Case Report

Toxic Effects of *Rhamnus alaternus*: A Rare Case Report

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In Tunisia, there are about 478 species of plants commonly used in folk medicine. Medicinal plants and herbal remedies used are responsible for 2% of intoxications listed by Tunisian National Poison Center. Most cases are related to confusion between edible plants and toxic plants lookalikes or to an excessive consumption of therapeutic plants. We report the case of a 58-year-old man admitted to the Emergency Department of the Regional Hospital of Zaghouan (Tunisia), with renal failure and rhabdomyolysis. The patient reported having daily consumption of a homemade drink based on *Mediterranean Buckthorn* roots, during the last 6 months, to control his blood glucose levels. The aim of this work was to establish an association between the consumption of the herbal remedy and the occurrence of both renal failure and rhabdomyolysis. No similar cases have been reported in recent literature.

1. Introduction

Herbal remedies have been used for centuries to treat a variety of diseases. *Mediterranean Buckthorn* (*Rhamnus alaternus*) has been used for therapeutic purposes and no toxicity effects have been documented. *Rhamnus alaternus* (Rhamnaceae) is a small tree located mainly in the north of Tunisia, where it is known as “Oud El-Khir.” It has traditionally been used as a diuretic, laxative, hypotensive drug and for the treatment of diabetes, hepatic, and dermatologic complications [1, 2]. Previous phytochemical studies have shown potent antioxidant, free radical scavenging, antimutagenic and antigenotoxic activities of flavonoids and phenol isolated from *Rhamnus alaternus* roots and leaves [3, 4].

2. Case Report

On February 1, 2013, a 58-year-old man was admitted to the Emergency Department of the Regional Hospital of Zaghouan (Tunisia), with dizziness, weakness, anorexia, and dyspnea. His blood pressure was 130/60 mmHg. The patient has a 15-pack-year history of smoking. He was a mason by occupation. He had 20-year back history of pulmonary tuberculosis and type 2 diabetes revealed one year ago. Two days before his admission, the patient experienced nausea, vomiting, anuria, and hematuria. He reported having daily consumption of a homemade drink based on *Rhamnus alaternus* roots, during the last 6 months, to control his blood glucose levels. On physical examination, the patient had myalgia. He had no other clinical signs.

Cytological reports and sputum smear were negative (three times) for pulmonary tuberculosis. Hepatitis B and hepatitis C serology were also negative. Chest X-ray was normal; blood and urine culture were negative. In renal ultrasonography, there was a significant difference in kidney sizes and the corticomedullary differentiation was altered. Laboratory tests showed glucose 14.44 mmol/L, creatinine 1190 μmol/L, blood urea nitrogen 66.77 mmol/L, creatine phosphokinase (CPK) 2129 UI/L, pH 7.10, a CRP of 8.7 mg/L, and a normal coagulation profile (Table 1). Three dialysis sessions were performed.

2.1. Toxicological Analyses. Samples of the herbal decoction were obtained from the patient’s wife. It was a dark brown
Table 1: Biochemical, hematologic, and blood gas parameters, before and after dialysis.

<table>
<thead>
<tr>
<th>Blood tests</th>
<th>Before dialysis</th>
<th>After dialysis</th>
<th>Normal ranges (adult male)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 4</td>
<td>Day 7</td>
<td>Day 9</td>
</tr>
<tr>
<td>Glucose</td>
<td>14.44</td>
<td>4.74</td>
<td>4.50</td>
</tr>
<tr>
<td>Urea nitrogen</td>
<td>66.77</td>
<td>46.04</td>
<td>39</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1190</td>
<td>756</td>
<td>853</td>
</tr>
<tr>
<td>Sodium</td>
<td>122</td>
<td>141</td>
<td>120.5</td>
</tr>
<tr>
<td>Potassium</td>
<td>4.88</td>
<td>2.44</td>
<td>3.61</td>
</tr>
<tr>
<td>Calcium</td>
<td>1.4</td>
<td>1.5</td>
<td>0.92</td>
</tr>
<tr>
<td>CPK</td>
<td>2129</td>
<td>2163</td>
<td>3399</td>
</tr>
<tr>
<td>CPK MB</td>
<td>484.1</td>
<td>481.5</td>
<td>154.8</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>8.7</td>
<td>8.2</td>
<td>7.4</td>
</tr>
<tr>
<td>WBC</td>
<td>3.1</td>
<td>2.86</td>
<td>1.68</td>
</tr>
<tr>
<td>Platelets</td>
<td>382.0</td>
<td>383.0</td>
<td>249.0</td>
</tr>
<tr>
<td>pH</td>
<td>7.10</td>
<td>7.29</td>
<td>7.32</td>
</tr>
<tr>
<td>HCO₃⁻</td>
<td>5.1</td>
<td>18.2</td>
<td>19.2</td>
</tr>
<tr>
<td>Anion gap</td>
<td>35.8</td>
<td>25.2</td>
<td>7.21</td>
</tr>
<tr>
<td>PaO₂</td>
<td>88</td>
<td>91</td>
<td>88</td>
</tr>
<tr>
<td>PaCO₂</td>
<td>16.2</td>
<td>26</td>
<td>27</td>
</tr>
</tbody>
</table>

2.2. Extraction Procedures. After the authenticity and the botanical identification of the species were confirmed according to the “Flore de la Tunisie” [6] phytochemical compounds were extracted from the medicinal decoction using routine methods including liquid-liquid extraction procedures with further analysis by gas chromatography/mass spectrometry (GC-MS). The solvents used were dichloromethane, ethyl acetate, and chloroform at different pH values (1.0, 7.0, and 9.0). The different extracts were dehydrated over anhydrous sulfate. The dry residue was diluted with 2 milliliters of ethyl acetate. One or 2 µL was analyzed by GC-MS. Dried roots of “Rhamnus alaternus” were reduced to small fragments and macerated in a water-methanol mixture (1:2) during 4 h with magnetic stirring. 24 hours later, the extract was filtered and the alcoholic layer was evaporated. The aqueous layer was collected in a separating funnel and had been alkalinized by the addition of ammonia (NH₄OH) and then extracted with dichloromethane by liquid-liquid extraction procedures. The organic phase was dehydrated over anhydrous sulfate and concentrated to 1 mL and then analyzed by GC-MS.

2.3. Chromatographic Conditions. The gas chromatograph-mass spectrometer used was a Hewlett Packard 5890-II (Agilent Technologies) fitted with a manual injector and HP5-MS (0.25-µm) capillary column (30 m long and 0.25 mm i.d.). The injection volume was 2 µL; the compounds were separated with helium (carrier gas) at a flow rate of 1 mL/min. The operating conditions were as follows: the injector was programmed to 250°C at 10°C·s⁻¹ and held for 2 min. The oven was programmed from 50°C (2 min) to 100°C at 25°C·min⁻¹ and then to 200°C at 10°C·min⁻¹ (2 min). MS detection was achieved in scan mode for qualitative analysis. Run time was 16 min.

3. Results

Screening by GC-MS of both Rhamnus alaternus roots and infusion extracts revealed the presence of anthraquinone glycosides such as 4,5-dihydroxy-9,10-dioxoanthrac`ene-2-carboxylic acid (rhein), 1,8-dihydroxy-3-(hydroxymethyl)-9,10-anthracenedione (aloe-emodin), and 1,8-dihydroxy-3-methoxy-6-methylanthracene-9,10-dione (physcion). The retention times were 8.95, 9.67, and 10.25 min, respectively (Figure 1).

Anthraquinone glycosides were detected in a dichloromethane extract and ethyl acetate extract at pH value = 9 and only in a dichloromethane extract at pH value = 7 by GC-MS analysis (Table 2).

4. Discussion

Blood chemistry tests performed before dialysis revealed renal nitrogen retention (serum creatinine of 1190 µmol/L and blood urea nitrogen of 66 mmol/L). Moreover, normochromic and normocytic anemia, hypocalcemia, and the loss of corticomedullary differentiation observed in our patient suggest a chronic renal insufficiency. From a biochemical point of view, major hyperglycemia (14.44 mmol/L) could be one of the underlying factors, which lead to the diagnosis of diabetic nephropathy. According to authors, this
Table 2: Qualitative screening by gas chromatography-mass spectrometry (GC-MS).

<table>
<thead>
<tr>
<th></th>
<th>Dichloromethane extract</th>
<th>Ethyl acetate extract</th>
<th>Chloroform extract</th>
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<tbody>
<tr>
<td></td>
<td>pH = 1</td>
<td>pH = 7</td>
<td>pH = 9</td>
</tr>
<tr>
<td>Rhein</td>
<td>ND</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Physcion</td>
<td>ND</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Aloe-emodin</td>
<td>ND</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

+: detected; ND: not detected.

Figure 1: Original chromatogram of herbal tea extract (scan mode).

Figure 2: Chemical structure of anthraquinone glycosides [5].
are concentrated [24, 25], causing hypovolemia and acute renal failure. Organic and phosphoric acids released from the muscle cell lead to metabolic acidosis and increase the anion gap due to the overproduction of organic acids [26]. In summary, the patient who refused to take any medication to control his blood glucose levels except herbal medication has an undiagnosed diabetic nephropathy aggravated by acute renal dysfunction and rhabdomyolysis. All metabolic disorders are mainly imputed to the toxic effects of the anthraquinone glycosides. We noticed that patient completely recovered and symptoms regressed completely when stopping herbal infusion ingestion. Blood chemistry tests performed after dialysis were all normal.

5. Conclusion

*Rhamnus alaternus* can be toxic when used in an abusive way beside its strong antibacterial, antioxidant, and antidiabetic activities. To our knowledge, this is the first report of a case of renal failure and rhabdomyolysis which is possibly associated with a chronic consumption of *Rhamnus alaternus* roots. We present this case to illustrate the role of both clinical and biological investigations in handling cases of herbal poisonings. We aimed also to increase awareness among emergency physicians about patients presenting to the Emergency Department with unexplained symptoms (renal failure, rhabdomyolysis, etc.) requiring prompt diagnosis so that such life-threatening complications can be avoided.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

References


