Licorice abuse: time to send a warning message

Hesham R. Omar, Irina Komarova, Mohamed El-Ghonemi, Ahmed Fathy, Rania Rashad, Hany D. Abdelmalak, Muralidhar Reddy Yerramadha, Yaseen Ali, Engy Helal and Enrico M. Camporesi

Abstract: Licorice extract has always been recognized as a sweetener and a thirst quencher. Its nutritive value is overrated by many who consume significant amounts and are prone to complications. Glycyrrhetic acid, the active metabolite in licorice, inhibits the enzyme 11-ß-hydroxysteroid dehydrogenase enzyme type 2 with a resultant cortisol-induced mineralocorticoid effect and the tendency towards the elevation of sodium and reduction of potassium levels. This aldosterone-like action is the fundamental basis for understanding its health benefits and the wide spectrum of adverse effects. Herein, we present a comprehensive review of licorice along with the reported complications related to excess intake. Despite its apparent use in a few clinical scenarios, the daily consumption of licorice is never justified because its benefits are minor compared to the adverse outcomes of chronic consumption. The review highlights the importance of investigating the dietary habits and herbal remedies which are being used worldwide on cultural and habitual bases rather than reliable scientific evidence. Licorice is a US Food and Drug Administration (FDA) approved food supplement used in many products without precise regulations to prevent toxicity. Increased awareness among the public is required through TV commercials, newspapers, internet sites, magazines and product labels regarding the upper limit of ingestion and health hazards associated with excess intake. We hope that this review will serve as a warning message that should be transmitted from physicians to patients to avoid excessive licorice intake as well as a message to the FDA to start regulating the use of this substance.

Keywords: Licorice, hyperaldosteronism, pseudo-hyperaldosteronism, hypokalemic myopathy, glycyrrhizin

Correspondence to:
Hesham R. Omar, MD
Internal Medicine Department, Mercy Hospital and Medical Center, 2525 South Michigan Avenue, Chicago, IL 60616, USA
hesham_omar2003@ yahoo.com

Irina Komarova, MD
Internal Medicine Department, Mercy Hospital and Medical Center, Chicago, IL, USA

Mohamed El-Ghonemi, MSc, MD
Critical Care Department, Cairo University, Cairo, Egypt

Ahmed Fathy, MSc
Cardiology Department, National Heart Institute, Cairo, Egypt

Rania Rashad, MD
Critical Care Department, Cairo University, Cairo, Egypt

Hany D. Abdelmalak, MD, Muralidhar Reddy Yerramadha, MD, Yaseen Ali, MD
Internal Medicine Department, Mercy Hospital and Medical Center, Chicago, IL, USA

Engy Helal, MB BCh
Emergency Department, Elagouza Hospital, Cairo, Egypt

Enrico M. Camporesi, MD
Department of Surgery/ Anesthesiology and Department of Molecular Pharmacology & Physiology, University of South Florida, Tampa, FL, USA

Introduction

Licorice is a popular sweetener found in many soft drinks, food products, snacks and herbal medicines. The habit of consumption of such a natural beverage is more popular in hot environments, especially during the month of fasting 'Ramadan'. The traditional belief that licorice is a healthy natural substance without side effects drives its liberal consumption which can occasionally be hazardous. Several characteristics allow the widespread utilization of licorice. Its sweet taste makes it attractive to many manufacturing companies as a sweetener for many products to mask its bitter taste. Its value as a thirst quencher promotes its excess consumption in certain climates. It is also used in several medical indications. Its main constituent, glycyrrhizic acid, mimics mineralocorticoids in its action (sodium reabsorption and potassium secretion). The extent of metabolic and acid–base derangement can occasionally be severe enough to cause serious complications. We present a detailed review of this substance and its health hazards illustrated with a case of quadriparesis that followed excessive licorice intake during Ramadan, which is the first reported case after the Egyptian drink 'erk soos'.

Historical background

Licorice has been present in various forms for a long period of time and has a rich history. It is an old remedy that was used by Egyptians and

Assyrians BC, although not in the forms that we know today. In ancient Egypt, licorice was not eaten as strips or ropes of candy but was made into a sweet liquid drink. The extract of the plant called *Glycyrrhiza* is derived from the ancient Greek term 'glykos', meaning sweet, and 'rhiza', meaning root. *Glycyrrhiza* was indulged upon by many prophets and pharaohs. Licorice extract has been utilized in the battlefields and the desert where soldiers and travelers drank it to suppress their thirst sensation on long marches.

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.

Sources of licorice

There are numerous licorice-containing products that are readily available in our everyday use and can be unintentionally consumed by the public in liberal amounts, putting them at risk of complications. Snacks containing licorice include licorice sticks and toffee bars, blackcurrant, Pontefract cakes, torpedos and stimorol chewing gums. Drinks containing licorice include the Egyptian drink 'erk soos', Belgian beers, pastis brands and anisettes (Raki, Ouzo, Pernod). Licorice is used by tobacco companies as a flavoring/sweetening agent. Sweet-flavored licorice tobacco twist, traditionally used by miners/sailors for chewing whilst working in 'no smoking' environments, is another source of licorice. Although exposure to glycyrrhizic acid via chewing tobacco has been previously reported to cause pseudo-hyperaldosteronism [Blachley and Knochel, 1980], extensive exposure to glycyrrhizic acid is not likely because of pyrolysis [Hoffmann and Hoffmann, 1997]. 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 (including cascara and compound licorice powder). Licorice extracts have been used for an extended period of time in China and
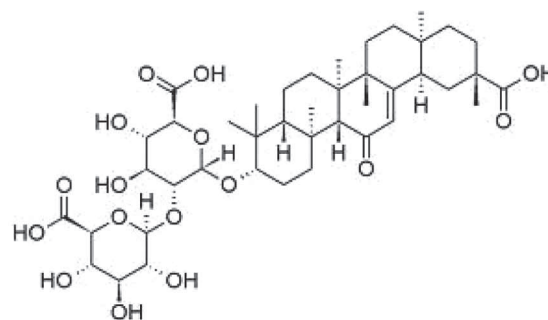

Figure 1. Chemical structure of glycyrrhizin.

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. Public awareness of licorice-containing compounds and their potential complications is mandatory to avoid the inadvertent use of such products.

Chemistry

The genus *Glycyrrhiza* consists of about 30 species of which *Glycyrrhiza glabra* is generally recognized as licorice because of its sweet taste. *G. glabra* is a member of the pea family and grows best in subtropical climates in deep, fertile, well drained soils, with full sun, and is harvested in the autumn, 2–3 years after planting. Glycyrrhizin (Figure 1), a triterpenoid compound, accounts for the sweet taste of licorice root and represents a mixture of potassium–calcium–magnesium salts of glycyrrhizic acid. The content of glycyrrhizin in licorice roots varies from 2 to 25%, depending on the particular species. Glycyrrhizin is 50 times sweeter than sucrose (cane sugar). Its sweetness has a slower onset than sugar but persists in the mouth for a longer time. Glycyrrhizic acid is composed of a hydrophilic part, two molecules of glucuronic acid, and a hydrophobic fragment, glycyrrhetic acid [Obolentseva *et al.* 1999]. Glycyrrhizic acid has an action resembling that of mineralocorticoids. The yellow color of licorice is due to the flavonoid content of the plant, which includes liquiritin, isoliquiritin, isoflavones, glabridin and hispaglabridins. The hispaglabridins A and B have significant antioxidant activity [Vaya *et al.* 1997], and glabridin and glabrene possess estrogen-like activity [Tamir *et al.* 2001].

Pharmacokinetics

Glycyrrhizin has a poor oral bioavailability and is detected at very low levels after a single oral dose administration. After oral ingestion of licorice in humans, its main constituent, glycyrrhizic acid, is hydrolyzed (pre-systemic hydrolysis) to glycyrrhetic acid by intestinal bacteria possessing a specialized ß-glucuronidase [Hattori *et al.* 1985]. Glycyrrhetic acid is a 200–1000 times more potent inhibitor of 11-ß-hydroxysteroid dehydrogenase (11-ß-HSD) than glycyrrhizic acid; therefore, its pharmacokinetics is more relevant after oral administration.

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 [Ploeger *et al.* 2000], which may lead to prolonged maintenance of pharmacologically active plasma levels. These conjugates are subsequently hydrolyzed by commensal bacteria [Ploeger *et al.* 2000, 2001]. 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 [Stewart *et al.* 1987]. 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) [Funder *et al.* 1988]. 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 [Calò *et al.* 2004]. 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 [Whorwood *et al.* 1993]. Glycyrrhetic acid also inhibits hepatic metabolism of aldosterone through suppression of 5-ß reductase activity [Latif *et al.* 1990]. Figure 2 illustrates the mechanisms of action of licorice.

Primary and secondary hyperaldosteronism

Hyperaldosteronism is classified into primary, secondary and pseudo-hyperaldosteronism. Primary hyperaldosteronism results from autonomous secretion of aldosterone from one or both adrenal glands and is associated with increased plasma aldosterone and low renin activity. In secondary hyperaldosteronism there is secondary activation of the renin–angiotensin system with subsequent increase in the aldosterone levels so the levels of renin and aldosterone are elevated.

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 [Palermo *et al.* 2003] due to an acquired reduction in the activity of 11-ß-HSD. Genetic causes include Liddle's syndrome due to a mutation of the gene encoding for β and γ subunits of the sodium channel leading to increased activity of this channel and subsequent increased sodium reabsorption [Scheinman *et al.* 1999]. Other genetic causes include MR abnormalities due to an activating mutation of the MR gene [Armanini *et al.* 2003] and the syndrome of apparent mineralocorticoid excess (SAME), which is an autosomal recessive disorder resulting from a mutation in 11-ß-HSD2. SAME is characterized by severe juvenile hypertension, low birth weight and failure to thrive in early childhood with extensive target organ damage [Potton *et al.* 1970]. Endocrinal causes of pseudo-hyperaldosteronism include congenital adrenal hyperplasia (especially due to 17-α hydroxlase and 11-hydroxylase deficiency), leading to accumulation of 11-deoxcorticosterone which has an aldosterone-like action. Figure 3 illustrates the various causes of hyperaldosteronism and the levels of renin and aldosterone in each category.
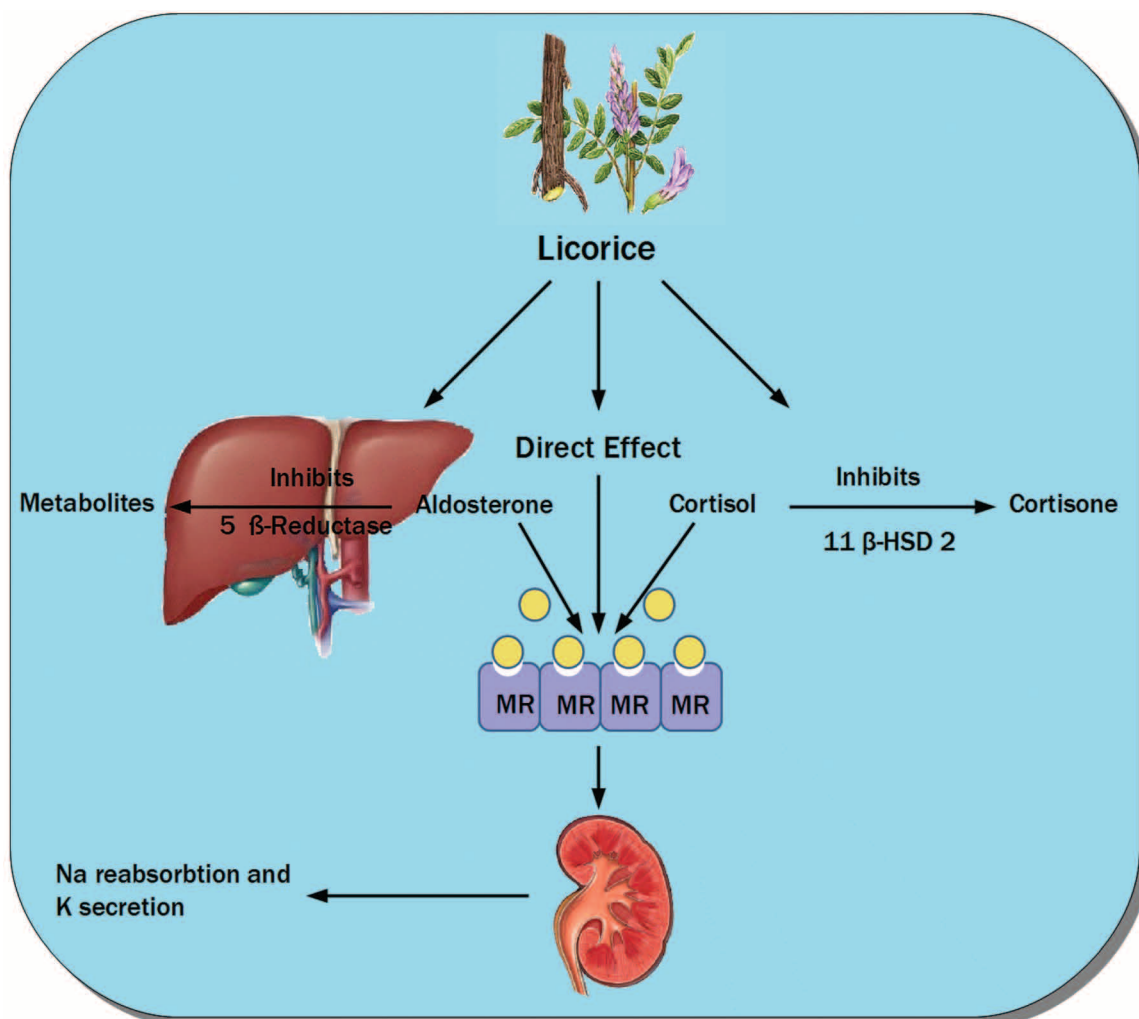
Figure 2. Demonstration of different mechanisms of action of licorice through inhibition of 11-ß-hydroxysteroid dehydrogenase type 2, 5 ß-reductase (which metabolizes aldosterone) and its direct action on the mineralocorticoid receptors causing sodium reabsorption and potassium secretion. MR, mineralocorticoid receptor; 11-ß-HSD 2, 11-ß-hydroxysteroid dehydrogenase type 2.

### Diagnosis of overconsumption

Licorice overconsumption should be suspected clinically in patients presenting with otherwise unexplained hypokalemia and muscle weakness. A clue is provided when dietary history reveals excessive licorice intake. 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. These effects are due to the affinity of glycyrrhetinic acid for MR in addition
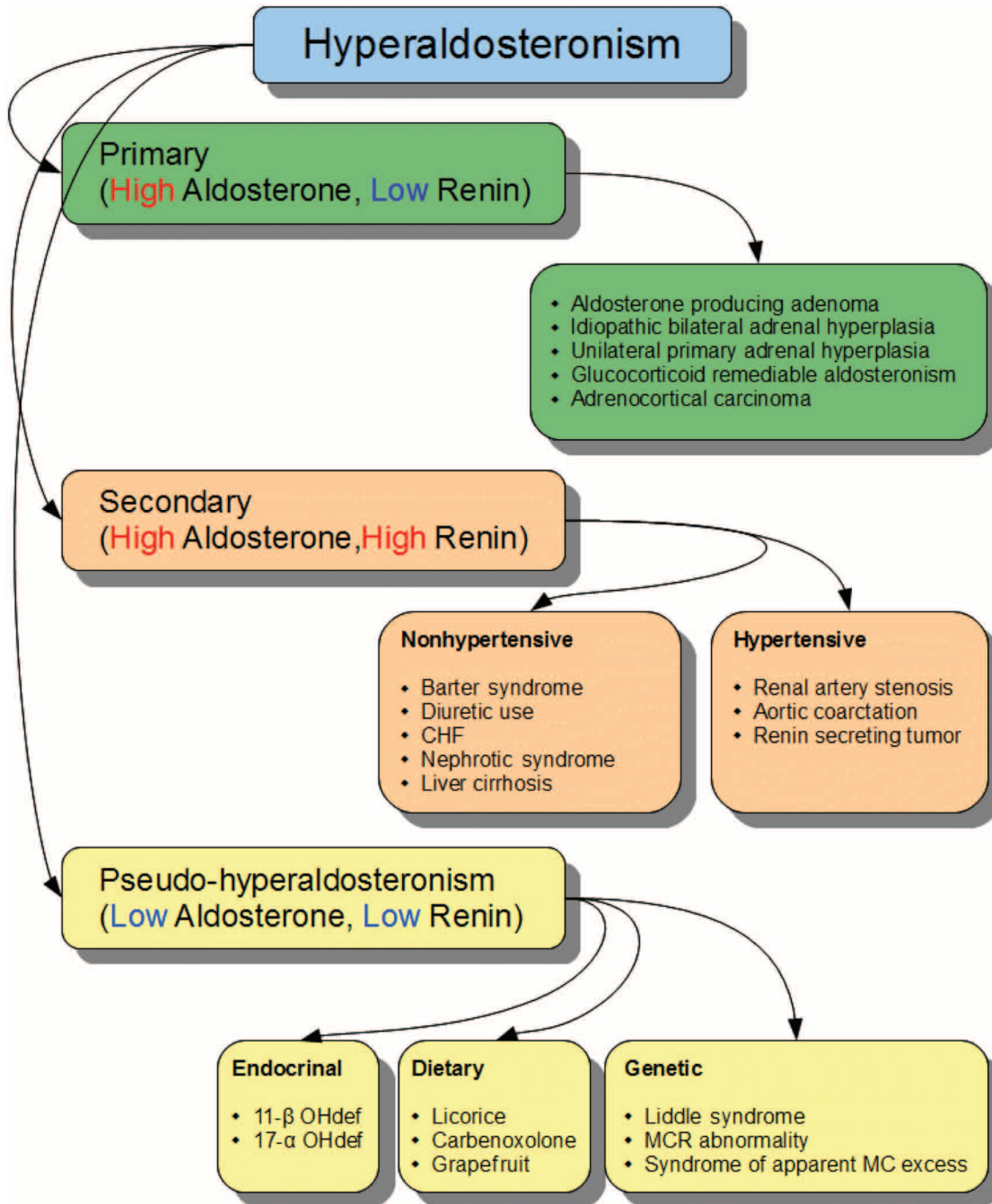
Figure 3. Illustration of the various causes of hyperaldosteronism and the levels of renin and aldosterone in each category. 11-β OHdef, 11 β hydroxylase deficiency; 17-α OHdef, 17 α hydroxylase deficiency; CHF, congestive heart failure; MC, mineralocorticoid; MCR, mineralocorticoid receptor.

to its plasma concentration being more than 5000 fold the concentration of aldosterone [Armanini *et al.* 1996]. Patients with postural hypotension caused by diabetic autonomic neuropathy have also shown improvement with licorice ingestion [Basso *et al.* 1994]. Bernardi and colleagues studied the effects of prolonged ingestion of graded doses of licorice on serum potassium level in healthy volunteers [Bernardi *et al.* 1994]. A significant fall in plasma potassium concentration from 4.3 to 3.5 mmol/liter was noticed, which occurred at the dose of 800 mg or more daily. 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 [Farese *et al.* 2009].

Licorice is one of the most widely prescribed herbs in Chinese medicine. It is used to treat gastric ulcers when administered 20 to 30 minutes before meals through lining the stomach wall. The processed form of licorice (DGL) is not associated with adverse effects and can be used to treat peptic ulcer disease in combination with antacids (this combination has been marketed as Caved-S). However, licorice is rarely used nowadays because of its side effects and the emergence of other more powerful classes of medications for treatment of peptic ulcers. In Japan, glycyrrhizin has been given intravenously for treatment of patients with chronic hepatitis B with improvement in liver functions and occasionally complete recovery. It was suggested that glycyrrhizin is able to suppress the secretion of both hepatitis B surface antigen and its intracellular transport [Sato *et al.* 1996; Takahara *et al.* 1994]. In women, licorice has been used in conjunction with spironolactone in the treatment of polycystic ovary syndrome (PCOS) [Armanini *et al.* 2007]. This estrogenic activity of licorice has been well documented [Oerter *et al.* 2003].

Other beneficial effects of licorice include its role in bone metabolism which was described by Mattarello and colleagues who demonstrated an increased parathyroid hormone and urinary calcium levels from baseline value in healthy women after 2 months of therapy. The postulated mechanism was the estrogen-like activity of isoflavans which are one of the constituents of licorice roots [Mattarello *et al.* 2006]. Armanini and colleagues described a reduction in body fat mass without a change in the body mass index in 15 normal weight subjects who consumed 3.5 g/day of licorice for 2 months. This suggested that licorice can reduce fat by inhibiting 11-ß-HSD type 1 at the level of fat cells [Armanini *et al.* 2003]. It was also demonstrated that licorice can reduce testosterone levels in healthy women due to the block of 17-HSD and 17–20 lyase. It was then concluded that licorice could be considered as an adjuvant therapy of hirsutism and PCOS [Armanini *et al.* 2004]. Agarwal and colleagues demonstrated the beneficial effect of licorice gargle in reducing the risk of postoperative sore throat [Agarwal *et al.*

2009]. The anticarcinogenic effects of glycyrrhizin and glycyrrhizinic acid have been thoroughly studied for their effects on mice, rat and human cancer cell lines. Prostate, breast, colon, liver and lung cancer cell lines have also been investigated. Most studies demonstrated a dose-dependent action on cell/tumor proliferation and apoptosis. Suggested mechanisms of action include its antioxidant activity, DNA-protective activity, suppressive action, cyclooxygenase inhibition and phyto-estrogenic and progesterone antagonist activity [Wang and Nixon, 2001; Dong *et al.* 2007; Lee *et al.* 2007; Chintharlapalli *et al.* 2007].

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 the United States, the manufacture of some dietary supplements, including licorice, is not closely regulated. 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) [Murphy *et al.* 2009]. In April 2003, the Scientific Committee on Food confirmed an upper limit of 100 mg/day [Scientific Committee on Food, 2003]. This was based on data from human volunteer studies. However, the Committee is still of the opinion that an average daily intake for glycyrrhizic acid and ammonium glycyrrhizinate cannot be derived because the new human toxicity studies are too limited (small experimental groups, short duration). The Dutch Nutrition Information Bureau advised against daily glycyrrhizin consumption in excess of 200 mg, assumed to correspond to 150 g of licorice confectionery [Fenwick *et al.* 1990].

Licorice fluid extracts contain approximately 10–20% glycyrrhizin; typical doses of 2–4 ml deliver 200–800 mg. A review concluded that about 2% of the regular consumers have a daily intake of glycyrrhizinic acid of over 100 mg/day [Maas, 2000]. In 1994, Walker and Edwards demonstrated that a daily oral intake of 1–10 mg of glycyrrhizin, which corresponds to 1–5 g licorice, has been estimated to be a safe dose for most healthy adults [Walker and Edwards, 1994]. Two studies on healthy volunteers were published. In 1994, Bernardi and colleges administered daily doses of 108, 217, 380 and 814 mg

Table 1. US Food and Drug Administration limitations for the use of licorice and its derivatives in foods (21 CFR 184.1408c) [World Health Organization, 2005].

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
1 = flavor enhancer; 2 = flavoring agent; 3 = surface-active agent.		

glycyrrhizic acid, as 'licorice pills' for 4 weeks to four groups of 3 male and 3 female healthy volunteers [Bernardi *et al.* 1994]. No observed-adverse-effect level (NOAEL) based on the study report was 217 mg/person/day. At higher dose levels, sodium retention and depression of plasma renin and aldosterone levels were observed. Female participants were slightly more sensitive to glycyrrhizinic acid than male participants. Two years later, in the double-blinded randomized placebo-controlled study by Bijlsma and colleagues, four groups of 10 healthy female volunteers received orally 0, 1, 2 or 4 mg of pure glycyrrhizinic acid/kg/day for 8 weeks [Bijlsma *et al.* 1996]. In this study the NOAEL for glycyrrhizinic acid was 2 mg/kg/day. The European committee considered that the NOAEL obtained in the study by Bijlsma and colleagues is more appropriate because this study comprised a larger group of volunteers (40 volunteers in contrast to 24 volunteers), a longer period of exposure (8 weeks in contrast to 4 weeks) and inclusion of a placebo control group.

Licorice and its derivatives, including ammoniated glycyrrhizin, are generally recognized as safe (GRAS) for use in foods by the US Food and Drug Administration (FDA) (21 CFR 184.1408). This chapter of regulations includes descriptions, specifications and maximum use levels (Table 1) for licorice and licorice derivatives. The FDA assumes that glycyrrhizin levels in foods do not pose a health hazard, provided that these foods are not consumed in excess.

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 [Sigurjonsdottir *et al.* 2003]. These subgroups comprise people with decreased 11-ß-HSD2 activity (the target enzyme of glycyrrhizic acid, for which genetic polymorphisms resulting in reduced basal activity have been described). Prolonged gastrointestinal transit time is another factor that increases sensitivity to glycyrrhizin. The amount of glycyrrhetic acid reabsorbed depends on its transit through the small and large intestines, therefore patients with prolonged gastrointestinal transit times and more prone to toxicity after repeated intake. 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 is seldom the sole cause of potassium depletion since the urinary excretion can be efficiently reduced to less than 15 mEq per day [Singer and Brenner, 2005]. Increased entry into cells as caused by B2 agonists, alkalosis or combined glucose and insulin therapy are other possibilities; however, the resulting hypokalemia is usually mild and transient. Other less common causes of hypokalemia include Cushing syndrome and Conn's syndrome. Anorexia nervosa is

Table 2. 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

another factor that increases glycyrrhizin sensitivity. Nightingale and colleagues reported a case of licorice-induced myopathy in a patient with anorexia nervosa with a diet comprising very low potassium levels [Nightingale *et al.* 1981]. Støving and colleagues demonstrated that glycyrrhizin sensitivity is increased in patients with anorexia nervosa suggested by the pronounced hypokalemic response to a relatively low daily dose of licorice [Støving *et al.* 2011]. Table 2 lists the various factors that can contribute to increased glycyrrhizin sensitivity.

Case presentation

A 35-year-old man from Egypt, with no past medical history, presented to the emergency room with progressive weakness that started in his lower extremities and quickly progressed to involve the upper limbs. There was no history of fever, chills, prior diarrhea, upper respiratory tract infection, back pain or trauma. On physical examination, the patient was fully conscious and oriented, had a blood pressure (BP) of 200/110 mmHg and a heart rate of 90/min. Neurological exam revealed bilateral symmetric flaccid paralysis (grade 1/5) of both upper and lower limbs with hypotonia and hyporeflexia. Examination of the sensory system and cranial nerves was unremarkable. Laboratory investigations were pertinent for a potassium level of 1.8 mmol/liter, sodium 144 mmol/liter and a normal CPK, thyroid and liver functions. Electrocardiography revealed a normal sinus rhythm, prominent U waves in the precordial leads and frequent atrial premature beats. A computed tomography scan of the brain was normal.

A provisional diagnosis of hypokalemic myopathy was presumed without a clear precipitating factor. Sodium nitroprusside infusion was initiated for control of BP together with intravenous potassium replacement. Initially, there was no improvement in his neurological status and he remained hypokalemic despite adequate supplementation. On further questioning, the patient admitted to drinking 1 liter daily of licorice, 'erk soos', during the whole month of Ramadan. Spironolactone therapy was started and potassium supplements were continued. The potassium level normalized slowly over the next 10 days with a gradual return of his motor function. The patient was discharged after regaining his full muscle power and was advised to avoid the excessive consumption of licorice.

Licorice-related complications

We reviewed all publications up to 2010 pertaining to complications previously described from excess licorice ingestion in any of its present forms. This review is based on data published in scientific journals indexed by the PubMed and Medline databases using the following keywords: 'licorice, hypokalemic myopathy, licorice induced hyperaldosteronism and pseudo-hyperaldosteronism'. 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 [Mumoli and Cei, 2008; Scali *et al.* 1990; Holmes *et al.* 1970; De Klerk *et al.* 1997] and hypokalemic myopathy [Yaguchi *et al.* 2008; Maresca *et al.* 1988; Caradonna *et al.* 1992; Lin *et al.* 2003a; Lin *et al.* 2003b; Gross *et al.* 1966; Tancevski *et al.* 2008]. 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 [Van der Zwan, 1993; Russo *et al.* 2000; Bramont *et al.* 1985]. One patient suffered a focal neurological deficit and completely recovered 5 months later [Van der Zwan, 1993], and another patient developed an ischemic stroke [Bramont *et al.* 1985]. 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 [Kasap *et al.* 2010].

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 [Campana *et al.* 2003; Arola, 2003; Böcker and Breithardt, 1991; Crean *et al.* 2009; Harris, 2000; Eriksson *et al.* 1999; Montoliu, 1977; Miyamoto *et al.* 2009; Bannister *et al.* 1977]. Some reports described a picture of heart failure and acute pulmonary edema which mostly followed a licorice binge [Chamberlain and Abolnik, 1997; Chamberlain, 1970; Hasegawa *et al.* 1998]. In these cases, recovery was the rule after implementing antifailure measures. A few cases presented with generalized edema which responded well to cessation of licorice and diuretic therapy [Sailler *et al.* 1993; Crampton, 1961; Francini-Pesenti *et al.* 2008].

Licorice was previously linked to increased incidence of preterm labor in a study performed on 95 women with preterm deliveries [Strandberg *et al.* 2001]. The study demonstrated that heavy consumption is associated with a twofold to threefold increase in the risk of preterm (<37 weeks) birth. However, these results were later questioned due to the retrospective collection of data and the possibility of confounding factors that might have biased the results [Hughes *et al.* 2003]. Several reports demonstrated the occurrence of ocular complications related to licorice ingestion [Hall and Clemett, 2004; Santaella and Fraunfelder, 2007; Dobbins and Saul, 2000; Fraunfelder, 2004]. The underlying pathogenesis involves vasospasm of the optic nerve blood vessels leading to transient monocular or binocular visual loss/aberrations. All patients who experienced transient visual loss/aberrations had resolution of their visual symptoms; the aid of hyperbaric oxygen was required for one patient.

There was another group of rare side effects. A young woman experienced an acute right upper limb embolic ischemia for which embolectomy was performed [Lozano *et al.* 2000]. Several reports demonstrated the interaction of licorice with drugs and the hepatic microsomal enzyme system. One patient exhibited digoxin toxicity due to hypokalemia induced by licorice intake [Harada *et al.* 2002]. Licorice root extracts not including glycyrrhizin causes inhibition of P450 and cytochrome P450 3A4 (CYP3A4) systems [Tsukamoto *et al.* 2005; Kent *et al.* 2002]. A study demonstrated the potentiation of warfarin effects due to the inhibitory effect of licorice on the hepatic microsomal enzyme system [Heck *et al.* 2000]. One patient presented with carpal tunnel syndrome with nerve conduction studies revealing bilateral median neuropathies likely attributed to licorice-induced water retention [Tacconi *et al.* 2009]. Other complications include hypersensitivity to glycyrrhizin [Kuriyama *et al.* 1975], occupational asthma [Cartier *et al.* 2002], myoclonus due to licorice-induced metabolic alkalosis [Ishiguchi *et al.* 2004] and licorice-induced contact dermatitis [Nugmanova and Kalitina, 1979; O'Connell *et al.* 2008]. Table 3 demonstrates the previously reported licorice-related complications.

Discussion

Licorice is a constituent in many food products and is available in various forms. The public often consume licorice because of a traditional belief in its health benefit with unawareness of the potential hazards of overconsumption. In Egypt, the consumption of erk soos (of which licorice is a main constituent) is a common tradition during Ramadan and especially during the warm summer where it acts as a thirst quencher. The presented case exemplifies one of the common complications of licorice toxicity when a patient without prior medical history presented with severe hypertension, hypokalemia and quadriparesis after prolonged heavy licorice intake.

The side effects of licorice were first described by Revers [Revers, 1948] following its use for the treatment of peptic ulcer disease. Consequently, other adverse effects were reported following exposure through candies or by ingestion of licorice-containing products such as the antituberculosis medication p-aminosalicylic acid [Cayley, 1950; Heard *et al.* 1950], the antipeptic ulcer medication carbenoxolone sodium [Baron, 1983], the French alcoholic beverage boisson de coco [Mollaret *et al.* 1960; Jenny *et al.* 1961], chewing tobacco [Blachley and Knochel, 1980] and some oriental herbal preparations [Sugimoto *et al.* 1984].

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, prevents upregulation of vascular endothelin-1,

Table 3. 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

CPK, creatine phosphokinase; CYP, cytochrome P450.

restores nitrous oxide mediated endothelial dysfunction and thus may advance as a novel and specific therapeutic approach in 11-ß-HSD2-deficient hypertension [Thomas *et al.* 2001]. 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 attributed to the long half life of glycyrrhetic acid and the long duration required for the renin–angiotensin–aldosterone axis to normalize, which can take up to 6 months [Epstein *et al.* 1977]. Because of its adverse effect profile, DGL has been manufactured in an attempt to avoid complications from glycyrrhizic acid.

This review creates awareness of the potential hazards of licorice. We emphasize the importance of a thorough and detailed dietary history, including licorice-containing products and herbal medicines, and the need for re-evaluating the traditional habits that promote excessive licorice consumption because of a belief of its health benefits. The FDA should start regulating the use of this substance and create public awareness through the media about its health hazards. We aim to send a warning message that licorice is not just a candy and that serious life-threatening complications can occur with excess use.

Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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