular coefficient; *b*, linear coefficient; R^2, determination coefficient; *LoD*, limit of detection; *LoQ*, limit of quantification

characteristics of the environment and the soil where they were grown [28, 29]. Normally, the soil is subject to contamination by atmospheric exposure to potentially toxic elements from point sources, including different environmental and industrial activities [30].

All samples analyzed contained Al, Cu, Fe, Mn, Se, Zn, Ca, K, Mg, Na, and P. Ba, Cr, Sn, and Sr were only detected, in medicinal plants samples. As, Cd, Co, Mo, Pb, and Sb presented values below LoQ, for all samples. Ni was determined, in only one sample of medicinal plant ("espinheira santa"). Si was not determined in the samples, as this element is found in the form of silicon oxide, in vegetables.

It is important to discuss the concentration of the essential nutrients (macro- and microelements) present in biological samples (medicinal plants and herbal medicines) considering that the main form of consumption occurs in the form of extracts or derived products. The results showed that the content of macroelements (Ca, K, Mg, Na, and P) and essential microelements (Ba, Co, Cu, Fe, Mn, Mo, Se, Sr, V, and Zn) varied among samples. Few data were found in the literature for the determination of macro- and microelements, using ICP OES, in herbal medicines containing *Maytenus ilicifolia* (Mart.) ex Reiss, *Cynara scolymus* L., and *Harpagophytum procumbens* D.C. Silva et al. [31] analyzed the elementary content of 59 medicinal plants (stand out, the species studied in this study) used in Brazil by instrumental neutron activation analysis (INAA) for As, Ba, Ca, Co, Cr, Fe, K, Mg, Mn, Na, Se, V, and Zn determinations and inductively coupled plasma optical emission spectrometry (ICP OES) and cold vapor atomic absorption spectrometry (CV AAS) for Cd, Cu, Ni, and Pb.

Among samples, the comparison of macroelements concentrations (Ca, K, Mg, Na, and P) showed a significant variation for medicinal plants and herbal medicines (Table 1). Higher concentrations were observed, especially for Ca (1593.32–19,957.40 µg/g) and K (1786.12–32,297.19 µg/g) in the medicinal plants, when compared with that of herbal medicines. Calcium is involved with the prevention of arterial hypertension, dyslipidemia, osteoporosis, and colorectal adenomas [32]. Potassium plays an important role, particularly, in excitable cells of the muscular and nervous systems [33]. The macronutrient content is the subject of research in different plant species. Küçükbay and Kuyumcu [34], using a microwave system for mineralization of samples (10 specimens of 7 *Thymus* species' leaves) growing naturally in Turkey, determined mineral and trace elements (Mg, Ca, K, Fe, Mn, Al, Zn, Cu, Cd, Ni, and Pb) by flame atomic absorption (F AAS) and graphite furnace atomic absorption spectroscopy (GF AAS). The mineral contents of *Thymus* species were influenced by climatic conditions, especially light and temperature, on growth rates and mineral ion utilization by plants. The concentrations of Ca, K, and Mg were in the range of 8383–25,570; 8470–18,187, and 2690–9453 µg/g, respectively.

Santos Júnior et al. [10] determined Ca and Mg and in herbal medicine samples from Brazil, in the mean concentrations of 275.62 ± 0.71 and 343.20 ± 0.52 µg/g, respectively, for herbal medicines containing *Maytenus ilicifolia* (Mart.) ex Reiss. Leal et al. [35] determined Ca (9647–9,877 µg/g), K (4200–8909 µg/g), Na (11.7–22.0 µg/g), and Mg (130–1256 µg/g) by neutron activation analysis technique (NAA-k0), in *Maytenus ilicifolia* (Mart.) ex Reiss (powders and teas) from Brazil. Silva et al. [31] determined Ca (0.7–2.3 µg/g), K (1.4–8.0 µg/g), Na (19–2255 µg/g), and Mg (0.11–0.68 µg/g) in *Maytenus ilicifolia* (Mart.) ex Reiss, *Cynara scolymus* L., and *Harpagophytum procumbens* D.C. (dried medicinal plants) by INAA. Therefore, in this study, higher levels of Ca, K, Mg, and Na were found for analyzed samples (medicinal plants and herbal medicines) when compared with data published in the literature. In addition, the phosphorus content was determined, and the herbal medicines showed a variation of 35.12–2,899.91 µg/g of this element. The results showed that medicinal plants and the herbal medicines analyzed can be potential sources of macronutrients (Ca, K, Mg, Na, and P), contributing to the treatment of disorders caused by deficiencies of these elements.

Micronutrients (Ba, Co, Cu, Fe, Mn, Mo, Se, Si, Sr, V, and Zn) can be incorporated into the plants mainly from soils and industrial activities (chemistry, engineering, and mining). In this study, Ba (18.90–63.18 µg/g) and Sr (52.33–84.31 µg/g) were determined only in samples of medicinal plants (Table 2). Barium and strontium are elements abundant on Earth (265 to 835 and 32 to 200 mg/kg dry weight, respectively) depending on the soil type and are not very mobile elements, as it forms insoluble salts in water [36]. Barium and strontium can accumulate and damage bones and teeth and cause skin damage [37]. Silva et al. [31] determined Ba (47–136 µg/g) in *Maytenus ilicifolia* (Mart.) ex Reiss, *Cynara scolymus* L., and *Harpagophytum procumbens* D.C. (dried medicinal plants) by INAA. Results indicated that the content of Ba was comparable with the literature, and Sr concentration ranges were lower than the levels found in soil.

Cu and Zn are essential metals for body functions as enzymatic cofactors, very important for central nervous, immune, skeletal, and reproductive systems [38]. Geographical and physical factors and Cu- and Zn-based pesticides could affect zinc and copper soil content. These metals can be potentially toxic in concentrations daily intake of 900 µg and 15 mg, respectively [39]. The Zn content for herbal medicines (2.60 ± 0.36 µg/g) containing *Maytenus ilicifolia* (Mart.) ex Reiss samples was lower than that found by Santos Júnior et al. [10] (3.98 ± 0.19 µg/g); Leal et al. [35] (20–22 µg/g) and Silva et al. [31] (17.3–23.1 µg/g). These latter authors determined Cu (5.52–6.11 µg/g) in *Maytenus ilicifolia* (Mart.) ex Reiss, *Cynara scolymus* L., and *Harpagophytum procumbens* D.C. (dried medicinal plants) by ICP OES and CV AAS. In this study, the Cu content was comparable with the literature, for

herbal medicines and higher for medicinal plants, in the 3 plant species studied.

Iron is a very important essential component of enzymes, for the binding, transporting, and release of oxygen in higher animals, and its deficiency when prolonged will be fatal. In excess, iron can promote nausea, vomiting, diarrhea, and hepatic disorders [37]. In this study, the content of Fe (8.54–627.49 μg/g) varied between samples. The iron content in medicinal plants was higher than of herbal medicines. Santos Júnior et al. [10] found higher content of Fe (13.83 ± 0.26 μg/g) than those found in this study (8.57 ± 0.93 μg/g) for herbal medicines containing *Maytenus ilicifolia* (Mart.) ex Reiss. Also, Leal et al. [35] determined Fe (210–240 μg/g) in *Maytenus ilicifolia* (Mart.) ex Reiss (powders and teas) from Brazil. Silva et al. [31] determined Fe (103–849 μg/g) in *Maytenus ilicifolia* (Mart.) ex Reiss, *Cynara scolymus* L., and *Harpagophytum procumbens* D.C. (dried medicinal plants) by INAA. This variation may be associated with differences in soil, climatic, and seasonal conditions.

Vanadium and selenium are probable essential trace elements, with importance for enzymatic and metabolic reactions. In humans, selenium deficiency can cause colonic, gastric, and pancreatic carcinoma and cirrhosis, and in excess was observed that selenium causes muscular complications [40]. The role of V is not clear, and this element enters the organism by digestive and respiratory tracts, through food and multivitamin medicines ingestion and air inhalation. Vanadium and related compounds have been investigated as potential therapeutic agents for the treatment of cancer, atherosclerosis, and diabetes [41]. In this study, the content of Se (1.52–3.71 μg/g) varied between samples. This element just was not found in the herbal medicine containing *Harpagophytum procumbens* D.C. (devil's claw). On the other hand, V was only found (0.24 ± 0.09 μg/g) in devil's claw (medicinal plant). In literature, no data were found on these elements on studied plant species.

Manganese is an essential trace element found the highest concentrations in nuts, grains, cereals, coffee, and tea, and its daily requirement is about 2–5 mg/day [40]. Mn is an important activator of enzyme and assists in the regulation of the oxidative phosphorylation, mucopolysaccharide, and cholesterol metabolism and urea cycle. In excess, it is potentially toxic to the body causing manganism and neurological effects [42]. Mn was found in all samples analyzed, medicinal plants (60.92–205.64 μg/g), and herbal medicines (0.40–26.69 μg/g). The results are in agreement with Santos Júnior et al. [10], who determined Mn (33.91 ± 0.10) in herbal medicines containing *Maytenus ilicifolia* (Mart.) ex Reiss by ICP OES. Also, with Leal et al. [35], who determined Mn (210–240 μg/g) in *Maytenus ilicifolia* (Mart.) ex Reiss (powders and teas) from Brazil by NAA-k0 and, Silva et al. [31] who determined Mn (23.5–47 μg/g) in *Maytenus ilicifolia* (Mart.) ex Reiss, *Cynara scolymus* L., and *Harpagophytum procumbens* D.C. (dried medicinal plants) by INAA.

Potentially toxic elements, present in plants, can be absorbed by living organisms and disrupt various physiological and metabolic functions. Table 3 presents data on the concentrations of the elements found in this study, the recommended daily exposure recommended for oral use, and the main effects of these elements on the human body.

For an assessment of acceptable exposure to potentially toxic elements, in food and drugs, the following items are required for medical analysis: (a) human data (preferred if there is good quality data) and animal toxicity associated with exposure to metal; (b) probability of the presence of metal in the sample to be analyzed; (c) level and pattern of use or consumption of the article or product; (d) level of exposure to metal; (e) other sources of exposure to metal; (f) other factors that can cause toxicity (for example, co-exposure to other metals); (g) data quality and individual variability; and (h) special promotions with an increased risk of toxicity. These considerations and other factors form a risk-free treatment base for selection of the metals control limits [45].

In Table 2, Al (20.24–1,261.64 μg/g) was the only potentially toxic element present in all samples, in highest concentrations. Aluminum is abundantly found in the soil, in various ionic forms (Al^{3+} is the most toxic). Aluminum has a negative impact on plants, as it makes the soil acidic, being considered a stress signaling agent [46]. Al has no biological role, and it is considered a potentially toxic element for living organisms. No data were found in the literature about the concentration of aluminum in herbal medicines containing the species studied in this study. The aluminum content varies according to climatic and geographical characteristics, as well as cultivation and plantation management techniques. Jurca et al. [47] determined Al (42.90–373.50 μg/g), in six types of capsules containing medicinal plants from the spontaneous flora of Romania, using ICP OES. Annan et al. [48] found aluminum varied between 105.53–23.3 μg/g for *Rauwolfia vomitoria* and 104.25–12.4 μg/g for *Paullinia pinnata* samples by atomic absorption spectrophotometry. Leal et al. [35] determined Al (31–298 μg/g) by NAA-k0, in *Maytenus ilicifolia* (Mart.) ex Reiss ("espinheira santa"), in samples of medicinal plants (powders and teas) from Brazil. Küçükbay and Kuyumcu [49] determined the mineral content (essential, non-essential, and toxic elements), in eleven medicinal plants employed to alleviate common cold symptoms in Turkey, using flame atomic absorption and emission spectrometry (F AAS and F AES) and GF AAS, after acid digestion, assisted by microwave radiation. Aluminium was determined in all samples (10.7–1670.0 μg/g), as well as Cd, Ni, and Pb. The authors emphasize that toxic element accumulation should be monitored, particularly when consumed in higher quantities. In this study, aluminum concentrations were found, in agreement with the aforementioned authors. However, there was a high concentration for devil's claw (1238.94 and 1261.64 μg/g, for medicinal plant and herbal medicine, respectively). The main

Table 3 Concentration of elements (μg/g) in medicinal plants and herbal medicines; daily exposure allowed for oral use and main effects on the human body

Element	Medicinal plants/herbal medicine concentration range found in this study (μg/g)	PDE (μg/day) [39, 43, 44]	Mains effects on the human organism
Al	20.24–1261.64	7200	Carcinogenic, reproductive and neurological toxicity
As	< LoQ	10–100	Skin damage, increased risk of cancer, and problems with circulatory system
Ba	18.90–63.18	-	Profound hypokalemia, severe acidosis, respiratory halt, and ventricular arrhythmias
Cd	< LoQ	10–200	Kidney dysfunction and osteomalacia
Co	< LoQ	10–200	Sialorrhea, nausea, vomiting, and diarrhea
Cr	0.28–15.99	250	Anemia and male reproductive system damage
Cu	4.16–21.99	13,000	Hepatic disorder and neurodegeneratives
Fe	8.57–627.49	13,000	Constipation, nausea, and vomiting
Mn	0.40–205.64	2500	Manganism and neurological effects
Mo	< LoQ	250	Joint pain, gout symptoms, and hyperuricosuria
Ni	0.99	250	Hematotoxicity, genotoxicity, and carcinogenicity
Pb	< LoQ	10–200	Neurological effects and carcinogenicity
Sb	< LoQ	10–200	Diarrhea, dermatitis, and cardiac disorders
Se	1.52–3.71	42	Nausea, vomiting, nail and hair changes, and diarrhea
Sn	1.53–12.43	10–200	Low toxicity (gastrointestinal effects)
V	0.24	250	Neurobehavioral changes and neurotoxicity
Zn	2.60–30.56	2500	Nausea, vomiting, anemia, neutropenia, and leukopenia

PDE permitted daily exposure for oral exposure; *LoQ* limit of quantification

concentration of aluminum is in the secondary roots and bark of this plant, and therefore, it is suggested that this species is rich in this element. The concentrations of the chemical elements may differ, in the same plant, collected in different geographical locations.

Cr (0.28–15.99 μg/g) and Sn (1.53–12.43 μg/g) were determined only in samples of medicinal plants. These elements are non-biodegradable and introduced and accumulate into the soil in different ways, such as lithogenic and anthropogenic sources. The growing use of pesticides, fertilizers, and disinfectants can also contribute significantly [50]. The micro- and macronutrients can be considered a supplementary nutritional source and toxic metals as a good environmental indicator of soil and urban contamination [51]. In the soil, Cr and Sn are present in the concentration range (0.05–3950 and 0–2.5 μg/g, respectively). The main effects of the Cr on the human organism are irritation and ulcers (stomach and small intestine), anemia, sperm, and male reproductive system damage [52]. Tin, despite having low toxicity, can cause cytotoxicity due to methylated tin compounds [53]. Therefore, determining Cr and Sn in herbal medicines is extremely important to ensure patient safety. Santos Júnior et al. [10], using ICP OES, did not find Cr and Sn in *Maytenus ilicifolia* (Mart.) ex Reiss ("espinheira santa") in the samples of herbal medicines from Brazil. Leal et al. [35] determined Cr (4.3–5.3 μg/g) by NAA-

k0, in *Maytenus ilicifolia* (Mart.) ex Reiss (powders and teas) from Brazil. Silva et al. [31] determined Cr (1.01–31 μg/g) in *Maytenus ilicifolia* (Mart.) ex Reiss, *Cynara scolymus* L., and *Harpagophytum procumbens* D.C. (dried medicinal plants) by INAA. In this study, a high amount of tin was found for the studied medicinal plants (*Cynara scolymus* L., *Harpagophytum procumbens* D.C., and *Maytenus ilicifolia* (Mart.) ex Reiss, about five times more found in the soil, which may indicate contamination of the samples.

In this study, none of the samples showed a concentration higher than the LoQ values (in μg/g), for As (0.169), Cd (0.059), Pb (1.125), and Sb (3.511). These data were in agreement with Silva et al. [31], who also did not find Cd and Pb (< LoQ) using ICP OES, in *Maytenus ilicifolia* (Mart.) ex Reiss, *Cynara scolymus* L., and *Harpagophytum procumbens* D.C. (dried medicinal plants). Caldas and Machado [54] also did not find these elements using F AAS in herbal medicine used in Brazil—*Maytenus ilicifolia* (Mart.) ex Reiss and *Cynara scolymus* L. *Maytenus ilicifolia* (Mart.) ex Reiss (medicinal plant) was the only sample that presented 0.99 ± 0.01 μg/g of Ni. Probably, the presence of Ni in this sample was due to contamination arising from the handling, before or during the preparation for commercialization (for example, cuts, drying, and packaging processes) [55]. Furthermore, also this can be attributed to nickel as one of the most mobile and bioavailable
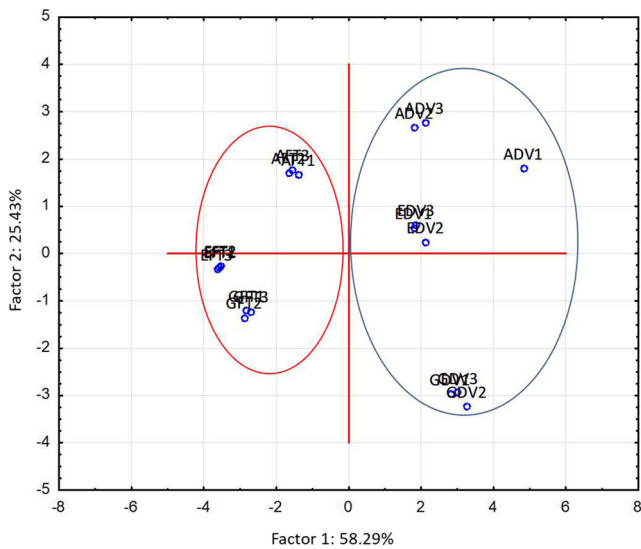
Fig. 1 Score plot PC1 × PC2 of samples obtained by principal component analysis

heavy metal ions that may be present in both industrially contaminated and pristine soils [56]. Silva et al. [31] determined Ni (0.70–5.0 μg/g) in *Maytenus ilicifolia* (Mart.) ex Reiss, *Cynara scolymus* L., and *Harpagophytum procumbens* D.C. (dried medicinal plants) from Brazil by ICP OES. Giacomino et al. [57], in Italy, determined the metal content in ayurvedic medicines by ICP OES, after sample mineralization in a microwave oven (3 mL of 65% HNO_3 and 3 mL of 30% H_2O_2). In one of the samples containing "global artichoke" (*Cynara scolymus* L.), high concentrations (in mg/Kg) of potentially toxic elements were found: As (6227 ± 49), Cr (7.4 ± 0.01), Ni (8.7 ± 2.71), Pb (134,971 ± 623), and Sn (1823 ± 240).

Table 4 Loadings of principal components (PC) for macro- and microelements in medicinal plants and herbal medicines

Element	PC 1	PC2	PC3
Al	0.11751	-0.0169	0.91714
Ba	0.96367	0.2279	0.08773
Cr	0.58290	-0.0717	0.731
Cu	0.82459	0.34199	0.34109
Fe	0.32987	0.43674	0.77547
Mn	0.55725	0.72639	-0.1212
Sn	0.78011	0.14893	0.49216
Sr	0.88818	0.41681	0.13547
Zn	0.31458	0.88271	0.34002
Ca	0.42197	0.89597	0.09509
K	-0.1219	0.93984	-0.0336
Mg	0.42727	0.79958	0.37759
Na	0.82666	-0.1408	0.41676
P	0.01475	0.98315	-0.093

Table 5 Correlation matrix for macro- and microelements in medicinal plants and herbal medicines

Element	Al	Ba	Cr	Cu	Fe	Mn	Sn	Sr	Zn	Ca	K	Mg	Na	P
Al	1.000000	0.217257	0.617755	0.416105	**0.724031**	0.043638	0.488647	0.254066	0.346032	0.117660	-0.13453	0.401786	0.434259	-0.14876
Ba		1.000000	0.587127	**0.900576**	0.497093	**0.723910**	**0.819276**	**0.969012**	0.533892	0.617477	0.073982	0.620133	**0.779263**	0.220199
Cr			1.000000	**0.714336**	**0.719561**	0.076436	**0.824387**	0.558312	0.356865	0.251444	-0.08257	0.463357	**0.851047**	-0.08379
Cu				1.000000	0.645831	0.634608	**0.808842**	**0.904625**	0.676964	0.671440	0.244318	**0.760774**	**0.798619**	0.323414
Fe					1.000000	0.477479	**0.729202**	0.587694	**0.743143**	0.617209	0.285424	**0.737769**	0.462364	0.349000
Mn						1.000000	0.480311	**0.814286**	**0.775366**	**0.882109**	0.505564	**0.749343**	0.196713	**0.682400**
Sn							1.000000	**0.803438**	0.535552	0.507787	0.038289	0.612274	**0.796554**	0.129245
Sr								1.000000	0.696695	**0.768613**	0.244220	**0.774268**	**0.712887**	0.392199
Zn									1.000000	**0.955558**	**0.778104**	**0.975051**	0.287458	**0.837139**
Ca										1.000000	**0.772106**	**0.934789**	0.254896	**0.872493**
K											1.000000	**0.694981**	-0.15885	**0.970633**
Mg												1.000000	0.427161	**0.753540**
Na													1.000000	-0.13009
P														1.000000

Multivariate Analysis of Medicinal Plants and Herbal Medicines

An analysis of the principal components was performed from a data matrix composed of 18 variables and 14 variables (18 × 14), and the data was autoscaled as a form of pre-processing. The first two main components (PC) explain 83.72% of the total variance, with PC1 contributing 58.29% and PC2 contributing 25.43% (Fig. 1).

From the visualization of Fig. 1 (PC1 × PC2), it is possible to verify that the samples separated into two large groups. In the first group (in blue) are the samples of medicinal plants, and in the second group (in red) are the samples of herbal medicines.

From Table 4, it can be seen that in PC1, the elements Ba, Cu, Sn, Sr, and Na stand out, while in PC2, the elements Mn, Zn, Ca, K, Mg, and P. However, Al, Cr, and Fe do not influence any of the first two PC. Table 5 shows a correlation matrix for macro- and microelements in the medicinal plants and herbal medicines.

From Table 5, it is possible to observe that there is a strong correlation between Cu, Ba, and Cr, whereas Fe has a correlation with Al and Cr. The Mn variable only correlated with the Ba variable. Tin showed a high correlation with Ba and Cu and with Cr and Fe variables, whereas Zn correlates only with Fe and Mn. Calcium was correlated with Mn, Sr, and Zn while K only with Zn and Ca. Mg was correlated with Cu, Fe, Mn, Zn, Ca, and K. Sodium is correlating with Ba, Cr, Cu, Sn, and Sr and P with Mn, Zn, Cu, K, and Mg.

In order to compare the results obtained through the PCA, an analysis of hierarchical groupings was performed using the Ward method and Euclidean distance (Fig. 2).

Based on Fig. 2, it can be inferred that the samples are divided into two groups, one formed by samples of medicinal plants and the other by samples of herbal medicines confirming the results found in the PCA.

Conclusions

Twenty-four elements (essential, non-essential, and potentially toxic) were determined in medicinal plants and herbal medicines from Brazil using axial view ICP OES, after a rapid and efficient microwave-assisted digestion procedure with adequate values of detection and quantification limits, precision, and accuracy.

International organizations recommend checking medicinal plants and herbal medicines for the amount of chemical elements in raw materials and final products. Multielement determinations are relevant to establish quality control criteria for these products, since high levels of contaminating elements are undesirable. In this study, it was observed that none of the analyzed samples (medicinal plants or herbal medicines) presented concentrations above or near, to daily exposure doses allowed for oral use. This indicates, preliminarily, that the doses consumed by the population are far from toxic doses, and therefore, both medicinal plants and herbal medicines can be supplementary sources of several essential elements useful for the human organism.

Fig. 2 Hierarchical cluster analysis of vegetable drugs and phytotherapics samples
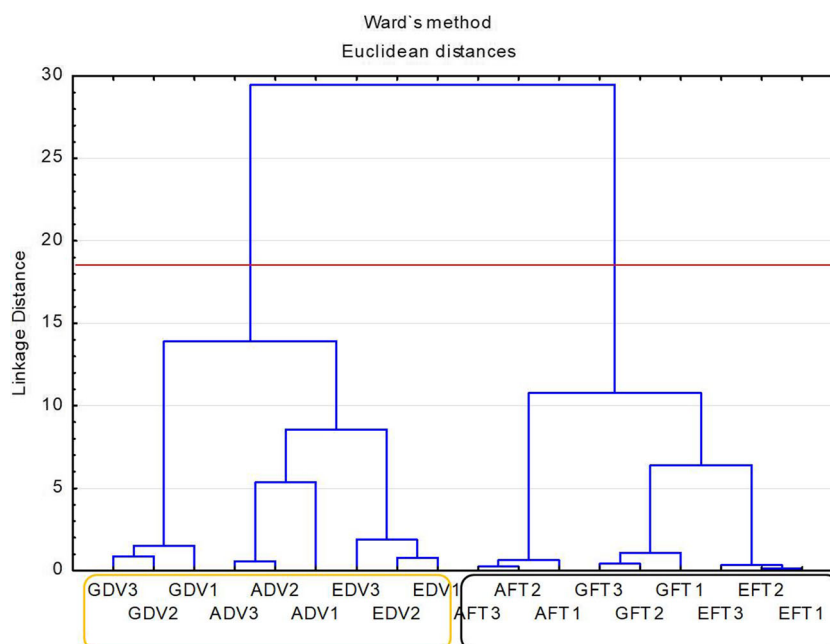
From the data obtained in that study, *Harpagophytum procumbens* D.C. (devil's claw), *Maytenus ilicifolia* (Mart.) ex Reiss ("espinheira santa"), and *Cynara scolymus* L. (global artichoke) are sources of Ca, K, Mg, Na, P, Cu, Fe, Mn, Se, and Zn. Despite being distant from the maximum recommended doses, all samples showed considerable levels of Al, and *Maytenus ilicifolia* (Mart.) ex Reiss (medicinal plant) presented Ni. PCA and HCA showed that the samples separated into two large groups (medicinal plants and herbal medicines).

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

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