- Management of collagen vascular diseases (lupus, psoriasis, Raynaud phenomenon) and promotion of symptomatic improvement in rheumatic disease.
- May prevent immunologic injury in pts with IgA nephropathy by retarding loss of renal function. May benefit renal transplant recipients treated with cyclosporine. Significant beneficial effects on diabetic nephropathy and macroangiopathy.
- Beneficial in chronic and severe mental disorders (bipolar disorder, depression, ADHD, dementia).
- Reduces inflammatory symptoms associated with inflammatory bowel diseases.
- Other uses: Dysmenorrhea, kidney stones, diabetic neuropathy, gout, migraine headaches, male infertility, osteoporosis, multiple sclerosis, cancer-related cachexia, modest reduction in cataract risks, may improve risk of depression.

Perioperative Risks

- Risks of long-term use not known. Variable increase in bleeding time with EPA (but not with DHA).

Worry About

- Coagulation disorders; >3 g/d can inhibit blood coagulation and potentially reduce platelet aggregability, thus increasing risk of bleeding.
- Large doses of fish oil have been linked to a theoretical increased incidence of cancer via an increase in free radicals and elevated oxidate stress (e.g., prostate cancer). However, it should be noted that another study has demonstrated that omega-3 fatty acids protect against death from prostate cancer.

Overview/Pharmacology

- Omega-3 fatty acids: EPA and DHA.
- Also known as cod liver oil, marine oil, menhaden oil, N-3 fatty acids, N3-polyunsaturated fatty acids, omega 3, omega-3 fatty acids, polyunsaturated fatty acids, salmon oil, W-3 fatty acids, algal DHA.
- Dietary supplements available in capsules or oil by brand names: Coromega, Solgar Omega 3 700, Nature Made, Spring Valley, Bounty, Barleans, LifeFitness DHA, Nature Made DHA, and others.
- Recent research has focused on omega-3 fatty acids and omega-6 fatty acids and their respective ratios, with 1:1 and 4:1 ratios having more omega-6 fats that appear to be beneficial (greater omega-3 fatty acids levels are associated with inflammation-mediated chronic disease).
- Fish oils and DHA supplements are not regarded as drugs and, except for Lovaza, are not regulated by the FDA.
- Have biologic effects on prostaglandins, thromboxanes, and leukotrienes; they increase levels of TXA_3 and decrease levels of TXA_2, thus stimulating formation of prostaglandin I_3, moderately reducing the formation of TXB_2 in platelet, and inhibiting aggregation and adhesion.
- Use results in reduced platelet aggregation (EPA) and vasoconstriction (DHA).
- Recent studies show a small increase in levels of LDL with large doses.
- Improves large artery endothelium-dependent dilation of hypercholesterolemics (both EPA and DHA) without affecting endothelium-independent dilation.
- Reduces blood viscosity by increasing deformability of RBCs.
- Substantial reduction of triglyceride levels; variable effects on cholesterol levels.

Drug Class/Usual Dose

- Not clear: Usual dosage is 2–9 g/d of fish oil or 20 mg per year of life up to age 45 (900 mg), where dose stays constant (DHA).

Assessment Points

System	Effect	Assessment by Hx	PE	Test
GI	Abdominal distention, belching, halitosis, heartburn, flatulence, diarrhea			
HEME	Prolongs bleeding time, inhibits platelet aggregation (EPA only)	Anticoagulant Rx, fatigue, weakness, bleeding problems	Vital signs	Bleeding time, Hct
ENDO	Mild glucose intolerance in pts with NIDDM	FBS		

Key References: Kris-Etherton PM, Harris WS, Appel LJ; American Heart Association Nutrition Committee: Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease, *Circulation* 106(21):2747–2757, 2002; Yurko-Mauro K, McCarthy D, Rom D, et al.: Beneficial effects of docosahexaenoic acid on cognitive function in age-related cognitive decline, *Alzheimers Dement* 6(6):456–464, 2010.

Perioperative Implications

Preoperative Concerns

- May reduce blood clotting and increase risk of bleeding (not an effect of DHA alone); pts on 3 g of fish oil per d can be switched to 900 mg of DHA a d with perhaps same antiarrhythmic and brain-function-preserving effects; half-life is variable depending on preparation. Ideally a pt having surgery or a pain procedure should be off fish oil for 7 d, allowing enough time for fish oil–induced blood thinning effects to be gone, but patient should also be switched to DHA at same time.

Induction/Maintenance

- No interactions known.

Adjuvants/Possible Drug Interactions

- Caution if pt is receiving heparin, warfarin, dipyridamole, ticlopidine, sulfinpyrazone, or aspirin.
- Can reduce vitamin E levels. Caution with herbals that have antiplatelet and/or anticoagulant constituents (angelica, clove, danshen, garlic, ginger, ginkgo, *Panax* ginseng, red clover, turmeric, willow, and others) with EPA, not DHA.

Anticipated Problems/Concerns

- Assess for possible adverse effects on the coagulation system.
- Rare side effects include abdominal pain with cramps, blurred vision, diarrhea, dizziness, fatigue, headache disorder, nausea.
- Medical-grade fish oil is now available (Lovaza), which reduces indirect risk of mercury polychlorinated biphenyls, dioxin, and dioxin-related compounds, as does DHA from algae (algal DHA).

Garlic *(Allium sativum)*

Amit Prabhakar | Alan David Kaye

Uses

- Administered orally and topically as a powder, oil, tablet, and raw clove. Allicin is the pharmacologically active component.
- Potentially beneficial to the CV system as an antihyperlipidemic (conflicting results in recent clinical trials); also useful as an antimicrobial (*Microsporum canis*, sporotrichosis, tinea pedis), antiplatelet (via increased thromboxane levels), fibrinolytic, antioxidant (increased catalase and glutathione peroxidase), antidiabetic, and vasoprotective agent (i.e., antihypertensive and protective of elastic properties of the aorta).
- Note: These indications are not approved by FDA, but garlic is generally recognized as safe. Interpretation of data must take into account publication bias (preferential publication of positive findings).

Perioperative Risks

- Increased bleeding diathesis via inhibition of platelets mediated by COX inhibition.

Worry About

- Major drug interactions: Anticoagulants, antidiabetic agents, ASA, NSAIDs, plt inhibitors, herbs (danshen, dong quai, feverfew, ginger, ginkgo biloba, ginseng, horse chestnut), thrombolytic agents.
- Garlic has dose-dependent side effects, including breath and body odor, possible stimulation of the uterus, GI irritation and heartburn, nausea, vomiting, diarrhea, allergic reactions, dermatitis, and other skin-related pathogenesis.

Overview/Pharmacology

- Intact cells of garlic bulbs contain alliin, an odorless, sulfur-containing amino acid. Crushed garlic causes the enzyme allinase to convert alliin to allicin—a potent antibacterial agent that is odoriferous and unstable. Ajoene, a self-condensation product of allicin, has antithrombotic activity. Fresh garlic releases allicin in the mouth during the chewing process. Dried garlic preparations lack allicin but contain alliin and allinase; they should be enteric-coated so that they will pass through the stomach into the small intestine, where alliin can be enzymatically converted to allicin. Allicin is unstable in oil. Allinase is inactivated by heat (cooking) and acid.
- Potency can vary substantially among manufacturers.
- Dosage: No clear consensus, but dosage varies with reason for use. Hypercholesterolemia/arteriosclerosis: German Commission E recommends 4 g/d (1.5–2 average-sized garlic cloves) of fresh garlic, or at least 5000 μg of allicin, or chewing one garlic clove daily. Extract standardized to 1.3% allicin is

recommended. For Htn or antibacterial effect, 2.5 g/d or 1 clove or 300 mg of extract.
- Treatment should be evaluated over a 3- to 6-mo period to determine efficacy. To treat *M. canis*, sporotrichosis, and tinea pedis, recommended oral dosage is 2–5 mg of allicin extract; topical treatment calls for applying sliced cloves or garlic extract (ajoene) to lesion 2–3 times daily for 1–2 wk.
- Usual dosage is 300 mg of extract 2–3 times daily standardized to at least 1.3% allicin (equivalent to approx 3 g or 1 fresh clove daily).
- Moderate daily consumption has no effects on normal individuals. Effects are not seen with cooked garlic.

Assessment Points

System	Effect	Assessment by Hx	PE	Test
CV	Reduced BP, reduced LDL cholesterol			BP, lipid profile
RESP		Halitosis, sulfuric odor		
ENDO	Hypoglycemia	Insulin, oral hypoglycemic use		Fasting blood glucose
HEME	Bleeding	Anticoagulant use, coagulopathy, dysfunctional platelets, bleeding disorders	Hematomas; poor surgical hemostasis	Prolonged PT, INR, plts, Hgb/Hct
GU		more than 5 cloves daily		
Low dose	Enhanced peristalsis	Dyspepsia, eructation, pyrosis (heartburn), flatulence		
Large doses	Inhibited peristalsis; possible reduction in stomach cancer	Constipation		
CNS	Spontaneous spinal epidural hematoma	Headache, paralysis	Neurologic examination	CT scan
ALLERGY/IMMUNE	Allergic reaction	Garlic oil contact dermatitis	Facial/tongue swelling	

Key References: Tsai CW, Chen HW, Sheen LY, et al.: Garlic: health benefits and actions, *BioMedicine* 2:17–29, 2012; Gardner CD, Lawson LD, Block E, et al: Effect of raw garlic vs. commercial garlic supplements on plasma lipid concentrations in adults with moderate hypercholesterolemia: a randomized clinical trial, *Arch Intern Med* 167(4):346–353, 2007.

Perioperative Implications

Perioperative Concerns/Possible Drug Interactions
- High consumption may cause significant antiplatelet activity; ASA, NSAIDs, other platelet inhibitors, thrombolytic agents, and certain herbs may cause risk of bleeding, but no clinical data are available.
- Hypoglycemia may be increased in individuals receiving antidiabetic agents.
- Garlic can interfere with oral contraceptives.
- Garlic is not recommended for individuals with thyroid disease.

Monitoring
- Preop PT (INR), blood glucose levels

Airway
- Malodorous breath and skin

Preinduction/Induction
- No special concerns

Maintenance
- Monitor blood glucose levels.

Extubation
- No special risks

Adjuvants
- No special risks

Postoperative Period
- Theoretically increased risk of bleeding and hypoglycemia

Anticipated Problems/Concerns
- Possible increased risk of bleeding and hypoglycemia
- Pts who are avid garlic consumers should not double up doses to make up for missed doses while undergoing surgery.
- If on warfarin postop, pts should be warned against heavy consumption.

Ginger *(Zingiber officinale)*

Mark R. Jones | Alan David Kaye

Uses
- Ginger ranks 18th in recent herbal supplement sales.
- Has long been used in Ayurvedic and Chinese medicine for a wide variety of conditions including arthritis, rheumatism, constipation, indigestion, nausea, vomiting, motion sickness, and diabetes mellitus.
- In vivo human studies show ginger to be effective in management of N/V postop and in association with pregnancy. Clinical research demonstrates potential effectiveness of ginger for dysmenorrhea, vertigo, morning sickness, and osteoarthritis.
- In vivo animal studies show ginger has significant anti-inflammatory, antithrombotic, hypotensive, glucose-lowering, and lipid-lowering effects.
- In vitro studies show ginger has significant antioxidant, antitumorigenic, anti-inflammatory, antiviral, and antimicrobial effects.
- Anecdotal or inconsistent evidence for ginger treatment in chemotherapy-induced nausea and vomiting, migraine headache, myalgia, and rheumatoid arthritis.

Perioperative Risks
- No toxic or unpleasant side effects reported in human studies with therapeutic doses.
- High doses may prolong bleeding time due to inhibition of thromboxane synthetase and stimulation of prostacyclin.
- High doses may lower BP.

Worry About
- Potential additive or synergistic effects with antiplatelet agents, heparin, or warfarin, which may increase bleeding risks.
- Potential hypotensive effect and additive effect with calcium channel blockers.
- Preliminary research demonstrates that ginger increases insulin levels. Therefore it could have an additive effect with any antidiabetes drugs and result in hypoglycemia (particularly important with NPO instructions).

Overview/Pharmacology
- Pungent constituents: Gingerol, shogaol, gingerdiols, vanilloids, sesquiterpene, monoterpene volatile oils, and diarylheptanoids. These constituents have a variety of pharmacologic properties, including antipyretic, antitussive, anti-inflammatory, sedative, antibiotic, and weak antifungal effects.
- Plasma concentration curve is defined by a two-compartment model with a terminal half-life of 7.2 min and total body clearance of 16.8 mL/min per kg.
- 92.4% of ginger is serum-protein–bound with elimination by the liver and gut flora.

Mechanism of Action
- Anti-5-HT_3 mediates antiemetic effects.
- Direct cholinergic agonist of postsynaptic M_3 receptors and an inhibitor of presynaptic muscarinic autoreceptors. May mediate GI prokinetic effects.
- The aqueous extract of red and white ginger rhizomes displays anticholinesterase inhibitory action, thereby increasing levels of Ach in the synaptic junction, which may improve cholinergic neurotransmission.
- Cyclo-oxygenase and lipo-oxygenase inhibition: Mediates anti-inflammatory and antithrombotic effects by decreasing levels of thromboxane B_2, prostaglandin E_2, and leukotrienes.
- Inhibition of cytokine and chemokine induction in vitro: Mediates anti-inflammatory effects.
- Insulin sensitization mediates hypoglycemic and lipid-lowing effects.
- Calcium channel inhibition mediates decrease in BP and negative inotropic and chronotropic effects.
- Vanilloid mediates induction of apoptosis: antitumorigenic effects.
- Antioxidant effects may be hepatoprotective and nephroprotective.

Usual Dosage/Indications
- Dosage: The total daily dose is typically 1–4 g with an onset of antiemetic effect within 25 min and duration up to 4 h.
- Doses as high as 15 g/d well tolerated in human trials.