Plant sterols for human health- A review

Tanu Jain* and Shikha Bathla

Department of Food & Nutrition, College of Home Science, Punjab Agricultural University, Ludhiana-141004 (Punjab), INDIA

*Corresponding author. E-mail: jain.tanu25@gmail.com

Received: May 15, 2015; Revised received: October 12, 2015; Accepted: November 10, 2015

Abstract: The aim of the article was to review phytosterols as functional food and its significance in lowering cholesterol as well as its specific effect on human health. Phytosterols has been known for its cholesterol lowering action long time back but the uprising of phytosterols in form of functional foods gained the interest once again. Fatty food matrix provides optimal solubility but fortification of phytosterols with other food matrices like low fat fermented milk, bread, juice are showing positive results. A dose of 2 g/day of either steryl or stanyl esters has been prescribed for an optimum effect which has been confirmed by FDA and EC. A number of studies have documented the safety and the efficiency of phytosterols. But there is still a big question mark on the use of it because of their adverse effect on body in form of Phytosterol oxidation products (POPs). It needs further investigation to elucidate effect of POPs within body.

Keywords: Cholesterol lowering agent, Phytostanols, Phytosterols, Sitosterolemia

INTRODUCTION

Plant sterols are nonnutritive compounds (or phytochemicals) which regulate the membrane fluidity of plant cells (Brufaua et al., 2008; Kritichevskya and Chen, 2005). The same function, cholesterol does in animals. Plant sterols include sterols and stanols and these are called phytosterols and phytostanols respectively but combinedly and generally they are called phytosterols. Structurally, both phytosterols and cholesterol have same sterol ring but the difference is in the side chain (Jong et al., 2003; Fernandes and Cabral, 2007; Cantrill and Kawamura, 2008) Phytosterols have additional alkyl substituents at C-24 and/or a double bond at C-22. More than 200 phytosterols (PS) have been identified in which β-sitosterol (65%), campesterol (32%), and stigmasterol (3%) are most abundant (Vannierlo et al., 2013). Ergosterol is mostly found in fungal cell. In plant tissues, PS occur in five common forms: free sterols, fatty-acid esters (steryl ester), steryl glycosides, acylated steryl glycosides, and hydroxycinnamic acid steryl esters (Moreau et al., 2002). Stanols do not have double bonds in the sterol ring and are called saturated sterols (Moreau et al., 2002.). Stanols are less abundant in nature than sterols. Main stanols are campestanol and sitostanol. Plant stanols are also produced by hydrogenating sterols (Chen et al., 2013). These phytosterols are normal constituents of the human diet.

Absorption and metabolism of phytosterols: Cholesterol absorption in humans varies from 30% to 60% but absorption of PS is rather low (Salen et al., 1989; Miettinen et al., 1990; Ling and Jones, 1995; Garcia-Llatasa and Rodriguez-Estrada, 2011). Absorption levels for campesterol (9.4–14.8%) are approximately 3 times higher than for β-sitosterol (3.1–4.5%) and stigmastanol (~4%). Absorption of campestanol and sitostanol has varies (0.1–2%) (Heinemann et al. 1993; Miettinen et al., 2000, Piironen et al., 2000; Sanders et al., 2000). The reason behind more cholesterol absorption is the presence of a double bond between C-5 and C-6 which increases the absorption rate. But in phytosterols, the Increase in the side chain length decreases its absorption. Phytostanols do not have double bond in sterol ring, which decreases the rate of absorption in body.

Mechanism of action of phytosterols: Phytosterols decrease absorption of cholesterol from diet which leads to suppressed feedback-regulation of enterohepatic cholesterol in circulation, resulting in increased production of cholesterol within body increasing the endogenous cholesterol synthesis. The absorbed phytosterols decrease the synthesis of cholesterol in body (Eisenberg, 2003; Shin et al., 2005; Micallef and Garg, 2008; Malinowski and Gehret, 2010). This way PS decreases both exogenous and endogenous production of cholesterol (Berge et al., 2000; Brufaua et al., 2008). The mechanism of cholesterol lowering action of phytosterols can be easily understood by the following ways:

Inhibition of cholesterol absorption in intestine: There is solubilization competition between cholesterol and PS in dietary mixed micelles (Wu et al., 2009; Gupta et al., 2011), in order to pass through the
There is competition for cholesterol transporters, such as done by two ways: intestinal brush border membrane (Davis and Mensink, 2005; Micallef and Garg, 2009). This is done by two ways:

- There is competition for esterase activity between cholesterol and PS, leading to a reduction of cholesterol in its absorbable form or its transport to more distal parts of the intestine where absorption is less efficient (Brufaua et al., 2008).
- There is competition for cholesterol transporters, such as the NPC1L1, between cholesterol and PS in the intestinal brush border membrane (Davis et al., 2004; Bergmann et al., 2005; Jakulj et al., 2005). Since PS and cholesterol structures are very similar (Otaegui-Arrazola et al., 2010), PS may be transported into the enterocyte, instead of cholesterol, thus reducing the uptake of cholesterol (Brufaua et al., 2008).

**Synthesis and excretion of cholesterol:** Intestinal ACAT re-esterifies the absorbed cholesterol in the mucosal cell. Since esterification of PS occurs in slow pace than that of cholesterol which encourages suppressed activity of ACAT and reduces cholesterol uptake (Rodwell et al., 1976).

- About 70–80% of the transported cholesterol is esterified, so it is possible that the incorporation into chylomicrons mainly depends on the esterification step (Ikeda et al., 1988). There is competition between cholesterol and PS for the incorporation into chylomicrons. Since PS is esterified in a minor degree than cholesterol, thus, lowers the cholesterol level.
- ABC transporters play a role in absorption of PS and cholesterol into mucosal cells. ABCG5 and ABCG8 are responsible for efflux of absorbed phytosterols and cholesterol back into intestinal lumen from enterocytes. From intestinal lumen, they are sent to large intestine where hydrolysis of cholesterol and phytosterols takes place (Berge et al., 2000).

**Food sources:** Nuts and vegetable oils can contain more than 1% of phytosterols. On the other hand, phytostanols occur in certain cereals (corn, wheat, rye, and rice), fruits and vegetables, but their concentrations are much lower than those of unsaturated PS. Oil and fat refining processes lead to a loss of PS (mainly free ones), which can vary from 10% to 70% depending on the applied conditions. PS are natural components of human diets (Weihrauch and Gardner, 1978; Phillips et al., 2005). An average daily intake of PS from natural sources is estimated between 150 and 440mg in Western countries (Ostlund, 2002; Jimenez-Escrig et al., 2006)

**Need of fortification:** Phytosterols has been known for its cholesterol lowering action since 1950s (Russel et al., 2002; Demonty et al., 2006; Ortega et al., 2006; Acuff et al., 2007; Earnest et al. 2007; Marangoni and Poli, 2010; Rocette et al., 2010). β-sitosterol had been used as a supplement and as a drug to lower serum cholesterol for a long time. But phytosterols extracted from oil is insoluble in water, relatively insoluble in oil and soluble in alcohol. So, due to its Poor solubility and bioavailability, serum cholesterol lowering effects were not always consistent and high doses and sometimes very High doses (up to 25–50 g per day) were required to show cholesterol lowering effect. After introducing effective anti-cholesterolemic drugs like statin, the use of β-sitosterol vanished (Pollak, 1953). But In 1990s, it regained interest as an idea of functional foods (Jones and Abu-Naoum, 2009). An accurate PS solubilization in the food vehicle is important for the best possible action on lipid serum levels. Foods provide a vehicle (matrix) to PS to be absorbed more efficiently. Various matrices, including fatty foods, low fat foods and non-fat food have been used. Fatty food matrix provides optimal solubility of added compounds.

**Safety level and frequency of consumption:** Government agencies, such as the FDA and in EC has confirmed about the safety level of PS. It is considered that a dose of 2 g/day of either steryl or stanyl esters should give an optimum effect (Berger et al., 2004; Jong et al., 2007; Naumann et al., 2008). 5–15% and 10–20% reduction in total cholesterol and LDL levels respectively can be expected by consuming 1.5–3 g of phytosterols or stanols (Nguyen, 1999; Tikkanen, M.J., 2005). Katan et al. (2003) reported that PS have to be present in the lumen for interference with cholesterol uptake which provided evidence of phytostanol’s independence upon number of meals (Matvienko et al., 2002; Wolfs et al., 2006; Madsen et al., 2007; Clifton et al., 2008) and doses per day (Rozner and Garti, 2006). So PS showed a long-lasting cholesterol lowering effect on its metabolism.

**Phytostanols vs. phytosterols:** No significant difference in the serum lipids reducing properties of both sterols and stanols was found when comparable studies were conducted (Jones et al., 2000; Normen et al., 2000; Noakes et al., 2002). The effects of sterols and stanols esters are also relatively equivalent (Law, 2000, Talati et al., 2010). No-observed-adverse-effect
Effect of phytosterols on different parameters:

**On fat-soluble vitamins:**
Antioxidants studies, have shown that daily consumption of 3.8 to 4.0 g plant stanols provided as fatty acid esters during a period of eight weeks significantly lowers serum concentrations of various carotenoids and tocopherols (Plat and Mensink, 2001). Plasma retinol (vitamin A) and vitamin D concentrations were not affected because the absorption or synthesis of these fat-soluble vitamins, are not transported by lipoproteins.

**On vitamin K concentrations:**
Effect on vitamin K concentration is not clear. Eight weeks of 3.8 g vegetable oil based plant stanols or 4.0 g wood based plant stanols had no effect on vitamin K dependent blood coagulation factors and fibrinolytic parameters (Nguyen and Dale, 1999). Study of Hendriks et al. (2003) contradicts the above results.

**On colon and prostate cancer:**
There is no strong and consistent evidence that sitosterol intake affects either colon or prostate cancer. (Kennedy, 1995, Klippel et al., 1997) but Woyengo et al. (2009) reported the inhibitory action of phytosterols on lung, stomach and ovarian cancer.

**On membrane properties:**
Plant sterols and stanols are incorporated into cellular membranes (Child and Kuksis, 1982) and may consequently influence membrane properties. Although one of the studies (Mora et al., 1999) showed no effects of sitosterol on the membrane fluidity, it has been suggested that plant sterols can incorporate in red blood cell membranes, replacing cholesterol, which made the erythrocytes less deformable and more fragile (Bruckerdorfer et al., 1969).

**On the immune system:**
Effects of plant sterols and stanols on immune function have not been studied in detail, but some studies do suggest that these compounds may have an effect. For example, plant sterol supplementation lowered serum interleukin-6 (IL-6) concentrations which assisted in lowering inflammatory response (Bouic et al., 1999).

**Sitosterolemia:**
It is a rare autosomal recessive disorder, with mutations in the ABCG5 or ABCG8 genes. In which there is Excessive accumulation of stanols / sterols in body because of reduced ability of liver to excrete plant sterols which is known to be associated with premature coronary artery disease tendon, tuberous xanthomas (Salen et al., 1992) and death.

**POPs:**
Phytosterols are susceptible to oxidation like cholesterol because of their inherent and close molecular structure to cholesterol (Yvonne et al., 2014). They form hydroxy, epoxy, keto and triol derivatives which are collectively known as Phytosterol Oxidation Products (POPs). It may be enzymatic or non-enzymatic (Ryan et al., 2009).

**Non-enzymatic oxidation:**
Sterol autoxidation is oxidation of the steroid nucleus through storage, processing and preparation of foodstuffs which is called non-enzymatic oxidation.

**Enzymatic oxidation:**
It is conversion of phytosterols to their oxides on application of enzymes vivo. Formation of cholesterol oxidation products (COP) is the result of enzymatic activity of the intestinal microflora (Hwang and Kelsey 1978). It may possible with the PS also, encouraging POP formation in vivo.

Four individual phytosterol oxides are: 7-ketocampesterol, 7-keto-b-sitosterol, 7-b-OH-campesterol and 7-b-OH-b-sitosterol.

Effect of POP on cholesterol uptake and its metabolism and other body organs is still to be uncovered. It requires future investigation to elucidate their specific effects on human health and to reduce their production in foods and in vivo.
Research should be done for effectiveness of PS for cation of PS in non-fat food should be encouraged. Tosterols should be preferred for consumption. Forti ifi cost of medicines. Natural and available form of phy- tients who have fear of intolerance, side effects a nd were reported. So it might be a better option for pa- ted with decreased level of fat soluble vitamins l ike phytosterols. No teratogenic effect and no toxicity carotene and tocopherol was seen on consumption of available in market. No adverse effect of risk associ- Earlier, the use of phytosterols were limited as dr ugs (2006) John al. Sridevi al. Quı´lez al. Hansel al. Oksana al. (2012) Sailaja al. (2014)

Table 2: Health benefits of phytosterols in different studies.

<table>
<thead>
<tr>
<th>Author</th>
<th>Outcome measures</th>
<th>Subjects</th>
<th>Product</th>
<th>Dose</th>
<th>Duration</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oksana et al. (2002)</td>
<td>Plasma TC and LDL cholesterol</td>
<td>Mild hypercholesterolemic young men</td>
<td>Round beef with 2.7 g of phytosterols</td>
<td>8 i n g l e dose per day</td>
<td>4 weeks</td>
<td>Lowered TC (9.3%), LDL (14.6%), TC:HDL cholesterol (9.1%) from baseline.</td>
</tr>
<tr>
<td>Qui´lez et al. (2003)</td>
<td>TC, LDL, TG lipoprotein</td>
<td>Normocholesterolemic subjects</td>
<td>PS, Croissant and muffin</td>
<td>two pieces daily (3.2 g of PS per day)</td>
<td>8 wk</td>
<td>Decrease in TC (8.9%) and LDL-C (14.7%) as compared to control. No changes in TG, HDL-C and lipoprotein.</td>
</tr>
<tr>
<td>Sridevi et al. (2004)</td>
<td>Plasma lipoprotein profile</td>
<td>Mild hypercholesterolemic healthy subjects</td>
<td>PS fortified orange juice</td>
<td>2g phytosterols per day</td>
<td>2 weeks, 8 weeks</td>
<td>Decreased total (7.2%), LDL (12.4%), and non-HDL cholesterol (7.8%) from baseline. Apolipoprotein B levels (9.5%) no changes in TG and HDL. Reduction in plasma total (4.7%), LDL cholesterol (6%), ratio of total and HDL (7.4%) as compared to control. No changes in HDL, TG, serum Vitamin A, E and serum β carotene.</td>
</tr>
<tr>
<td>John et al. (2006)</td>
<td>Total, LDL cholesterol, vitamin A and carotenoids</td>
<td>Hypercholesterolemic subjects</td>
<td>Cocoa flavanol-enriched snack bar containing 1.5 g phytosterol</td>
<td>2 serving per day</td>
<td>6 weeks</td>
<td>Plasma LDL-cholesterol concentrations were reduced by 7.8% as compared with control. No significant changes in TG, HDL-C and β carotene.</td>
</tr>
<tr>
<td>Hansel et al. (2007)</td>
<td>LDL-C, HDL-C, TG, β carotene, Moderate Hypercholesterolemic subjects</td>
<td>low-fat Fermented milk (FM) enriched with 0.8 g PS ester per portion</td>
<td>2 low-fat portions</td>
<td>6 weeks</td>
<td>Decreased plasma TG, TC and LDL-C, hepatic TG and TC as compared with control.</td>
<td></td>
</tr>
<tr>
<td>Qianchun et al. (2012)</td>
<td>Changes in antioxidant defence capacities and lipid profile</td>
<td>Male Wistar rats</td>
<td>Diets containing phytosterol fortified flaxseed oil</td>
<td>2000mg/100g</td>
<td>4 weeks</td>
<td>Decrease in serum TC (6.12%), TG (6.21%) and LDL-C (9.05%) as compared to control.</td>
</tr>
<tr>
<td>Sailaja et al. (2014)</td>
<td>TC, TG and LDL-C</td>
<td>Normocholesterolemic and mildly hypercholesterolemic</td>
<td>PS incorporated (1.5%) papaya fruit bar</td>
<td>30 g (fruit bar) per day</td>
<td>30 days</td>
<td>Decrease in serum TC (6.12%), TG (6.21%) and LDL-C (9.05%) as compared to control.</td>
</tr>
</tbody>
</table>

Conclusion
Earlier, the use of phytosterols were limited as drugs for lowering cholesterol, later, it was fortified with fat matrix but now positive results have been reported for phytosterols as functional foods in other matrices also. many fortified products including spread, orange juice, pasta, yogurt, snack bars and milk drinks are available in market. No adverse effect of risk associated with decreased level of fat soluble vitamins like carotene and tocopherol was seen on consumption of phytosterols. No teratogenic effect and no toxicity were reported. So it might be a better option for patients who have fear of intolerance, side effects and cost of medicines. Natural and available form of phytosterols should be preferred for consumption. Fortification of PS in non-fat food should be encouraged. Research should be done for effectiveness of PS for general population. Role of phytosterols on colon, ves-

REFERENCES
fects of β-sitosterol (BSS) and β-sitosterol glucoside (BSSG) mixture on selected immune parameters of marathon runners: inhibition of post marathon immune suppression and inflammation. *Int. J. Sports Med.*, 20 : 258-262.


Noakes, M., Clifton, P., Ntanios, F., Shrapnel, W., Record, I.


