Licorice and kidney

Dr.B.Ghiasi
Assistant Professor of Ilam Medicine University

Historical background

The monks first introduced licorice into ***Pontefract,*** West Yorkshire, UK in **1562** and George Dunhill, a local chemist, added sugar to it and named it Pontefract cake.

Severe cases of hypokalemia, rhabdomyolysis and tetraparesis have been reported due to these cakes..

England began using the extract and turned it into licorice candy which then became well known throughout the country.

Licorice recipes were brought by the early settlers to America which have been producing and importing licorice products ever since

Licorice extracts are often used as flavoring agents to mask the bitter taste in medicinal preparations.

Health products that contain licorice include herbal and licorice-flavored cough mixtures, throat pearls, licorice tea, licorice-flavored diet gum, laxatives .

Licorice extracts have been used for an extended period of time in China and Japan as herbal medicines.

In the United States, glycyrrhizin is generally recognized as a safe flavoring agent.

De-glycyrrhizinated licorice (DGL) has been manufactured to avoid the side effects of licorice by removing the active compound glycyrrhizin and is available in capsules, lozenges, wafers and liquid

Chemistry

Glycyrrhizic acid is composed of a hydrophilic part, two molecules of glucuronic acid, and a hydrophobic fragment, **glycyrrhetic acid .**

Glycyrrhizic acid has an action resembling that of mineralocorticoids.

Pharmacokinetics

After oral ingestion of licorice in humans, glycyrrhizic acid, is hydrolyzed to glycyrrhetic acid by intestinal bacteria .

Glycyrrhetic acid is a 200–1000 times more potent inhibitor of 11-ß-hydroxysteroid dehydrogenase (11-ß-HSD) than glycyrrhizic acid.

Glycyrrhetic acid is then rapidly absorbed and transported via carrier molecules to the liver.

In the liver it is metabolized to glucuronide and sulfate conjugates which are transported efficiently and excreted into the bile and are then subjected to **entero-hepatic circulation** , which may lead to prolonged maintenance of pharmacologically active plasma levels.

The transit rate of gastrointestinal contents through the small and large intestines predominantly determines to what extent glycyrrhetic acid conjugates will be reabsorbed.

Therefore in subjects with prolonged gastrointestinal transit times, glycyrrhetic acid might accumulate causing toxicity after repeated intake.

Mechanism of action

The active metabolites in licorice extract which are glycyrrhizic acid and glycyrrhetic acid can lead to a syndrome known as ***apparent mineralocorticoid excess .***

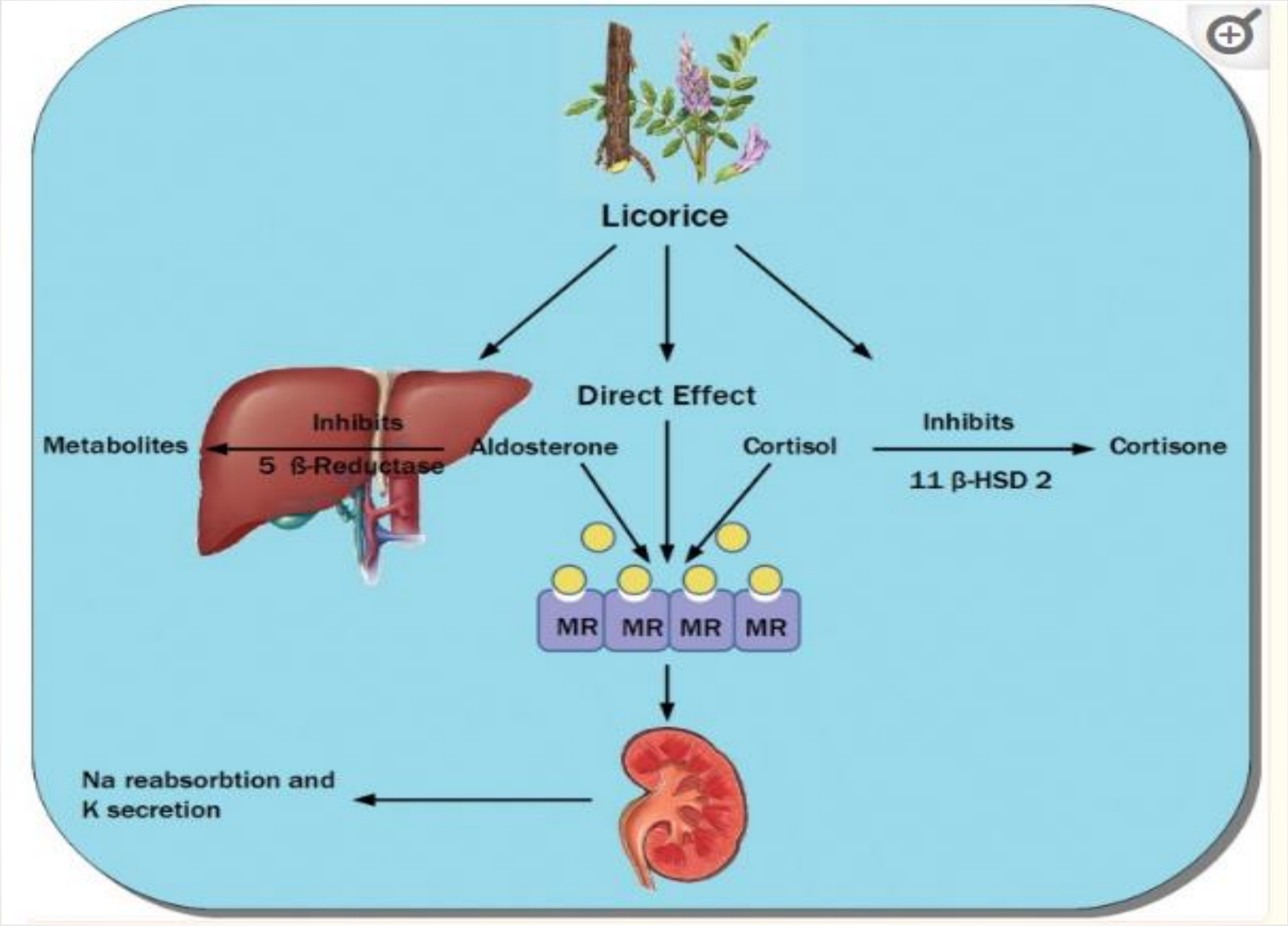
These side effects arise from the inhibition of the enzyme 11-ß-HSD and subsequent increase in the activity of cortisol. This effect is physiologically important because cortisol binds as avidly as aldosterone to the mineralocorticoid receptor (MR) .

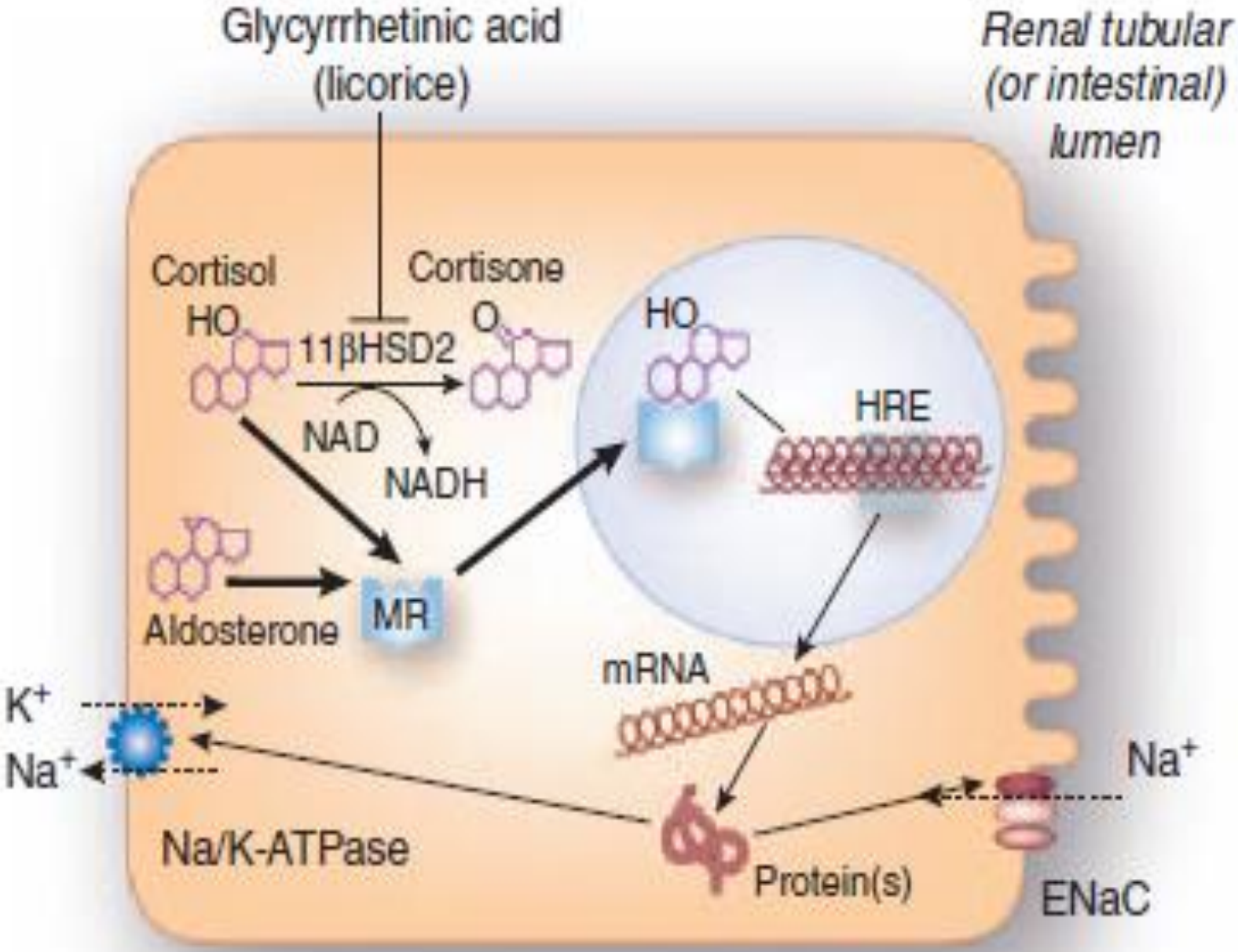
One form of this enzyme 11-ß-HSD type 2 (11-ß-HSD2) is mainly restricted in the kidneys to the aldosterone-sensitive sites in the collecting tubules.

Licorice also has a mineralocorticoid-like activity not only by blocking 11-ß-HSD2 but also by directly binding to MR .

Although initial studies suggested that this was the main mode of action, subsequent studies confirmed that its affinity to the MR is by far less than that of aldosterone and that the main contributing mechanism is through inhibition of 11-ß-HSD2

Glycyrrhetic acid also inhibits hepatic metabolism of aldosterone through suppression of 5-ß reductase activity .


Licorice
Direct Effect
Inhibits
Metabolites
5 ß-Reductase
Aldosterone
Cortisol
Inhibits
Cortisone
11 β-HSD 2
MR
MR
MR
MR
Na reabsorbtion and
K secretion


Glycyrrhetinic acid
(licorice)
Renal tubular
(or intestinal)
lumen
Cortisol
HO
11βHSD2
Cortisone
O
NAD
NADH
HO
HRE
Aldosterone
MR
mRNA
K+
Na+
Na+
Na/K-ATPase
Protein(s)
ENaC

Hyperaldosteronism is classified into primary, secondary and pseudo-hyperaldosteronism

Pseudo-hyperaldosteronism is a condition that clinically mimics hyperaldosteronism with suppression of plasma renin activity and aldosterone levels.

Causes of pseudo-hyperaldosteronism can be categorized into dietary, genetic and endocrinal causes.

Dietary causes include prolonged overconsumption of **licorice**, carbenoxolone or grapefruit juice due to an acquired reduction in the activity of 11-ß-HSD

Diagnosis of overconsumption

Licorice overconsumption should be suspected clinically in patients presenting with otherwise unexplained hypokalemia and muscle weakness.

Due to its aldosterone-like action, laboratory investigations reveal hypokalemia and metabolic alkalosis.

Creatine phosphokinase (CPK) may be elevated in cases with rhabdomyolysis (due to severe hypokalemia) which may be complicated with acute tubular necrosis.

The inhibition of 11-ß-HSD by licorice will cause reduction in the conversion of cortisol to cortisone.

Therefore, in conditions causing pseudo-hyperaldosteronism (as licorice excess), the **cortisol:cortisone** ratio in the peripheral venous plasma is sharply raised.

Moreover licorice-induced hypertension is also accompanied by reduction **in plasma renin** as well as **aldosterone level**, which is not the case in primary or secondary hyperaldosteronism.

Health benefits of licorice

Understanding the mechanism of action of licorice promoted its therapeutic benefit in several groups of patients.

The binding of licorice to the MR explains its utility in patients with Addison's disease.

Patients with postural hypotension caused by diabetic autonomic neuropathy have also shown improvement with licorice ingestion

A significant fall in plasma potassium concentration from 4.3 to 3.5 mmol/liter was noticed.

An important clinical application for this was provided by Farese and colleagues, who demonstrated the use of licorice as an important tool to maintain predialysis potassium levels within a safe limit to decrease the risk of hyperkalemic arrhythmias in patients on chronic dialysis

Licorice: a sweet alternative to prevent hyperkalemia in dialysis patients?

Paolo Ferrari[1]

In patients on hemodialysis, Farese *et al.* report that inhibition of the enzyme 11β-hydroxysteroid dehydrogenase type 2 by glycyrrhetinic acid, the active compound of licorice, reduces serum potassium concentration and the frequency of hyperkalemia, possibly by enhancing intestinal potassium loss. This finding could be an important tool to maintain predialysis [K^+] within safe limits in some dialysis patients at risk of hyperkalemic arrhythmias.

In a 6-month prospective, doubleblind, placebo-controlled crossover study:

10 hemodialysis patients received cookies or bread rolls supplemented with either GA (500 mg / d) or placebo.

Th e ratio of plasma cortisol to cortisone increased significantly in all patients given GA as compared with placebo.

7 On GA, mean [K +] was on average 1 mmol / l lower than on placebo,

The frequency of hyperkalemia (6 mmol/ l) was reduced from 9 % to 0.6 % .

The changes were not related to increased urinary potassium excretion in these patients.

Hence, the suggested mechanism underlying the persistent reduction in [K +] is colonic loss of potassium, most likely by activation of the MR by hydrocortisone as a consequence of the inhibition of 11 HSD2 by GA.

Although the authors did not measure fecal potassium excretion.

lowers [K +] in dialysis patients without inducing weight gain or hypertension.

Thus providing an appealing treatment alternative to minimize the risk of hyperkalemia in end-stage kidney disease patients

Farese *et al.* suggest that treatment with GA for up to 6 months is safe with no evidence of significant toxicity.

In humans, 11 HSD2 enzyme is also expressed in the heart and vessels.

Given that patients with end-stage kidney disease have a high cardiovascular burden, some questions may arise with regard to the long-term safety of MR overstimulation in other organs.

Treatment of peptic ulcers.

In women, treatment of polycystic ovary syndrome (PCOS)

Licorice extract ameliorates diabetic nephropathy in rats

Article in Planta Medica · July 2009

DOI: 10.1055/s-0028-1084734

How much is too much?

The main difficulty with licorice dosing lies in its availability in various forms such as candies, beverages, supplements and extracts that contain different amounts of the active components of licorice.

In 1991, the European Union proposed a provisional figure of 100 mg/day as the upper limit for ingestion of glycyrrhizin (approximately the amount found in 60–70 g licorice)

In April 2003, the Scientific Committee on Food confirmed an upper limit of 100 mg/day

Food category	Maximum allowable levels in foods as % glycyrrhizin content	Functional use
Baked goods	0.05	1, 2
Alcoholic beverages	0.1	1, 2, 3
Nonalcoholic beverages	0.15	1, 2, 3
Chewing gum	1.1	1, 2
Hard candy	16.0	1, 2
Soft candy	3.1	1, 2
Herbs and seasonings	0.15	1, 2
Plant protein products	0.15	1, 2
Vitamin or mineral dietary supplements	0.5	1, 2
All other foods, except sugar substitutes	0.1	1, 2

Factors that increase sensitivity to glycyrrhizin

Susceptibility to glycyrrhizin is influenced by the baseline health status, with some patients developing manifestations of toxicity with intake of **smaller amounts** than those expected to cause toxicity

These subgroups comprise people with decreased 11-ß-HSD2 activity.

Prolonged gastrointestinal transit time.

Other factors include old age, female sex and hypertension.

Licorice toxicity is also potentiated by factors known to predispose to hypokalemia.

Common causes include :

Gastrointestinal losses due to diarrhea or renal losses due to diuretic therapy.

Diminished intake

Increased entry into cells as caused by B2 agonists, alkalosis or combined glucose and insulin therapy

However, the resulting hypokalemia is usually mild and transient.

Factors that increase sensitivity to glycyrrhizin.

Hypokalemia
Prolonged gastrointestinal transit time
Decreased 11-ß-hydroxysteroid dehydrogenase-2 activity
Hypertension
Anorexia nervosa
Old age
Female sex

Licorice-related complications

It was evident that most of the published complications are linked to the aldosterone-like action of licorice.

The two main categories of complications were licorice-induced hypertension and hypokalemic myopathy

In reports of licorice-induced hypertension, prognosis was favorable with good response after cessation of licorice and starting antihypertensive medications.

However, there were a few patients who experienced hypertensive encephalopathy with a trend towards a longer recovery period.

One patient suffered a focal neurological deficit and completely recovered 5 months later, and another patient developed an ischemic stroke

Hypertensive emergency induced by licorice tea

Jean-Pierre Falet MD, Arielle Elkrief MD, Laurence Green MD

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The second main category of complications is hypokalemic myopathy manifesting with flaccid paralysis.

This group also had a good prognosis and full recovery was the rule in the majority of cases after cessation of licorice and potassium replacement.

Some cases experienced delayed recovery after correction of hypokalemia and a few others exhibited acute renal tubular damage leading to acute renal failure from myoglobinuria

Acute Renal Failure After Licorice Ingestion: A Case Report

Research Article

Radmila M Velickovic-Radovanovic[1,2], Branka Mltic[1,2], Dusanka Kitic[1], Svetislav Kostic[1,2], Tatjana Cvetkovic[1,2], Vidojko Djordjevic[1,2]

[1] *Faculty of Medicine, University of Nis, 18000 Nis, Serbia*

[2] *Clinic of nephrology and haemodialysis, Clinical centre, 18000 Nis, Serbia*

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Abstract: A 39-year-old female presented to the nephrology clinic emergency department with a complaint of muscle weakness and stomach pain. A detailed personal history revealed ingestion of 50-100 g herbal products which contained licorice, every day for 8 weeks to treat sterility. The herbal product was studied and determined to contain 'licorice' containing glycyrrhizic acid. Licorice (a plant which contains glycyrrhizic acid) induced hypokalemia which usually has a mild progression. However, it may cause critical failure in physical action by means of weakness followed by paralysis and may cause rhabdomyolysis, acute renal failure and hyperaldosteronism. This report presents the first case with acute renal failure due to licorice consumption from Serbia. In addition, the report aims to emphasize the importance of obtaining the detailed personal history of a patient for precise diagnosis.

Keywords: *Licorice • Hypokalemic myopathy • Renal damage • Hyperaldosteronism*

Licorice Ingestion; An Unusual Cause of Rhabdomyolysis and Acute Renal Failure

Meyan Kökü; Rabdomyoliz ve Akut Böbrek Yetmezliğinin Beklenmeyen Bir Nedeni

ABSTRACT

Licorice root has glycyrrhizic acid as the active ingredient and is responsible for a primary hyperaldosteronism-like syndrome with hypokalemia, metabolic alkalosis, and hypertension, typically accompanying low aldosterone. Herein, we present a rare complication of licorice consumption with acute renal failure.

A 49-year-old male patient was admitted to emergency department with generalized muscle pain/weakness, nausea, and dark urine. He was suffering from confusion and somnolence and the general condition was moderate. At laboratory assessment, potassium was 2.3 mEq/L, sodium 141 mEq/L, urea 146 mg/dl , creatinine 6.24 mg/dl, and total creatine kinase 4597 U/L. He had metabolic alkalosis (pH 7.59, HCO^{3-} 37.2 mmol/L). Hemodialysis was performed because of uremic neurological symptoms. His detailed anamnesis revealed consumption of herbal medication for the last 1.5 years to treat gastric complaints. The herbal medication included 16 gr licorice root powder (~600-750 mg glycyrrhizic acid) per 100 gr. The plasma aldosterone concentration was significantly suppressed [1.6 pg/ml (normal; 38.1-300 pg/mL)]. Under these conditions, our final diagnosis was hypokalemic rhabdomyolysis and acute renal failure due to licorice ingestion.

We present a rare life-threating effect of licorice ingestion in this report. Furthermore, we want to draw attention to the importance of a detailed medical history, including the use of herbal medications and regional traditional characteristics to confirm the diagnosis.

Ramazan DANIŞ[1]
Çağlar RUHİ[1]
Nuh BERKETOĞLU[2]
Ali Veysel KAYA[2]
Barış YILMAZER[3]
Sedat KAYA[4]

1 Diyarbakır Training and Research Hospital, Department of Nephrology, Diyarbakır, Turkey
2 Diyarbakır Training and Research Hospital, Department of Internal Medicine, Diyarbakır, Turkey
3 Diyarbakır Training and Research Hospital, Department of Rheumatology, Diyarbakır, Turkey
4 Diyarbakır Training and Research

The complication associated with most fatalities is the arrhythmogenic effect of licorice mediated by hypokalemia and subsequent QT prolongation and possible torsade de pointes.

The prognosis in the reported cases was poor, with six out of nine cases experiencing cardiac arrest

- Some reports described a picture of heart failure and acute pulmonary edema which mostly followed a licorice binge .

- A few cases presented with generalized edema which responded well to cessation of licorice and diuretic therapy

Complications related to excess licorice intake.

Cardiovascular	Hypertension
	Hypertensive encephalopathy
	Cardiac arrhythmias and death due to QT prolongation
	Heart failure and pulmonary edema
	Generalized edema
	Embolic ischemia
Neurological	Hypokalemic myopathy Stroke
	Rhabdomyolysis
	Carpal tunnel syndrome
	Licorice-induced myoclonus
	Occular deficits
Electrolyte and renal abnormalities	Hypokalemia
	Metabolic alkalosis
	Elevated CPK
	Acute tubular necrosis due to myoglobinuria
Allergic reactions	Occupational asthma
	Contact dermatitis
Drug interaction	Inhibition of the P450 and CYP3A4 systems
	Potentiation of the effect of warfarin therapy
	Digoxin toxicity due to licorice-induced hypokalemia

Treatment

Licorice-induced mineralocorticoid effect can be abated after cessation of intake, adequate potassium replacement and spironolactone therapy.

A previous study demonstrated that aldosterone receptor antagonism with either spironolactone or eplerenone normalizes blood pressure

A considerable period of time is usually required for the reversal of licorice's mineralocortecoid-like effects as was demonstrated in the presented case

This is attrof glycyrrhetic acid and the long duration required for the renin–angiotensin–aldosterone axis to normalize, which can take up to 6 months

Thanks