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RESEARCH ARTICLE

AN INSIGHT IN TO PHYTOSTEROLS: A REVIEW ON ITS BENEFITS AND POTENTIAL CONCERNS

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ABSTRACT

Phytosterols are the phytoconstituents resembling cholesterol in structure with a slight difference in side chain configuration and function. As human body cannot synthesize phytosterols, they can be obtained from the diet. The most common phytosterols include stigmasterol, Campesterol and β-sitosterol. Phytosterols have many health beneficial effects including hypocholesterolemic effect, protection from cardio vascular disorders, anti-cancer, anti-inflammatory, immunomodulatory, antioxidant activity. The most important and studied effect of phytosterols is its antihyperlipidemic activity. Many preclinical and clinical studies have been performed in order to prove this activity. Now-a-days, many functional foods are being enriched with phytosterols for its cholesterol lowering abilities. Phytosterol supplementation is also combined with the therapy of statins as well as ezetimibe in order to enhance its effectiveness. Also, a self-GRAS (Generally Recognized As Safe) procedure has been followed for them, to which USFDA raised no objections. However, some side effects of phytosterols include decrease in absorption of certain amounts of fat soluble vitamins like tocopherols and carotenoids. But this effect can be minimised by adjusting the levels of these vitamins in diet. Phytosterolemia is a rare, genetic disease due to mutation in genes coding for $ABCG_5$ and $ABCG_8$ which results in excessive absorption and high plasma levels of phytosterols.

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INTRODUCTION

Nature is an invaluable source for obtaining various natural products and phytoconstituents like alkaloids, glycosides, flavonoids, saponins, Phytosterols, Terpenoids, etc. (Bhanot *et al*., 2011). Phytosterols are phytoconstituents which are steroidal alcohols in nature and resemble mammalian cholesterol in function with a slight difference in structure (side chain configuration). Cholesterol has 8 carbon atoms in the side chain while Phytosterols contain 9 or 10 carbon atoms in their side chain (Kritchevsky and Chen, 2005). Human body cannot synthesize Phytosterols on its own and hence they are obtained from the diet (Jones and AbuMweis, 2009). Phytosterols can be naturally obtained through foods like nuts, fruits, vegetables, oils, seeds, cereals, etc. (Raju *et al*., 2013). Phytosterols have many health beneficial effects. There are mainly two types of Phytosterols present viz. - sterols and stanols with sterols being most commonly found in foods.(MacKay and Jones, 2011) The most common Phytosterols are Campesterol, β-sitosterol and Stigmasterol. Others include Brassicasterol, Avenasterol, Campestanol, β-sitostanol, etc. (Bradford and Awad, 2007).

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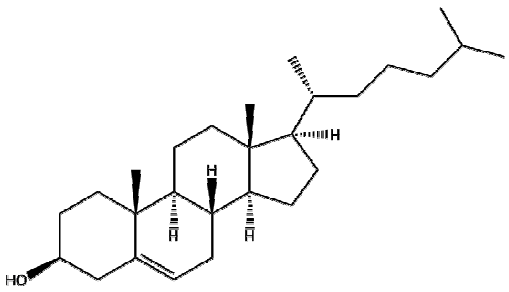
The most studied and scientifically proven health beneficial effect of Phytosterols is its cholesterols lowering ability. Other therapeutic benefits of Phytosterols include antioxidant, anti-inflammatory, anticancer, antibacterial, antifungal activities and ability to reduce cardiovascular disease risk. Because of all these health benefits, Phytosterols are now a days gaining importance as functional food ingredients.

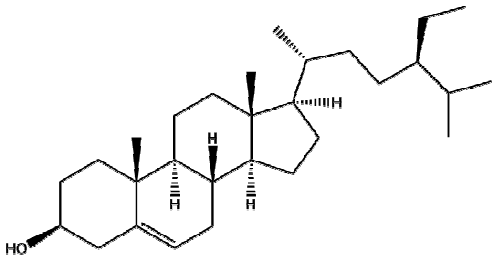
Present review will talk about the structure of phytosterols, its health benefits and potential side effects in brief.

Structure of phytosterols

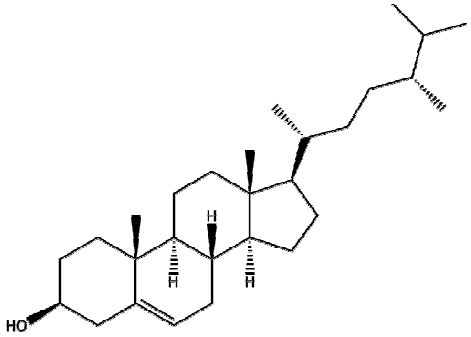
The structure of Phytosterols is almost similar to cholesterol with the difference being the presence of methyl or ethyl group at C24 and double bond between C22 and C23 in case of most commonly occurring sterols (Hovenkamp *et al*., 2008;Lagarda *et al*., 2006). Saturated forms of sterols are known as stanols (eg. Sitostanol). Phytosterols not only resemble cholesterol in structure but also in function that is to stabilize cell membrane. Figure 1 shows structure of most commonly found Phytosterols (Lagarda *et al*., 2006).



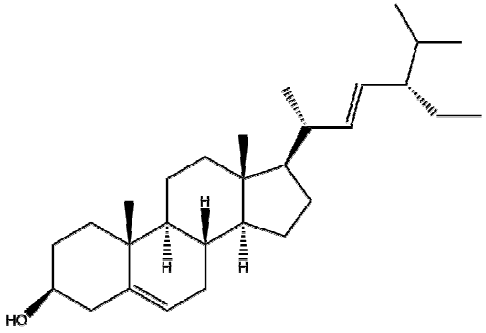
Cholesterol



Beta-sitosterol



Campesterol



Stigmasterol

Patents of Phytosterols

S.No.	Title of the Patent	Inventors	Patent No. and Date of Patent	Field of Invention	Summary
1.	Process of isolating a phytosterol composition from pulping soap	James P. Kutney, Vancouver; Egon Novak, Richmond; Peter J. Jones, Montreal, all of Canada	5,770,749 Date: Jun. 23, 1998	preparation and purification of sterol compositions item pulping soaps to the actual compositions per se and their use in dyslipidemias	The invention provides a process for purifying and preparing phytosterol compositions from pulping soap to form a unique phytosterol composition (Kutney *et al*., 1998).
2.	Topical delivery system for phytosterols	Shyam K Gupta, Scottsdale, AZ (US)	US 7,615,546 B2 Date: Nov. 10, 2009.	It relates to certain sugar esters of phytosterols which are useful for topical application.	The invention relates to sugar esters of said phytosterols which are conjugates of phytosterols with certain sugar lactones and their usefulness in some skin disorders (Gupta, 2009).
3.	Dispersion of Phytosterols	Thomas Francis Harting Glade, Santiago (CL); Miguel Fuenzalida Diaz, Santiago (CL); Alejandro Markovits Rojas, Santiago (CL)	US 2012/0046254 A1 Date: Feb. 23, 2012	Method for the production of highly stable aqueous dispersions of phytosterols, phytostanols and derivatives.	The invention relates to a process to produce an aqueous phytosterol dispersion comprising of two steps (Glade *et al*., 2010).

Biological effects

Antihyperlipidemic effect

Hyperlipidemia is one of the metabolic disorders which is characterized by alterations in lipid levels i.e. increase in Total Cholesterol (TC), Very Low Density Lipoprotein Cholesterol (VLDL-C), Low Density Lipoprotein Cholesterol (LDL-C), Triglycerides (TG) level and subsequent decrease in High Density Lipoprotein Cholesterol (HDL-C) level (Rohilla *et al*., 2012). According to WHO (World Health Organization) report, raised cholesterol level is estimated to cause 2.6 million deaths (4.5 % of total) and 29.7 million disability adjusted life years (DALYs), or 2% of total DALYs. In 2008, the global prevalence of raised total cholesterol among adults was 39%("WHO | Raised cholesterol," n.d.). Increased cholesterol levels may lead to various cardiovascular complications like hypertension, atherosclerosis, etc. Hyperlipidemia is associated with a variety of risk factors like cholesterol rich food, overweight, high alcohol consumption, stress and diabetes (Rohilla *et al*., 2012). At present, five major classes of

medications are used for hyperlipidemia therapy: statins-HMG-COA Reductase inhibitors, nicotinic acid derivatives, Fibric acid derivatives, Bile acid binding resins and cholesterol absorption inhibitors (Katzung *et al*., 2012).

Up till now, Phytosterols have been extensively studied for their ability to reduce cholesterol levels. Hence, now a day's many products in the market have added phytosterol content in them.

This cholesterol lowering ability of sterols and stanols can be attributed to several mechanisms but the main mechanism is the competition to cholesterol for solubilisation into mixed micelles at the intestinal level (Santas *et al*., 2013). Intestinal cholesterol absorption of both dietary and biliary cholesterol begins with the micellar solubilisation in the intestinal lumen. Around 50% of intestinal cholesterol is absorbed in humans in which about 2/3rd derived from the bile and other from the diet (Davis and Altmann, 2009). After the incorporation of cholesterol into the micelles, it is then transferred to the surface of the brush border membrane of intestinal enterocytes and its uptake is actively mediated by transporters mainly NPC1L1 (Niemann-Pick C1-Like1) located in the brush border membrane (Jia *et al*., 2011; Davis and Altmann, 2009). Then cholesterol is esterified with fatty acid by acyl-CoA, ACAT-2 (Cholesterol-O-acyl transferase -2) incorporated into chylomicrons and then secretion to the lymph through the basolateral membrane of the enterocyte (Nguyen *et al*., 2012). Unesterified cholesterol can be pumped back to the intestinal lumen by ABC (ATP Binding Cassettes) transporters G_5 and G_8 ($ABCG_5$/ $ABCG_8$) in direct opposition to NPC1L1 (Brown and Yu, 2009). As cholesterol absorption is a complex process and involves many different molecular targets, recent studies have proposed that phytosterol can play vital role in the process. ABCA1 can mediate the incorporation of sterols into nascent HDL (High Density Lipoprotein) leads to their secretion into the lymph. Phytosterols have greater affinity to micelles involved in fat digestion as compared to cholesterol thereby reducing intestinal cholesterol absorption. However, there are several other mechanisms by which phytosterols and stanols reduce cholesterol levels (Santas *et al*., 2013).

One of the possible mechanisms of reduction of plasma cholesterol by phytosterols can be competition of phytosterols with cholesterol for esterification in the enterocyte by ACAT-2 enzyme, hence reducing its incorporation into chylomicrons. Recently, it has been reported that a route exists in the body for cholesterol removal that does not involve the hepato-biliary system. This is called as Trans intestinal cholesterol excretion (TICE). It has been found that plant sterol feeding results in stimulation of cholesterol excretion via TICE. Hence, it can be said that this route might be important for the cholesterol-lowering properties of phytosterols in humans (Brufau *et al*., 2011). However, further research is necessary in order to know exact molecular mechanism by which phytosterols reduce cholesterol levels in human.

Protection from Cardio Vascular Diseases (CVD)

Cardiovascular diseases like coronary heart diseases, hypertension, congenital heart diseases, heart failure, etc. are the number one cause of death globally. As per WHO (World Health Organisation), estimated 17 million people died from CVD in 2005, representing 30% of all global deaths. By 2030, WHO has estimated 23.6 million people will die from CVD. Major causes of CVD are tobacco use, unhealthy diet and physical inactivity (WHO, n.d, Cardiovascular Diseases). As stated earlier, plant sterols have ability to reduce serum cholesterol levels and NCEP ATP- III (National Cholesterol Education Programme Adult Treatment Panel-III) report recognizes LDL-C (Low Density Lipoprotein- Cholesterol) as the main atherogenic lipoprotein and identifies it as the primary target of cholesterol lowering therapy. ATP- III introduced the principle of maximal dietary therapy, the primary aim of which is to achieve as much LDL lowering as possible, short of drug therapy. According to ATP- III, maximum dietary therapy includes reducing dietary cholesterol to < 200 mg/day, however additional LDL lowering can be obtained by adding ≥10 gm/day of viscous fibre and 2 gm/day of plant sterols or stanols. It was found that conversion of plant sterols to stanols increased lowering of serum LDL. Several clinical trials with plant stanols esters have proven that 1-3 gm/day of stanols will reduce LDL-C levels by up to 15%, but the optimal intake of plant stanols esters is approximately 2gm/day (Grundy, 2005).

However, Phytosterolemia which is a rare autosomal recessive genetic disorder which leads to accumulation of plant sterols in the body because of an inability to clear absorbed plant sterols from the blood. This disorder results in 50-100 fold increase in plant sterol levels. Several individuals with phytosterolemia have developed premature coronary heart disease which suggests that the presence of high serum levels of phytosterols can be atherogenic (Mackay and Jones, 2013).

Anticancer activity

Cancer is one of the most dreaded disease is characterized by loss in the normal control mechanisms that governs cell survival, proliferation and differentiation and leads to uncontrolled multiplication of abnormal cells (Katzung *et al*., 2012). Cancer continues to be one of the leading causes of fatality worldwide. According to WHO, there were approximately 14 million new cases and 8.2 million cancer related deaths in 2012. The number of new cases is expected to rise by about 70% over the next two decades ("WHO | Cancer," 2015.). It has been evaluated that phytosterols can reduce cancer risk, by various trials. Various studies suggests that phytosterols can play an important role in the prevention of several types of cancer such as lung, stomach, prostate, ovarian and breast cancer (Santas *et al*., 2013). Numerous studies have been performed in order to assess cancer protective effects of phytosterols. A series of case control studies were carried out at major hospitals in Uruguay to investigate the role of dietary phytosterols in the risk of some cancers like lung, breast, stomach, oesophageal. These studies included from 100 to 500 newly diagnosed and histologically verified cases of specific cancers and frequency matched control patients of similar age, gender, residence and urban/rural status. All the patients were interviewed using food frequency questionnaires based upon 64 food items considered representative of local diet. Published data were used to evaluate specific intakes of β-sitosterol, Campesterol, stigmasterol and total phytosterols. Total

phytosterol intake was associated with specific protective effects in lung, breast, ovarian, stomach and oesophageal cancer (Mendilaharsu *et al*., 1998; Ronco *et al*., 1999; McCann *et al*., 2003; De Stefani *et al*., 2000)

Studies were performed on immune deficient mice (SCID mice). They were fed with 2% phytosterol, 2% cholesterol or the 0.2% cholic acid vehicle. Then the mice were injected with MDA-MB-231 estrogen receptor negative human breast cancer cells into their inguinal mammary fat pads. At 8 week, the tumor sizes in the animals fed with the phytosterol diet were 33% smaller than those in animals fed with cholesterol diet. There was 40-43% reduction in tumor size in animals (SCID mice) fed with phytosterol diet versus the cholesterol diet against the proliferation and metastasis of PC-3 human prostate cancer cells (Awad *et al*., 2000).

There are many mechanisms by which phytosterols show protective effect against cancer such as inhibition of the production of carcinogens, cancer cell growth, invasion and metastasis and promote apoptosis of cancerous cells (Woyengo *et al*., 2009).

Anti-inflammatory activity

Inflammation can be defined as the immune response to infection or injury which can be characterized by pain, rise in temperature and edema. There are number of inflammatory mediators released by monocytes including cytokines, chemokines, adhesion molecules as well as secreted by visceral adipose tissue like TNF-α (Tumor Necrosis Factor-α), PAI-I (Plasminogen activator inhibitor-I), IL-1β(Interleukin), IL-6, IL-8, IL-10, IL-15, complement factors and PGE2 (Prostaglandin E2); these mediators stimulate the secretion of acute phase protein, CRP (C-reactive protein) by the liver. CRP is positively related with the risk of future cardiovascular events (Katzung *et al*., 2012. Pg. 635-636). Inflammation plays an important role in the process of atherogenesis. Various in-vitro and in-vivo studies have been carried out to evaluate anti-inflammatory effect of phytosterols. Majority of in-vitro studies and in-vivo studies in animals suggests anti-inflammatory effects of phytosterols, however results of most of the in-vivo studies in humans are inconsistent. Hence long term and well controlled intervention studies of phytosterol supplementation on inflammation are required.

The possible mechanism behind the anti-inflammatory activity of phytosterols is unknown. In mice, a decrease in edema and pro inflammatory cytokines suggests anti-inflammatory activity. As the effect of these compounds on the inflammatory markers like IL-6, TNF-α, CRP in human are not consistent and hence be tested in long term, well controlled intervention studies (Brull *et al*., 2009).

Immunomodulatory activity

The immune system has evolved to protect host from pathogens and to eliminate disease. There are two types of immune systems viz. innate and adaptive immune systems. Th (T-helper) cells are very important in the initiation and regulation of the adaptive immune response and can be divided into various subtypes viz. Th1, Th2 and Th17 cells, and CD^{4+}/CD^{25++} and $Foxp^{3+}$ regulatory T cells (Katzung *et al*., 2012 pg. 977-978). Various ex-vivo and in-vivo studies have been performed on mice in order to check the effects of phytosterol supplementation on Th1/Th2 balance. It has been demonstrated that phytosterols might induce a Th1 shift in in-vivo animal study. Results of human study indicate that phytosterols can shift the Th1/Th2 balance towards a more Th1 dominant response, however the mechanism behind this effect is unclear.

Apart from these biological effects, phytosterols also show antioxidant activity (Wang *et al*., 2002), antibacterial activity (Sharma, 1993) and also tested for their benefit in the patients with benign prostatic hyperplasia (CARBIN *et al*., 1990).

Phytosterols as functional food ingredients

Functional foods are generally used to enhance certain physiological functions, in order to prevent or to cure diseases (Varela *et al*., 2002). Various studies support significant cholesterol lowering ability of phytosterols. The United States National Cholesterol Education Programme has recommended a dose of 2 gm/day for reduction of LDL cholesterol and evidences suggests around 10% reduction in LDL cholesterol depending upon phytosterol dose (Ostlund, 2007). Hence, in recent years functional foods enriched with phytosterols gained huge popularity (Eussen *et al*., 2011).

The first pharmaceutical product containing phytosterol was Cytellin marketed by Eli Lilly from 1954 to 1982 for the treatment of elevated cholesterol. The active ingredient in Cytellin was a mixture of free phytosterols, mainly β- sitosterol suspended in oil or methyl cellulose. Cytellin was discontinued in 1985 due to lack of palatability which was likely due to the difficulty in dissolving high doses of free sterols in an aqueous mixture hence yielding an unpleasant gritty texture and taste(Dutta, 2004; McKay *et al*., 2011). The first functional food containing phytosterols was margarine first launched in the Finnish market in 1995. In addition to margarines, now a days there are several other phytosterol enriched foods such as yoghurt drinks, dairy-free drinks, low or reduced fat milk, soft cheese, bread, salad dressing, snack bars, etc. (De Jong *et al*., 2004; Gylling *et al*., 2014). Even though there are limited number of studies investigating the long term effects of phytosterol enriched functional foods, there is no evidence to suggest their consumption to be unsafe, making them effective for management of hypercholesterolemia (Micallef and Garg, 2009). In USA, a self-GRAS (Generally Recognized As Safe) procedure has been followed for phytosterols, to which USFDA raised no objections (Cantrill *et al*., 2008).

Combination therapy

In order to enhance the effectiveness of phytosterols in lowering the cholesterol level, they can be used in combination with other drugs such as statins, ezetimibe, fibrates, etc (Santas *et al*., 2013). Statins are the compounds which competitively inhibit the conversion of HMG-CoA (3-Hydroxy-3-methyl glutaryl coenzyme-A) to mevalonate by the enzyme HMG-CoA reductase (Tripathi, 2008). As phytosterols and statins

reduce plasma cholesterol by two different mechanisms i.e. inhibition of cholesterol absorption and inhibition of synthesis of cholesterol respectively, the added benefit of combination therapy of phytosterols and statins has been evaluated in recent clinical trial (Micallef and Garg, 2009). Several studies demonstrate the additive effect of the phytosterols and statin combination resulting in incremental decreases in LDL cholesterol from about 10-20%. Hence this combination may provide sufficient improvement to total and LDL cholesterol level (Thompson, 2002).

Ezitimibe is a compound which decreases cholesterol absorption by blocking the NPC1L1 (Niemann-Pick C1-Like1) transporter. Phytosterols also decreases absorption of cholesterol but by a different mechanism, phytosterol displace cholesterol from intestinal micelles. Hence ezetimibe can be considered as competitor of phytosterols at molecular level. But clinical data are limited to prove advantage of combination therapy including ezetimibe and Phytosterols (Carr *et al*., 2010; Gylling *et al*., 2014). Clinical studies showed an additive effect on LDL-C levels when phytosterols are consumed with fibrates. Fibrates are mainly used to lower serum TG (Triglycerides) and as a secondary effect, raise HDL cholesterol. Hence the combination of fibrates and phytosterols has been studied as a therapeutic option to simultaneously lower TG and LDL cholesterol levels, but there is limited data suggesting an additive effect of phytosterols with fibrates (Gylling *et al*., 2014; Carr *et al*., 2010).

Safety of phytosterols

As mentioned earlier, phytosterols, stanols and their supplements are most commonly used now-a-days for their hypocholesterolemic effect. Hence, substantial interest has focused on the safety of plant sterols and stanols when used as hypocholesterolemic agents. The amount of plant sterol or stanols that is required for cholesterol lowering ranges from 1-3 gm/day which is well above typical consumption patterns which rarely exceed 400-600 mg/day (Gylling *et al*., 2014).
The first toxicity study with phytosterols was performed for preparations containing phytosterols to be marketed in the 1950s for cholesterol lowering, containing about 65-90 % of sitosterol. No detectable effects were observed in rats, rabbits and dogs fed with large amounts of phytosterols over a 2 year period with regard to growth, serum proteins, blood urea nitrogen, gross and microscopic appearance. The lack of toxicity and genotoxicity has been evaluated for phytosterols in rats fed mixed phytosterols at levels of 0.1-5.0% (w/w) for 90 days (Lea and Hepburn, 2006).

The safety and tolerability of phytosterols was assessed in an 8-week study in 48 free-living men and women consuming phytosterols up to 9 gm/day (Carr *et al*., 2010). No adverse effects were observed in various body systems as well as there were no psychiatric effects. In a long-term study, men and women consuming 2.7 gm/day phytosterols for 1 year exhibited lower LDL-C concentration with no change in the concentration of liver enzymes, albumin, glucose, sex hormones or iron (Hendriks *et al*., 2003). Also studies concluded that phytosterols do not result in deleterious effects in reproduction or cancer risk (St-Onge and Jones, 2003). Hence, from overall evidence from long-term monitoring trials and experimental models indicate that plant sterols or stanols present a favourable safety profile to be incorporated into diet for cholesterol lowering (Gylling *et al*., 2014).

Side effects of phytosterols

The most important concern about intake of phytosterols is their interference with the absorption of carotenoids, it decreases the carotenoid levels in the blood (QuÍlez, 2003). Several studies have reported that there is a parallel decrease in plasma carotenoid levels on consumption of high amount of Phytosterols (Santas *et al*., 2013). A review of some randomized trials, showed plant sterols and stanols lower blood levels of β-carotene by about 25%, α-carotene by 10% and that of vitamin E by 8% (Law, 2000). Kritchevsky *et al*. combined 9 different studies in humans that were administered with pure stanols (0.8- 3.2gm/day), pure sterols (0.8- 3.6 gm/day), wood derived stanols (2.3 gm/day) or vegetable derived stanols (2.6 gm/day) during a variable period. Results of these studies showed relevant dose-dependent decrease in plasma total cholesterol and LDL-C, which was correlated with a parallel decrease in carotenoid concentration, up to 20% in some cases (Santas *et al*., 2013).

Carotenoids are fat soluble and they circulate with the LDLs and whatever that lowers the levels of LDL will also lower the levels of carotenoids. The key role of vitamins like tocopherols and carotenoids is to protect LDL-C from oxidation. Phytosterols reduce the amount of LDL-C and lipophilic vitamins are associated with LDL particles. Hence blood concentration of these vitamins needed to be adjusted for lower LDL-C concentration (Jones and AbuMweis, 2009). Serum carotenoid levels can be adjusted either by increasing the intake of carotenoid rich foods or by taking supplements containing these carotenoids. This has been attempted in one clinical study which was proven to be effective (Noakes *et al*., 2002). The addition of carotenoids in the diet in the form of the recommended 5 servings of fruit and vegetables per day effectively maintains carotenoid levels in normal range in subjects supplemented with phytosterols (Marangoni and Poli, 2010).

A recent study showed that consumption of phytosterol-fish oil ester resulted in higher vitamin levels than other phytosterol esters (Jones *et al*., 2007). Hence it has been noted that consumption of free phytosterols and phytostanols may not induce malabsorption of fat-soluble vitamins and antioxidants as much as that caused from consumption of fatty acid ester form.

Phytosterolemia

Phytosterolemia or sitosterolemia is a rare, genetic, autosomic recessive disease which is characterised by excessive absorption and high plasma levels of plant sterols and stanols with normal or moderately increased cholesterol levels (Gylling *et al*., 2014). Patients with sitosterolemia absorb between 15-60% of sitosterol as compared to less than 5% absorbed in normal subjects (Marangoni and Poli, 2010). In this disease, there is an accumulation of phytosterols not only

in plasma but also in adipose tissue, skin, aorta and other tissues (Santas *et al*., 2013).

It occurs due to complete mutation in 2 adjacent oppositely oriented genes coding for the ATP-binding cassette transporters G_5 and G_8 ($ABCG_5$/ $ABCG_8$) located in a head-to-head organization on human chromosome 2p21(Izar *et al*., 2011). $ABCG_5$ and $ABCG_8$ play important role in regulating intestinal phytosterol absorption by excreting phytosterols that have already taken up from the enterocytes back into intestinal lumen (Marangoni and Poli, 2010). Some serious clinical manifestations of phytosterolemia include premature atherosclerosis, xanthomas (Patel and Thompson, 2006). Phytosterols have been shown to accumulate in atherosclerotic lesions of phytosterolemic subjects in the same ratio as present in serum. But, the phytosterol/cholesterol ratio is higher in phytosterolemia that in normal subjects in plasma and tissue (Gylling *et al*., 2014).

Conclusion

It is well established by evidences that Phytosterols decreases blood levels of total and LDL cholesterol which can be useful in hypercholesterolemic patients. Phytosterols and stanols also show wide array of other beneficial effects such as protection from tumor growth, anti-inflammatory, Immunomodulatory and antioxidant activity, etc. But Phytosterols exhibit these biological activities at high doses and hence cannot be considered as the main component of medicinal preparations (Mehtiev and Misharin, 2008). Although, phytosterol intake is generally considered safe to date, side effects are reported in sitosterolemic and also in nonsitosterolemic subjects and which requires further investigation (Brufau *et al*., 2008). Current research on health benefits of Phytosterols is providing valuable insights with regard to the pathways associated with the beneficial effects of Phytosterols, but their exact mechanism is not fully clear. Hence more studies are needed in this regard (Santas *et al*., 2013). Also there is no study on synthetic preparation of phytosterols.

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