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Anzaroot (*Astragalus sarcocolla* dymock) is associated with Acute hepatitis and hepatic encephalopathy in children

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Abstract

Anzaroot (*Astragalus sarcocolla* dymock) herbal remedies, which are known in Arabic countries as Anzaroot, are widely available in Saudi Arabia and are used to treat several conditions, such as the common cold, respiratory infections, gastrointestinal disease and wound bleeding. However, several species of Anzaroot that are considered to be safe in adults have unknown safety parameters in children. We report two pediatric cases with hepatic problems that were possibly induced by Anzaroot.

One case is a 9-month-old child who developed hepatic encephalopathy after drinking Anzaroot-soaked liquid and was then treated with N-acetyl cysteine. The other case is a 9-year-old patient who was admitted to the hospital with acute hepatitis due to consumption of liquid steeped with Anzaroot.

Anzaroot has been mentioned as having hepatoprotective properties. However, we found that in children there is potential for treating hepatic injury.

Keywords

Anzaroot; *astragalus sarcocolla* dymock; hepatic encephalopathy; acute hepatitis; hepatic injury; roussel UCLAF causality assessment scale

Introduction

Astragalus sarcocolla dymock herbals grow in high mountainous regions in several countries in Asia, including Iraq and Iran. *Astragalus sarcocolla* is mentioned by several names in Indian Medicinal Plant books, such as Anzaroot, Gujar, and Kohal Kirmaani [1].

Astragalus sarcocolla dymock (Anzaroot) has been used in traditional Arabic and Chinese medicine to protect the body against cancer, diabetes, and cardiac problems as well as to support the immune system. Furthermore, it is used to treat eye redness, eye itching, abscesses and curing wounds [2]. Anzaroot is used on the Arabian peninsula as an anti-inflammatory and antibacterial as well as to minimize cold symptoms [1,2].

The medicinal component of *Astragalus* are its roots, and the active constituents of *Astragalus* root are flavonoids, saponins (astragolosides), polysaccharides, triterpenes, glycosides, amino acids, fatty acids, sterols, tragacanth and other trace element [3,4].

According to traditional Chinese medicine, *Astragalus* is used to alleviate liver injury by reducing elevated alanine transaminase (ALT), restore the loss of righting reflex and to protect hepatic cells against pathological changes [2,5]. The several species of *Astragalus sarcocolla* dymock are considered to be safe in adults, but their safety in children is unknown [1,6]. However, there are claims that the side effects of *Astragalus* could be due to the adulteration and contamination of herbs, which may be associated with liver injury [7].

Case 1

A 9-month old baby girl was referred from a peripheral hospital with diarrhea and vomiting. According to her history, she had taken two cups of soaked Anzaroot (*Astragalus sarcocolla* dymock) daily for 3 days without any history of previous medications or other herbal products. The patient did not suffer from any liver disease or epilepsy, nor did her family. Three days later, the patient suffered respiratory distress, disturbed consciousness, mild fever, dyspnea and vomiting. Moreover, upon examination, she was jaundiced with tenderness of the upper right quadrant of her abdomen, yellowish skin discoloration, unstable vital signs (heart rate 157/min), abdominal distension and an enlarged liver (4 cm).

The laboratory results showed a normal complete blood count (CBC), aspartate aminotransferase (AST) 111 U/L, alanine aminotransferase (ALT) 1089 U/L, alkaline phosphatase (ALP) 357 µ/L, and gamma glutamyl transferase 145U/L, partial thromboplastin time (PTT) 47 s, prothrombin time 29.45 s, international normalized ratio (INR) 2.55, blood urea nitrogen (BUN) 1.5 µmol/L, ammonia 45 µmol/L, and glucose 6.9 µmol/L (Table 1).

An abdominal ultrasound showed an enlarged liver without bile duct obstruction. Serology for hepatitis A, B, C, and E; cytomegalovirus (CMV); and Epstein-Barr virus (EBV) were all negative.

An electroencephalography (EEG) test showed an abnormal front-temporal focus with a secondary generalized pattern, which was suggestive of seizure.

The patient was diagnosed with hepatic encephalopathy due to herbal toxicity and treated with 600 mg of N-acetyl cysteine intravenous every 12 hours; 2 mg of vitamin K intravenous every 12 hours; 15 microgram fentanyl intravenous every 2 hours, which was increased to 16 microgram; 15 mg of phenobarbitone intravenous once daily; 5 ml of lactulose syrup oral every 12 hours; 3 g of human albumin intravenous every 12 hours; regular insulin (sliding scale); and 1 mg of salbutamol nebulizer every 3 hours. See the laboratory results during treatment (**Table 1**).

After 3 months of treatment, the patient developed epilepsy and speech and neuro-motor delay. The patient is now taking 40 mg of sodium valproate syrup orally every 12 hours with physiotherapy. The patient's liver condition has improved.

Case 2

A 9-year-old female was referred to a referral hospital from a peripheral hospital (which was more than 300 km away from the location of the first case) with vomiting, abdominal pain, mild dehydration and jaundice. The patient suffered from these symptoms over a period of seven days prior to admission. According to her history, the patient had taken three cups of soaked Anzaroot (*Astragalus*

sarcocolla dymock) daily for 2 days. The physical examination showed a liver enlargement 4 cm below the costal margin with a smooth surface and tenderness without ascites or splenomegaly.

Upon admission, the laboratory values were as follows: CBC, normal; AST, 1727 U/L; ALT, 3558 U/L; ALP, 693 U/L; TBIL, 124 mmol/L; direct bilirubin, 119.64 mmol/L; prothrombin time, 18.2 sec; INR, 1.4; osmolarity, 268; sodium, 127 µmol/L; potassium, 4.5 µmol/L; and a urine analysis showing acetone +3 and amorphous +3.

The patient had an abdominal CT scan that confirmed the presence of hepatosplenomegaly, a thickened gall bladder wall and no evidence of biliary or vascular obstruction, viral hepatitis (A, B, C), cytomegalovirus, Epstein-Barr virus, or herpes simplex virus. The anti-nuclear antibody, anti-smooth muscle antibody and liver-kidney microsome antibody were all negative.

The treatment team initiated 15 ml of lactulose syrup orally every eight hours, 750 mg of cefuroxime intravenous every eight hours, 5 ml of multivitamin syrup orally once daily, 2 meq of potassium chloride in 10% dextrose with 70 ml of 0.45% sodium chloride every hour and 2 mg of vitamin K intravenous every 12 hours.

Two days after admission, the laboratory results showed alkaline phosphatase, 666 U/L; AST, 4231 U/L; total bilirubin, 173 µmol/L; BIL-D, 114.69 µmol/L; ammonia, 52 µmol/L; prothrombin time, 15.02 sec; and INR, 1.3. One week later, the patient was diagnosed with acute hepatitis induced by herbal intake. The patient's condition stabilized and her liver enzymes began to reverse to normal: ALP, 518 U/L; ALT, 503.9 U/L; AST, 174.8 u/L; total bilirubin, 35.5 µmol/L; direct bilirubin, 26.1 µmol/L; and normalized coagulation parameters. After 2 months of treatment, the patient improved and her liver function returned to normal.

Discussion

Astragalus sarcocolla dymock has been widely used in the northern region of the Arabian peninsula because of the general belief that it is safe, especially when used in cases of common cold, flu and colic. Anzaroot consumption explains the cause of the two cases. Despite the lack of evidence, Anzaroot is widely used in this area as an alternative treatment for various diseases.

According to the Physicians' Desk Reference for herbal medicine, the daily dosage of dried *Astragalus* root in adults is 2 to 6 g in divided doses or an oral ingestion of an *Astragalus* decoction at7.5 g/kg, indicating very low inherent toxicity [3,8].

In our cases, Anzaroot induced hepatic injury associated with neurological complications, prolongation of coagulation factor and hyperglycemia in the first case. In other reports, extracts of *Astragalus* may cause respiratory depression, excitatory cardiac effects, palpitations, abnormal kidney function, alterations in blood pressure, diarrhea, dizziness, dehydration, rash, rhino sinusitis, stimulation of the immune system and, at high doses, lead to blindness [2,3,9,10].

In our cases, the neurological dysfunctions could be due to the selenium content of the herbal. The fact that *Astragalus* acts as a diuretic and causes dehydration as well as metabolic abnormalities also increased the fibrinolysis effect and potentiated the risk of bleeding [3].

Based on the literature, Anzaroot might have a hepatoprotective effect through the reduction of

elevated SGPT levels [3]. It is considered to be safe for most adults according to the literature. On the other hand, liver injury induced by herbals may occur due to differences in personal susceptibility, including age, genetic abnormalities and underlying disease [11]. However, we present two pediatric cases. This age group could be a potentiating factor for the toxicity of Anzaroot. Moreover, contamination or adulteration of Anzaroot herbals could have caused liver injury in these cases. However, the occurrence of these two cases at different times and sites as well as the absence of similar cases in the same time period makes this unlikely.

Diagnosis of herbal hepatotoxicity is difficult, and the mechanism of toxicity remains unknown [11]. However, while there is no exact mechanism of Anzaroot-induced hepatotoxicity, other known herbals can cause hepatotoxicity due to a hypersensitivity reaction (immune – mediated mechanism). This could be a possible mechanism due to the short period of ingestion. However, hypersensitivity manifestations, such as eosinophilia, fever and rash, were absent in these patients [11]. In addition, a direct hepatotoxic effect (hepatocellular injury) by *Astragalus* or its metabolites may also be the cause. Accumulation of metabolites may lead to an increase of the concentration of cytochrome p450 and depletion of glutathione in the liver, which can cause changes in hepatocyte histology. This is the best and most logical reason for the mechanism of toxicity [11,12].

The patients in our cases were not taking any medication or herbals when administered Anzaroot treatment, so the possibility of liver injury due to an interaction is unlikely.

Moreover, based on the recommendation by the American College of Gastroenterology, we used the Roussel Uclaf Causality Assessment (RUCAM) scale, which is the most commonly used tool to assess adverse hepatic drug reactions associated with herbal and dietary supplements [13,14].

The RUCAM system contains 7 categories including 8 separate factors that can be induce liver injury. These categories are time to onset, subsequent course of illness, risk factors (age, alcohol and pregnancy), concomitant drugs, nondrug causes of liver injury (acute hepatitis A, B, C, biliary obstruction, alcoholic liver disease) ischemic hepatitis, previous information on the hepatotoxicity of the drug and response to rechallenge . The total score ranges from -9 to +14without the rechallenge score, but 2 points are added for special risk factors, so the total range is actually -7 to +11. A score of 0 or less means that the drug is excluded as a cause, a score of 1 to 2 means that the drug is unlikely to be the cause, a score of 3 to 5 means that an ADR is possible, 6-8 means that an ADR is probable and a score greater than 8 means that ADR is highly probable [13,15].

The R ratio should be calculated before calculating the RUCAM scores. The R ratio is calculated by dividing ALT by ALP to determine whether the injury is hepatocellular (R > 5.0), cholestatic (R < 2.0), or mixed (R = 2.0 – 5.0), and should use the upper value of the normal range for ALT and ALP. The first 3 of 7 categories are determined by the R ratio. In our hospital, the ULN of ALT was 40U\L and the ULN of ALP was 115U\L .We calculated the R ratio for the first case as 8.7 and 14.77 for the second case, implicating *Astragalus* induced hepatocellular injury in both cases. Thus, RUCAM for *Astragalus* was 8 points in for first case and 7 point for the second case.

In the first case, the patient was given 600 mg of N-acetyl cysteine intravenous every 12 hours. N-acetyl cysteine was used as an antidote to help restore depleted intrahepatic glutathione levels.

However, this treatment has not been approved until now in pediatric groups. Still, N-acetyl cysteine had a good result in our first case **(Table 2)**.

In our cases, we also used vitamin K to reduce the fibrinolysis effect of *Astragalus*, although there was no active bleeding and this indication is not recommended. Further, we administered cefuroxime in the second case as a prophylactic because patients with acute liver failure are more susceptible to bacterial infection, especially sepsis, due to immune system dysfunction [16].

Tables

Table 1: Lab Results during Treatment

Date	3rd Day	1 Week	2 Week	Normal Range
Na	143	135	134	135-155 µmol/L
K	2.4	2.1 ↓	5	3.6-5.5 µmol/L
Glucose	6.9↑	3.8 ↓	4.71	3.9-6.1 µmol/L
Albumin	25 ↓	38 ↓	43	30-50 g\l
Ca	-	2.22	2.68	2.12-2.52 µmol/L
Ammonia	45	25	17	9-33 µmol/L
BUN	1.5↓	1.2	3.4	2.5-6.4 µmol/L
ALT	1089↑	162 ↑	62	30-65 U\l
AST	111 ↑	64 ↑	35	15-37 U\l
ALP	357 ↑	262 ↑	-	21-232U\l
TBIL	-	68 ↑	22 ↑	0-17 µmol/l
PT	29.45↑	19.65 ↑	12.5	11-16 sec
INR	2.55↑	1.8 ↑	1.1	0.8-1.2
PTT	↑47	↑52.3	↑ 37.8	18-28 sec

Table 2: Effect of N-Acetyl Cysteine Intravenous on Liver Enzymes.

Date	Before used	1 Week, after used	Normal Range
Albumin	25 ↓	38 ↓	30-50 g\l
Ca	-	2.22	2.12-2.52 µmol/L
Ammonia	45	25	9-33 µmol/L
BUN	1.5↓	1.2 ↓	2.5-6.4 µmol/L
ALT	1089↑	162 ↑	30-65 U\l
AST	111 ↑	64 ↑	15-37 U\l
ALP	357 ↑	262 ↑	21-232U\l
TBIL	-	68 ↑	0-17 µmol/l
PT	29.45↑	19.65 ↑	11-16 sec
INR	2.55↑	1.8 ↑	0.8-1.2
PTT	↑47	↑52.3	18-28 sec

Conclusion

Astragalus sarcocolla dymock is widely used in the Arabian peninsula and is believed to be safe as well as to provide a hepatoprotective effect. However, the potential for hepatic injury, especially in children, should be noted.

The Roussel UCLAF causality assessment scale indicated that Astragalus induced hepatocellular injury in two pediatric cases.

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