Multielemental analysis of pharmaceuticals derived from plant seeds by energy dispersive X-ray fluorescence spectrometry

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Multielemental analysis of pharmaceuticals derived from plant seeds by energy dispersive X-ray fluorescence spectrometry

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AbstrAcT
The concentrations of elements in pharmaceuticals derived from plant seeds were determined by energy dispersive X-ray fluorescence. The concentrations of Ca, Si, Cl, K, S, Ti, Cr, Mn, Fe, P, Cu, Zn, Br, Rb, Sr, Hg, and Zr were quantified; only Si (10 ± 1 to 70,000 ± 10 mg kg⁻¹), S (10 ± 2 to 12,400 ± 243 mg kg⁻¹), K (4,000 ± 58 to 24,000 ± 70 mg kg⁻¹), Ca (2200 ± 35 to 87,000 ± 150 mg kg⁻¹), Mn (21 ± 4 to 1956 ± 17 mg kg⁻¹), and Fe (100 ± 7 to 5150 ± 70 mg kg⁻¹) were present in all samples. These results may validate the use of these pharmaceuticals for the treatment of disease due to high concentrations of essential elements Mn, Ca, Mn, K, Mg, Zn, Cl, Fe, and P. Mercury was present in some products below standard values. The results also have quality control applications because of the widespread use of these pharmaceuticals.

KeYwoRDS
Cancer; disease; EDXRF; elemental analysis; energy dispersive X-ray fluorescence; pharmaceuticals; seeds

IntrOducTioN
Medicinal plants are widely used for the treatment of disease. Approximately 80% of the world’s population consumes plants and their products to treat disease. Medicinal plants are commonly used to maintain the human body and for treatment of diabetes, respiratory problems, skin infections, bacterial infections, diarrhea, fungal infections, and malaria. Studies on the toxicity of medicinal plants, including their elemental composition, may increase their applications.

Approximately 21 elements are essential for the human body. Deficiencies of these elements causes symptoms. The required mass varies from 50 µg to 18 mg. Biochemical processes in the human body are affected by elemental concentrations. Several trace elements play essential roles in the formation of the active constituents responsible for therapeutic activity.
Trace elements are essential due to their functions and metabolic characteristics\textsuperscript{[4]} and contribute to regulatory and structural functions by interacting with pro-hormones, biological membranes, and enzymes.\textsuperscript{[5]} Some minerals are needed in high quantities, such as Ca, K, Fe, Mg, and Na, and are deemed macroelements. Others, such as Zn, Mn, and Cr, are required in lesser amounts and are deemed trace elements.\textsuperscript{[4,5]}

Some elements interact with organic ligands to enhance available to the human body.\textsuperscript{[5]} The medicinal activity of some plants may be due to the presence of Zn, K, Ca, Cu, Cr, Mg, and Fe\textsuperscript{[6]} that are components of biological molecules.\textsuperscript{[7]} Because the quality of many medicines depends on the concentrations of elements, the quantitative analysis in plants is necessary.\textsuperscript{[8]}

Excess or deficiency of elements may cause disorders\textsuperscript{[9]} that include metabolic disorders, nervous system disorders, bone diseases, and muscle abnormalities. Cancer patients have low concentrations of Fe, Mg, Zn, Ca, Mn, and Cu in their hair.\textsuperscript{[10]} A low concentration of Zn may induce pathogenesis of lung cancer.\textsuperscript{[11]} Furthermore, one-third of the world’s population is affected by anemia due to low iron consumption.\textsuperscript{[12]} On the other hand, toxic elements, even at low concentrations, may be harmful to the human body.\textsuperscript{[13]} Therefore, it is necessary to determine these elements as well.\textsuperscript{[1]} Consequently, elemental analysis of plant pharmaceuticals is significant.\textsuperscript{[14]}

The determination of elements in pharmaceuticals is a part of quality control to evaluate their efficacy, safety, and purity according to the World Health Organization.\textsuperscript{[15]} Several studies have been reported the determination of elements in medicinal plants.\textsuperscript{[16]} However, these investigations are incomplete in Jordan. Plant pharmaceuticals are ingested as tablets, infusions, and powders.

The determination of elements has been performed by various techniques.\textsuperscript{[17–19]} Energy dispersive X-ray fluorescence (EDXRF) spectrometry is commonly used because it is reliable, rapid, accurate, sensitive, nondestructive, and simultaneous.\textsuperscript{[1,7,19]} Appropriate sample preparation may reduce limits of detection, with values below 1 mg kg\textsuperscript{-1} for many elements.\textsuperscript{[18]}

The goal of this article was to determine elements in pharmaceuticals derived from plant seeds by EDXRF. The determination of elemental concentrations in these materials is essential to understand their therapeutic and toxic activity.\textsuperscript{[13]}

**Materials and methods**

**Sampling**

Nine pharmaceuticals derived from plant seeds were obtained from local markets in Jordan. The materials were powders of various seeds. Their ethnomedical uses and recommended daily dosages are listed in Table 1. The samples were dried in an oven at 70°C for 48 hr to remove water. 5 g of each dried sample was milled using an agate mortar and sieved to below
Table 1. Pharmaceutical properties of pharmaceuticals derived from plant seeds.

<table>
<thead>
<tr>
<th>Applications</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
<th>VI</th>
<th>VII</th>
<th>VIII</th>
<th>IX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia, hemorrhoids</td>
<td>3000</td>
<td>1500</td>
<td>650</td>
<td>1000–4000</td>
<td>Hypertension, stress, removal of toxins, depression. 350–600</td>
<td>1500</td>
<td>1000–2500</td>
<td>1500–2000</td>
<td>Diabetes, gastrointestinal disease</td>
</tr>
<tr>
<td>Joints</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2000</td>
</tr>
<tr>
<td>Heartburn, bowel disorders, gout, colic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastritis, anorexia, urinary problems</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastroparesis, urinary problems</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disease</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes, gastrointestinal disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
80 µm to obtain a fine powder. The sample was pressed into a pellet by a 15-ton hydraulic press for 5 min. The pellets had a 27 mm diameter and intermediate thickness. The powdered samples were stored in polyethylene vials for 24 h to avoid contamination before analysis.

**EDXRF spectrometry**

Analysis by EDXRF spectrometry was performed using a MiniPal spectrometer (PW4025 2004). The spectrometer was equipped with rhodium anode X-ray tube and silicon diode detector with resolution of 160 eV at 5.9 keV. The X-ray detection subsystems were computer-controlled. The rhodium target was air-cooled and a set of aluminum filters were used in the system at an operational voltage up to 30 kV.

The spectrometer was designed to operate under appropriate conditions with an enhanced signal-to-noise ratio by the selection of the suitable combinations of the filters as secondary targets. The samples were irradiated under three conditions. For light elements (Na to Cl), a tube voltage of 4.09 kV was used without a beam filter and a tube current of 1000 µA. A voltage of 15 kV with a thin aluminum filter was used for Ca to Cu using K-lines. The elements from Ba to Sn were determined using L-lines. A tube voltage of 30 kV and a tube current of 1 mA were employed for these elements. Spectrum acquisition required 110 s per sample with a dead time of approximately 50%. Replicate measurements were performed for each sample.

**Data analysis**

Three conditions were employed for the analysis of the specimens. The spectrometer was calibrated before each analysis. For each measurement, the intensity was converted to elemental concentration by the sensitivity curve. Furthermore, a check standard for peak position was employed in the energy calibration. The beam stop contained a reference sample composed of an aluminum-copper alloy. Copper was employed for the gain correction and copper Kα and the aluminum Kα lines were used for energy calibration. The peak intensities were converted into concentrations.

The MiniPal software was utilized for the acquisition of the X-ray fluorescence (XRF) spectra. Qualitative analysis was performed to identify elements. Quantitative analysis was performed to determine the concentrations of the elements. The software package used data libraries for the profiles of K- and L-lines with the curves of concentration sensitivity to correlate X-ray intensity at a specific tube current with concentration.

Deconvolution of the spectra was performed using an internal algorithm to determine the intensities of the elements in each sample. Therefore, each element in the sample had an appropriate profile. The precision of the method
was characterized by triplicate measurements. The accuracy was verified by the analysis of a 31X B20/Leaded brass/Mbh Analytical Limited certified reference material. The limit of detection (L_{od}) was obtained by:

\[ L_{od} = \frac{4.65 \times C_i}{I_{peak} - \bar{I}_{back} \left( \frac{t}{2} \right)^{1/2}}, \]  

where \( C_i \) is the concentration of element \( i \) in the standard, \( \bar{I}_{back} \) is the average of the background intensity, \( I_{peak} \) is the peak intensity of element \( i \), and \( t \) is the acquisition time. For the elements not in the standard, their spectra were recorded, and the following expression was applied to estimate the limits of detection:

\[ L_{od} = \bar{I}_{back} + 3.29 \sigma_{back}, \]  

where \( \sigma_b \) is the background standard deviation. The results demonstrated good accuracy, with relative errors less than 10% for most elements. The precision, determined as the relative standard deviation, was less than 10%.

**Biological activity of elements**

Twenty-three elements have physiological activities in the human body.\(^{[22]}\) Eleven of these elements are trace elements,\(^{[13]}\) and eight are in the period 4 of the periodic table. These elements include Co, Mn, V, Fe, Mo, Cu, Zn, Cr, F, Se, and I. The human body requires less than 100 mg day\(^{-1}\) for elements considered to be micronutrients. Elements required in larger amounts, such as P, Cl, Na, Ca, and Mg, are considered macronutrients.\(^{[13]}\) Trace elements are crucial for various biological functions but may be toxic at high concentrations.\(^{[13]}\) According to the Agency for Toxic Substances and Disease Registry, biological systems are able to recognize and transport the metal to the target and minimize toxic reactions.\(^{[23]}\) Proteins are primarily responsible for transport and recognition. However, the association of most elements with other biological molecules may induce deleterious modification of the compounds.

**Results and discussion**

**Elemental analysis**

Elemental concentrations in pharmaceuticals derived from plant seeds are significant because several elements participate in medicinal properties. In addition, some elements are necessary for human metabolic processes.\(^{[24]}\) Metal ions affect the availability of other elements in the body. Excess or deficient levels may affect the concentrations essential elements and result in biological disorders.\(^{[25]}\)
### Table 2. Elemental concentrations in plant seed pharmaceuticals by energy dispersive x-ray fluorescence.

<table>
<thead>
<tr>
<th>Element</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
<th>VI</th>
<th>VII</th>
<th>VIII</th>
<th>IX</th>
<th>Mean ± standard deviation</th>
<th>Recommended daily dietary intake (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cr</strong></td>
<td>Not detected.</td>
<td>9 ± 2</td>
<td>8 ± 1</td>
<td>Below limit of detection.</td>
<td>Below limit of detection.</td>
<td>Below limit of detection.</td>
<td>Below limit of detection.</td>
<td>Not detected.</td>
<td>694 ± 20</td>
<td>237 ± 396</td>
<td>0.02–0.2</td>
</tr>
<tr>
<td><strong>Fe</strong></td>
<td>5150 ± 70</td>
<td>9 ± 2</td>
<td>890 ± 30</td>
<td>400 ± 15</td>
<td>250 ± 10</td>
<td>100 ± 5</td>
<td>Below limit of detection.</td>
<td>Below limit of detection.</td>
<td>Below limit of detection.</td>
<td>Not detected.</td>
<td>2900 ± 57</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>9 ± 2</td>
<td>900 ± 22</td>
<td>1700 ± 35</td>
<td>142 ± 8</td>
<td>100 ± 7</td>
<td>1940 ± 18</td>
<td>4000 ± 63</td>
<td>1910 ± 13</td>
<td>6030 ± 83</td>
<td>2079 ± 2033</td>
<td>800</td>
</tr>
<tr>
<td><strong>Zn</strong></td>
<td>Below limit of detection.</td>
<td>Below limit of detection.</td>
<td>Below limit of detection.</td>
<td>Below limit of detection.</td>
<td>21 ± 3</td>
<td>30 ± 5</td>
<td>35 ± 4</td>
<td>3120 ± 65</td>
<td>802 ± 1546</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td><strong>S</strong></td>
<td>65000 ± 160</td>
<td>2030 ± 43</td>
<td>4000 ± 51</td>
<td>300 ± 17</td>
<td>124000 ± 243</td>
<td>10 ± 2</td>
<td>3910 ± 55</td>
<td>3020 ± 47</td>
<td>6480 ± 80</td>
<td>23194 ± 43078</td>
<td>Not available</td>
</tr>
<tr>
<td><strong>Cl</strong></td>
<td>49680 ± 98</td>
<td>30020 ± 82</td>
<td>3020 ± 57</td>
<td>Below limit of detection.</td>
<td>130000 ± 279</td>
<td>Below limit of detection.</td>
<td>40000 ± 87</td>
<td>7250 ± 88</td>
<td>43328 ± 46189</td>
<td>750</td>
<td></td>
</tr>
</tbody>
</table>

*Continued*
<table>
<thead>
<tr>
<th>Element</th>
<th>Concentration (mg kg(^{-1}))</th>
<th>Mean ± standard deviation</th>
<th>Recommended daily dietary intake (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sr</td>
<td>Below limit of detection.</td>
<td>34 ± 3</td>
<td>146.74 ± 10</td>
</tr>
<tr>
<td>Hg</td>
<td>Below limit of detection.</td>
<td>30 ± 3</td>
<td>1.5 ± 2</td>
</tr>
<tr>
<td>K</td>
<td>9050 ± 75</td>
<td>34 ± 3</td>
<td>12911 ± 6270</td>
</tr>
<tr>
<td>Ca</td>
<td>Not detected.</td>
<td>Below limit of detection.</td>
<td>30 ± 3</td>
</tr>
<tr>
<td>Zr</td>
<td>Not detected.</td>
<td>Below limit of detection.</td>
<td>30 ± 3</td>
</tr>
<tr>
<td>Si</td>
<td>10750 ± 64</td>
<td>Below limit of detection.</td>
<td>30 ± 3</td>
</tr>
<tr>
<td>Br</td>
<td>Not detected.</td>
<td>Below limit of detection.</td>
<td>30 ± 3</td>
</tr>
<tr>
<td>Mn</td>
<td>159 ± 6</td>
<td>Below limit of detection.</td>
<td>30 ± 3</td>
</tr>
<tr>
<td>Ti</td>
<td>206 ± 5</td>
<td>Below limit of detection.</td>
<td>30 ± 3</td>
</tr>
<tr>
<td>Cu</td>
<td>7040 ± 26</td>
<td>Below limit of detection.</td>
<td>30 ± 3</td>
</tr>
</tbody>
</table>
Table 1 lists nine pharmaceuticals derived from plant seeds with their medical applications and recommended daily dosages. Table 2 lists elemental concentrations with mean and standard deviation (σ) of the pharmaceuticals determined by EDXRF. Ti, Rb, Mn, K, S, Ca, Cr, Cl, Fe, P, Hg, Zr, Br, Si, Sr, Cu, and Zn were determined. Moreover, some elements were not detected or were below the limit of detection in some samples.

The standard deviation (σ) is higher than the mean for the studied pharmaceuticals (Table 2), showing that these pharmaceuticals are heterogeneous. Every pharmaceutical is a mixture of several plant seeds. The heterogeneity of the ingredients resulted in large relative standard deviations. Furthermore, the sample size was reduced because concentrations below the limit of detection were excluded from the calculation of the mean.

The presence of Si, S, K, Ca, Mn, and Fe in all samples may be attributed to the presence of multiple species of seeds in each pharmaceutical product. Si, S, Cl, K, and Ca were present at the highest concentrations (Table 2). The highest level of chlorine in product V was 130,000 ± 279 mg kg$^{-1}$. This result may be due to the addition of chlorine to this material.

Recommended daily dietary intakes of the nutrients are included in Table 2.[26,27] In order to control the daily intakes of the pharmaceuticals, the allowed daily intake of the pharmaceutical in grams is defined to be as

\[
\text{Allowed daily intake} = 10^3 \times \frac{\text{Recommended daily dietary intake}}{\text{Element concentration}},
\]

where the recommended daily dietary intake is in mg and the element concentration is mg kg$^{-1}$. Based on this calculation, the allowed daily intake of Cl was 750 mg (see Table 2). Accordingly, the allowed daily intake of the pharmaceutical V should be 5.8 g. The value of 5.8 mg is higher than the recommended daily intake of the pharmaceutical V, which is between 0.35 and 0.6 mg (Table 1). Thus, the recommended daily dosage of the pharmaceutical V does not supply the human body by its required daily amount of Cl. Chlorine helps the liver to filter waste, stimulate the production of hydrochloric acid, and regulate the acid alkali equilibrium.[28]

Manganese was determined in all pharmaceutical products with concentrations from 21 ± 4 to 1956 ± 17 mg kg$^{-1}$ and a mean of 289 ± 626 mg kg$^{-1}$. Therefore, the allowed daily intake was 0.5–2.6 g for pharmaceutical VIII and 47.6–238.1 g for pharmaceutical IX. This implies that a large amount of the pharmaceutical IX (47.6 – 238.1 g) must be consumed to provide the human body with its daily quantity of Mn, while a lower amount of pharmaceutical VIII (0.5–2.6 g) is required. Excess consumption of Mn may induce Parkinsonism.[13] Manganese deficiency increases the probability of cardiovascular disease, myocardial infarction, and bony disorders in children and infants.[29] Sources of Mn include nuts, rice, grains, and tea.
Iron was present in all samples with a concentration from 100 ± 7 to 5150 ± 70 mg kg\(^{-1}\) with an average of 1443 ± 1812 mg kg\(^{-1}\). The highest concentration was for pharmaceutical I, with the lowest values in pharmaceuticals V and VI. According to the recommended daily dietary intake, the daily allowance of Fe is 10–18 mg. Thus, the allowed daily intake of the pharmaceutical I is 1.9–3.5 g, which concurs with the recommended daily intake of this product (3 g). In addition, pharmaceuticals IX and VIII contained Fe at concentrations of 2900 ± 57 mg kg\(^{-1}\) (allowed daily intake = 3.4–6.2 mg) and 3000 ± 50 mg kg\(^{-1}\) (allowed daily intake = 3.3–6 g), respectively. According to the values of the ethnomedical uses (Table 1), pharmaceuticals of I, VIII, and IX are utilized to treat anemia. Iron is an essential element as it is a part of hemoglobin and plays a role in electron transport. Iron also facilitates the oxidation of fats, proteins, and carbohydrates to regulate body weight. Rhizomes or roots of the plants are known as storage centers of the trace elements.\(^{30}\) Hemoglobin and myoglobin from animals are sources of heme. Some sources of the non-heme iron are vegetables, fruits, seeds of leguminous plant, and dairy products. Excessive intake of Fe, repeated blood transfusions, and the genetic diseases are commonly related to the chronic iron poisoning.\(^{31}\)

The zinc concentration had a maximum value of 3120 ± 65 mg kg\(^{-1}\) (allowed daily intake = 4.8 g) with a mean of 802 ± 1546 mg kg\(^{-1}\). Zinc was present in all pharmaceuticals except III. The explanation for the high value in pharmaceutical IX may involve direct addition of zinc. Since the allowed daily intake (4.8 g) is higher than the recommended daily dosage of the pharmaceutical IX (2 g), it may be concluded that it does not supply the human body the recommended daily amount of Zn. Therefore, the intake of the pharmaceutical IX must be increased. Because elevated levels of Zn may influence the retention of the toxic elements in the body,\(^{32}\) one must be careful in consuming pharmaceutical IX due to its high zinc concentrations. Zinc may be used for the treatment of the gastric ulcers.\(^{33}\) Its deficiency may be associated with the impairing of DNA synthesis, wound healing, malnutrition, and senses of taste and smell. Zinc is an essential nutrient for protein manufacturing and wound healing, and may be toxic at elevated concentrations.\(^{34}\) Zinc is incorporated in more than 270 enzymes and contributes in several physiological tasks.\(^{35}\) Furthermore, it is involved in the system, fetus growth, and sperm production.\(^{36}\) Its deficiency in an organism is correlated with multisystem dysfunction. A high or low zinc intake was found to produce a variety of diseases.\(^{35}\) Sources of Zn include beans, nuts, and grains.

Concentrations of potassium in the pharmaceuticals were between 4,000 ± 58 (pharmaceutical IV, allowed daily intake = 137.5–1406.3 g) and 24,000 ± 70 (pharmaceutical V, allowed daily intake = 23–234.4 g) mg kg\(^{-1}\) with a mean of 12,911 ± 6270 mg kg\(^{-1}\). Comparison with the recommended daily intake of the pharmaceuticals shows that neither pharmaceutical IV...
(recommended daily dosage = 1 to 4 g) nor the pharmaceutical V (recommended daily intake = 0.35–0.6 g) may provide the human body with recommended daily intake of K. Therefore, an additional amount of these pharmaceuticals are need to provide sufficient potassium. K contributes to the protection of the cardiac rhythm. High levels of K in plants are needed to regulate water usage, enzyme activation, and photosynthesis.

Copper concentrations were between 17 ± 3 (pharmaceutical VIII, allowed daily intake = 59–176 g) and 7040 ± 26 (pharmaceutical I, allowed daily intake = 0.14–0.43 g) mg kg⁻¹ with an average of 1548 ± 3079 mg kg⁻¹. Comparison of the recommended daily dosage of the pharmaceutical I (3 g) with the allowed daily intake shows that the recommended consumption exceeds the control limits. Hence, its daily dosage should be reduced to a daily intake of 0.14–0.43 g. Many plants do not contain elevated copper concentrations as in pharmaceutical I (7040 ± 26 mg kg⁻¹), suggesting copper may have been added. Copper plays an important role in the production of collagen, melanin, hemoglobin, and myelin. High consumption of soybeans, which contain high levels of Cu, may cause iodine deficiency. Elevated Cu concentrations may cause Zn or Fe deficiency. Excess Zn or Fe may cause a decrease in Cu absorption. Seeds, oysters, dark chocolate, nuts, and grains are good Cu sources.

Calcium concentrations were from 2,200 ± 35 (pharmaceutical III, allowed daily intake = 363.6–545.5 g) to 87,000 ± 150 (pharmaceutical V, allowed daily intake = 9.2–13.8 g) mg kg⁻¹ with an average of 17,876 ± 27244 mg kg⁻¹. Four pharmaceuticals had calcium concentrations higher than 10,000 mg kg⁻¹: pharmaceuticals I, V, VI, and IX (Table 1). Their allowed daily intakes were higher than their recommended daily dosages, suggesting they do not provide sufficient calcium. Therefore, their intake should be increased to obtain their calculated allowed daily intakes. High calcium concentrations may increase the retention of toxic elements in the body. Hence, the recommended daily intake of the pharmaceutical V should be monitored. Calcium is the principal component of the skeleton and regulates cellular mortality, hormonal action, and muscle function. It has been reported that Ca increases beneficial cholesterol in the blood.

The concentration of bromine in pharmaceutical III was 30 ± 85 mg kg⁻¹ (pharmaceutical III, allowed daily intake = 50–83 g). Based on this allowed daily intake, the recommended daily dosage of this product (650 mg) does not provide the recommended amount of Br (1.5–2.5 mg). One has to consume 50–83 g of pharmaceutical III to meet the need for Br. This consumption is impractical and unsafe based on other elemental concentrations. Bromine is an essential element.

The concentrations of phosphorus were between 9 ± 2 (pharmaceutical I, allowed daily intake = 88,889 g) and 6,030 ± 83 mg kg⁻¹ (pharmaceutical IX, allowed daily intake = 133 g) with an average value of 2,079 ± 2,033 mg kg⁻¹.
Since the recommended daily dosages of the pharmaceutical I and IX were 3 and 2 g, respectively (Table 1), these values are lower than the allowed daily intake. Hence, other sources of P are required. Since P is present in every cell, it contributes to most reactions in the human body. Phosphorus is anti-osteoporotic and estrogenic.

Rubidium concentrations were from $40 \pm 6$ to $469.4 \pm 13 \text{mg kg}^{-1}$ with a mean value of $186 \pm 245 \text{mg kg}^{-1}$. Pharmaceuticals of I, II, III, VI, VII, and IV had Rb concentrations lower than the limit of detection, whereas the pharmaceutical IX had the highest concentration. Rb is not an essential element for the human body.\[33\]

Concentrations of chromium were from $8 \pm 1$ (pharmaceutical III, allowed daily intake $= 2.5–25 \text{g}$) to $694 \pm 20$ (pharmaceutical IX, allowed daily intake $= 0.03–0.3 \text{g}$) $\text{mg kg}^{-1}$ with an average of $237 \pm 396 \text{mg kg}^{-1}$. The other pharmaceuticals contained relatively low chromium concentrations. Since the recommended daily intake of the pharmaceutical IX was 2 g (Table 1) and its allowed daily intake was 0.03–0.3 g, it was concluded that the pharmaceutical IX supplies the human body with excess chromium. The other pharmaceuticals do not provide the human body with the required daily amount of Cr. Chromium cleans arteries by reducing triglyceride and cholesterol levels.\[41\] Chromium also has a central role in the metabolism of heart disease and cholesterol.\[42\] Furthermore, its deficiency leads to disorders in protein metabolism and glucose lipids.\[43\] The presence of Cr in plants may have therapeutic effects against cardiovascular disease.\[42\] Toxic effects of high chromium concentrations may include bleeding, upset stomach, nose irritation, and kidney damage.

Zirconium concentrations were from $9 \pm 1$ to $162.8 \pm 7 \text{mg kg}^{-1}$ with a mean of $56 \pm 72 \text{mg kg}^{-1}$. Its concentration varied to below the limit of quantification to $20 \pm 3 \text{mg kg}^{-1}$. Pharmaceutical IX had the highest Zr concentration.

Strontium concentrations were between $34 \pm 3$ and $411 \pm 21 \text{mg kg}^{-1}$ with a mean of $137 \pm 136 \text{mg kg}^{-1}$. Strontium was present in all pharmaceuticals except V and VI. Pharmaceutical IX had the highest concentration of Sr. Strontium is known to be present in most plants. It has no known biological role, but elevated concentrations in the body may be problematic.\[44\]

Titanium levels were between $10 \pm 1$ and $920 \pm 16 \text{mg kg}^{-1}$ with an average of $255 \pm 378 \text{mg kg}^{-1}$. The biological role of Ti is not completely known, but it is suspected to cause cancer. It also acts as a stimulant.\[45\]

Mercury was present at concentrations from $10 \pm 1$ (pharmaceutical IV, allowed daily intake $= 222–500 \mu\text{g}$) to $9050 \pm 75$ (pharmaceutical I, allowed daily intake $= 2–6 \mu\text{g}$) $\text{mg kg}^{-1}$ with an average of $4020 \pm 4606 \text{mg kg}^{-1}$. Since the allowed daily intakes of the pharmaceuticals were lower than their recommended daily dosages (Table 1), it was deduced that these pharmaceuticals are safe with respect to mercury. However, according to the World Health
Organization, Hg concentrations of 0.5–0.22 µg kg\(^{-1}\) may be harmful.\[^{46}\] Therefore, the amounts of Hg in these pharmaceuticals exceed the standard levels of the World Health Organization and one should monitor intake. Mercury is not normally in plants; therefore, its presence in the pharmaceuticals may be due to contamination. This contamination may be avoided by preparation of the pharmaceuticals in a clean environment.

The results show the consumption of these pharmaceuticals is safe when following the recommended daily dosage. These pharmaceuticals contain high concentrations of S, Fe, K, Cu, P, Zn, Cl, Mn, and Ca, nutrients that have pharmacological activity. The presence of excess or insufficient concentrations of elements may induce problems in the human body. These pharmaceuticals contain high concentrations of some elements that may affect physiological processes Consequently, there is a need for additional investigation of the elemental composition of these materials to verify their safety.\[^{13}\]

**Figure 1.** Correlation of the concentration of Ca with the concentration of P in plant pharmaceuticals.

**Figure 2.** Correlation of the concentration of K (mg kg\(^{-1}\)) with the concentration of P in plant pharmaceuticals.
**Correlation study**

In general, the investigated pharmaceuticals were enriched with Si, S, Cl, K, Ca, Mn, and Fe. It has been reported that there is a relationship between the concentrations of some elements.\[18,47–49\] The ratios between these elements in the human body must remain constant to maintain balance between their concentrations. Additionally, some elements may substitute for each other.

Figure 1 shows the relationship between the concentration of Ca (mg kg\(^{-1}\)) vs. the concentration of P (mg kg\(^{-1}\)). Most of pharmaceuticals exhibited ratios of Ca/P less than 10 except for pharmaceutical I that had a ratio of 3333. The highest ratio may imply that the calcium was added to pharmaceutical I. Pharmaceutical IV exhibited a ratio of 22. In general, Ca was poorly correlated with other metals.

The relationship between the concentration of K (mg kg\(^{-1}\)) vs. the concentration of P (mg kg\(^{-1}\)) is shown in Figure 2. Pharmaceutical I had a ratio of K/P of 1633, while the ratios for pharmaceuticals IV and II were 28 and 10, respectively. For the other pharmaceuticals, the ratio was less than 10. The highest ratio of 1633 may indicate that potassium was added to pharmaceutical I.

**Conclusions**

Knowledge of the elemental concentrations of plant pharmaceuticals is necessary to understand their pharmacological actions. Also, high concentrations of some elements are toxic. EDXRF was employed to determine these elements in seed derived pharmaceuticals. The concentrations of Mn, Cu, Cl, Cr, Sr, Si, Zr, P, S, K, Ca, Hg, Ti, Fe, Rb, Zn, Br, and Ti varied from below the limit of detection to 130,000 mg kg\(^{-1}\). Plant seeds are important sources of elements that may be involved in the therapeutic properties of these products. The results showed that many pharmaceuticals contained significant concentrations of essential elements. The detected elements with their concentrations in the investigated pharmaceuticals are below the permissible levels if they are taken according to the allowed daily intakes of the pharmaceuticals and may not form a health hazard for the consumers. The obtained data have proved that the EDXRF spectrometry is able to provide rapid and effective analysis for the elements in the studied pharmaceuticals.

**References**


