upon successful completion of this article, the pharmacist should be able to:
1. Evaluate fasting lipid panels and establish goals for therapy based on patient specific information.
2. Identify natural products used for dyslipidemias.
3. Outline role in therapy, adverse effects, and drug interactions for each product.
4. Select/recommend safe and effective natural products for patients with dyslipidemias.
5. Educate patients on appropriate use of natural products for dyslipidemias.

INTRODUCTION
More than 100 million Americans age 20 and older have high cholesterol. The Third Report of the National Cholesterol Education Program (NCEP III) Expert Panel established guidelines for identifying, diagnosing and treating these patients. The lipid goals and medications of choice are outlined in Table 1 (page 40). Prescription options for dyslipidemias are numerous and include: hydroxymethylglutaryl coenzymeA (HMG-CoA) reductase inhibitors or statins, cholesterol absorption inhibitors, bile acid sequestrants, fibrates, extended release niacin (Niaspan), and omega 3 fatty acid (Lovaza).

With all these options, why would consumers seek alternative treatments? First, some patients may need additional agents to assist them in achieving the stricter lipid goals being driven by recent literature. NCEP III is already eight years old, and many significant trials have been published to support lower LDL-C goals in certain patient subsets since that time. Lower LDL-C goals for a larger population are anticipated when NCEP IV is released in the spring of 2010. Although the most potent statin at the highest dose can lower LDL-C by up to 63 percent, patients with higher baseline values and low LDL-C goals may require combination treatment to achieve a higher degree of reduction. Second, efficacy and tolerability of these medications varies. Statins have plentiful data to support their use for primary and secondary prevention of heart disease. Unfortunately, some patients cannot tolerate them at all or require low doses to avoid dose-related adverse effects such as myalgias and hepatic enzyme elevations. Third, patients may not be able to afford some brand name products and may be seeking a cheaper alternative. Lastly, Americans are replacing or supplementing traditional medicine with alternative and complementary approaches more than ever before.

A provocative survey released in December 2008 found that 38 percent of all adults 18 and older used some form of complementary and alternative medicine (CAM) in the past year. The use of CAM specifically for cholesterol is increasing. It is currently the fifth most likely disease to be treated with natural medications in the United States, being surpassed only by orthopedic ailments and anxiety indications. Five years earlier, cholesterol was not even in the top 10. Now, three out of the top 10 CAM products used in this survey are for cholesterol—fish oil (1), flax seed (4), and garlic (9). Garlic is the only product to show reduced popularity; possible reasons for this will be discussed later.

Community pharmacists are in the driver’s seat when it comes to educating the public about over-the-counter products. They can assist patients by navigating them through misleading media and direct-to-consumer advertising. Pharmacists armed with knowledge of the pros and cons of CAM for cholesterol are a useful resource in reducing the epidemic of dyslipidemia effectively and safely. Table 2 (page 41) outlines free Web sites that are useful to pharmacists needing more information.
The Basics

Medications do not substitute for a low fat, low cholesterol, high fiber diet and physical activity, also known as therapeutic lifestyle changes, or TLC. Pharmacists can encourage patients to comply with TLC and offer tips on compliance and identify potential barriers to success, including identification of medications associated with weight gain. Discourage natural products for managing cholesterol in patients who are pregnant, planning to become pregnant, nursing, or under the age of 18 without direct supervision from their physician. Evaluate patients’ motivation to seek alternative treatment. If it is to avoid their provider or traditional medicine approaches, encourage them to maintain open communication with their provider. If they choose to initiate a natural product, emphasize the importance of telling all of their providers that they are taking the product. “Natural” doesn’t necessarily mean “safe.” Inform them that supplements are not required to demonstrate safety or efficacy to the Food and Drug Administration (FDA) prior to being released on the market.

It is also not the job of the FDA to verify that what the label says on the container is actually what is in the product. Good manufacturing practices are supposedly met, but quality of the product is not completely reviewed as it would be for prescription medications. Tell them that the FDA does not specifically define the terms “standardized”, “verified”, or “certified” on a label. Manufacturers may use them without an explicit guarantee of quality or consistent ingredient. The FDA does intervene if a product shows safety issues once it is marketed. Screen patients’ past medical history and current medications for pertinent drug-disease interactions, and interactions with prescription, over the counter, and natural products.

Case 1

Medicay Shun is a 39-year-old slightly overweight female who comes into your pharmacy looking for something to lower her cholesterol. She recently had her fasting lipid panel checked at work and thinks she should do something about it. She hasn’t seen a doctor in a year or two but walks a half mile daily to keep healthy. She shares the results with you and they reveal the following: Her total cholesterol is 226 mg/dL; triglycerides, 167 mg/dL; HDL 49 mg/dL; and LDL 170 mg/dL. She has no family history of heart disease, doesn’t smoke, and reports having a blood pressure at the screening of 110/80 mmHg. She is on no medications and has a history of seasonal allergies to ragweed but is not taking any.
medications right now. Using Table 1, what are her goal lipid values?

NCEP III states that when TG are less than 400 mg/dl, LDL should be the first target for treatment. This patient does not have any cardiovascular risk factors—she does not smoke, has normal blood pressure, is under 55 years old and has no family history. Based on her history, she does not have heart disease or a risk equivalent. Therefore, her LDL-C should be less than 160 mg/dL so she is above her goal. The patient’s TG and HDL are slightly out of goal range also and her TC is elevated by about 10 percent. What advice do you give her?

First, you need some to ask some questions. Determine if she is pregnant, nursing, or planning to become pregnant. This is important because cholesterol management with these scenarios are best handled in conjunction with their primary care provider or lipid specialist. She tells you she is not. At this point, it is prudent to emphasize TLC, which includes a low fat (saturated fat < 7 percent calories), low cholesterol (< 200 mg daily), high soluble fiber (10-25 grams per day) diet and increased physical activity. Typically, three months are needed to see an effect. She is aware that her diet is “a mess,” and you have some information printed off from the American Heart Association and the National Institutes of Health that further detail heart healthy diet plans. You remind her that it might be a good idea to check in with her doctor and a nutritionist if needed. She agrees, and you tell her to get her fasting lipid panel rechecked in three months.

Medicay Shun returns to the pharmacy in three months with a new lipid panel. She admits that she was really com-

<table>
<thead>
<tr>
<th>Table 2: Useful Web Sites (All information on each site is free and readily accessible.)</th>
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<tbody>
<tr>
<td><strong>Web Site</strong></td>
</tr>
<tr>
<td><a href="http://www.nhlbi.nih.gov/guidelines/cholesterol/">http://www.nhlbi.nih.gov/guidelines/cholesterol/</a></td>
</tr>
<tr>
<td><a href="http://www.americanheart.org/presenter.jhtml?identifier=2158">http://www.americanheart.org/presenter.jhtml?identifier=2158</a></td>
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<tr>
<td><a href="http://nccam.nih.gov/">http://nccam.nih.gov/</a></td>
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<tr>
<td><a href="http://www.nlm.nih.gov/medlineplus/druginformation.html">http://www.nlm.nih.gov/medlineplus/druginformation.html</a></td>
</tr>
<tr>
<td><a href="http://www.mayoclinic.com/health/drug-information/DrugHerbIndex">http://www.mayoclinic.com/health/drug-information/DrugHerbIndex</a></td>
</tr>
<tr>
<td><a href="http://www.cfsan.fda.gov/~dms/supplmnt.html">http://www.cfsan.fda.gov/~dms/supplmnt.html</a></td>
</tr>
</tbody>
</table>
pliant with a heart healthy diet and is proud to tell you she increased walking to one mile daily. She does note that her mother just passed away from a heart attack at 60, and that she started smoking again because it helps her eat less and deal with stress. Update lipid panel reveals the following: total cholesterol, 219 mg/dL; triglycerides, 149 mg/dL; HDL 47 mg/dL; and LDL 149 mg/dL. She asks you (now that her LDL is at goal), is there anything else over the counter she can take to improve her lipid panel?

First, you should congratulate her on the progress made with diet and exercise. You will need to clarify to the patient that her LDL is NOT at goal. Her family history and resumption of smoking moves her into the LDL goal category of < 130 mg/dL. Use this as a motivating factor to encourage smoking cessation. She should also be educated that smoking reduces HDL, so all of that extra exercise she is doing, which normally raises HDL, is being lowered by cigarettes. Encourage her to continue walking and the heart healthy diet. What other products can be recommended to her today? As her greatest need right now is to lower LDL-C and TC, we will review natural products typically used for that purpose. Table 3 (page 43) summarizes products for both LDL and TG lowering that are better supported by evidence and may be therapeutic options.

**NATURAL PRODUCTS USED FOR LOWERING TOTAL CHOLESTEROL**

**Artichoke Extract**

Artichoke extract contains chemicals that may block hydroxymethyl glutaryl coenzyme A reductase, similar to statins. Artichoke extract produced an impressive 23 percent reduction in LDL-C in a six-week trial. Although the data is promising, there isn’t enough information available to recommend this to everyone just yet. Also, patients with ragweed allergy should not use artichoke extract since it is derived from the same plant family. Flatulence is the most common side effect reported with use.

**Soluble Fiber**

There are two types of fiber: soluble and insoluble. Soluble fiber is the only type that will lower cholesterol, and according to NCEP, is a dietary staple for all patients with dyslipidemias. Soluble fiber lowers the amount of cholesterol in the liver and also upregulates LDL receptors to facilitate removal.

Ten to 12 grams of soluble (also known as viscous) fiber is associated with a 5–10 percent reduction in LDL-C, and a 3–14 percent reduction in total cholesterol. As many patients will require a larger reduction than what fiber can do alone, it’s best used in combination with other strategies. Fiber may help to achieve cholesterol goals at lower doses of prescription products, which may spare some of the dose-dependent adverse effects of many of these agents.

Fiber supplements are helpful for patients that have difficulty getting in the right amount of dietary fiber daily. Examples of high fiber foods include whole grains, oats, and fruits and vegetables. There are a few product disparities a pharmacist should consider. First, some products list the maximal dose of soluble fiber to be six grams per day, lower than the recommended dose defined by NCEP III. Also, not all fiber supplements contain the cholesterol-lowering type of fiber. Check that the label indicates soluble fiber—possible sources include psyllium, wheat dextrin and methylcellulose. Table 4 (page 45) lists some examples of soluble fiber supplements. Product availability includes powder, capsule and wafer formulations. Different formulations may contain varying amounts of fiber. Wafer formulations typically have a higher fiber content; unfortunately their higher calorie and fat content contributes to increased intake in patients already on a restricted diet. Sugar-free formulations are available for patients with diabetes. Remind patients the dose must be taken with an eight ounce glass of water. Different textures (smooth, coarse) and flavors are also available.

Adverse effects of soluble fiber supplements include gastrointestinal upset, bloating, flatulence, diarrhea, and constipation. Titrating the dose up slowly and taking the dose with plenty of water will help to improve tolerability. Fiber supplements may impair absorption of medications and should be separated from other oral medications by two hours or more.
Pharmacists should inform patients that soluble fiber should be incorporated into the management of dyslipidemia. Patients not getting enough fiber from dietary sources are candidates for supplements. Assist patients in the selection of a fiber supplement that is right for them. Patients may need to take more over time to reach the goal amount or preferably can combine the supplement with dietary sources. Labeling for fiber supplements can be confusing as the amount from the source (ex psyllium husk) is not necessarily equivalent to the amount of soluble fiber in the product. Pharmacists can help to clarify that dosing should be based on the amount of soluble fiber in the product. Pharmacists can help to clarify that dosing should be based on the amount of soluble fiber (such as the “active” ingredient) so patients get the appropriate dose. Some formulas can add an additional 10 grams of fat and 240 calories to the diet and should not be first choice. Fiber total daily doses are typically split into three doses per day to avoid bloating if too much is taken at once. Tell patients to start low and titrate up for better tolerability. Pharmacists may need to assist patients in designing a regimen that avoids concomitant administration of fiber with other medications. Emphasize that they must take the dose with water for most formulations.

Flaxseed

Flaxseed was the fourth most common natural product used among adults and children in 2007. It contains alpha linoleic acid, fiber mucilage and lignans. Flaxseed oil does not contain the latter two substances. Alpha linolenic acid is a precursor to omega-3 fatty acids found in fish oil. Data is not as strong for flaxseed as it is for omega-3 fatty acids, and therefore flaxseed should not be considered a substitute for fish oil. The mechanism is not known but it may be similar to fiber. TC and LDL-C are modestly reduced by 5–8 percent, respectively. One 10-week study noted that the reduction in LDL-C was not long lasting, and more information is needed before a conclusion can be made. The largest male representation in a trial using 40 grams of ground flaxseed suggested that HDL is lowered along with LDL; HDL in women on flaxseed was not affected. More data is welcome to determine the effects on HDL.

There is not much information reviewing the safety of flaxseed in adults despite the widespread use. Overall, flaxseed appears to be well tolerated. It is best to take flaxseed with water. Patients with gastrointestinal disorders that might be exacerbated by the laxative effects of flaxseed should avoid its use (such as those with irritable bowel or diverticulitis). Very high doses have been associated with bowel obstruction but high doses (>0.3 mg/kg) should be avoided anyway due to concern with cadmium accumulation with certain sources. Some products are advertised to be cadmium-free. The lignans in flaxseed may have some estrogen-like effects (not oil)—avoid use in patients with breast, uterine, and ovarian cancer, uterine fibroids, and endometriosis until additional information is available. A few studies noted an association between men that take alpha linolenic acid supplements and prostate cancer. Although PSA levels do not appear to increase, avoid in men with or at risk for prostate cancer for now. Glucose control may be impaired; patients should have glucose monitored more frequently when starting on flaxseed. Severe allergic reactions have been reported.

Similar to fiber, flaxseed administration should be separated from other medications to avoid reduced absorption. Flaxseed specifically reduces absorption of psyllium, and vitamins and should be separated by an hour before or two hours after taking the dose. Tamoxifen levels may be increased when used concomitantly. Advise patients on tamoxifen to avoid flaxseed for cholesterol lowering as the association is not clear and the cholesterol lowering

<table>
<thead>
<tr>
<th>Product</th>
<th>Dose</th>
<th>Expected lipid reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soluble fiber</td>
<td>10–12 grams daily</td>
<td>LDL decrease 5–10%</td>
</tr>
<tr>
<td>Plant stanol/sterol esters</td>
<td>2 grams daily</td>
<td>LDL decrease 9–20%</td>
</tr>
<tr>
<td>Omega 3 fatty acids</td>
<td>2–5 grams of EPA/DHA</td>
<td>TG decrease up to 50%</td>
</tr>
</tbody>
</table>

Table 3: Lipid Parameter Reductions Associated With Recommended Natural Products for Dyslipidemia
benefit is small. Effects on oral contraceptives are not known. Flaxseed may increase the risk of bleeding in patients on anticoagulants or antiplatelets. Avoid adding flaxseed to a regimen that already contains antidepressant herbs such as St. John’s Wort.

Dosing is not well defined, but doses up to 50 grams daily have been evaluated. Approximately one tablespoon of unground flaxseed can be mixed in six to 12 ounces of liquid and taken orally up to three times a day. Flaxseed oil comes in a variety of forms and has been taken in doses ranging from 10–250 grams.

Based on what you have learned so far about artichoke extract, soluble fiber, and flaxseed, what would you recommend for the case patient? Soluble fiber is the best studied and endorsed by national guidelines—it is the best choice so far. The patient’s diet could be screened to determine if higher fiber can be included. Consultation with the patient to determine the best soluble fiber supplement is warranted; avoid supplements with higher fat and calories. As she is not on any other medications, there is no need to worry about interactions, but she should be warned to separate future medications from the fiber. Artichoke extract does not have enough data to date to recommend and she also reports a ragweed allergy which may predispose her to an allergic reaction. Flaxseed is an option but because of similar adverse effects (GI) and absorption interference between the two it will not be recommended just yet.

Garlic

As mentioned previously, garlic is losing popularity but is still in the top 10 of all CAM products used in the United States. Garlic contains an amino acid known as alliin that converts to allicin when crushed. This compound further breaks into additional chemicals that block various enzymes involved in cholesterol synthesis, including HMG Co-A reductase.

Earlier studies of small duration suggested that garlic supplements reduced LDL, TC, and also TG. Most of this research used a garlic powder that contained a specific amount of alliin (1.3 percent). Recently, a large National Institutes of Health-sponsored study noted that when several studies were pooled together, garlic only contributed to a modest drop in TC of 4–6 percent. Some have suggested that the reductions are temporary (<six months). Limited data suggest that dehydrated garlic preparations improve cholesterol reductions at one to three months better than other formulas.

Garlic has several adverse effects and drug interactions of clinical relevance. Minor adverse effects include stomach upset, heartburn, and breath odor. Garlic has antiplatelet effects, so patients on other antiplatelet and/or anticoagulant medications should be warned about a potential for increased bleeding. Increased monitoring is suggested. Garlic is also a known inducer of cytochrome P450 3A4. Therefore, medications that use the 3A4 pathway may have lower levels in patients taking garlic, making them less effective. Review each garlic product for the amount of allicin—this is the main ingredient thought to promote drug interactions. The more allicin in a garlic preparation, the more likely an interaction will occur. Some potential interactions occur include oral contraceptives, cyclosporine, and simvastatin, lovastatin and atorvastatin.

Inform patients about the change in thinking about garlic supplements. Labeling can be particularly misleading. Caution patients about the potential drug interactions with a large amount of medications and the increased risk of bleeding when used with other antiplatelets and anticoagulants. Advise them to consider agents with more proven lipid lowering properties.

If we return to our case patient, would we want to consider garlic for her? No. Better designed trials suggest that garlic has minimal effect on cholesterol. Advise her against purchasing garlic supplements.

Plant Stanols/Plant Sterols

Two types of phytosterols are plant sterols and plant stanols. Plant sterols and stanols closely resemble the structure of cholesterol, differing only by their side chains. Plant sterols are normal ingredients of the diet that are present in small amounts in plant sources such as fruits, vegetables, nuts, seeds, legumes, and vegetable oils. The three most common varieties
of plant sterols are sitosterol, campesterol, and stigmasterol, though more than 40 types exist. Plant stanols are simply hydrogenated or saturated versions of plant sterols and are found in similar dietary sources. Theoretically, removal of a double bond from the sterol to create a stanol improves the LDL lowering capacity, but this has never been proven in a direct comparative trial.

Plant stanols/sterols are thought to reduce the amount of cholesterol going into the cell and more recently, increase the amount of cholesterol coming out of the cell. Sterols compete with dietary and biliary cholesterol for absorption in micelles. Although the product should be taken during meals for incorporation into micelles, it appears the type of meal (high fat, low fat) does not influence effectiveness. Once in the small intestine, cholesterol reductase hydrolyzes the structure and the free form is available to work. When compared to cholesterol, sterols and stanols are absorbed much less.

Manipulation of the physical characteristics of plant stanols and sterols helps to improve the dissolution of the product in the small intestine. Esterification of plant stanol/sterols improves lipid solubility into foods, and may also improve the availability of free plant stanol/sterols in the small intestine. The majority of products available today are in the esterified form.

Two grams of plant sterol ester is associated with an LDL-C reduction of 9–20 percent. The FDA allows product labeling for free phytosterols, plant stanol, and sterol esters that provide 800 mg, 3.4 grams, and 1.3 grams respectively to claim that use is associated with a reduced risk of coronary heart disease.

Minimal adverse effects are reported with plant stanol/sterols. Some have observed lower levels of plasma alpha and beta carotene, alpha tocopherol, and

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**Table 4: Sample Soluble Fiber Preparations**

<table>
<thead>
<tr>
<th>Product</th>
<th>Comments</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benefiber/wheat dextrin</strong></td>
<td>Powder: sugar free, grit free Dissolves in food and liquid</td>
<td>2 tsp in 4–8 oz of beverage or soft food (not carbonated drink) up to three times a day</td>
</tr>
<tr>
<td>Powder (2 tsp = 3 grams soluble fiber)</td>
<td>Expires 6 months once opened</td>
<td></td>
</tr>
<tr>
<td>15 cal per dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Benefiber chews and caps</strong></td>
<td>Sugar free</td>
<td>3 chews up to three times a day</td>
</tr>
<tr>
<td>Chews/caps (3 chews/caps = 3 grams soluble fiber)</td>
<td>Caps expire in 6 months</td>
<td></td>
</tr>
<tr>
<td>30 cal per dose–chews</td>
<td>Assorted flavors</td>
<td></td>
</tr>
<tr>
<td>15 cal per dose–caps</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Citrucel with Smart Fiber</strong></td>
<td>Does not ferment; may cause less gas and bloating</td>
<td></td>
</tr>
<tr>
<td>1 scoop powder = 2 grams SF</td>
<td>Do not mix with carbonated beverages, milk or hot liquids</td>
<td></td>
</tr>
<tr>
<td>4 caps = 2 grams soluble fiber</td>
<td>Hot liquids may cause the active ingredient to be reduced</td>
<td></td>
</tr>
<tr>
<td>4 chews = 2g (also 600 mg cal)</td>
<td>Swallow one cap at a time</td>
<td></td>
</tr>
<tr>
<td>Regular powder = 70 cal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SugarFree = 37 calories</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caps = 5 calories</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chews = 65 calories, 2 grams fat</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Metamucil powder</strong></td>
<td>Expiration date stamped on bottle</td>
<td>Some may be allergic if inhaled</td>
</tr>
<tr>
<td>1 Tablespoon flavored mixed with water = 2 grams soluble fiber</td>
<td>Start with one dose per day and titrate up</td>
<td></td>
</tr>
<tr>
<td>40–45 calories per dose</td>
<td>Dose differences between flavored and non flavored</td>
<td></td>
</tr>
<tr>
<td>1 rounded teaspoon unflavored /sugar free flavored</td>
<td>Not 100% soluble fiber-add more water if becomes thick</td>
<td></td>
</tr>
<tr>
<td>= 2 grams soluble fiber</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 calories per dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Metamucil wafers</strong></td>
<td>Note higher calories and fat</td>
<td></td>
</tr>
<tr>
<td>2 wafers = 3g sol fiber in 8 oz hot or cold beverage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>120 calories, 5 grams fat, 1 g saturated fat</td>
<td></td>
<td></td>
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lycopene when these products are used. Although the reductions do not appear to be significant, it may be helpful to ensure that patients are also getting plenty of fruits and vegetables (and possibly a multivitamin) to ensure that normal vitamin levels are maintained.

Advise patients on ezetimibe to avoid these products at this time. Theoretically, both products work at similar sites in the gut and may compete. There is also some information that suggests the addition of sterols to ezetimibe therapy does not provide additional lipid lowering.

Pharmacists can educate patients about lowering LDL using plant stanol/sterols. Their use is endorsed by the American Heart Association, NCEP III, and the FDA allows claims for reduced risk of heart disease. Dosing depends on the product formulation and is outlined in Table 5 (page 47). More evidence on the efficacy of LDL lowering used the esterified versions and is preferred. Two grams of plant stanol/sterol esters daily is recommended. Food sources may contribute to additional fat and calories and should be accounted for as part of total daily intake. Vitamins containing these products require twice daily administration. This should be clarified to patients since most take vitamins only once a day.

**Policosanol**

Policosanol is a combination of several carbon alcohols. No one knows for sure how it works, but there may be some inhibition of HMG CoA reductase. Limited but promising data suggested that 10 mg policosanol is comparable to 10 mg simvastatin or 20 mg fluvastatin for LDL and TC reduction. Direct comparisons with phys-tosterols suggest that policosanol may work better (24 percent reduction versus 11 percent). Most of the positive findings originated in Cuban trials that used a particular type of sugar cane. Cuban derivative policosanol is not available in the United States.

Similar to garlic and flaxseed, increased bleeding may occur in patients on antiplatelets and anticoagulants. Most common adverse effects include increased urination, insomnia, and weight loss. There is limited information on drug interactions.

The usual starting dose is 510 mg daily up to 40 mg daily. Although promising, additional data need to accumulate to demonstrate similar effectiveness with products available in the United States. Tell patients to hold off for now.

**Red Yeast Rice**

Red yeast rice is yeast that is grown on rice. Products contain compounds known as monacolins of which there are several types. One of these chemicals is actually lovastatin, a prescription statin. LDL reductions of 20–26 percent have been reported.

The fermentation process is important for the integrity of the product. The process can be manipulated to produce more lovastatin. According to the FDA, if the fermentation is done incorrectly, a substance called citrinin can be formed, which causes kidney problems. Taken with statins, you might see increased risk of myopathy and hepatic enzyme elevation.

Although not well defined, other interactions of statins may be similar to red yeast rice and include fibrates, niacin, and perhaps other medications that inhibit cytochrome p450 system. Red yeast rice may also increase bleeding risk in patients on antiplatelets and anticoagulants.

Red yeast may cause mild headache and abdominal discomfort. Side effects may be similar to statins. Patients with a history of liver disease or unexplained elevations in their liver enzymes should not use red yeast rice. Cholesterol management and liver disease is best reserved for a specialist.

Counsel patients that safer prescription alternatives are available. Steer patients away from red yeast rice. Numerous drug interactions, lack of monitoring, and questionable product safety make this one of the most dangerous choices available for patients with high cholesterol.

**Soy Protein**

Inconsistent information exists on the benefits of soy protein for lipids. Consuming between 25–135 grams of soy protein daily used in place of regular protein may reduce LDL-C by about 10 percent, presumably through upregulation of LDL receptors. The FDA believed enough in the findings to allow soy products to list on the label that 25 grams of soy protein daily lowers heart disease risk.

Soy can be incorporated into the diet from
various food sources such as soy milk and tofu. Minor stomach upset can occur, and allergy has been reported. It is unknown whether soy can affect outcomes in women with hormone sensitive cancers. Patients with these diseases should consult with their doctor first. Soy is a healthy source of dietary protein for patients with high cholesterol. Advise patients that isoflavone supplements are ineffective for lowering cholesterol.

The case patient returns, this time with her sister Choles Terol who has a question for you. Her sister is 45 years old and sees a physician regularly, but wanted to know about some options for managing her high triglycerides. She typically runs in the 300s. She had a good response to fenofibrate but couldn’t pay for it, and gemfibrozil gave her such terrible constipation that she doesn’t want to go back on it. Is there anything you can suggest over the counter that might be beneficial?

First, we do not know enough about this patient to make an informed decision. We would need to make sure that she is not pregnant, planning to become pregnant, or nursing. We would want to find out about other medications and disease states. It would be helpful to ask about other lipid panel findings to see if an LDL goal evaluation is needed. She tells you she is not pregnant, nursing, has no past medical history and reports an LDL of 80, HDL of 50, and a TC of 150 mg/dl. She has a questionable allergy to shrimp—she breaks out in a rash when she eats shrimp scampi at a local restaurant (she eats it anyway because it tastes so good). Therefore, she appears to be a candidate to treat the TG first.

Niacin

Niacin is the best product available, prescription and nonprescription, for elevating HDL. It raises HDL from 15–35 percent. The mechanism of action is not fully understood but an enzyme called lipoprotein lipase that removes triglycerides from plasma may be increased.

Formulations influence adverse effects. For example, although immediate release is cheap and may increase HDL more than other products, multiple doses and adverse effects such as flushing limit use. Sustained release products available over the counter may increase the risk of liver damage and should be avoided. Extended release niacin available only by prescription is preferred but can be expensive. Products advertised as No flush niacin (inositol hexanicinate) may not work as well some

| Table 5: Plant Stanol/Sterol Esters and Free Phytosterol Products |
|------------------|------------------|------------------|
| **Product**      | **Amount**       | **Comment**      |
| Cholestoff       | 900 mg/2 caplets | Recommended to take 15–30 minutes before a meal; may still work if taken with meals |
| Promise Activ Super Shots (yogurt) | 2 grams of plant sterols per serving | Works best after meals |
| Promise Activ    | 1 gram sterols per tablespoon | Margarine type spread  
|                  |                   | Choose light version for lower fat content  
|                  |                   | Additional fat must be accounted for in daily intake |
| Benecol Smart Chews or spread (1T) | 2 grams plant stanols/4T or 2 chews | Margarine type spread  
|                  |                   | Fat content  
|                  |                   | Chews only available online |
| Minute Maid Heart Wise orange juice | 1 gram sterols/8 oz | Account for additional carbohydrate intake in diabetes  
|                  |                   | May worsen heartburn |
| One a day cholesterol plus | 100 mg free phytosterols per tab | Free formulation not studied as much as other products |
| Centrum cardio   | 800 sterol/2 tabs | Twice a day vitamin |
| Bayer with heart advantage | 400 sterols + 81 mg asa | As a dose per day 162 mg  
|                  |                   | Dosing on label for analgesic use of asa (max 4/24 hrs) |
preparations were found to contain no free nicotinic acid. There is no evidence that it is better tolerated and therefore should be avoided.

Adverse effects include flushing and stomach upset. Doses over two grams daily may be associated with increased glucose, liver toxicity, and elevated uric acid levels. The American Diabetes Association recommends restricting the dose of niacin to less than or equal to two grams daily. More frequent glucose monitoring may be warranted. Use should be avoided in patients with gout, liver, and peptic ulcer disease. Increased myopathy may result when used in combination with a statin.

Counseling patients on proper use of omega-3 fatty acids is very important. Many patients (even pharmacists) may be confused with how to take omega-3 supplements.

The different types of niacin available can be confusing to a consumer. There are three formulations—immediate release (crystalline), long-acting (also called sustained release, controlled release or timed release), and extended release. The first two products are available OTC. Avoid sustained release niacin (Slo-Niacin). Despite marketed effects of less flushing, its slowed metabolism is associated with increased hepatic effects. No flush niacin, inositol hexaniacinate, should also be avoided because of questionable efficacy and product content. There is also no evidence that it is better tolerated, and therefore should be avoided. Niacinamide does not affect cholesterol and should not be recommended. Educate patients to report muscle pain and weakness to their provider.

Pharmacists can also clarify proper use to patients. Immediate-release niacin starts low and titrates up (50–100 mg po three times a day with meals as initial). Proper administration is a must. Advise patients that to reduce flushing, 325 mg of aspirin may be used a half hour before or one hour before if using enteric coated formulation. Alcohol, hot beverages, hot environments, and spicy foods are best avoided immediately after taking the dose. Continued use is associated with tolerance to flushing effects. Patients with a history of noncompliance should not take niacin due to increased flushing with inconsistent use.

Omega-3 fatty acids
Omega-3 fatty acids are the number one reported natural product used among adults and the second most commonly used natural product in children. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are common sources in supplements. Combined doses of 2–4 grams daily of EPA and DHA may reduce TG by up to 50 percent, with an average of 30 percent. Although certain types of fatty fish also contain EPA/DHA, the amount of fish required for consumption and the risk of mercury exposure precludes dietary sources as a main treatment. Lower doses of 0.5–1.8 grams (as EPA and DHA) have been associated with a reduction in death from all causes and heart disease. The way omega 3 fatty acids work are not completely known, but EPA and DHA may reduce TG synthesis in the liver. EPA and DHA may serve as alternative substrates for enzymes needed to make TG. Fish oil supplements may be used alone or in combination with fibrates or niacin to lower triglycerides. These products are not associated with liver toxicity and represent a viable first line choice in patients that cannot take niacin or fibrates. However, fish oil is not associated with increased HDL like niacin and fibrates. Patients on higher fish oil doses may also experience average increase in LDL-c of 5–10 percent, though elevations up to 75 percent have been reported.

Although certain types of fish contain some EPA/DHA, the amount of fish consumed to reach this dose would be excessive. Unlike nicotinic acid and fibric acid derivatives, omega 3 fatty acids do not appear to raise “good” cholesterol, high density lipoprotein (HDL). Similar to fibrates, patients with higher baseline TG levels may be predisposed to an average increase in LDL-C of 5–10 percent, but elevations of up to 75 percent have been reported. The clinical significance of this is unknown, but may be associated with the development of larger LDL-C particles that are possibly not as atherogenic as the smaller dense LDL particles.

Dosing omega 3 fatty acids can be confusing to patients. Pharmacists should
educate patients that the dose on the front label is not how the product should be dosed. Educate patients to turn the bottle over and look at the EPA/DHA content to determine the correct regimen. For example, most capsules contain 120 mg and 180 mg of EPA/DHA, but the label may indicate 1,000 mg. According to the American Heart Association, a patient would require a minimum of seven caps a day of this formulation to lower triglycerides. Many patients may have difficulty complying with a large pill burden. If so, advise them to speak with their doctor about a prescription omega 3 product, Lovaza, which contains 840 mg of EPA/DHA in a one gram capsule; four grams once or twice daily is recommended.

Common adverse effects associated with fish oil include stomach upset, diarrhea, and reflux. Some patients may complain of a fishy taste, especially with higher doses. Some patients find it beneficial to use enteric coated formulations or to freeze the capsules to reduce fishy taste/odor. Stability of fish oil supplements when frozen is not fully studied. Use with caution in patients with fish allergy, as the source of fish varies between products and is not always on the label. These products do not appear to affect hemoglobin A1c in patients with diabetes, but nutritional information should be consulted to determine the formulation with lower carbohydrate and fat content. Molecular distillation of impurities removes most of the mercury content of the fish. Unfortunately, of the 200 types of fish oil preparation available over the counter, less than 10 are USP verified.

Fish oil supplements do not appear to interact with other prescriptions used for cholesterol lowering. Higher doses may be associated with impaired platelet aggregation. Patients on more than three grams daily should consult their provider before taking fish oil in conjunction with antiplatelets and warfarin.

Counseling patients on proper use of omega 3 fatty acids is very important. Many patients (even pharmacists) may be confused with how to take omega-3 supplements. Labeling on the products can be misleading as the dose on the front of the bottle does not reflect the total amount of EPA/DHA in each capsule which may predispose a patient to take less than the recommended amount. Calculate proper doses for patients using the EPA/DHA content on the back of the bottle. Avoid cod liver oil because of Vitamin A overload. Choose products that have higher EPA/DHA content with USP verification. Educate patients that the doses needed to lower TG are not typically provided on the bottle. Evaluate products for vitamin E content. Higher doses of fish oil may increase daily intake of vitamin E and may require adjustment of vitamin supplementation.

“Pill burden” may also be a barrier to compliance. For example, a patient taking the minimum recommended TG lowering dose of EPA/DHA would be required to take 2–3 capsules three times a day. Starting low and titrating up (for example, 1–2 caps twice daily for a few days) to the goal dose and taking the supplement with food may counteract GI effects.

After reviewing niacin and omega 3 fatty acids, what do you recommend to Ms. Tirol to lower TG? First, she may be counseled to limit alcohol intake and implement TLC as her sister did. Her HDL is close to goal of > 50, so omega 3 fatty acids will be a good choice. If her HDL was lower, niacin would be considered for its HDL raising qualities. An allergy to shrimp does not necessarily preclude the use of fish oil supplements, but verify the source of omega-3 on each supplement to be sure. Typical fish sources include salmon, mackerel, anchovy, and sardines. The product selected contains 120 mg EPA and 180 mg DHA, so she would be advised to take one capsule three times a day for three days, then increasing to 2–3 capsules three times a day. Doses should be taken with food to improve tolerability. If the enteric formula is not available, she may consider freezing the capsules to limit fishy taste. If she agrees to comply with the regimen, advise her to have her fasting lipid panel checked in eight weeks for follow up.

CONCLUSION
Patients are using alternative treatments for dyslipidemia more than ever. Pharmacists armed with appropriate knowledge on these natural products can educate patients to make informed decisions about their care. Pharmacists should be familiar with efficacy, safety,
drug interactions, monitoring and dosing strategies for commonly used complementary therapies.

Natural product types supported by national guidelines include soluble fiber, plant stanols/sterols, immediate release niacin products and omega 3 fatty acids. Policosanol, soy protein, flaxseed, and artichoke extract may have a role with additional study. Pharmacists should avoid recommending red yeast rice, garlic, inositol hexaniacinate, sustained release niacin, and niacinamide.

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Editor’s Note: To obtain the complete list of references used in the article, contact Chris Linville at NCPA (703-838-2680), or at chris.linville@ncpanet.org.

CONTINUING EDUCATION QUIZ

Select the correct answer.

1. Identify which lipid goal is appropriate:
   a. TG should be less than 250 mg/dL
   b. HDL should be < 40 mg/dL in men
   c. TC should be less than 200 mg/dL
   d. LDL should be less than 200 mg/dL in patients with two cardiovascular risk factors

2. The LDL goal for patients with diabetes is:
   a. < 100 mg/dL
   b. < 130 mg/dL
   c. < 160 mg/dL
   d. < 200 mg/dL

3. Preferred medications for lowering LDL include:
   a. Bile acid sequestrants
   b. Fibrates
   c. Statins
   d. Niacin products

4. Patients seek alternative treatments for high cholesterol because:
   a. Combination therapy may be needed to achieve goal
   b. Tolerability of traditional treatments vary
   c. They may be looking for less expensive options.
   d. All of the above

5. The number one natural product reported in the United States is:
   a. Garlic
   b. Flaxseed oil
   c. Omega 3 fatty acids
   d. Red yeast rice
6. What statement below is true about natural products?
   a. They have been tested in pregnant and nursing mothers.
   b. The food and drug administration requires efficacy data to be submitted before they are marketed.
   c. Products labeled “standardized” indicates that the labeling and product composition is accurate.
   d. All of the above statements are false.

7. Patients using soluble fiber supplements should be:
   a. Screened for ragweed allergy
   b. Educated to take the dose with carbonated beverages
   c. Titrated up slowly to avoid bloating
   d. Reassured that it is okay to take them at the same time as other medications

8. Which of the following is true regarding flaxseed products?
   a. Flaxseed and flaxseed oil contain different ingredients.
   b. Should be avoided in patients with gastrointestinal disorders such as diverticulitis and irritable bowel disease
   c. Flaxseed should be avoided in patients with or at risk for hormone sensitive cancers
   d. All of the above

9. Garlic supplements:
   a. Are the best choice for naturally lowering cholesterol
   b. May interact with medications that are substrates for cytochrome p450 3A4 enzyme
   c. Should be kept in the freezer
   d. May inhibit the anticoagulant effects of warfarin

10. Plant stanols/sterols:
    a. Are thought to lower the amount of cholesterol going into the cell
    b. May be esterified to improve lipid solubility
    c. May lower LDL 9–20 percent
    d. All of the above

11. Red yeast rice:
    a. May contain lovastatin in varying amounts
    b. Causes increased urination
    c. Is a combination of several carbon alcohols
    d. Is a staple of a low cholesterol diet

12. Which of the following is true regarding soy protein?
    a. It is best at increasing HDL.
    b. Soy isoflavone supplements are preferred for lowering LDL.
    c. It is unknown whether soy affects outcomes in women with hormone sensitive cancers.
    d. It is associated with flushing.

13. Which of the following statements is true regarding adverse effects of niacin?
    a. Immediate release niacin causes flushing the most.
    b. Sustained release niacin is associated with more hepatotoxicity.
    c. It may increase uric acid levels.
    d. All of the above

14. Appropriate patient education tips on niacin include:
    a. Take with food.
    b. Avoid alcohol immediately after taking the dose.
    c. Avoid hot beverages and spicy foods
    d. All of the above are appropriate.

15. Which of the following is true regarding fish oil supplement dosing and administration?
    a. Supplements should be taken on an empty stomach.
    b. Dosing is based on EPA and DHA content.
    c. One capsule a day is appropriate for lowering triglycerides.
    d. Each capsule should be administered with a full glass of water.

16. Common adverse effects of fish oil include:
    a. Stomach upset
    b. Constipation
    c. Heart attack
    d. Hyperuricemia
17. Which natural product may be associated with excessive vitamin exposure?
   a. Plant stanols
   b. Cod liver oil
   c. Artichoke extract
   d. Soy protein

18. Which of the following products are associated with increased risk of bleeding if taken in conjunction with antiplatelets and anticoagulants?
   a. Fish oil supplements
   b. Garlic
   c. Flaxseed
   d. All of the above

19. Natural product for cholesterol that should be avoided in liver disease:
   a. Plant stanol/stereols
   b. Soluble fiber
   c. Flaxseed
   d. Niacin

20. Natural products that should be avoided include:
   a. Red yeast rice
   b. Garlic
   c. Inositol hexaniacinate
   d. All of the above should be avoided.