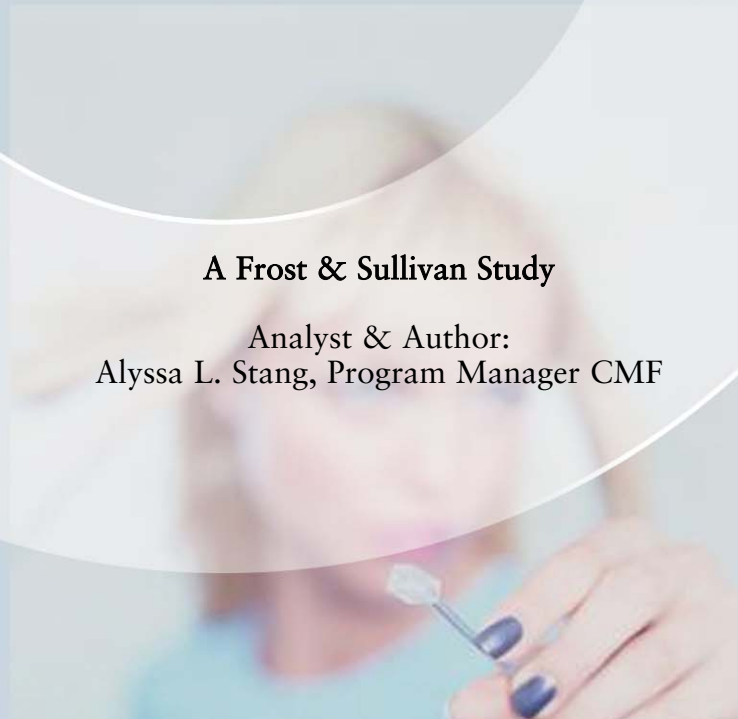


NEW EXCITEMENT IN THE NATURAL CHOLESTEROL REDUCING PRODUCTS MARKET



A Frost & Sullivan Study

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INTRODUCTION

Dietary supplements remain a popular way for Americans to maintain and promote good health. Cholesterol reducing dietary supplements are becoming an important part of this product array. In the following paper, the success of cholesterol reducing dietary supplements is discussed in relation to prescription products. An overview of natural ingredients, and the cholesterol reducing products that contain these ingredients, are addressed. Finally, a new ingredient is discussed that appears to be at the forefront of the natural cholesterol reducing products discussed in this study. This conclusion is based on publicly, readily available information for the competitive products analyzed.

OVERVIEW OF CHOLESTEROL REDUCING PRODUCTS: PRESCRIPTION & NATURAL

High blood cholesterol levels are a major risk factor for heart disease. The Center for Disease Control states that heart disease is the leading cause of death in the United States, and about 17 percent of adult Americans (29 million) have high blood cholesterol.

Controlling cholesterol levels can be an important factor in reducing a person's risk of heart disease. Cholesterol levels can be controlled by several methods. These methods would include diet, exercise, prescription medication, and over-the-counter dietary supplements.

For the vast majority of health professionals, prescription drugs are the preferred method for reducing cholesterol, even for patients with slightly elevated cholesterol levels. Most of the prescription cholesterol drugs are statins like Lipitor, Zocor, and Pravachol. These drugs work by blocking the enzyme the liver needs to produce cholesterol. A drawback to using most prescription cholesterol lowering drugs is they mainly impact the lowering of LDL cholesterol and have almost no effect on HDL or "good" cholesterol. In addition to this limitation, there can be negative side effects. Statin drugs may be necessary for individuals with significantly elevated LDL or "bad" cholesterol, but there may be natural alternatives for individuals with moderately elevated LDL cholesterol.

Using a natural cholesterol reducing product may help lower blood cholesterol without the side effects of a prescription drug. In addition to lowering LDL, some of these products may also increase HDL. These products are being used by an increasingly health conscious America. Heart health supplements are growing at a compound growth rate (CAGR) of 12.4 percent. The market for heart health supplements was around \$0.80 billion in 2005. It is expected to grow to \$1.81 billion by 2012 (*Source: F&S study*).

NATURAL INGREDIENTS OVERVIEW

About 65 percent of Americans use dietary supplements. The over-the-counter (OTC) natural ingredient market is estimated to be \$20.00 billion in 2005 (Source: F&S study). Several factors have contributed to the success of the natural ingredient market. These market drivers have fueled continued growth in the dietary supplement market.

One of the important drives in this market is the availability of information to the consumer. More product advertising and media attention in this area has aided in increasing the accessibility and quantity of information available to health conscious consumers. This has made consumers more aware and better educated about dietary supplements and their health benefits, creating an increase in demand for well designed dietary supplements. To maintain this consumer interest, well executed and communicated clinical trials must be performed in order to help the consumer understand the benefits of the dietary supplement.

Low barriers to entry that characterize this market have also driven an explosion of product offerings. Compared to prescription drugs, there are very few regulations that surround the dietary supplement category, making it easier for a manufacturer to enter this market. There are as many as 1000 dietary supplements introduced every year into the US market (Source: *Frost & Sullivan Study*). A manufacturer needs to support its product offering with good clinical trial data.

A growing portion of the OTC dietary supplements are natural ingredients that claim to lower cholesterol. The use of natural ingredients to lower cholesterol has many benefits. These benefits include possibly lowering LDL and increasing HDL. The natural ingredients found in some OTC natural supplements that claim to lower cholesterol are: Garlic, Vitamin E, Fenugreek, Artichoke extract, Guggulipid, Red Yeast Rice, Pantethine, Plant sterol/stanol and Polymethoxylated Flavones and Phellodendron extracts.

These natural ingredients have had varying levels of proposed success according to various clinical trial results. For the purpose of the following discussion on claimed cholesterol lowering effects of natural ingredients, only results from human studies that are readily available are included. In addition, the focus is on the ability of these ingredients to lower LDL cholesterol with only a secondary focus on the impact of HDL cholesterol. With these limitations in mind, Table I shows the possible LDL lowering capabilities of some natural ingredients (see next page for Table I).

TABLE 1: Natural ingredients possible LDL lowering capabilities

Natural Ingredient	Possible LDL Cholesterol Lowering Capability (%) <i>(from readily available, public, complete studies)</i>
Garlic	11.4 *
Vitamin E	7.9 *
Fenugreek	18 to 38 *
Artichoke ext	22.9 *
Guggulipid	16 – 36 *
Red Yeast Rice	22-32 *
Plant sterol/stanol	8-15 **
Pantethine	NA ***
Polymethoxylated Flavones	NA ****
Polymethoxylated Flavones + Phellodendron	45% *****

- * The Journal of Family Practice, June 2003 Vol 52, No 6
- ** Progress in Lipid Research, March 22 2002
- *** No studies with only Pantethine as the natural ingredient
- **** No published studies or trial papers
- ***** Clinical trial report available, submitted for publication

In addition to the above claimed LDL lowering capabilities of these natural ingredients, there has been some evidence of adverse side effects for several of these ingredients. These include Fenugreek, Guggulipid, and Red yeast rice. Red yeast rice, for instance, has been noted to have some of the same side effects as prescription statin drugs. These include allergic reaction, unexplained muscle pain, and tenderness. Less serious side effects could be gastrointestinal issues or dizziness.

NATURAL INGREDIENT CHOLESTEROL REDUCING PRODUCTS OVERVIEW

Heart health is an increasing concern for consumers. The use of natural ingredient products that address heart health is increasing. Some of the drivers behind this market increase are an aging population, increasing body of research supporting the health claims of natural ingredients, and Food and Drug Administration (FDA) approved health claims for ingredients such as soy protein, omega 3 fatty acids, and plant sterols.

Vitamin supplements that claim to lower cholesterol are an important part of the natural reducing cholesterol products market. There are many over-the-counter vitamin supplements that claim to lower cholesterol. As stated previously many of the ingredients used in these products have some evidence that they will reduce LDL, and in some cases, increase HDL. A consumer has many choices, and this can be very daunting and confusing. As with all health supplements, make sure you consult your physician or other qualified medical professional before taking any cholesterol lowering supplements.

To understand the product array better, the following selection of possible dietary supplements and their natural ingredients will be discussed: Resterol, Cholestin®, Reducol™, Pantestin®, and Flavoxine™. Table 2 shows the products and a listing of their cholesterol reducing natural ingredients.

Table 2: Natural Ingredient Cholesterol Reducing Products

Resterol	Cholestin®	Reducol™	Pantestin®	Flavoxine™
Vitamin E, Policosanols, Pantethine, Garlic, Turmeric, Guggul	Red Yeast Product	Sterols/Stanoles	Pantethine	Polymethoxylated Flavones, Phellodendron Extract

Out of the 5 competitive products, Resterol has the widest variety of ingredients. It is made by Progressive Health Inc. who claims their product has a synergistic blend of ingredients. Other than the studies on the individual ingredients discussed earlier, there are no published clinical studies on the cholesterol lowering effect of the product.

Cholestin® is made by Pharmanex who claims that their product is a breakthrough all-natural solution for individuals concerned with maintaining cholesterol levels already in the normal range. The main natural ingredient in Cholestin® is red yeast product, and although

this ingredient has been shown to lower LDL cholesterol levels, there have been side effects associated with this natural ingredient. The possible side effects include allergic reaction, unexplained muscle pain and tenderness. Less serious side effects could be gastrointestinal issues or dizziness.

Reducol™ is made by Forbes Medi-Tech is based out of Vancouver, Canada. Forbes Medi-Tech is a life-sciences company that researches, develops, and commercializes products for the prevention and treatment of cardiovascular disease (CVD). According to Forbes Medi-Tech, Reducol™ is a unique, patented blend of naturally occurring compounds found in plants known as phytosterols and phytostanols. In November 2004, Novel Food Approval was gained for Reducol™ use in yellow fat spreads. Reducol™ gained Substantial Equivalence Food Approval in March 2005 for use in fermented milk-type products, soy drinks, low-fat cheese-type products, yogurt-type products, spicy sauces, and salad dressings. Reducol™ is generally recognized as safe (GRAS) by the United States Food and Drug Administration, and according to Forbes Medi-Tech, it is clinically proven to significantly lower 'bad' cholesterol levels when used in conjunction with a low fat diet and exercise.

Pantesin® is made up of the natural ingredient Pantethine. Pantethine has shown some evidence that it may help lower LDL cholesterol, but there are no conclusive studies publicly available that focus only on the natural ingredient pantethine. Pantesin® is a trademark of Daiichi Fine Chemical Co., Ltd. and sub-licensed to Tomen America, Inc. for the North American market. According to Daiichi, many studies have been conducted under their guidance that supports both the benefits and safety of the use of pantethine.

Flavoxine™ is made by Next Pharmaceuticals and is a patented, proprietary blend of plant extracts. Next Pharmaceuticals indicates that it is the combination of the Polymethoxylated Flavones from orange peel, and a proprietary extract from Phellodendron amurense, in their dietary supplement that work together to lower LDL cholesterol by 45 percent and increase HDL cholesterol by 12 percent. This impact was shown to be statistically significant in their recent clinical study.

PROMISING NEW INGREDIENT SET TO STORM THE MARKET

Flavoxine™ is the newest ingredient to hit the dietary supplement market and appears to be at the forefront of the natural cholesterol reducing products discussed in this study. This conclusion is based on publicly available information for the products analyzed. Next Pharmaceuticals recent clinical study showed a highly significant lowering of LDL cholesterol, a significant elevation of HDL cholesterol, and it caused significant weight loss in the overweight subjects. The Flavoxine™ ingredients are covered by two patents: U.S. Patent No. 6,987,125 and No. 6,184,246.

In a double-blind, placebo-controlled clinical trial with 80 subjects divided into overweight (experimental and placebo) and normal weight (experimental and placebo) groups, Flavoxine™ exhibited extraordinary results for both experimental groups; however, the statistical significance between the overweight groups was superior.

Flavoxine™ significantly ($p < 0.001$) lowered weight and BMI by 5 percent in the overweight subjects. Lipid lowering was seen in both groups in all measurements. Flavoxine™ significantly reduced circulating LDL-cholesterol by 45 percent in 8 weeks in the overweight group ($p < 0.001$) and by 17 percent in the normal weight group ($p < 0.01$). Flavoxine™ significantly increased HDL-cholesterol in the overweight subjects by 12 percent after 8 weeks ($p < 0.05$). A statistically significant increase ($p < 0.05$) was also shown in the normal weight subjects. C-reactive protein, an indicator of inflammation that is now considered to be a positive risk factor for coronary artery disease, was significantly ($p < 0.001$) reduced by Flavoxine™ in the overweight group by 48 percent at 8 weeks and in the normal weight group by 44 percent ($p < 0.001$). Flavoxine™ after 8 weeks also significantly ($p < 0.05$) reduced the concentration of triglycerides by 18 percent in the overweight group and by 15 percent ($p < 0.001$) in the normal weight group. Blood pressure was significantly lowered in both Flavoxine™ groups at 8 weeks. The overweight group lowered their systolic blood pressure by 6 percent ($p < 0.05$) and their diastolic blood pressure by 13 percent ($p < 0.001$), while the normal weight group dropped their diastolic blood pressure by 12 percent ($p < 0.01$).

When compared with the other natural ingredient cholesterol reducing products, Flavoxine™ appears to be an exciting new entry into the growing market of natural products for maintaining heart health. According to researchers at the Veterans Administration Palo Alto Health Care System, one of the primary actives in Flavoxine™ lowers LDL cholesterol by increasing the receptors in the liver for LDL cholesterol (Kong et al., Nature Medicine, Volume 10, Number 12, December 2004). This is a different mechanism of action than the statin drugs, and could position Flavoxine™ as a complementary strategy to drug therapy for individuals that require prescription drugs.

Note: Information and analysis on products mentioned in this paper (Restero!, Cholestin®, Reducol™, Pantestin®, and Flavoxine™) is based on publicly, readily available information.

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