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Ingredients, Formulations, and Applications
Pathak Yashwant, Steven J. Schapiro

Nutraceuticals for the Cardiovascular System

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CHAPTER 11

Nutraceuticals for the Cardiovascular System

Hieu T. Tran and Kimberly K. Daugherty

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The number one cause of death in the United States is cardiovascular disease. One of every 2.8 deaths in the United States in 2005 was attributable to cardiovascular disease or a cardiovascular event [Lloyd-Jones et al. 2008]. Patients are turning more and more to herbal medications to treat their cardiovascular diseases. The market for herbal medications in the United States was around $590.9 million in 2001 [Izzo et al. 2005]. Various studies report 3–93% usage of herbal medications [Vora and Mansoor 2005]. A 1990 survey showed that 34% of U.S. adults used at least one alternative therapy, and, by 1997, the CAM therapy usage had increased by 25%. Less than 30% of patients tell their physicians, however, that they are taking alternative medications [Miller, Liebowitz, and Newby 2004]. These statistics just underline the importance of understanding what alternative medications are available to treat cardiovascular diseases, what are the data regarding these treatments, what cardiovascular adverse effects are associated with these treatments, and what, if any, drug interactions that patients and healthcare professionals should be aware of.
GARLIC

*Allium sativum* (garlic) has been studied for a variety of cardiovascular benefits and is the most widely used supplement in the world [DeBusk 2000; Knox and Gaster 2007].

**Content and Effects**

Garlic has been shown in numerous studies to lower lipids and blood pressure, reduce atherosclerosis, decrease coagulation and platelet aggregation, and increase fibrinolysis of blood clots [DeBusk 2000; Hermann 2002].

Garlic is made up of two different active ingredients: allicin and alliin [Hermann 2002]. Garlic bulbs contain an odorless, sulfur-containing amino acid known as alliin. After garlic is crushed, alliin is converted by alliinase to allicin, which is highly odoriferous. Allicin seems to be the component that causes the cardiovascular benefits seen with garlic [Frishman, Grattan, and Mamtni 2005]. Garlic is thought to lower blood pressure by opening calcium ion channels in the vascular smooth muscle, resulting in vasodilatation [Khosh and Khosh 2001]. The hyperlipidemic properties of garlic are thought to be attributable to garlic’s HMG-CoA reductase activity, increased catabolism of fatty acids such as triglycerides, and retardation of the absorption of cholesterol from the intestine [Caron and White 2001; Mamtni and Mamtni 2005].

**Usage**

There have been a variety of garlic doses and products studied. The recommended dose seems to depend on the indication the drug is being used for and the product being used (see Table 11.1). The following doses and product(s) are the most commonly effective in clinical trials [Bordia 1981; Lau, Lam, and Wang-Cheng 1987; Vorberg and Schneider 1990; Jain et al. 1993; Adler and Holub 1997; Morcos 1997; Kannar et al. 2001; Durak et al. 2004; Jeyaraj et al. 2005]:

1. Hyperlipidemia: garlic powder (Kwai®), 900 mg/day (1.3% alliin = 0.6% allicin release)
2. Hypertension: garlic powder (Kwai®), 900 mg/day

**Adverse Drug Effects**

Garlic’s number one side effect is its odor and taste, which makes it hard to do blind, controlled studies. Other side effects include flatulence, halitosis, and GUI upset. It has also been shown to cause more serious adverse effects, such as anaphylaxis, spontaneous bleeding, asthma, myocardial infarction, and small intestinal obstructions [Bordia 1981; Lau, Lam, and Wang-Cheng 1987; Vorberg and Schneider 1990; Jain et al. 1993; Adler and Holub 1997; Morcos 1997; Caron and White 2001; Kannar et al. 2001; Durak et al. 2004; Frishman, Grattan, and Mamtni 2005; Jeyaraj et al. 2005].
Table 11.1 Garlic Studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th>Key Findings</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kannar et al. 2001</td>
<td>Double-blind, randomized, placebo-controlled</td>
<td>Garlic: significant reduction in total cholesterol</td>
<td>Diet counseling</td>
</tr>
<tr>
<td></td>
<td>46 patients</td>
<td>(−4.2%) and LDL (−6.6%)</td>
<td>Small sample</td>
</tr>
<tr>
<td></td>
<td>12 weeks</td>
<td>Placebo: nonsignificant increase in total cholesterol</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Enteric coated Australian garlic powder tablets</td>
<td>(−2.0%) and LDL (−3.7%); HDL was significantly</td>
<td>Short time period</td>
</tr>
<tr>
<td></td>
<td>(2.4 mg alliin-releasing per tablet); 22 patients,</td>
<td>increased in placebo (−0.9%) compared with garlic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 tablets twice daily</td>
<td>group (decrease of 0.9%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo: 24 patients</td>
<td>No significant change in triglycerides in either</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>group</td>
<td></td>
</tr>
<tr>
<td>Jeyaraj et al. 2005</td>
<td>Randomized, placebo controlled, unblinded</td>
<td>Significant reductions were seen in all parameters</td>
<td>Diet counseling</td>
</tr>
<tr>
<td></td>
<td>32 patients (16 each group)</td>
<td>except for HDL, which was nonsignificantly increased</td>
<td>Small sample size</td>
</tr>
<tr>
<td></td>
<td>30−60 years old</td>
<td>with placebo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>60 days</td>
<td>Total cholesterol: combination, −20% compared</td>
<td>Short time period</td>
</tr>
<tr>
<td></td>
<td>600 mg of fish oil + 500 mg of garlic pearls (garlic</td>
<td>with placebo, +1.8%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>oil per day</td>
<td>LDL: combination, −21% compared with placebo, +3.4%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>Triglyceride: combination, −37% compared with</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>placebo, −0.9%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HDL: combination, +5.1% compared with placebo,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>−1.6%</td>
<td></td>
</tr>
<tr>
<td>Bordia 1981</td>
<td>Group A: 20 healthy volunteers garlic for 6 months</td>
<td>Group A: serum cholesterol decreased 17%;</td>
<td>No diet</td>
</tr>
<tr>
<td></td>
<td>and then 2 months without garlic</td>
<td>triglycerides decreased 20%, HDL increased by 41%;</td>
<td>mentioned</td>
</tr>
<tr>
<td></td>
<td>Group B (62 patients): divided randomly and blinded</td>
<td>changes were statistically significant.</td>
<td>Small sample size</td>
</tr>
<tr>
<td></td>
<td>into two groups for 10 months; one group received</td>
<td>Group B: total cholesterol significantly decreased</td>
<td></td>
</tr>
<tr>
<td></td>
<td>garlic and other placebo</td>
<td>by 18% by end of study in garlic arm; triglycerides also</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Garlic dose: 0.25 mg/kg oil per day divided into</td>
<td>were significantly decreased in garlic arm; little change</td>
<td></td>
</tr>
<tr>
<td></td>
<td>two doses in gelatin capsules</td>
<td>in the control group.</td>
<td></td>
</tr>
<tr>
<td>Morcos 1997</td>
<td>Single-blind, placebo-controlled crossover study</td>
<td>Supplementation for 1 month resulted in 11% decrease</td>
<td>No true diet control</td>
</tr>
<tr>
<td></td>
<td>40 subjects</td>
<td>in cholesterol, 34% decrease in triglycerides, and 10%</td>
<td>Small sample size</td>
</tr>
<tr>
<td></td>
<td>4 week washout between arms</td>
<td>decrease in LDL. Also trend toward increase in LDL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Each arm was 4 weeks</td>
<td>(32%).</td>
<td>Short study period</td>
</tr>
<tr>
<td></td>
<td>Placebo for 1 month and then fish oil (1,800 mg</td>
<td>No significant effect while on placebo: cholesterol, −1%;</td>
<td>Crossover study</td>
</tr>
<tr>
<td></td>
<td>EPA/1,200 mg DHA) + garlic powder 1,200 mg</td>
<td>triglycerides, −2%; LDL, −4%; HDL, −2%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>capsules daily for 1 month</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Adler and Holub 1997
- **Study Design:** 50 male subjects
- **Intervention:**
  - 12 weeks
  - Placebo group: 900 mg of garlic placebo per day + 12 g of fish oil placebo per day
  - Intervention group: 900 mg of garlic per day + 12 g of fish oil per day
  - Control group: 900 mg of garlic placebo per day + 12 g of fish oil placebo per day
  - Additional group: 900 mg of garlic per day + 12 g fish oil placebo per day

### Results
- **Placebo group** showed no significant change in total cholesterol, LDL, or triglycerides compared with baseline.
- **Total cholesterol** was significantly lower with garlic + fish oil (−12.2%) and garlic (−11.5%) but not with fish oil alone.
- **LDL concentrations** were also significantly reduced with garlic + fish oil (−9.5%) and with garlic (−14.2%) but were raised with fish oil (+8.5%).
- **Triglycerides** were significantly reduced with garlic + fish oil (−34.3%) and fish oil alone (−37.3%); garlic group was not significantly changed.

### Limitations
- Diet controlled
- Small sample size
- Short study period

### Durak et al. 2004
- **Study Design:** 23 subjects
  - Hypertensive group (13) and normotensive group (10)
  - 4 months
  - Garlic extract 1 ml/kg/day (about 10 g garlic/day)

### Results
- Serum total, LDL, triglycerides were significantly lower after extract use and HDL was elevated; no changes in liver function, bilirubin, urea, creatinine, protein, electrolytes, or calcium levels.

### Limitations
- Small sample size
- Short time period

### Jain et al. 1993
- **Study Design:** Double-blind, placebo-controlled
- **Participants:** 42 health adults
  - 12 weeks
  - Standardized garlic powder tablets 300 mg three times a day
  - Placebo

### Results
- **Garlic treatment** significantly lowered total cholesterol levels (262 ± 34 to 247 ± 40 mg/dl)
  - LDL reduced by 11% and placebo lowered them by 3%
- No significant changes in HDL or triglycerides

### Limitations
- No diet control
- Healthy patients
- Short time periods

### Lau, Lam, and Wang-Cheng 1987
- **Study Design:** Randomized, placebo-controlled
- **Intervention:**
  - Liquid garlic extract at 250 mg dry weight/ml of active garlic component; 4 capsules (1 ml/capsule) per day
  - 6 months
  - 56 subjects (32 male and 24 female)
  - Three studies: hyperlipidemic group (32 patients), normolipidemic group (14 patients), additional hyperlipidemic group (10 patients with no placebo group)

### Results
- **Hyperlipidemic arm:** serum cholesterol increased at 1 month in 10 subjects, and at 2 months 13 of 15 subjects showed increased in cholesterol in the garlic arm; by 6 months, 11 subjects had more than a 10% lowering of cholesterol (−12–31%); only 2 of 12 had a drop in cholesterol over 10%
  - Normolipidemic patients: there were no significant changes noted for either the garlic or placebo groups
  - Additional hyperlipidemic group: 6 of the 10 subjects had a greater than 10% drop from baseline in their cholesterol levels

### Limitations
- Normal diet habits
- Small sample sizes
- No placebo group in last arm

(Continued)
### Table 11.1 (Continued)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th>Key Findings</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Garlic-positive studies</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Vorberg and Schneider 1990</td>
<td>Double-blind, placebo controlled</td>
<td>Garlic showed significantly lower total cholesterol (21% versus 3%), triglycerides (25% versus 5%), and blood pressure than placebo</td>
<td>No mention of diet Small sample size</td>
</tr>
<tr>
<td></td>
<td>40 patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Garlic powder 900 mg/day (equivalent to 2700 mg fresh garlic/day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Garlic-negative studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peleg et al. 2003</td>
<td>Randomized, prospective, double-blind, placebo-controlled</td>
<td>No significant changes were seen in total cholesterol, LDL, HDL, or triglycerides</td>
<td>Diet counseling Small sample size Short time period High drop out rate in the garlic group</td>
</tr>
<tr>
<td></td>
<td>16 weeks</td>
<td>Garlic versus placebo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>33 patients</td>
<td>Total cholesterol, −0.7 ± 9.9 versus −2.8 ± 11.2%; LDL, −0.1 ± 14.7 versus −2.7 ± 15.1%; HDL, −77 ± 10.7 versus −0.2 ± 9.8%; triglycerides, +30.1 ± 53.3 versus −6.9 ± 29.0%</td>
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<tr>
<td></td>
<td>2 tablets twice daily (13 patients)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Placebo (20 patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gardner et al. 2007</td>
<td>Parallel, randomized, placebo-controlled</td>
<td>No statistically significant effect from the 3 forms of garlic on LDL: raw garlic, +0.4 mg/dl; powdered garlic, +3.2 mg/dl; aged garlic extract, +0.2 mg/dl; placebo, −3.9 mg/dl</td>
<td>Diet controlled Diet counseling Small sample size</td>
</tr>
<tr>
<td></td>
<td>192 patients</td>
<td>No statistically significant effects on HDL, triglycerides, or total cholesterol</td>
<td></td>
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<tr>
<td></td>
<td>Raw garlic, 4.0 g blended</td>
<td>Raw versus powdered versus aged versus placebo</td>
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<tr>
<td></td>
<td>Powdered garlic, 4 Garlicin tablets</td>
<td>HDL, +2.3 versus +1.0 versus −0.3 versus −0.8 mg/dl</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aged garlic extract, 6 tablets</td>
<td>Triglycerides, −5.2 versus −6.6 versus −2.0 versus +6.4 mg/dl</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>Total cholesterol, −0.11 versus −0.02 versus 0.0 versus −0.04 mg/dl</td>
<td></td>
</tr>
<tr>
<td></td>
<td>All products were taken 6 days/week for 6 months</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Garlic component in each arm was equivalent to an average-sized garlic clove</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tanamai, Veeramanomai, and Indrakosas 2004</td>
<td>Randomized, double-blind crossover</td>
<td>No significant differences were found in total cholesterol between the two groups at the end of three or six months</td>
<td>No specific dose given for the garlic Crossover study No washout period mentioned</td>
</tr>
<tr>
<td></td>
<td>100 subjects (45 in trial group and 55 in control)</td>
<td>Side effects: headache, itching, garlic smell; no effects related to liver, kidney function, or hematologic effects</td>
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<tr>
<td></td>
<td>Garlic tablets each contained 1.5% allcin</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Trial group took garlic tablets in first 3 months then placebo for 3 months then nothing for 3 months Control group took 3 months of placebo then 3 months of garlic then 3 months of placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Patients</td>
<td>Duration</td>
</tr>
<tr>
<td>------------------------------</td>
<td>-----------------------------</td>
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<td>----------</td>
</tr>
<tr>
<td>Berthold, Sudhop, and Bergmann 1998</td>
<td>Randomized, double-blind, placebo-controlled, crossover</td>
<td>25 patients</td>
<td>12 weeks with washout periods of 4 weeks</td>
</tr>
<tr>
<td>Isaacsohn et al. 1998</td>
<td>Randomized, double-blind, placebo-controlled, parallel</td>
<td>28 patients</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Superko and Krauss 2000</td>
<td>Double-blind, randomized, placebo-controlled</td>
<td>50 patients</td>
<td>3 months</td>
</tr>
<tr>
<td>Dhawn and Jain 2004</td>
<td>Double-blind, randomized</td>
<td>Two groups: essential hypertension (EH) and normotensive (control)</td>
<td>40 patients</td>
</tr>
</tbody>
</table>

**(Continued)*
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th>Key Findings</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Garlic-negative studies</strong></td>
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<tr>
<td>Simons et al. 1995</td>
<td>Double-blind, placebo-controlled, randomized, crossover 30 patients 12 week cycles 28 day washout period Garlic powder tablets 300 mg three times daily Placebo</td>
<td>No significant differences in total cholesterol, LDL, HDL, or triglycerides</td>
<td>Diet controlled Crossover Short time period Small sample size</td>
</tr>
<tr>
<td>Neil et al. 1996</td>
<td>Double-blind, randomized, parallel 6 month 115 subjects Dried garlic tablets (1.3% allicin) 300 mg three times daily Placebo</td>
<td>No significant difference was seen in any lipid parameter between the garlic and placebo group</td>
<td>Diet controlled</td>
</tr>
<tr>
<td>Plengvidhya et al. 1988</td>
<td>Double-blind, randomized 30 patients Group 1 (16 patients): Placebo capsule twice daily for 2 months then 1 capsule twice daily for 2 months Group 2 (14 patients): Garlic capsules given first then placebo Sprayed garlic preparation</td>
<td>Group 1: no statistically significant changes were seen in total cholesterol, triglycerides, or HDL Group 2: same results</td>
<td>Diet controlled No specifics given on the type of garlic Small sample size Short time period</td>
</tr>
<tr>
<td>Luley et al. 1986</td>
<td>Randomized, double-blind 6 weeks Study 1: 34 patients, 198 mg three times daily Study 2: 51 patients, 450 mg three times daily Dried garlic</td>
<td>No change was seen in any lipid parameter studied</td>
<td>Small sample size Short time period</td>
</tr>
</tbody>
</table>
Drug Interactions

It may inhibit multiple isoforms of the P450 enzyme system, which means it may have multiple drug interactions, including warfarin [Knox and Gaster 2007].

Overall Recommendation

Other than some potential drug interactions, overall garlic appears to be safe and somewhat effective. Patients should be encouraged to only take products that contain an appropriate amount of allicin and should alert their physician they are taking garlic, particularly if they are receiving other medications.

GUGGULU

Commiphora mukul (guggulu) belongs to the Burseraceae family of plants, which are native to India. This plant resembles a gum-like resin when cut. This plant was used in ancient times as a treatment for obesity and skin disease. It is now thought to contain the presence of antihyperlipoproteinemic compounds called guggulsterones [Singh, Niaz, and Ghosh 1994; Caron and White 2001; Szapary et al. 2003; Mamtani and Mamtani 2005; Knox and Gaster 2007].

Content and Effect

Guggulu has been studied to treat hyperlipidemia mainly. Guggulsterones are thought to exert their antihyperlipoproteinemic properties by antagonizing the farnesoid X receptor, which is activated by bile acids. The farnesoid X receptor controls the levels of bile acids, thus regulating cholesterol levels. Guggulsterones are also thought to increase LDL receptor reuptake and increase receptor binding sites. Guggulsterones are also thought to inhibit platelets and have anti-inflammatory properties [Singh, Niaz, and Ghosh 1994; Caron and White 2001; Szapary et al. 2003; Mamtani and Mamtani 2005; Knox and Gaster 2007].

Usage

There is no consistent dose or product that has been studied (Table 11.2).

Adverse Drug Effects

Guggulu has not been shown to have many side effects. The most common side effects seen in the clinical trials performed to date include diarrhea, loose stools, hiccups, and rashes. These side effects are usually mild and infrequent. One major problem with most guggulu supplements is the potentially dangerous levels of heavy metals that they may contain [Knox and Gaster 2007].
Table 11.2  Guggulu Studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th>Key Findings</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Kuppurajana et al. 1978 | Randomized, placebo controlled
Three treatment groups (total of 120 patients): obese (>20% of ideal weight), hypercholesterolemic (total cholesterol >300 mg/100 ml), and hyperlipidemic (total lipids >750 mg/100 ml)
Given for 21 days
1. Purified guggulu 2 g three times daily
2. Fraction A' petroleum ether guggulu 0.5 g twice daily
3. Placebo 2 g three times daily
4. Clofibrate 500 mg three times daily | Obese: Cholesterol: purified guggulu statistically lower on day 10 but not significantly lower by day 21; no significant change at any point for the petroleum guggulu or clofibrate
Lipids: no significant change in any group
Hypercholesterolemic: Cholesterol: purified guggulu was statistically lower at day 10; petroleum guggulu was statistically significant at both days 10 and 21; clofibrate was statistically significant at both days 10 and 21
Petroleum guggulu showed a significant decrease in both cholesterol and total lipids compared with placebo at both day 10 and day 21
Lipids: Decrease in total lipids by both purified guggulu and petroleum guggulu was statistically significant.
No significant difference between groups
Final conclusion: Petroleum guggulu significantly lowers serum cholesterol and serum lipids significantly. Results are similar to those seen by clofibrate. | Not applicable |
| Agarwal et al. 1986 | Phase I study: 21 patients (14 males and 7 females) Mean age 44 years 400 mg three times daily for 4 weeks
Phase II study: 19 patients (13 male and 6 female) 30–65 years
Primary hyperlipidemia (total cholesterol >250 mg/dl and triglycerides >200 mg/dl 500 mg three times daily for 12 weeks followed by 6 weeks of dietary control) | Phase I: 1 patient complained of epigastric fullness three days after starting therapy; no abnormalities were seen in the hematological parameters, liver function tests, blood urea, or blood sugar levels
Phase II: 78.9% of patients were responders to drug therapy by the end of the 12 week treatment (fall in cholesterol and triglycerides at the end of 12 weeks was greater than the day-to-day variation without treatment)
Cholesterol level started falling within 2–4 weeks of starting treatment; levels tended to rise after withdrawal of the drug, although they were still statistically lower
Average total cholesterol decrease was 17.5 ± 9.9%; average decrease in triglycerides was 30.3 ± 18.4%
Phase I: drug is safe and does not produce changes in hepatic or renal function, blood sugar levels, hematological parameters, or electrocardiograms.
Phase II: gugulipid significantly lowered serum cholesterol and triglycerides | Small sample size
Phase I and II studies only
No good explanation of how the gugulipid was prepared |

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<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Szapary et al. 2003</td>
<td>Double-blind, randomized, placebo-controlled, parallel design</td>
<td>103 patients</td>
<td>Guggul extract (2.5% guggulsterones) standard dose (1000 mg) (33 patients) versus high dose (2000 mg) (34 patients) versus placebo (36 patients); all three times daily</td>
<td>Placebo: LDL decreased by 5% Standard dose and high dose guggulipid raised LDL levels by 4%; the results were significantly different compared with placebo No significant changes in total cholesterol, HDL, triglycerides, or very LDL 6 guggulipid patients developed a rash Guggulipid does not appear to improve serum cholesterol over the short term and might even raise LDL; it may also cause a hypersensitivity rash</td>
</tr>
<tr>
<td>Singh, Niaz, and Ghosh 1994</td>
<td>Double-blind, randomized, placebo-controlled</td>
<td>61 patients</td>
<td>Guggulipid (25 mg of guggulsterones) 50 mg twice daily</td>
<td>Guggulipid decreased total cholesterol by 11.7%, LDL decreased by 12.5%, triglycerides decreased by 12.0% Placebo levels were unchanged; results were significantly different compared with the treatment group Levels increased substantially in the guggulipid during the washout period (cholesterol increased 6.5%, LDL increased 6.6%, and triglycerides increased 7.7%) compared with insignificant changes in the control group Side effects of guggulipid: headache, mild nausea, eructations, and hiccups</td>
</tr>
<tr>
<td>Verma and Bordia 1988</td>
<td>Randomized, placebo-controlled</td>
<td>40 patients</td>
<td>Purified gum guggulu 4.5 grams in 2 divided doses</td>
<td>Gum guggulu results: Cholesterol: decreased by 78% end of 4th week, 15.78% end of 8th week, and 21.78% end of 16th week (significant decrease by 16th week) Triglycerides: decreased by 6.7% end of 4th week; 17.1% end of 8th week, and 27.1% end of 16th week (significant decrease by 16th week) HDL gradually increased by 35.8% by end of 16th week (significant change)</td>
</tr>
</tbody>
</table>
### Table 11.2 (Continued)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th>Key Findings</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malhotra, Ahuja, and Sundaram 1977</td>
<td>Randomized, active comparator</td>
<td>Both agents decreased cholesterol and triglycerides significantly. Guggulu at 71–80 weeks: cholesterol, 36.8% decrease; triglycerides, 50.4% decrease. Clofibrate at 71–80 weeks: Cholesterol, 43.5% decrease; triglycerides, 50.2% decrease. No significant difference was seen between the two agents. Side effects: diarrhea in 5 of the Guggulu patients. Study concluded that both agents were equally effective in treating hyperlipidemia.</td>
<td>No specific diet requirements. Small number of subjects.</td>
</tr>
</tbody>
</table>

1. 75 weeks
2. 51 subjects (45 male and 6 females)
3. 75 weeks

Fraction A' guggulu 1.5 g/day (41 subjects)
Clofibrate 2 g/day (10 subjects)
Drug Interactions

This agent has also been show to induce CYP3A4 genes, leading to many drug interactions [Knox and Gaster 2007].

Overall Recommendation

Although this product does show some promising results in clinical trials, there is no specific dose or product that can be recommended. This product also has numerous side effects and potential drug interactions.

HAWTHORN

Hawthorn is derived from the berries of the *Crataegus oxyacantha* L. plant, which has different species such as *laevigata* and *monogina*. The plant consists of leaves with flowers or fruit and is in the family Rosaceae [Fishman, Grattan, and Mamtani 2005].

Potential Indications

Hawthorn has been used in Europe for years to treat hypertension, myocardial dysfunction, and tachycardia [Walker et al. 2006]. Studies have demonstrated significant improvement in patients with congestive heart failure, New York Heart Association classification II and III [Tauchert 2002; Degenring et al. 2003].

Pharmacology

The therapeutic effects of Hawthorn are thought to be attributable to oligomeric procyanidins, in addition to flavonoids, catechin, and epicatechin, which cause direct vasodilation of the coronary vascular smooth muscles [Walker et al. 2002, 2006]. These effects are slow to develop. This herbal also has some inotropic and chronotropic effects with the potential to irritate the myocytes [Tauchert 2002; Degenring et al. 2003].

Dosing Recommendations/Products Studied

The dosing recommendations and products studied are as follows [Tauchert 2002; Degenring et al. 2003]: flavones, 5 mg; total flavonoids, 10 mg; oligomeric procyanidin as epicatechin, 5 mg. For congestive heart failure, the ethanolic extract ratio is used.

Adverse Drug Effects

The treatment was well tolerated by patients; however, because of potential hypotensive effects, close monitoring is recommended [Tauchert 2002; Walker et al. 2002, 2006; Degenring et al. 2003].
Overall Recommendation

Although this herbal has shown some promising results, the use of this agent is debatable and should only be used under close supervision of a healthcare professional.

DIGITALIS

Digitalis, also known as *Digitalis purpurea* L. and *lanata* belongs to the Scrophulariaceae family. Digitoxin is from both *D. purpurea* and *D. lanata*. Digoxin is only found from *D. lanata*. The dry leaves of the plant are thought to contain the pharmacologic action [Frishman, Grattan, and Mamtani 2005].

Potential Indications

This agent is used mainly for treatment of heart failure [Fishman, Grattan, and Mamtani 2005].

Pharmacology

This herbal is thought to work through positive ionotropic effects on the heart [Frishman, Rattan, and Mamtani 2005].

Dosage Recommendation/Products Studied

This agent requires professional titration and kinetic dosing for use [Frishman, Grattan, and Mamtani 2005]

Overall Recommendation

This agent has numerous studies showing its positive effect, but, because of its need for close kinetic monitoring, it should only be used under the supervision of a healthcare provider trained in its use.

Other Plants with the Same Effects

Other plants with the same side effects include the following: *Adonis vernalis*, *Apo-cynum cannabinum*, *Helleborus niger* L., *Selenicereus grandiflorus* L., *Convallaria majalis* L., *Nerium oleander* L., *Urginea maritima* L., and *Strophantus kombe*.

GINKGO

*Ginkgo biloba* belongs to the family Ginkgoaceae. Clinical trials have been conducted using a standardized, concentrated acetone-water extract of dried leaves, prepared to a potency of 24% flavone glycosides and 6% terpenes [DeBusk 2000].
Potential Indications

This agent has been officially declared by the German E Commission to be used in cerebral and peripheral arterial circulatory disturbances [DeBusk 2000].

Pharmacology

This agent is thought to work because of its mixture of flavonol and flavone glycosides (of quercetin and kaempferol, also rutin). The effects from the mixture of these ingredients include reduction of capillary fragility and free radical scavengers. This agent is also thought to work through inhibition of the platelet-activating factor from ginkgolides [DeBusk 2000].

Dosage Recommendation/Products Studied

Dosage recommendation/products studied include the following: extract as tablet, liquid, and intravenous forms; one tablet (40 mg/tab) is to be taken three times a day with meals.

Adverse Drug Effects

Adverse drug effects are thought to not be significant but may include GI disturbances, headache, and allergic skin reactions [DeBusk 2000].

Overall Recommendation

This agent is approved for use as food supplement in the United States. It can be recommended for consumers.

HORSE CHESTNUT SEED

Horse chestnut seed (Aesculus hippocastanum L.) belongs to the family Hippocastanaceae. This herbal is a large, globular, brown seed [DeBusk 2000].

Potential Indications

This herbal has been studied and approved by the German Commission E for improvement of venous tone and to reduce the risk of varicose vein formation [DeBusk 2000].

Pharmacology

Horse chestnut seed is a complex mixture of triterpenoid saponin glycosides (aescin) with the flavonoids quercetin and kaempferol. Aescin can reduce lysosomal activity by 30% (stabilize the cholesterol-containing membranes of the lysosomes).
and restrict edema (reduce water and protein leakage with light diuretic effect) [DeBusk 2000].

**Dosing Recommendations/Products Studied**

Dosing recommendations/products studied [DeBusk 2000] include the following:
for varicose veins, as an aqueous-alcoholic extract of aescin; initial dosage, 90–150 mg of aescin orally; with improvement, reduce to 53–70 mg daily, oral administration; questionable use of ointment, liniment, and of hydroalcoholic extract.

**Adverse Drug Effects**

Adverse drug events effects include GI disturbances, such as constipation with oral consumption (rare), isolated reports of renal and hepatic toxicity, and anaphylaxis reaction after intravenous administration [DeBusk 2000].

**Drug Interactions**

This agent has been shown to have a coumarin content; therefore, it should not be used with warfarin or other blood thinners attributable to the risk of increased bleeding [DeBusk 2000].

**Overall Recommendation**

Despite this agent’s drug interaction with warfarin and other blood thinners, it is considered safe for use by the German Commission E. Healthcare professionals should counsel patients about its potential drug interaction.

**BUTCHER’S BROOM**

Butcher’s broom (*Ruscus aculeatus* L.) affects are thought to be from the rhizome and root of the plant [DeBusk 2000].

**Potential Indications**

The main indication for this herbal is treatment of venous insufficiency [Frishman, Grattan, and Mamtani 2005].

**Pharmacology**

This agent is thought to work because of its mixture of steroidal saponins, which have anti-inflammatory and vasoconstricting effects on the venous vasculature [Frishman, Grattan, and Mamtani 2005].
Dosage Recommendation/Products Studied

Dosage recommendation/products studied include the following [Frishman, Grattan, and Mamtani 2005]: capsule or tablet of approximately 300 mg of dried extract; ointment and suppositories for hemorrhoids.

Overall Recommendation

Clinical safety and efficacy remain to be established.

GINSENGS

Ginsengs (Panax ginseng, P. quinquefolius L. [American ginseng], Ginseng Radix Rubra [Korean ginseng, are made by drying several species from China, Korea, Russia, and Japan and are of the family Araliaceae [Hammond and Whitworth 1981; Han et al. 1998; Sung et al. 2000; Stavro et al. 2005].

Potential Indications

This agent is being studied for use in hypertension [Hammond and Whitworth 1981; Han et al. 1998; Sung et al. 2000; Stavro et al. 2005]

Pharmacology

Triterpenoid saponin glycosides consist of ginsenosides or panaxosides [Hammond and Whitworth 1981; Han et al. 1998; Sung et al. 2000; Stavro et al. 2005]. The content of ginsenosides varies with the age of the root, the habitat, the harvesting season, and the method of curing or drying. In Chinese usage, the whole root is better than any of its parts.

In general, ginseng properties include a tonic or adaptogenic effects. Animal studies have shown these effects: increase endurance, prevent stress-induced ulcer, stimulate hepatic ribosome production, boost the immune system, and stimulate protein synthesis [Sung et al. 2000].

Red ginseng might be used to improve vascular endothelium because of the release of NO [Sung et al. 2000].

Dosage Recommendation/Products Studied

Dosage recommendation/products studied include the following [Hammond and Whitworth 1981; Han et al. 1998; Sung et al. 2000; Stavro et al. 2005]: tea, capsules, extracts, tablets, roots, chewing gum, cigarettes, and candies; for red ginseng, 1.5 g three times per day (each capsule contains 300 mg of red ginseng) orally.
Adverse Drug Effects

Ginseng abuse syndrome, which consists of potential hypertension, has been associated with Chinese ginseng [Hammond and Whitworth 1981]. Other potential adverse effects include nervousness and irritability. Usually, ginseng is not associated with serious adverse reactions [Han et al. 1998; Sung et al. 2000; Stavro et al. 2005].

Overall Recommendation

Ginseng can be used moderately. However, it should be used with caution in patients prone to hypertension or nervousness.

TREE BARK

Tree bark (Terminalia arjuna) is derived from Combretaceae family. Tree bark used has been used in Indian Pharmacopoeia [Gupta et al. 2001; Bharani et al. 2002].

Potential Indications

The bark extract is supposed to have cardiotonic, anti-ischemic and anti-heart failure properties [Gupta et al. 2001; Bharani et al. 2002].

Pharmacology

Tree bark is a combination of arjunic acid and terminic acid. Bark extract also contains strong antioxidants (flavones, tannins, and oligomeric proanthocyanidins), glycosides (arjunetin arjunosides I–IV), and minerals [Gupta et al. 2001; Bharani et al. 2002].

Dosing Recommendations/Products Studied

Clinical studies have shown that Arjuna potentially has displayed anti-ischemic effects similar to isosorbide mononitrate at 40 mg/day [Bharani et al. 2002] and also possessed potent antioxidant action compared with vitamin E as well as significant hypcholesterolemic effects [Gupta et al. 2001]; for anti-ischemic effect, bark extract at 500 mg every 8 h by mouth; for antioxidant and hypocholesterolemic effect, capsule of 500 mg pulverized powder of Arjuna bark daily by mouth.

Adverse Drug Effects

The bark extract or powder were well tolerated, and no side effects were reported [Gupta et al. 2001; Bharani et al. 2002].
Overall Recommendation

This agent can be used with monitoring for angina and high cholesterol levels (used independently or in association with vitamin E).

REFERENCES


