Phytosterols and Its Effect on Human Health

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Abstract
Phytosterols or stanols are large group of compounds found exclusively in plants. These are naturally present in plants and are structurally similar to cholesterol. A daily intake of 3 g of phytosterol (or their reduced form stanols) is associated with consistent and reproducible reduction in LDL cholesterol concentrations up to 10% and reduces the risk of coronary heart disease by 20% over a lifetime. Studies have concluded that the effective doses for reduction of cholesterol are between 1.5 and 3g/day, leading to decrease in 8% and 15% of LDL-cholesterol. The principal mechanism of action is based on interference with the solubilization of the cholesterol in the intestinal mucosa. Several studies have validated the cholesterol lowering effect of phytosterols and stanols along with its role in prevention of coronary heart diseases. Phytosterols and stanols fortified foods and formulations should pave the greater use of such ingredients for promotion in human health.

Keywords: Phytosterol, LDL cholesterol, coronary heart diseases mechanism of action, functional foods

Introduction
The term phytosterols is generally used to describe plant sterols and plant stanols collectively. Phytosterols are natural components of plant origin forming cell membrane and occur in small quantities in many fruits, vegetables, nuts, seeds, cereals, legumes, vegetable oils and other plants. Plant stanols occur in even smaller quantities in many of the same sources. It is estimated that 2500 tonnes of vegetable oil needs to be refined to produce 1 tonne of plant sterols (IFST 2005). All sterols are waxy colorless solids, soluble in most organic solvents and insoluble in water (Anon 2011a).

Structure of phytosterols:
Chemically, the phytosterols are classified as 4-desmethylsterols of the cholestan-4-one series. Structurally, plant sterols fall into one of three categories: 4-desmethylsterols (no methyl groups); 4-monomethylsterols (one methyl group) and 4, 4-dimethylsterols (two methyl groups). However, most of the major phytosterols such as β-sitosterol, campesterol, stigmasterol, avenasterols and plant stanols belong to the group of 4-desmethylsterols (Christie 2011; Wasowicz 2002). Phytosterols differ very slightly in structure from the cholesterol by the presence of an ethyl or methyl group at C-24 position in the side chain (Scheme 1). There are over 40 phytosterols known today, but β-sitosterol is the most abundant one, comprising about 50 per cent of dietary phytosterols (Anon 2012a). The next most abundant phytosterols is campesterol (about 33%) and stigmasterol (about 2 to 5%). Other phytosterols found in the diet include brassicasterol, α-7-stigmasterol and α-7-avenasterol. Structurally, β-sitosterol differs from cholesterol by the presence of an ethyl group at the 24th carbon position of the side chain, whereas in the case of campesterol, a methyl group occupies the same position. The fully saturated form of phytosterols (containing no double bond at the 5,6 position) are the phytostanols, which are present in only trace amounts but can be formed by hydrogenation of phytosterols.

Scheme 1. Structure of cholesterol and phytosterols.

<table>
<thead>
<tr>
<th>R</th>
<th>Compound</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Cholesterol</td>
</tr>
<tr>
<td>CH₃</td>
<td>Campesterol</td>
</tr>
<tr>
<td>C₂H₅</td>
<td>β-sitosterol</td>
</tr>
<tr>
<td>C₂H₅Δ22</td>
<td>Stigmasterol</td>
</tr>
</tbody>
</table>
Sources Of Phytosterols And Its Intake:

Phytosterol is abundantly present in the fat soluble fractions of all plants and foods containing plant based raw materials including principally oils, cereals, pulses and dried fruits (Piironen et al. 2000). Phytosterols may exist as free sterols (FS’s), esterified with fatty acids (SE’s) or phenolic acids (SPHE’s) or as glycosides (SG’s) and acylated glycosides (Moreau et al. 2002; Piironen and Lampi 2003). Some packaged foods, such as specially formulated orange juices, low fat yogurts and milks are available in the market being fortified with phytosterol. However, major sources of phytosterols for fortification in current foods and for the preparation of dietary supplements include tall oil and vegetable oil deodorizer distillate. Vegetable oils are richest source of free phytosterols and their fatty acid esters. These, in crude forms, contain 1-5 g/kg of phytosterols (Weihrauch and Gardner 1978; Johansson 1979; Piironen et al. 2000; Gunstone 2005). However, fewer oils such as corn oil (7.8-11.1 g/kg) and rapeseed oil (6.8-8.8 g/kg) are exceptions of this category. Tall oil contains a higher proportion of plant stanols than do vegetable oils (IFST 2005). The amount of available phytosterols in different vegetable oils is shown in Table 1. Refining of oils leads to significant lowering of phytosterol content (Ferrari et al. 1997) and therefore, it is very essential to develop industrial methods to minimize these losses (Quilez et al. 2003).

Distribution of phytosterols to free sterols and steryl fatty acid esters account for different proportion in different oils (Johansson 1979; Ferrari et al. 1996; Verleyen et al. 2002; Phillips et al. 2002; Worthington and Hitchcock 1984; Gordon and Griffith 1992) for example- free sterols accounts for nearly 54-85% of total phytosterols in soybean, sesame, olive, cotton seed, coconut, safflower, and peanut oil whereas the proportion varies for 32-44% in canola, rapeseed, corn, avocado and sunflower oil (Phillips et al. 2002).

Cereals such as rye, barley, wheat and oats are generally considered as good source of phytosterol wherein germ and bran fractions are known as the best reservoirs among other fractions. The total phytosterol content of various cereals varies from about 350-1200 mg/Kg (on wet basis). In cereals, sitosterol dominates among all phytosterols and its proportion ranges from 49-64% in wheat, rye, barley and oats (Piironen et al. 2003). Table 2 shows the composition of major phytosterol in different cereal grains.

Vegetables, fruits and berries are not as good source of plant sterols as vegetable oils and cereals, on a fresh weight basis. However, the variation in their sterol contents is remarkable when the results are calculated on dry weight basis. Piironen et al. (2000) have analyzed various vegetables for total sterols and reported a range of 5-37mg/100 g (on fresh weight).
and 25-410 mg/100g (on dry weight) available in them.

**Absorption Of Phytosterols**

Initially, it was demonstrated that phytosterols are unabsorbable in rodents and rabbits. However, Salen et al. (1989) estimated 1.5-5% absorption of sitosterol in human beings. Ostlund et al. (2002) reported about 0.5% of sitosterol and 1.89% of campesterol absorption in human beings which reduced by 91% when the saturated form i.e. stanols was used. With the development of newer analytical techniques, various animal species showed phytosterols absorption ranging from 0-4% in rabbit & rats and 6% in human beings (Pollak and Kritchevsky 1981). Reported data also shows that some phytosterols get metabolized into acidic products (Kritchevsky and Chen 2005).

**Cholesterol lowering effect of phytosterols and coronary heart diseases:**

The cholesterol-lowering effect of phytosterol/stanol enriched foods has been well documented (Law 2000 & Plat et al. 2000). Systematic reviews studying the efficacy of phytosterols have shown that phytosterol/stanol enriched foods can significantly lower LDL cholesterol (Law 2000; Normen et al. 2005). Daily intake of phytosterols helps to prevent heart disease by lowering HDL cholesterol levels by as much as 14% (Anon 2011b).

A number of studies using phytosterols have been carried out and showed significant lowering of blood cholesterol levels. A summary of 52 studies revealed that an average of 13±1 g of phytosterol intake daily for 3-5 weeks, showed a 20% decrease in blood cholesterol level (Pollak and Kritchevsky 1981). Miettinen et al. (1995) prepared an esterified sitosterol (i.e. sitostanol) based spread which exhibited lowering of serum cholesterol in subjects with hypercholesterolemia. Unesterified sterols and stanols also exhibited a similar degree of low-density lipoprotein (LDL) cholesterol lowering effects (Vanstone et al. 2002). The efficacy of phytosterol esters as a hypocholesterolemic agent has recently been affirmed in a review by Katan et al. (2003). In a meta-analysis of 41 trials with various enriched food products, these authors found that the optimal daily dosage of sterols or stanols is 2g/day can result in a 10% reduction in LDL cholesterol, whereas higher doses provide only a small additional effect.

Phytosterols compete with cholesterol absorption and uptake in the small intestine thereby reducing the supply of cholesterol in the blood stream. Since high blood total cholesterol and low-density lipoprotein (LDL) cholesterol levels are the main risk factors for coronary heart disease (CHD) and other diseases related to atherosclerosis, thus reducing cholesterol levels reduces the risk of CHD as well. According to recent data, cardiovascular disease (CVD) is a leading cause of death and a major cause of disability in Australia. One recent data reports that nearly 47,000 Australians died from CVD in 2007 (Australian Bureau of Statistics 2009) and in India according to a report generated by India Today, CVD is at the top position among the top ten causes of deaths in India with a percentage of 24.8 (Anon 2012). In this context phytosterols have no effect on the levels of triacylglycerol or HDL cholesterol. Studies showed daily intake of 2-3 g sterols and stanols lowers LDL level by 10% and likely lowers CHD by 12-20% in the first 5 years and by 20% over a life time (Weststrate, and Meijer 1998). Phytosterols are absorbed from the blood into the body at a rate of 5-10%, whereas cholesterol is absorbed at a rate of 50% (Awad et al. 2000).

Studies have also been conducted to investigate the effect of spreads containing phytostanol and sterol esters when used in conjunction with cholesterol lowering drugs i.e. Statins and Fiberates. These studies showed that phytosterol and stanol esters can be used safely, to provide an additional cholesterol lowering effect to that of the medication alone (Neil et al. 2001; Nigon et al. 2001). Since then, a large number of clinical studies with phytosterols have been conducted. Studies have shown that without adherence to a controlled diet, the consumption of 20 g phytosterol/stanol-enriched margarine has been shown to have a lipid lowering effect (Hendriks et al. 2003 and Geelen et al. 2002) and to augment the LDL cholesterol-lowering effect of other cholesterol-lowering strategies (Nestel et al. 2001). Phytosterols lower serum cholesterol by decreasing cholesterol absorption in the small intestine with a consequential increase in fecal excretion of cholesterol.

In an efficacy study on plant stanols, a daily consumption of 24 g of spread, containing 2-3 g of plant stanol esters resulted in lowering of total serum cholesterol and LDL cholesterol by 6.4 per cent and 10.1 per cent respectively (Nguyen et al. 1999; St-Onge et al. 2003). A dose dependent decrease in total and LDL cholesterol was observed with increasing levels of plant stanol esters up to a level of 1.6 g per day. However, increasing the dose from 2.4 g to 3.2 g did not provide any clinically important additional effect (Hallikainen et al. 2000a; 2000b).

To examine the effect of a food enriched with phytosterols on blood levels of cholesterol and nutrients, researchers randomly assigned 67 people with high cholesterol to eat two snack bars containing 1.5 grams of phytosterols each every day for six weeks or two bars that did not contain phytosterol. The subjects who had enriched bar showed 5 percent reduction in total cholesterol and 6 percent reduction in LDL cholesterol after six weeks. Also, an increase in the amount of HDL or "good" cholesterol in relation to total cholesterol was observed. However, the phytosterol enriched bars did not affect vitamins A or E levels in blood but at the same time reduction in β-carotene levels had also
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Phytosterols and Cancer:

As plant components, phytosterols (PS) may offer protection against cancer by several different means (Rao and Koratkar 1997; Awad and Fink 2000). These include inhibiting cell division, stimulating tumor cell death and modifying some of the hormones that are essential to tumor growth (Awad et al. 2000). Long-term studies showed an association between the amount of plant sterol consumed in the diet and developing cancer. It is estimated that about 9 million new cancer cases are diagnosed every year and over 4.5 million people die from cancer each year in the world (Reddy 2012). However, the estimated number of new cancer patients in India per year is about 7 lakhs and over 3.5 lakhs people die of cancer each year.

Phytosterols have been found useful in treating other conditions, including rheumatoid arthritis, but their widest application is in protecting the heart. However, reports also suggest that excessive intake of dietary phytosterols and stanols in plasma and tissues may contribute to the increased blood pressure (Chen et al. 2010).

Safety of phytosterols:

Based upon results of clinical studies, plant sterols appear to be safe (Katan et al. 2003; Hendriks et al. 2003; Hepburn et al. 1999) and non-toxic (Christiansen et al. 2001; Hendriks et al. 1999) and no adverse effect has been found on the reproductive system (Baker et al. 1999; Waalkens et al. 1999). The U.S. Food and Drug Administration (FDA) granted GRAS “Generally Recognized as Safe” status for plant sterols/stanols, and the European Union Scientific Committee on Foods has concluded margarines and dairy products containing phytosterol esters are safe for human consumption. The FDA has also approved a health claim that foods containing plant sterols/stanols esters may reduce the risk of coronary heart disease (European food safety agency 2003) by reducing blood cholesterol levels as part of a diet low in saturated fat and cholesterol. However, the only drawback with phytosterols is that these require fat based medium to get solubilize and the problem can be overcome by emulsification with lecithin and delivering in non-fat or low-fat foods and beverages. This can reduce the amount of fat in fat-based preparations substantially with retention of bioactivity and reduction in cholesterol (Ostlund 2004). Table 3 depicts the potential uses of phytosterol along with its future applications in non-fat dairy products.

Phytosterols in products:

Due to increasing consumer knowledge in functionality and health benefits, market of phytosterols containing products is growing continuously and various ready to eat products are available in market containing the phytosterols and stanols as novel ingredients as in yellow fat spreads (Wolfs et al. 2006). Also, their effectiveness in lowering both total and LDL-cholesterol in human subjects when incorporated to other foods matrices (yoghurt, milk, salad dressing and lean ground beef) has also been successfully demonstrated and indicated no side effects (Volpe et al. 2001; Davidson et al. 2001). These results have led to the market introduction of several foods enriched or fortified with phytosterols. Since fats are necessary to solubilize sterols, hence foods with majority of the fat phase eg. Butter or margarines are an ideal vehicle for them, although cream cheese, salad dressing, and yogurt can also be used.

**Conclusion**

The availability of phytosterol containing products is gradually becoming more widespread due to awaken awareness and education of mass. Also, regulatory hurdles governing their use in foods are steadily overcoming. However, the only dark side effect of such products is with the interference with the absorption of carotenoids, which can be compensated by adding these compounds in appropriate carriers. Phytosterols also has anti-cancerous properties and act as immune system modulators. There are several possible future lines of research, as finding raw materials containing phytosterol content in abundance, minimization of losses during recovery processes and addition of purest form in ready bio-available product in the market and its easy availability. These ingredients should be incorporated in diet in sufficient amounts to reap the potential benefits of phytosterols. At the same time, the genetic bases of their action must be elucidated, synergic effects with other compounds must be studied along with its minimal side effects and the effects of long-term treatment must be defined precisely.
### Table: 1

**Phytosterol Content In Various Vegetable Oils**

<table>
<thead>
<tr>
<th>Sr. no.</th>
<th>Source</th>
<th>Amount present (g/kg)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Crude vegetable oil</td>
<td>1-5</td>
<td>Weihrauch and Gardner, 1978; Piironen et al., 2000.</td>
</tr>
<tr>
<td>2</td>
<td>Corn oil and rapeseed oil</td>
<td>8-22 and 5-11</td>
<td>Gunstone, 2005</td>
</tr>
<tr>
<td>3</td>
<td>Wheat germ and corn germ oil</td>
<td>17-26 and 10.7</td>
<td>Homberg and Bielefeld, 1989</td>
</tr>
<tr>
<td>4</td>
<td>Palm oil and coconut oil</td>
<td>0.7-0.8 and 0.7</td>
<td>Verleyn et al. 2002</td>
</tr>
<tr>
<td>5</td>
<td>Crude soybean oil</td>
<td>3-4.4</td>
<td>Moreau et al., 2002</td>
</tr>
</tbody>
</table>

### Table: 2

**Composition Of Phytosterols In Different Cereals (Mg/Kg)**

<table>
<thead>
<tr>
<th>Sample</th>
<th>Campesterol</th>
<th>Sitosterol</th>
<th>Stigmasterol</th>
<th>Avenasterol</th>
<th>Stanols</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barley</td>
<td>150-192</td>
<td>437-484</td>
<td>24-36</td>
<td>56-69</td>
<td>17-19</td>
<td>720-801</td>
</tr>
<tr>
<td>Buck wheat</td>
<td>93</td>
<td>775</td>
<td>Tr</td>
<td>40</td>
<td>23</td>
<td>963</td>
</tr>
<tr>
<td>Corn</td>
<td>--</td>
<td>375</td>
<td>18</td>
<td>87</td>
<td>ND</td>
<td>770</td>
</tr>
<tr>
<td>Millet</td>
<td>112</td>
<td>371</td>
<td>18</td>
<td>87</td>
<td>ND</td>
<td>770</td>
</tr>
<tr>
<td>Oats</td>
<td>32-46</td>
<td>237-321</td>
<td>11-21</td>
<td>15-56</td>
<td>8-9</td>
<td>350-491</td>
</tr>
<tr>
<td>Rice</td>
<td>146</td>
<td>375</td>
<td>104</td>
<td>20</td>
<td>32</td>
<td>723</td>
</tr>
<tr>
<td>Rye</td>
<td>128-210</td>
<td>358-607</td>
<td>22-37</td>
<td>5-42</td>
<td>122-220</td>
<td>707-1134</td>
</tr>
</tbody>
</table>

(Source: Piironen and Lampi, 2003)

ND: Not Detected; Tr= Traces, -- Not reported

### Table: 3

**Phytosterol: Applications And Opportunities**

<table>
<thead>
<tr>
<th>Current uses</th>
<th>Potential uses</th>
<th>Novel forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Margarines, fat spreads, soft spreadable cheeses, mayonnaise, salad dressings, low fat dairy products, milk, yogurt and cheeses, snack and energy bars, frying oils, breakfast cereals etc.</td>
<td>Baked pastry products, egg noodles and pasta, custard, ice cream, frozen desserts, muesli bars and soups, meat products, rice beverages, cereal grains and flours, food flavourings etc.</td>
<td>Encapsulation with egg proteins to increase bioavailability in foods</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Water soluble powders for inclusion in beverages (orange juice) and non fat foods.</td>
</tr>
</tbody>
</table>

(Source: Anon, 2008)
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