

EVALUATION OF MINERAL AND TOXIC ELEMENTS IN AN IMPORTANT HERBAL MEDICINE (SCHINUS TEREBINTHIFOLIUS RADDI) IN BAHIA, BRAZIL

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ABSTRACT

Schinus terebinthifolius is a well-known medicinal plant that occurs in South and Central America and it is employed in folk medicine mainly as antimicrobial, anti-inflammatory and antipyretic, it is also commercialized as herbal medicines. Samples of *S. terebinthifolius* were collected in different habitats of the Brazilian semi-arid region. In this paper were evaluated the micro (Co, Cu, Fe, Mn, Mo, Ni and Zn), macro (Ca, Mg, Na and P) and toxic elements (As, Cd, Pb and Cr) by ICP OES and ICP-MS. The results were submitted to multivariate analysis, principal component analysis (PCA), and hierarchical cluster analysis (HCA). The multivariate analysis showed the the composition

of *S. terebinthifolius* is altered seasonally. The developed methods were promising to evaluate the minerals, toxic elements, and the results indicate that they can be added as a potential nutritional supplement in the human diet.

KEYWORDS: Minerals, Toxic elements, Chemometric, Brazilian pepper.

1. INTRODUCTION

Schinus terebinthifolius Raddi is a tree belonging to the Anacardiaceae family, and it is predominantly distributed in tropical and subtropical regions of Central and South America (Correia et al., 2006). It is popularly known as “aroeira vermelha” or brazilian pepper due to the appearance of its fruits and also because it is used as a food condiment in most of Brazil (Bendaoud et al., 2010; Feuereisen et al., 2014).

The employment of different parts of this plant in folk medicine is indicative of the importance of *S. terebinthifolius* from social and commercial points of view. Since the first edition of Brazilian Pharmacopoeia (1929), (Cavalher-Machado et al., 2008; Leite et al., 2011) its bark has been indicated as a vegetal drug, although recent studies demonstrate that leaves and fruits also present active compounds (Kweka et al., 2011).

In Brazil, the high cost of manufactured drugs, the dissatisfaction with traditional medicine, the difficulties to access the health public system are some aspects of the growing use of medicinal plants (Peron *et al.*, 2008; Simões *et al.*, 2003; Souza-Moreira et al., 2010; WHO, 2002). However, the lack of an efficient control system and quality assessment of such products may contribute to exacerbate the health public problems in the country (Leal *et al.*, 2006; Veiga et al., 2005).

The presence of foreign materials in the herbal medicines may compromise the quality of the drug and interfere in their effectiveness (Balbino, Dias, 2010; Carvalho *et al.*, 2011; Freire, 2005; Melo *et al.*, 2004; Tobias *et al.*, 2007). The major concern for human health is the long-term exposure to chemicals nonessential to humans, even at low concentrations (Fergusson, 1990; Remington, Genaro, 2000).

Plants could accumulate metals essential to their growth and developed from the soil and water - such as, Mg, Fe, Mn, Zn, Cu, Mo and Ni (Langille, MacLean, 1976). Some plants even could accumulate metals that have no known biological function to them, as Hg, Cr and others. The excessive accumulation of metals is toxic to most plants (Memon *et al.*, 2001).

Heavy metal contamination is one of the most pressing concerns for food security and food safety (Guo et al., 2010; Juo et al., 1995; Motesharrei et al., 2016) because of their detrimental effects on human health (Stavins, 2012). Heavy metals enter the human body through a wide variety of pathways (e.g., ingestion of soil, inhalation of dust, dermal contact with soil, and consumption of food crops grown in contaminated soil) (Friedlingstein et al., 2014; United Nations, 2014), and are associated with an increased risk of cardiovascular, kidney, and neurological diseases (Ostrom, 2009; Pimm, 1982; Zhao et al., 1992).

Non-invasive quality control is a critical step in getting an herbal medicine at an acceptable level of consumer quality. It is believed that the increased demand for medicinal plants and herbal medicines, in itself, has led to a reduction in the quality of the product being offered.

Lack of information among manufacturers on the care required at each stage of production, from the harvest or acquisition of raw materials to final processing, as well as the lack of trained professionals in the industry, also contributes to the low quality of products or products of poor quality (Carvalho *et al.*, 2010; Zaroni *et al.*, 2004). A large range of analytical techniques, such as, Atomic Absorption Spectroscopy (AAS), Mass Spectrometry Inductively Coupled Plasma (ICP-MS) and High Performance Liquid Chromatography (HPLC) have been employed in the evaluation of herbal drugs (Gautam *et al.*, 2010; Yuan *et al.*, 2011).

Considering this issue, the objective of this study was to determine the elementary composition *S. terebinthifolius* bark in terms of As, Ca, Cd, Co, Cr, Cu, Fe, Mg, Mn, Mo, Na, Ni, P, Pb and Zn concentrations by ICP OES and ICP-MS.

2. MATERIAL AND METHODS

2.1 Instrumentation

For the digestion of samples and CRMs (apple leaves, peach leaves and spinach leaves), a TE-040/25 (Tecnal, São Paulo, Brazil) digester block was used. Multi-element determination was performed by using a Vista PRO inductively coupled plasma optical emission spectrometer (ICP OES – Varian Mulgrave, Australia), with axial viewing and a charge-coupled device detector. The instrumental parameters for multi-element determination were as follows: radiofrequency (RF) power of 1.0 kW, plasma gas flow rate of 15.0 Lmin⁻¹, auxiliary gas flow rate of 1.5 L min⁻¹ and nebulizer gas flow rate of 1.5 L min⁻¹. The elements and analytical spectral lines (nm) were as follows: Ca II (422.673), Cu I (324.754), Fe II (259.940), Mg I (285.213), Mn II (257.610), Na I (589.592), P I (177.434), Pb II (220.353) and Zn I (213.857). Inductively coupled plasma mass spectrometry (ICP-MS) with quadrupole (XSeriesII – Thermo Electron Corporation, Germany), was used for trace element determination. The following isotopes were chosen for each element: ⁷⁵As, ¹¹¹Cd, ⁵³Cr, ⁵⁹Co, ⁹⁸Mo and ⁶⁰Ni. Aiming to compensate any transport interference, it was used the internal standards (Ge, Rh, Sc and Tl). The instrumental conditions for trace element determination without CC mode were as follows: RF incident power of 1300 W, plasma argon flow rate of 13 Lmin⁻¹, auxiliary argon flow rate of 0.7 Lmin⁻¹, nebulizer argon flow rate of 0.89 L min⁻¹, scanning mode peak jump, standard resolution, dwell time of 10 ms, sweeps of 100, number of readings per replicate of 3 and conditions of ¹⁴⁰Ce¹⁶O⁺ / ¹⁴⁰Ce⁺ < 2% and ¹³⁷Ba⁺⁺ / ¹³⁷Ba⁺ < 3%.

2.2 Reagents

All chemical reagents for the digestion procedure were of analytical grade obtained from Merck (Darmstadt, Germany). For sample digestion, concentrated nitric acid, concentrated sulfuric acid and 30% (v/v) hydrogen peroxide were used. Ultrapure water (resistivity of 18.2 MΩ cm), obtained from a Milli-Q purification system (Millipore, MA, USA), was used for the preparation of all solutions. Stock solutions of the elements As, Ca, Cd, Co, Cr, Cu, Fe, Mg, Mn, Mo, Na, Ni, P, Pb and Zn (1000 to 4000 mgL⁻¹) were used to prepare working standard solutions.

2.3 Sample collection

Samples de *S. terebinthifolius* were obtained from April to August of 2014 in ten different spots in the Bahia State (Brazil). They were bought in street markers of Salvador (12°57'11.2"S 38°30'08.1"W), Ilhéus (14°47'14.7"S 39°02'51.2"W), Porto Seguro (16°26'38.2"S 39°04'30.0"W), Jequié (13°51'48.7"S 40°05'02.8"W), Guanambi (14°13'39.5"S 42°46'47.2"W), Barreiras (12°08'41.3"S 44°59'50.7"W), Irecê (12°08'41.3"S 44°59'50.7"W), Euclides da Cunha (10°30'31.9"S 39°00'49.8"W), Juazeiro (9°26'40.5"S 40°29'28.4"W), Paulo Afonso (9°24'12.5"S 38°12'60.0"W).

2.4 Acid digestion

The collected material was separated. After sorting, the barks were packed in paper bags, identified, and dried in a forced circulation oven at 70 °C until reaching constant weight. Afterward, they were weighed on a semi-analytical balance to determine the dry mass. From these data, the percentage of each litter fraction was estimated. The samples (about 0.2 g) were digested, and the organic matter was efficiently oxidized in a digestion block using 2.0 mL of concentrated HNO₃ and 3.0 mL of H₂O₂. The digestion conditions of the digester block were 5h and a temperature of 120 °C. After being cooled, the solutions were filtered on filter paper, black band, and their volumes complete to 15 mL.

2.5 Evaluation of accuracy of the method

The accuracy of the procedure was confirmed by the analysis of three different certified reference materials from the National Institute of Standards and Technology (NIST): apple leaves (1515), spinach leaves (1570a) and peach leaves (1547). The digestion of these materials was performed by the same procedure applied to samples.

2.6 Data analysis

In the data analysis, multivariate techniques, such as principal component analysis (PCA) and hierarchical cluster analysis (HCA), were used to describe the similarity between the samples considering the total set of variables and the correlations between them. In these statistical analyses, the data set was organized in a matrix consisting of 10 samples (lines) and 14 variables (columns) representing the determined metals. Before multivariate analysis, autoscaling of the matrix was carried out, aiming to give the same weight for all variables. The analysis was performed, and graphs were plotted using the OriginPro^{8®}.

2.7 Analytical validation

All samples and standards were analyzed in triplicate and precision was evaluated by the performance of intra-day and inter-day assays by six replicated injections of the standard solutions. Intermediate precision was obtained by comparing the values obtained using ICP OES acquired in two different days, one day with analyst change. Limits of detection (LOD) and quantification (LOQ), detected as the injection concentration provided peak heights 3- and 10-fold the signal-to-noise ratio (S/N), were acquired. Multi-element solution stability and samples were evaluated for 24 h at room temperature and kept at 37 °C for 2 h at 0.01 and 0.1 mol L⁻¹ HCl by checking changes in the analytical signal after the analysis by ICP OES.

3. RESULTS AND DISCUSSION

3.1 Validation of the analytical method

The analytical method adopted for the determination of metal in the *S. terebinthifolius* was validated obtaining some parameters of merit such as the limit of quantification (LOQ), precision expressed as repeatability (percentage of relative standard deviation, %RSD), linearity (expressed as determination coefficient, R²). The results for these parameters are presented in Table 1.

The LOQ values found were adequate to determine these elements. Relative standard deviation values ranged from 0.13 to 3.5%. Typically, methods that quantify compounds in macro quantities require a RSD of 1 to 2%. For trace or impurity analysis methods, RSDs up to 20% are accepted depending on sample complexity. Linearity was evaluated as the correlation coefficient (R). According to the Brazilian National Institute of Metrology, Quality and Technology (INMETRO) R-values above 0.90 are recommended. Thus, these values show that these analytical curves present adequate linearity (Ribani et al., 2004).

Accuracy was evaluated by the analysis of three Certified Reference Materials, whose results showed good agreement with the certified values shown in Table 2 at 95% confidence. The samples were digested and analyzed by ICP OES and ICP-MS to determine the concentrations of the analytes As, Ca, Cd, Co, Cr, Cu, Fe, Mg, Mn, Mo, Na, Ni, P, Pb and Zn. The results are shown in Table 3.

3.2 Evaluation of the mineral composition in *S. terebinthifolius* bark

The results obtained for the toxic elements are shown in Table 3. Brazilian and international legislation do not have maximum allowable limits of toxic elements for edible flowers. However, based on the RCD Resolution, No 42/2013 on technical regulation of inorganic contaminants in foods of the National Health Surveillance Agency (ANVISA), the maximum permitted levels for vegetables, expressed in mg kg^{-1} range from 0.1 to 0.3 for As and 0.05 to 0.2 for Cd. Therefore, the content of arsenic in the St 6 sample was $1,23 \text{ mg kg}^{-1}$ and other samples had a concentration below the limit of quantification. In relation to Mo, all samples had levels lower than the LOQ.

According to the literature data, referring to the plant samples generally, the main matrix elements (Ca, K, Mg ...) are present in concentrations superior to 0.1%, minor elements (Fe, Al ...) lower than 0.1%, trace elements in mg/kg and ultra-trace elements below $\mu\text{g/kg}$ or lower (Hoenig & Kersabiec, 1996; Hoenig et al., 1998).

The ingestion of various elements by plants from the soil to the root system depends on the specific plant, the botanical structure of the particular tissue, the type of soil and the element. In addition, microelements can enter the plant from external environmental compartments. On the other hand, the content of essential elements in organisms depends on physiological processes, which is part of the regulatory mechanisms that can place elements below the toxic level. This is consistent with data obtained in this work and literature data as well (En et al., 2003).

The most inevitable elements in the human body are dust and tea from production, cutting processes, dry matter, soil management or climate pollution (Ernest, 2002; Fraga, 2005; Ng et al., 2012). Metals Methods used in packaging and transport of plants and related products are the major stages of heavy metals and heavy pollutants (Carvalho et al., 2010; Freire, 2005).

The toxic effects of metals on human health depend on many variables, including the affected organism, their temporal state and exposure parameters. The results presented here indicate the need to evaluate the quality of commercial herbal remedies due to the toxicity of the elements found in them (Azevedo, Chasin, 2003). The toxicological effects of these elements are difficult to quantify because they are not mentioned in the reference material of the nutritional diet (Carvalho et al., 2006).

Data evaluation by HCA using Ward's method was performed to obtain the minimum variance between vectors that comprise each group, as well as the Euclidean distances, in order to check the similarity between samples, as shown in the dendrogram of Figure 1.

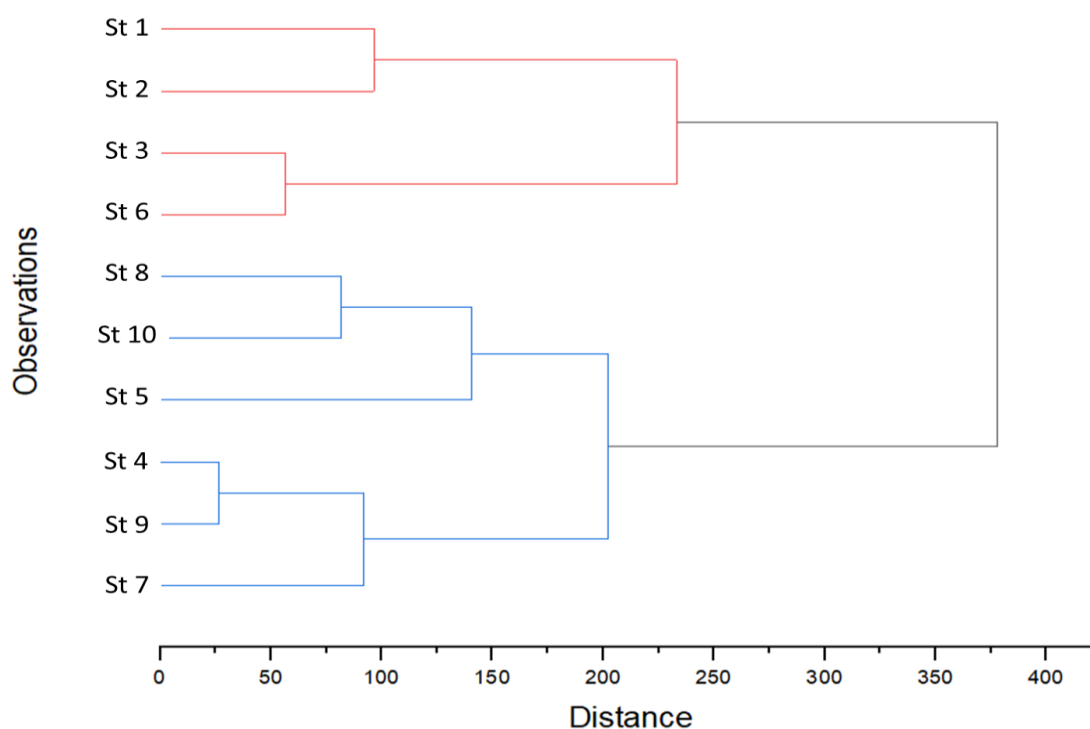


Figure 1: Dendrogram of the data obtained after metals determination in *S. terebinthifolius* collected in Bahia, Brazil.

Evaluating the dendrogram (Figure 1), it can be seen that nutrient contents and distributions discriminate between two main groups. The first group formed only by samples collected in Atlantic forest and savannah and the second group formed by the other samples collected in transition zone and caatinga. This result corroborates with the one found in the principal component analysis (Figure 2), which shows this difference of the samples St 6 and St 1, St 2 and St 3 with the others. Also, the tendency of the samples to be grouped climate types,

The evaluation of the distribution of the analytes in the samples was carried out by PCA which a 10 x 15 matrix was organized with the obtained concentration and analyte were disposed of in lines and columns, respectively. To assess the relative contribution of each component in total data variability, an explanation was the discretion of eigenvalues, where only PCs with eigenvalues greater than 1 are considered important. Thus, two PCs are significant to explain data variability for and, together, they account for 69,58% of data variability.

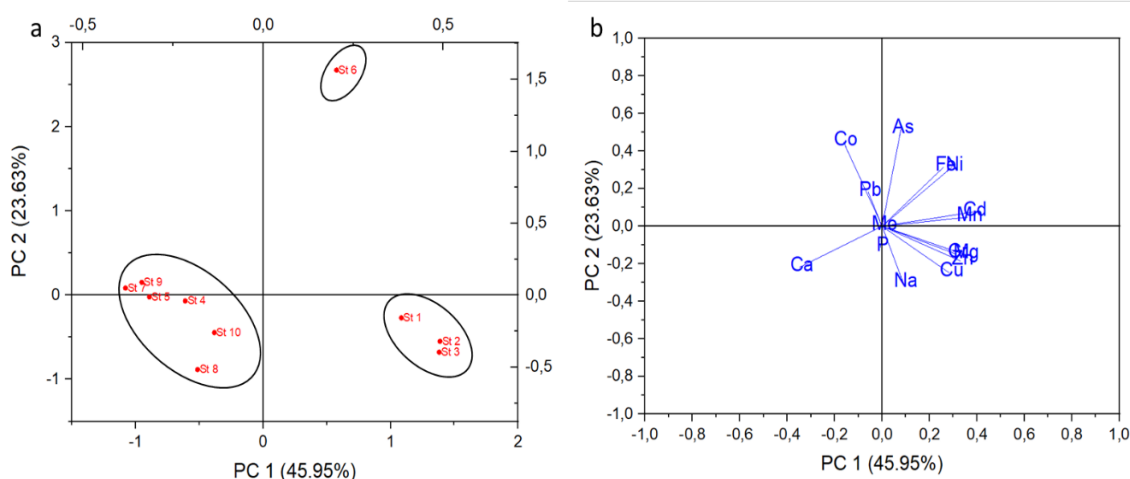


Figure 2: (a) Score and (b) loading plots for principal component analysis of the data obtained after metals determination in *S. terebinthifolius* collected in municipalities of Bahia, Brazil.

The interpretation of PCA is often performed by graphical analysis of the scores (associated with the objects: *S. terebinthifolius* samples) and loadings (represented by the variables: analytes). The obtained graphs represent the samples in a Cartesian system, whose axes are the PCs.

According to the projection of the score graph PC1 and PC2 (Figure 2a) all samples of *S. terebinthifolius* were grouped and the results are in accordance with HCA (Figures 1). The projection of the loadings on the PCs provides the chart of loadings, which is shown in Figure 2B. This chart makes it possible to assess the contribution of each variable/analyte in group separation. The correlation between the variables is described by the angle cosine between the vector loadings. The more significant loadings positive, were related to As, Fe, Ni, Cd, Mn, Cr, Mg, Cu, Zn and Na in PC1 whereas Co, Pb, As, Fe, Ni, Cd and Mn in PC2.

The score graph presented in the Figure 2a shows the separation between the samples collected in diferentes hotspot in Bahia. This separation is due to the greater concentrations of Na, Cu, Cr, Zn and Mn in St 1, St 2 and St 3 collected in Atlantic florest, and they have negative values in PC1. Only for St 6 (collected at Savannah), an anomalous behavior was observed; positive value in PC1 and PC2 was verified for As, and As was the only element present in St 6 sample. On the other hand, Ca has the greater concentrations in St 4, St 4, St 7, St 8, St 9 and St 10 collected in transition zone and caatinga, and they have negative values in PC1 and PC2.

The differences between samples collected confirm that hotspots are a crucial factor to increase or decrease the absorption of micro- and macronutrients. It depends directly on the production rate of secondary metabolites containing the phenolic compounds, which are strongly influenced by some factors such as seasonality, temperature, water availability, solar radiation and others (Souza et al., 2007; Calixto, 2000; Czelusniak et al., 2012) once most of them are wild material then, the plant may not present uniform composition (Gutés et al., 2005).

In addition, plants can accumulate metals essential to their growth and developed from the soil and water - such as, Mg, Fe, Ms, Zn, Cu, Mo and Ni (Langille, MacLean, 1976). Some plants even can accumulate metals that have no known biological function to them, as Hg, Cr and others. The excessive accumulation of metals is toxic to most plants (Memon *et al.*, 2001).

Table 1: Analytical characteristics of the methodology used in the determination of metals in samples of *S. terebinthifolius*.

Elements	LOQ ^a (mgkg ⁻¹)	RDS ^b (%)	Linearity (R ²)
As	1.21	2.2	0.9954
Ca	11.0	1.2	0.9984
Cd	1.33	2.4	0.9956
Co	0.14	1.5	0.9945
Cr	0.25	1.6	0.9974
Cu	0.72	2.4	0.9955
Fe	3.15	3.5	0.9968
Mg	2.25	3.1	0.9963
Mn	1.02	1.8	0.9987
Mo	0.45	2.1	0.9973
Na	5.16	2.2	0.9967
Ni	0.14	1.1	0.9991
P	4.78	1.9	0.9989
Pb	0.14	0.13	0.9958
Zn	1.48	2.3	0.9971

^aLOQ: limit of quantification for a sample mass of 0.2g; ^bRSD: relative standard deviation for a 0.5 mg L⁻¹ metal solution (n = 10).

Table 2: Comparison between the results of the analysis of the certified sample apple leaves (1515), spinach leaves (1570a) and peach leaves (1547) with their certified values.

Elements	Certified value (mgkg ⁻¹)	Found value (mgkg ⁻¹)	Recovery (%)*
As ²	0.06 ± 0.018	0.061 ± 0.017	101.67
Ca ³	1.527 ± 0,041	1.546 ± 0.015	101.24
Cd ²	0.03	0.03 ± 0.02	100.00
Co ²	0.07	0.068 ± 0.01	97.14
Cr ²	1	1.1 ± 0.1	110.00
Cu ²	3.7 ± 0.4	3.5 ± 0.2	94.59
Fe ¹	80	84 ± 0.6	105.00
Mg ¹	0.271 ± 0.008	0.274 ± 0.006	101.11
Mn ¹	54 ± 3	55 ± 0.8	101.85
Mo ²	0.06 ± 0.008	0.06 ± 0.01	100.00
Na ²	24 ± 2	26 ± 0.8	108.33
Ni ²	0.69 ± 0.09	0.75 ± 0.03	108.70
P ³	0.518 ± 0.011	0.544 ± 0.11	105.02
Pb ²	0.869	0.866 ± 0.017	99.65
Zn ¹	12.5 ± 0.3	12.3 ± 0.1	98.40

* Values in mm⁻¹ %. ¹Apple leaves (1515), ²Peach leaves (1547), ³Spinach leaves (1570^a). Mean ± standard deviation, n=3.

Table 3: Determination (mgkg⁻¹) of the mineral composition, trace and toxic elements of *S. terebinthifolius*.

Sample	As	Ca	Cd	Co	Cr	Cu	Fe	Mg	Mn	Mo	Na	Ni	P	Pb	Zn
St 1	<LOQ	240±12	2.30±0.2	0.23±0.01	0.46±0.01	1.60±0.35	8.57±0.65	32±2	3.82±0.09	<LOQ	7.12±0.98	2.30±0.15	452±32	0.23±0.01	5.45±1.03
St 2	<LOQ	250±11	2.35±0.05	0.33±0.02	0.44±0.03	1.90±0.15	9.45±0.45	46±1.3	3.99±0.45	<LOQ	9.15±1.23	2.40±0.42	567±15	0.26±0.02	5.25±1.25
St 3	<LOQ	245±2	2.31±0.04	0.28±0.03	0.48±0.01	2.40±0.66	6.48±0.74	39±1.6	4.02±0.15	<LOQ	8.15±1.02	2.90±0.62	648±17	0.25±0.03	4.99±1.16
St 4	<LOQ	401±35	1.40±0.03	0.85±0.01	0.33±0.02	1.12±0.45	5.26±0.56	26±3	2.56±0.01	<LOQ	8.03±1.35	1.45±0.13	780±22	0.48±0.02	3.65±1.35
St 5	<LOQ	345±21	1.35±0.04	0.45±0.04	0.21±0.04	1.02±0.12	3.66±0.48	23±1	2.4±0.35	<LOQ	6.25±0.78	0.89±0.12	214±45	0.36±0.02	3.15±0.89
St 6	1.23±0.02	199±16	2.11±0.06	1.35±0.03	0.35±0.02	0.99±0.26	12.54±1.02	24±0.5	3.45±0.05	<LOQ	6.38±0.64	3.58±0.24	365±36	0.34±0.01	3.25±0.87
St 7	<LOQ	409±13	1.41±0.08	0.79±0.03	0.22±0.01	1.45±0.24	5.66±0.84	13±0.9	1.48±0.06	<LOQ	5.48±0.59	1.56±0.22	698±29	0.16±0.01	2.56±0.47
St 8	<LOQ	385±28	1.36±0.06	0.52±0.02	0.36±0.01	1.35±0.25	4.56±0.68	25±1.2	1.65±0.12	<LOQ	9.65±0.93	0.99±0.08	254±27	0.21±0.02	4.15±0.54
St 9	<LOQ	378±24	1.42±0.02	0.99±0.05	0.33±0.02	1.06±0.36	3.89±0.12	14±0.8	2.36±0.31	<LOQ	8.26±1.02	1.69±0.14	589±41	0.33±0.02	1.89±0.16
St 10	<LOQ	379±13	1.39±0.07	0.560.03	0.45±0.02	0.99±0.13	8.26±0.66	19±0.7	3.04±0.19	<LOQ	8.77±0.04	1.03±0.18	793±68	0.19±0.02	2.67±0.28

* St 1- Salvador, St 2 – Ilhéus, St 3 – Porto Seguro, St 4 – Jequié, St 5 – Guanambi, St 6 – Barreiras, St 7 – Irecê, St 8 – Euclides da Cunha, St 9 – Juazeiro, St10 – Paulo Afonso. Mean ± standard

4. CONCLUSION

Determination of 15 elements in *Schinus terebinthifolius* was performed. Complete procedures, sample preparation and measurements were validated by using certified reference material. Good recovery values for all elements in all samples were obtained thus confirming complete mineralization and dissolution, as well as the absence of any problem in measurements. Chemometric approach was used to recognize the patterns and thus possible influences of outer or inner sources. Tracer elements are not unique to a certain source category. Moreover, markers and source profiles change with time; as the environment is a very dynamic and changeable system, it requires frequent monitoring. In addition, it was possible to observe that the metal content in the samples was seasonal.

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