components have been removed. Unfortunately preparation and advertising of these compounds is unregulated by the FDA.
- Licorice is taken in the following manner
  - Dried root: 1–5 g PO 3 times daily up to 6 wk (indication: general use).
  - Extract: (1:1 preparation) 2–5 mL PO 3 times daily up to 6 wk (indication: general use)
  - DGL extract: 1.5–3 g/d for peptic ulcer
  - DGL extract: 380–760 mg PO 20 min before meals for peptic ulcer

Assessment Points

System	Effect	Assessment by Hx	PE	Test
CNS	Headache Visual changes Paresthesias	Exposure/use of licorice	Visual acuity Sensory exam	Neurologic consult, possible MRI
CV	Hypovolemia Hypervolemia Htn Arrhythmia	Exposure/use of licorice	BP/HR, consider orthostatics	ECG rhythm strip
GI	Black stools (rare) Laxative effect	Report of loose dark stool	Abdominal exam	Stool guaiac
HEME	Decreased clotting (rare)	Bleeding problems	Plts, PT/PTT	
ENDO	Hyperglycemia Hypernatremia Hypokalemia	Exposure/use of licorice Weight gain, increased urination		Serum chemistries

Key References: Kaye AD, Clarke RC, Sabar R, et al.: Herbal medicines: current trends in anesthesiology practice—a hospital survey, *J Clin Anesth* 12(6):468–471, 2000; Ruetzler K, Fleck M, Nabecker S, et al.: A randomized, double-blind comparison of licorice versus sugar-water gargle for prevention of postoperative sore throat and postextubation coughing, *Anesth Analg* 117(3):614–621, 2013.

Possible Drug Interactions

Preoperative Period

- Multiple adverse drug interactions reported in pts using licorice preparations and prescription medications. Licorice can interfere with the function of hormone supplements (e.g., birth control pills), oral hypoglycemic agents, and corticosteroids. Lyte imbalances and GI symptoms can be worsened by usage of licorice with diuretics and laxatives. Digoxin usage and licorice-induced hypokalemia can be potentially arrhythmogenic.
- Lyte abnormalities of hypokalemia, hypernatremia, and metabolic alkalosis should be sought and corrected before surgery in high-dose frequent users.
- Pt should be instructed to discontinue use of the herbal medicine approx 2 wk before elective surgery.

Induction/Maintenance

- No known interactions with licorice metabolites. However, pseudohyperaldosteronism should be considered and anesthetic management directed at the problems of hypokalemia, Htn, and fluid status. Placement of an arterial line and/or central venous line should be considered in symptomatic pts. (See Hyperaldosteronism, Secondary.)

Adjuvants/Regional Anesthesia/Reversal

- No known interactions. Consider pros and cons of NSAID use intraop, especially if no assessment of renal function. Careful attention to neurologic exam and/or paresthesias before initiation of regional technique.

Emergence/Extubation

- No known interactions. Acute topical preop and postop administration (by gargle) has been used without adverse effect to prevent postop sore throat. However, hypokalemia with or without a Hx of muscle weakness could potentially modify response to nondepolarizing muscle relaxants.

Postoperative Concerns

- Failure of resolution of preop symptoms attributed to licorice use with D/C of licorice-containing compound should prompt investigation of other causes.
- Continued monitoring of fluid and lyte status. If problems with hypokalemia continue despite potassium supplementation, consider potassium-sparing diuretics (e.g., triamterene) or a competitive aldosterone antagonist (e.g., spironolactone); investigate other possible causes.

Melatonin (*N*-Acetyl-5-Methoxytryptamine, Bevitamel, Vitamist, Melatonex)

Ori Gottlieb

Uses

- Regulates sleep-wake cycles.
- Prescribed for jet lag, shift work, depression.
- Use as antineoplastic, antidelirium, and anticonvulsant is under investigation.
- Questionable benefit in treating breast cancer and migraines.
- Categorized as a nutraceutical (unregulated).

Risks

- Not controlled by FDA; therefore quality and potency may vary.
- May interact with other CNS-acting medications such as hypnotics, sedatives, or psychotropics.
- Not recommended in children or pregnant/breast-feeding women owing to insufficient data
- May cause excessive somnolence.
- Use of animal-source melatonin products is not recommended because of risk of viral contamination or infection.

Overview/Pharmacology

- Secretion modulated by hypothalamic enzymes in response to a dark environment.
- Exogenous routes of administration: Oral tablets, capsules, lozenges, teas, sprays.
- Unlike endogenous melatonin, oral doses undergo first-pass hepatic metabolism with a bioavailability of 30–50%.
- Crosses the blood-brain barrier.
- Mean elimination half-life is 45 min. Only 0.01% of melatonin is excreted unchanged in urine.
- Pharmacologic tolerance to melatonin has not been described.
- Alcohol may potentiate side effects.

Usual Dose

- Taken 1–2 h before usual sleep time.
- Significant individual dose variation.
  - Insomnia: 1–4 mg PO in evening.
  - Insomnia with depression: 5–10 mg PO in evening.
  - Jet lag: 3–6 mg PO in evening on the destination's sleep schedule; may require up to 5 nights to become effective.
  - Tinnitus: 3 mg PO in evening.
  - Circadian disruption/blindness
  - Adults: 5–7 mg PO in evening.
  - Children: 2.5–7.5 mg PO in evening.

Endogenous Actions

- Secreted by the pineal gland in response to the absence of photic stimuli (known as the "darkness hormone").
- Reduces the body's core temperature in preparation for sleep.
- Secretion peaks during the pediatric years and decreases with age.
- Is involved in some way with reproductive function. Receptors have been found in reproductive tissues.
- Endogenously produced melatonin may have a significant role in deferring a number of free radical–related diseases and some pathophysiologic changes associated with aging.

Exogenous Actions

- Resets the body to the environmental clock and allows pts to normalize physiologic and behavioral sleep patterns.
- Used commonly as a preventive and therapeutic agent against jet lag.
- Useful in individuals with poor circadian synchrony, such as the visually impaired.

Perioperative Implications

- The ASA recommends that all herbal medications be D/C 2–3 wk prior to elective surgery because it takes 5–6 half-lives for an agent to leave the body; moreover, these substances lack uniform data regarding uptake, distribution, and elimination as they are not considered drugs by the USA FDA. Over 90 herbal products are associated with bleeding; this can be a specific problem intraop or when placement of a regional anesthetic is being considered for postop pain management.

Phytosterols

Lee A. Fleisher

Uses

- Naturally occurring in human diet.
- Used as supplements, especially in margarines, to reduce cholesterol levels.
- May also possess anti-inflammatory, antipyretic, antineoplastic, and immune-modulating properties.
- Some recent evidence questions the beneficial effect of phytosterols and the potential for increased CV risk.

Perioperative Risks

- None known

Worry About

- Pts may be taking phytosterols because of hypercholesterolemia and occult CAD.

Overview/Pharmacology

- Phytosterols (including plant sterols and stanols) are natural components of edible vegetable oils such as sunflower seed oil; as such, they are natural constituents of the human diet.
- It is difficult to incorporate free sterols into edible fats and/or oils because of their insolubility, whereas sterols esterified to fatty acids are more fat soluble.
- In the intestine, most sterol esters are hydrolyzed to free sterols as part of the normal digestive process.
- Plant stanols are hydrogenation products of the respective plant sterols (e.g., campestanol and/or campesterol, sitostanol and/or sitosterol) and are found in nature at very low levels.
- Enrichment of foods such as margarines with plant sterols and stanols is one of the recent developments in functional foods to enhance the cholesterol-lowering ability of traditional food products.
- May reduce the absorption of some fat-soluble vitamins. Randomized trials have shown that plant sterols and stanols lower blood concentrations of β-carotene by about 25%, concentrations of α-carotene by 10%, and concentrations of vitamin E by 8%.

Drug Class/Usual Dose

- Consumption of plant sterols and stanols lowers blood cholesterol levels by inhibiting the absorption of dietary and endogenously produced cholesterol from the small intestine. Plant sterols and/or stanols are only very poorly absorbed themselves.
- This inhibition is related to the similarity in physicochemical properties of plant sterols and stanols and cholesterol and may be related to two mechanisms:
  - The greater the amount of plant sterols and/or stanols, the lower the solubility and perhaps the greater the amount of cholesterol precipitated. Cholesterol in the crystalline form cannot be absorbed.
  - Competition for space in mixed micelles.
- Being marketed in new margarine formulations.

Assessment Points

System	Effect	Assessment by Hx	PE	Test
CV	Hypercholesterolemia	CAD, angina	Chest pain	ECG
GI	Malabsorption of some vitamins			

Key References: Weingärtner O, Böhm M, Laufs U: Controversial role of plant sterol esters in the management of hypercholesterolaemia, *Eur Heart J* 30(4):404–409, 2009: Rocha VZ, Ras RT, Gagliardi AC, et al.: Effects of phytosterols on markers of inflammation: a systematic review and meta-analysis, *Atherosclerosis* 248:76–83, 2016.

Possible Drug Interactions

- No known drug interactions

Anticipated Problems/Concerns

- None known

Red Yeast Rice (Cholestin)

Alan David Kaye | John N. Cefalu | Amit Prabhakar

Uses

- Chinese traditional medicine for therapy of pts with cardiovascular diseases
- Hypercholesterolemia
- Prevention of coronary events, stroke, and TIA
- Treatment of dyslipidemia in statin-intolerant pts
- Prostate and colon cancer
- Possible diabetes treatment

Perioperative Risks

- Obtain adequate Hx to determine indication for taking red yeast rice.

Worry About

- Chemical composition of red yeast rice is not controlled by the FDA and may vary by manufacturer.
- Relatively contraindicated in liver disease. Hepatotoxicity is worsened in combination with other hepatotoxic drugs.

Overview

- Prepared by growing red yeast (*Monascus purpureus*) on rice to produce a red product.
- Contains 10 mevinic acids include monacolin K, also known as lovastatin.
- Popular in Asian countries.
- Available in several preparations in USA.

Drug Class/Mechanism of Action/Usual Dose

- HMG-CoA reductase inhibitor, essentially a natural statin and its homologues, additionally contains unsaturated fatty acids, flavonoids, plant sterols, and other biologically active substances.
- Inhibits conversion of HMG-CoA to mevalonic acid, an early precursor of cholesterol.
- Usual dose is 600–2400 mg daily.
- Xuezhikang (from red yeast rice) reduces expression of mediators of oxidative stress induced in diabetes mellitus and protects pancreatic islet cells from hyperglycemic injury. Xuezhikang, which is purified from cholestin, has been shown to decrease blood glucose levels by improving glucose tolerance and insulin secretion in db/db mice. Xuezhikang has also been shown to protect islets from hyperglycemic injury with conserved β-cell content and microenvironment. Xuezhikang potently inhibits the expression of key factors in oxidative stress and causes an upregulated expression of glucose-sensing tissue.
- Reduces matrix metalloproteinases 2 and 9 and CRP levels involved in vascular remodeling.
- Red yeast rice can significantly increase adiponectin and can significantly lower LDL-C and total cholesterol levels. Adiponectin correlates positively with HDL-C while serum leptin correlates negatively with triglycerides. Therefore red yeast rice has a potentially protective effect in obesity-related and cardiovascular diseases.
- Xuezhikang from red yeast rice has been shown to upregulate eNOS expression in vascular endothelia and RBCs, increasing plasma nitric oxide and improving abnormal hemorheology in high cholesterol diet–induced atherosclerotic rats. Therefore the elevated eNOS/NO and improved hemorheology may be beneficial in atherosclerosis.