β-Sitosterol: Predominant Phytosterol of Therapeutic Potential

32

Ena Gupta

Abstract

In plant cell membranes, there is a group of naturally occurring compounds referred to as phytosterols (plant sterol and stanol esters). Phytosterols are structurally similar to cholesterol, occurring in plants and vary in absence or presence of a double bond in carbon side chain. These phytosterols does not produce undesirable side effects and are generally recognized as safe (GRAS). There are around more than 200 sterols, and allied compounds have been identified. The plants exclusively made the most predominant phytosterol that is β-sitosterol, a white waxy powder in its pure form. A deoxyxylulose and mevalonate pathway promotes its biological synthesis. It is majorly found in plant kingdom (nuts and seeds, fruits, fresh vegetables, and higher concentration in unrefined plant oils such as flaxseed, olive, canola, corn, and sesame oil). Some clinical and preclinical studies suggest that β-sitosterol provides many significant health benefits. It lowers the level of bad cholesterol (LDL) and reduces the risk of coronary artery disease, heart attack, and atherosclerosis, preventing many types of cancers along with supporting body's natural recovery process. This review article is aimed at the chemistry of β-sitosterol, biosynthetic pathways, and their metabolism along with wide-range pharmacological and therapeutic applications.

Keywords

Phytosterols · β-sitosterol · Therapeutic applications

E. Gupta (✉)
Department of Home Science, University of Allahabad, Prayagraj, Uttar Pradesh, India

P. Mishra et al. (eds.), *Innovations in Food Technology*,
https://doi.org/10.1007/978-981-15-6121-4_32

32.1 Introduction

In plants various types of chemicals are present that are nonnutritive but possess disease-preventive properties. The major chemicals which are produced by plants through primary and secondary metabolism are termed as "phytochemicals." It is a Greek word named *phyton*, which means "plant." There are more than thousands of phytochemicals, and plants produce these chemicals for growth or to protect themselves against pathogens or competitors. In 1994 the term phytochemicals was first introduced, and quickly it became a topic of interest among scientists and researchers. One of the important classes of bioorganic molecules is phytosterols (a subgroup of the steroids). Plant-derived compounds (sterols and stanols) are commonly known as phytosterols having structural similarity to cholesterol, and it is widely spread among plants, animals, and fungi group (Fig. 32.1). The third most important class of lipid are sterols which are considered as membrane reinforcers as they maintain the domain structure of cell membranes and also regulate the important biological processes (Ribeiro et al. 2007; Yin et al. 2018). The major sterols present in vertebrates are cholesterol (CHO) mainly found in animal's cell membrane. In developmental signalling it serves as secondary messenger and also affects the cell membrane's fluidity (Akhisa and Kokke 1991).

In plant species the embryonic growth is due to the presence of most important constituents of the sterol profiles such as two 24-ethyl sterols, sitosterol (SIT), campesterol, and stigmasterol (STI). In plants majorly two classes of plant sterols have been identified (Fig. 32.2): (I) campesterol, β-sitosterol, and stigmasterol are the most abundant sterols found in plant and human diet, and there is a presence of double bond in the sterol ring of these plant sterols. (II) campestanol and sitostanol are some important stanols that comprise of 10% of the total dietary phytosterols, and these plant stanols do not have a double bond in the sterol ring; These saturated sterols show unique health benefits by promoting embryonic growth of plants and involved in forming liquid-ordered (*lo*) lipid domains (lipid rafts) important for biological processes like polarized growth of root hair and pollen tube, cytoskeleton reorganization, secondary messenger in signal transduction, cellular sorting, asymmetric distribution of membrane components, and infectious diseases. This review article is aimed at the chemistry of β-sitosterol, biosynthetic pathways, and their metabolism along with wide-range pharmacological and therapeutic applications.

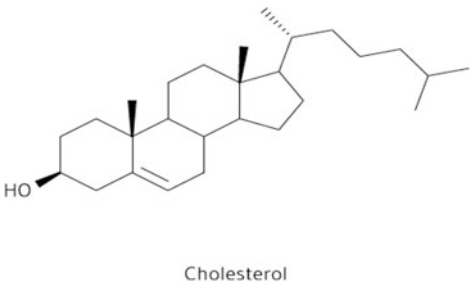

Fig. 32.1 Chemical structure of cholesterol

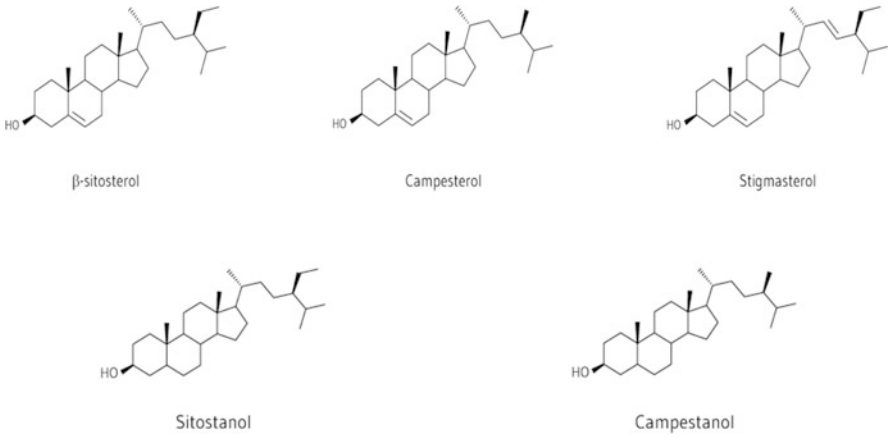

Fig. 32.2 Chemical structure of plant-derived sterols and stanols

Table 32.1 High phytosterol-rich foods (mg/100 g) (Kritchevsky 1997)

Food sources	Total phytosterol content (mg/100 g)
Oils	
Rice bran	1055
Corn	952
Wheat germ	553
Nuts	
Cashew	158
Almond	143
Pecan	108
Legumes	
Pea	135
Kidney bean	127
Broad bean	124
Vegetables	
Beet root	25
Brussels sprout	24
Cauliflower	18
Fruits	
Orange	24
Banana	16
Apple	12

These phytosterol-rich metabolites constitute health-promoting functions in natural foods and being constantly marketed for decades worldwide. Significantly high phytosterol content was found in plant oils or products made from them, whereas in fruits and vegetables, it is present in lesser extent as depicted in Table 32.1 where the sum of phytosterol content is due to presence of campesterol, stigmasterol, and beta-sitosterol. In plants phytosterols are mostly present in free forms (in plants, vegetable

oils, corn oil, rice bran oil, wheat germ oil) and esterified forms (whole wheat, wheat germ oil, vegetable oils, corn oil, Promise activ® spreads (sterol esters), Benecol® spreads (stanol esters), whereas in some foods, it is in the glycosylated form that has an attached glucose molecule like bran, seeds, legumes, nuts, whole grains, wheat germ, vegetables, fruits, and unrefined plant-derived lecithin (Moreau et al. (2002)). Many clinical studies assessed the beneficial effects of number of food products enriched in plant sterols/stanols found on the market, such as spreads, margarines, yogurts, and milk (Gylling and Simonen 2015).

32.2 Structure

β-sitosterol is an optically active steroidal compound. Optical activity is reflected in its chemical name (3S,8S,9S,10R,13R,14S,17R)-17-[(2R,5R)-5-ethyl-6-methylheptan-2-yl]-10,13-dimethyl-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-ol. Like mammalian sterols, phytosterols possess same tetracyclic core structure, for example, cholesterol, but there is a difference in the nature of the substitution at C_{24} and absence or presence of a double bond at C_{22}. Plants contain mixture of phytosterols; the most predominant sterols include β-sitosterol ($C_{29}H_{50}O$, molecular weight 414.71 g/mol, unsaturated sterol with one double bond in sterol ring structure), campesterol (structurally similar to β-sitosterol but instead of an ethyl group, it has a methyl substituent at C_{24} position), and stigmasterol (is an unsaturated sterol, having one double bond in the side chain and one double bond in the sterol ring structure); another important saturated sterol is stigmastanol with sterol ring structure and side chain, whereas the major phytosterol present in most plant foods is β-sitosterol, and the second abundant is campesterol comprising 95% of isolated phytosterols, and there is a significant contribution of other sterols specifically in seeds and nuts (Phillips et al. 2005); examples are shown in Fig. 32.2.

32.3 Synthesis

Until now β-sitosterol has not been totally synthesized; its production is through pure stigmasterol by two ways. Firstly, β-sitosterol was produced together with fully saturated stigmastanol and different levels of stigmasterol by hydrogenation of side-chain $\Delta_{22–23}$ alkene, whereas in the second approach, this selective hydrogenation is followed by protection of $\Delta_{5–6}$ alkene to produce cyclopropylcarbinyl ether. Hydrogenation of the $\Delta_{22–23}$ double bond should be followed in this process along with solvolyzation of the cyclopropane for the production of $\Delta_{5–6}$ alkene and C3 alcohol. The second method synthesizes high purity β-sitosterol. In reality, semi-synthesis of β-sitosterol is still a challenge due to production of the methyl ether by products whose elimination is quite difficult (Hang and Dussault 2010; Khripach et al. 2005).

32.4 Biosynthesis

During membrane biogenesis biosynthesis of sterols and particular lipids occurs through 13C-labeling patterns. Research studies suggest that in the synthesis of β-sitosterol, both deoxyxylulose and mevalonate pathways are involved (De-Eknamkul and Potduang 2003). Most accurate mechanism involved for the formation of β-sitosterol comes from cycloartenol which varies according to the organism used. The beginning of cycloartenol biosynthesis is by joining of one molecule of isopentenyl diphosphate (IPP) and two molecules of dimethylallyl diphosphate (DMAPP) to produce farnesyl diphosphate (FPP). Later, tail-to-tail attachment of two molecules of FPP forms a triterpene (squalene). Finally through a cyclization, cycloartenol is produced by reaction of squalene with an intermediate 2,3-oxidosqualene.

32.5 Acceptable Daily Intake (ADI)

β-sitosterol is the most common plant sterol having minimal potential for adverse effects in the organism, and it has been considered as natural, effective, and safe nutritional supplement. A report was published by international organizations such as USFDA, EFSA, and JECFA on phytosterols as food additives or supplements without emphasizing specifically on any individual compound. British Dietetic Association (2012) recommended the daily dietary intake of phytosterols (200–400 mg/day) and plant stanols (30–50 mg/day) from natural sources (Ras et al. 2014). The Joint FAO/WHO Expert Committee on Food Additives (*JECFA*) in 2009 recommended the approximate calculated values from phytosterol mixtures, not specific information on β-sitosterol separately; the acceptable daily intake (ADI) is 40 mg/kg_BW/day; no-observed-adverse-effect level (NOAEL) is 4200 mg/kg_BW/day; margin of safety (MOS) is 210 mg/kg_BW/day; and for the systemic and cosmetic products is 8.3 mg/kg_BW/day, respectively (Schneider et al. 2009). The scientific opinions of European Food Safety Authority (EFSA) were published on phytosterols but not solely on β-sitosterol (Raport 2008).

32.6 Therapeutic Applications

β-sitosterol has been shown to possess multiple roles and plays an important part in biomedical world as it is a natural bioactive compound found in cells and membranes of all oil-producing plants, trees, grains, vegetables, fruits, and seeds. It is known to possess potential health benefits by being nontoxic, safe, and valuable nutritional supplement with diverse therapeutic applications against different communicable and noncommunicable diseases.

32.6.1 Antimicrobial Activity

Higher plants are resistant to various bacteria due to presence of antibacterial substances in their plant tissues. Antibacterial and antifungal property was shown by β-sitosterol obtained from different plants without causing any toxicity in brine shrimp lethality assay (Kiprono et al. 2000). Antitrypanosomal and mosquito larvicidal activities were shown by plant extracts or formulation containing β-sitosterol (Rahuman et al. 2008; Nweze 2011). In the bioactive compound (β-sitosterol-3-*O*-glucoside), a derivative of β-sitosterol shows wide-spectrum antimicrobial activity and was isolated from *Lannea kerstingii* Engl. and *K. Krause* (Anacardiaceae) using dry vacuum liquid chromatography. Antimicrobial activity of β-sitosterol-3-*O*-glucoside (200 μg/ml) was determined and found active against *S. aureus*, *S. typhi*, *E. coli*, *K. pneumonia*, *B. subtilis*, and *P. mirabilis* with zone of inhibition ranging from 24 mm to 34 mm. The compound was equally active against the fungi *C. tropicalis* and *C. albicans* with MIC ranging from 25 μg/ml to 50 μg/ml, while minimum bactericidal and minimum fungicidal concentration (MBC/MFC) ranged from 50 μg/ml to 200 μg/ml (Njinga et al. 2016). In another study bioassay-guided fractionation was used to isolate β-sitosterol from *Vitex agnus-castus* (Verbenaceae), commonly called (chasteberry), and was found to inhibit the growth of pathogenic bacteria *S. epidermidis*, *S. aureus*, *B.subtilis*, *E. faecalis*, and *E.coli* (Arokiyaraj et al. 2011).

Antimicrobial activity of β-sitosterol derivative (β-sitosterol-D-glucopyranoside) obtained from *Desmostachya bipinnata* (L.) Stapf was identified in combination with antibiotics; results of time kill curve shows that most of the pathogens are killed within 5–10 h with (MIC 6–50 μg/ml) working synergistically with most antibiotics, mainly with ciprofloxacin (Subramaniam et al. 2014).

32.6.2 Antioxidant Activity

Research studies suggest that β-sitosterol has been shown to possess antioxidant property as it can modulate human estrogen receptor/PI3-kinase-dependent pathway and antioxidant enzymes. It works as a potent ROS scavenger by maintaining the glutathione peroxidase (GSH) and GSH/total glutathione ratio (Vivancos and Moreno 2005). β-sitosterol isolated from *Vitex agnus-castus* has been shown to possess antioxidant property by preventing the free radicals generation at 50 and 100 μg/ml (58% and 67%) (Arokiyaraj et al. 2011). β-sitosterol is recommended as chemopreventive drug for colon carcinogenesis as it has been shown to be effective against colon carcinogenesis in rats induced by 1,2-dimethylhydrazine and elevates enzymatic and nonenzymatic antioxidant by preventing lipid peroxidation (Baskar et al. 2012). From the medicinal herb, *Solanum surattense*, β-sitosterol (BS) was isolated for studying the antioxidant potential using an experimental rat model with diabetes-induced oxidative damage. Results showed that different doses of BS (10, 15, and 20 mg/kg, p.o.) decrease the thiobarbituric acid-reactive substances (TBARS) with increase in pancreatic antioxidant levels (Gupta et al. 2011). The

antioxidant activity of the methanolic extract of *Eulophia campestris* Wall was studied by 1,1-diphenyl-2-picrylhydrazyl (DPPH) method; obtained results showed the moderate to potent antioxidant activity with the ED50 value of 1.593 μg/ml. The high antioxidant activity of the plant might be due to the presence of high alkaloids content (Rao et al. 2013).

32.6.3 Neuroprotection

Plants containing β-sitosterol show anxiolytic, antinociceptive, and tranquillizing effects in rats, although such results were not found in case of humans (Santos et al. 1995; López-Rubalcava et al. 2006). Till now no such studies have been performed related to the brain region or the pathways affected by β-sitosterol. Findings suggest that β-sitosterol has similar effect like diazepam; however, the exact mechanism of action behind this effect has not been studied yet (Aguirre-Hernandez et al. 2007). Incorporation of β-sitosterol into cell membrane can prevent lipid peroxidation and glucose oxidase-induced oxidative stress which is helpful in curing neurodegenerative disorders like Alzheimer's disease (Shi et al. 2013). Research studies suggest that β-sitosterol or its extract increases the proliferation of neural stem cell, although it is recommended to perform additional studies on its possible applications in the area of tissue engineering (Hamedi et al. 2015).

32.6.4 Angiogenic Effect

The angiogenic component (β-sitosterol) was isolated from the *Aloe vera* gel, and its effect was examined upon damaged blood vessels of the Mongolian gerbil, through a chick embryo chorioallantoic membrane assay; it was established that intraperitoneal administration of beta-sitosterol for a period of 19 days at a dosage of 500 microg/kg/day significantly enhances the formation or motion recovery of new vessel in gerbil brains damaged by ischemia/reperfusion Choi et al. (2003). Research findings suggest that β-sitosterol plays a potential role in healing chronic wound and in the formation of new blood vessels, but till now not a single experimental study was reported on the exact mechanism of wound healing. According to Moon et al. (1999), β-sitosterol in the presence of heparin stimulated the motility of human umbilical vein endothelial cells in an in vitro wound migration assay and stimulated neovascularization in the mouse Matrigel plug assay.

32.6.5 Cardioprotective

Research studies suggest that phytosterols and their derivatives (β-sitosterol) reduce the cholesterol levels in the blood and also inhibit the dietary cholesterol absorption and biliary cholesterol. The correct mechanism for this interference in cholesterol absorption is not clear, but it has been recognized that it might be due to three

different possibilities such as co-crystallization in the so-called mixed micelles in the small intestine and competitive solubilization or combination with other statins and its effect at absorption site (hydrolysis by esterases and lipases). β-sitosterol have been approved and recommended by US Food and Drug Administration (FDA) for the treatment of hypercholesterolemia or hyperlipidemia and prevention of different cardiovascular diseases (Hu 2003; Retelny et al. 2008).

β-sitosterol and its hydrogenated product (sitostanol) was compared for their hypocholesterolemic activity in young male rats. Results demonstrated that sitostanol significantly lowers cholesterol more efficiently than sitosterol, but their effects were similar on liver concentration of triglyceride and cholesterol. It was concluded from the study that hydrogenation of plant sterols improves their hypocholesterolemic activity without affecting their safety (Sugano et al. 1977).

Another study shows that β-sitosterol (6 g/day) was added to a group of 30 patients (16 men, 14 women) for the treatment of hypercholesterolemia followed by lovastatin for 12 weeks; it was found that in β-sitosterol group, the LDL cholesterol decreases by 35.3–37.1%, whereas there was decrease in total cholesterol by 27.3–29.2% (Richter et al. 1996).

32.6.6 Glucoregulation

Gupta et al. (2011) studied the antioxidant and antidiabetic potential of β-sitosterol in streptozotocin-induced diabetic rats; administration of β-sitosterol protects the pancreatic tissue and enhances the pancreatic insulin and antioxidant level followed by reduction in blood glucose, nitric oxide (NO), and HbA1c levels. It ameliorates diabetic complications (arthritis) by preventing development of diabetes. However, oral administration of β-sitosterol increases glucose-induced insulin secretion and also increases fasting plasma insulin levels while decreasing fasting glycemia, and these effects of β-sitosterol are comparable to standard antidiabetic drug (glibenclamide) Ivorra et al. (1997). Phytosterol derivatives (stigmasterol and sitosterol-3-*O*-β-D-glucopyranoside) extracted from leaves of *Pseuderanthemum palatiferum* were orally administered to diabetic rats at a doses of 0.25 and 0.50 mg/kg for 21 days, it was found that fasting blood glucose (FBS) levels were decreased significantly (p ? 0.05) with a constant increase in serum insulin, and the highest hypoglycemic effect was shown by sitosterol-3-*O*-β-D-glucopyranoside at a dose of 0.50 mg/kg (Padee et al. 2010). β-sitosterol stimulates adipogenesis in differentiating preadipocytes which increase glucose uptake in adipocytes. In contrast it induces adipocytes lipolysis which was not attenuated by insulin; it downregulates GLUT4 gene (Akt and PI3K) expression like insulin. β-sitosterol shows it's potential in weight management and diabetes due to its unique characteristics like regulating glucose uptake, lipolysis in adipocytes and adipogenesis (Chai et al. 2011).

32.6.7 Fertility

Research finding shows contradictory results for β-sitosterol on the reproductive system. Studies on rat model shows sex hormone levels such as estradiol in females and testosterone in males were increased due to intake of β-sitosterol (Ryokkynen et al. 2005). The bioactive compound β-sitosterol extracted from roots of *Barleria prionitis* was used to determine the antifertility potential in the male albino rats; dose-dependent treatment of β-sitosterol shows marked alterations in the male reproductive organs by suppressing spermatogenesis and fertility, which reflects the potential of β-sitosterol in development of cheap, nontoxic herbal male-contraceptive drug (Singh and Gupta 2016). High-dose level (5 mg/kg per day per rat subcutaneously) of β-sitosterol shows more pronounced antifertility effect than long-term low-dose treatment (0.5 mg/kg per day per rat subcutaneously) in male albino rats. Accessory sex tissues, weight of testis, and sperm concentrations were reduced after time-dependent high-dose treatment with β-sitosterol. Following withdrawal of treatment for 30 days, weights of accessory sex tissues can be restored to normal conditions (Malini and Vanithakumari 1991).

32.6.8 Carcinogenicity

β-sitosterol is an important constituent of human diet; it interacts with different cellular pathways and targets to show anticancer properties (Novotny et al. 2017). This compound shows no genotoxic effects and inhibits mutagenicity by preventing chromosomal breaks. Naturally known phytoesterogen β-sitosterol was isolated from *Cyrtandra cupulata* Ridl. (Gesneriaceae) through bioactivity-guided purification produced growth inhibitory effect on MCF-7 cells which are positive breast cancer cell line with estrogen receptors in a dose-dependent manner. Addition of β-sitosterol to the cell line dose dependently showed an increase in 1.53-fold of DEVDase activity, signifying elevated caspase activity which results in caspase-induced apoptosis (Chai et al. 2008). In addition, β-sitosterol also inhibits the increase of MDA-MB-231 human breast cancer cells and tumor growth formation; it also increases the apoptosis in cell culture which shows its antiproliferative nature in the prevention of breast cancer (Awad et al. 2000). β-sitosterol and taraxasterol reduce the development of breast and colon cancer; both of these compounds affect the development of different levels of tumors, for example, inhibition of tumor cells invasion and metastasis along with producing inhibitory effects on creation, promotion, and induction of cancerous cells. β-sitosterol supplementation decreases E2-induced MCF-7 tumor growth along with circulating 17β-estradiol (E2) levels in ovariectomized athymic nude mice. Thus, results suggest that positive effects are seen in women with breast cancer who are supplemented with high dietary phytosterols (Ju et al. 2004). In another study cytotoxicity of important phytosterols (β-sitosterol and its glycoside daucosterol) was examined against cancers cell lines by MTT assay. Results revealed that daucosterol inhibits the K-562 cell line (leukemia), whereas β-sitosterol was more active against HT-29 cell line (colon

carcinoma) (Manayi et al. (2013)). Recent findings have shown that there is a reduced risk of prostate cancer especially in men consuming huge amounts of plant products rich in phytosterols. It was established that β-sitosterol increases the apoptosis of prostate cancer cells by producing a cellular signalling molecule ceramide, which regulates the differentiation, proliferation, apoptosis of cells, and programmed cell death (Von Holtz et al. 1998).

32.6.9 Immunomodulation

β-sitosterol works as an active immune modulator by targeting definite T-helper (Th) lymphocytes and improving the activity of natural killer (NK) cells and T lymphocytes. However, a small dose of β-sitosterol and its glycoside daucosterol promotes in vitro proliferative activity of T lymphocytes, after being stimulated by lower concentrations of phytohaemagglutinin (PHA). A significant increase in the expression of HLA-Dr antigens and CD25 expression on T lymphocytes was observed caused by essential sterolin formulation (ESF) which promotes the growth in the secretion of gamma interferon and IL-2 (Bouic 2001). In AIDS there was a slight decrease in the apoptosis of CD4 lymphocytes. It was found that in AIDS, stable CD4 cell counts were maintained by β-sitosterol, and slight decrease in the apoptosis of CD4 lymphocytes was observed, thus slowing HIV. In infected cells viral replication rates are slowing down due to significant decrease in IL-6 levels which overall decrease the viral load in HIV cases (Bouic 1997).

32.7 β-Sitosterol Herbal Dietary Supplement-Drug Interactions

β-sitosterol is one of the most dominant phytosterol consumed (200–400 mg daily) in human diets, found in large quantities in nonpolar fractions of plants and marines. β-sitosterol should be consumed in caution, or doses may be adjusted when using with supplements or herbs that may lower blood sugar levels. β-sitosterol should not be consumed with the drugs that increase the bleeding risk such as antiplatelet drug like clopidogrel (Plavix®), anticoagulants (blood thinners) like warfarin (Coumadin®) or heparin, and nonsteroidal anti-inflammatory drugs like ibuprofen (Motrin®, Advil®) or naproxen (Naprosyn®, Aleve®) and aspirin. Beta-sitosterol may also interact with agents (herbs and supplements) that affect the immune system or the heart, antiarthritic agents, anticancer agents, alpha1-blockers, cholesterol-lowering agents, cyclooxygenase inhibitors, diosgenin, cholestyramine, dalcetrapib, ezetimibe, beta-lactoglobulin tryptic hydrolysate (LTH), rifampin, lifibrol, and statins. It may also interact with lycopene, sterols, lutein, olestra, and vitamins A, D, and E (Saeidnia et al. 2014).

32.8 Conclusion

β-sitosterol commonly known as "plant sterol ester" are majorly found in plants and possess diverse applications in different fields such as in medicinal world and global food industry. There is a vital role of chemistry, biochemistry, and biotechnology in understanding the structure, biosynthesis, and behavior of β-sitosterol. This compound is structurally similar to cholesterol and has huge impact on human physiology. It is a well-known natural sterol with reported potential therapeutic mode of applications in cancer, diabetes, cardiovascular, immunomodulatory, neurological, and reproductive system. It is considered as the remarkable drug of the future with higher efficacy. There is a requirement to cover a broad spectrum of scientific applications for understanding the potential benefits presented by this remarkable phytosterol.

References

Aguirre-Hernández E, Rosas-Acevedo H, Soto-Hernández M, Martínez AL, Moreno J, González-Trujano ME (2007) Bioactivity-guided isolation of beta-sitosterol and some fatty acids as active compounds in the anxiolytic and sedative effects of Tilia americana var. Mexicana Planta Med 73:1148–1155

Akhisa T, Kokke W (1991) Naturally occurring sterols and related compounds from plants. In: Patterson GW, Nes WD (eds) Physiology and biochemistry of sterols. American Oil Chemists' Society, Champaign

Arokiyaraj S, Vimalarasan A, Hemachandran M, Priya D (2011) Antibacterial activity of beta-sitosterol of Vitex agnus castus. Int J of Appl Biol 2:12–15

Awad AB, Downie AC, Fink CS (2000) Inhibition of growth and stimulation of apoptosis by beta-sitosterol treatment of MDA-MB-231 human breast cancer cells in culture. Int J Mol Med 5:541–546

Baskar AA, Al Numair KS, Paulraj MG, Alsaif MA, Al Muamar M, Ignacimuthu S (2012) β-Sitosterol prevents lipid peroxidation and improves antioxidant status and histoarchitecture in rats with 1,2-dimethylhydrazine-induced colon cancer. J Med Food 15:335–343

Bouic PJ (1997) Immunomodulation in HIV/AIDS: the Tygerberg/Stellenbosch University experience. AIDS Bull 6:18–20

Bouic PJ (2001) The role of phytosterols and phytosterolins in immune modulation: a review of the past 10 years. Curr Opin Clin Nutr Metab Care 4:471–475

British Dietetic Association (2012). https://www.bda.uk.com/foodfacts/plantstanolsandsterols. Accessed 22 June 2014

Chai JW, Kuppusamy UR, Kanthimathi MS (2008) Beta-sitosterol induces apoptosis in MCF-7 cells. Malays J Biochem Molecular Bio 16:28–30

Chai JW, Lim SL, Kanthimathi M, Kuppusamy UR (2011) Gene regulation in β-sitosterol-mediated stimulation of adipogenesis, glucose uptake, and lipid mobilization in rat primary adipocytes. Genes Nutr 6:181–188

Choi YH, Kong KR, Kim Y, Jung KO, Kil JH, Rhee SH, Park KY (2003) Induction of bax and activation of caspases during β-sitosterol-mediated apoptosis in human colon cancer cells. Int J Oncol 23:1657–1662

De-Eknamkul W, Potduang B (2003) Biosynthesis of β-sitosterol and stigmasterol in Croton sublyratus proceeds via a mixed origin of isoprene units. Phytochemistry 62:389–398

Gupta A, Sharma AK, Dobhal MP, Sharma MC, Gupta RS (2011) Antidiabetic and antioxidant potential of β-sitosterol in streptozotocin-induced experimental hyperglycemia. J Diabetes 3:29–37

Gylling H, Simonen P (2015) Phytosterols, phytostanols, and lipoprotein metabolism. Nutrients 7:7965–7977

Hamedi A, Ghanbari A, Razavipour R, Saeidi V, Zarshenas MM, Sohrabpour M, Azari H (2015) Alyssum homolocarpum seeds: phytochemical analysis and effects of the seed oil on neural stem cell proliferation and differentiation. J Nat Med 69:1–10

Hang J, Dussault P (2010) A concise synthesis of beta-sitosterol and other phytosterols. Steroids 75:879–883

Hu FB (2003) Plant-based foods and prevention of cardiovascular disease: an overview. Am J Clin Nutr 78:544S–551S

Ivorra M, D'ocon M, Paya M, Villar A (1997) Antihyperglycemic and insulin-releasing effects of beta-sitosterol 3-beta-D-glucoside and its aglycone, beta-sitosterol. Arch Int Pharmacodyn Thér 296:224–231

Ju YH, Clausen LM, Allred KF, Almada AL, Helferich WG (2004) β-sitosterol, β-sitosterol glucoside, and a mixture of β-sitosterol and β-sitosterol glucoside modulate the growth of estrogen-responsive breast cancer cells In vitro and in ovariectomized athymic mice. J Nutr 134:1145–1151

Khripach VA, Zhabinskii VN, Konstantinova OV, Khripach NB, Antonchick AV, Antonchick AP, Schneider B (2005) Preparation of (25R)- and (25S)-26-functionalized steroids as tools for biosynthetic studies of cholic acids. Steroids 70:551–562

Kiprono PC, Kaberia F, Keriko JM, Karanja JN (2000) The in vitro anti-fungal and anti-bacterial activities of β -sitosterol from Senecio lyratus (Asteraceae). Z Naturforschung C 55:485–488

Kritchevsky D (1997) Phytosterols. In: Kristchevsky, Bonfield (eds) Dietary fiber in health and disease, vol 427. Plenum Press, New York, pp 235–242

López-Rubalcava C, Piña-Medina B, Estrada-Reyes R, Heinze G, Martínez-Vázquez M (2006) Anxiolytic-like actions of the hexane extract from leaves of Annona cherimola in two anxiety paradigms: possible involvement of the GABA/benzodiazepine receptor complex. Life Sci 78:730–737

Malini T, Vanithakumari G (1991) Antifertility effects of beta-sitosterol in male albino rats. J Ethnopharmacol 35:149–153

Manayi A, Saeidnia S, Ostad SN, Hadjiakhoondi A, Shams Ardekani MR, Vazirian M, Akhtar Y, Khanavi M (2013) Chemical constituents and cytotoxic effect of the main compounds of Lythrum salicaria L. Z Naturforsch 68:367–375

Moon EJ, Lee YM, Lee OH, Lee MJ, Lee SK, Chung MH, Park YI, Sung CK, Choi JS, Kim KW (1999) A ncovel angiogenic factor derived from aloe vera gel: β-sitosterol, a plant sterol. Angiogenesis 3:117–123

Moreau RA, Whitaker BD, Hicks KB (2002) Phytosterols, phytostanols, and their conjugates in foods: structural diversity, quantitative analysis, and health-promoting uses. Prog Lipid Res 41:457–500

Njinga NS, Sule MI, Pateh UU, Hassan HS, Abdullahi ST, Ache RN (2016) Isolation and antimicrobial activity of β-Sitosterol-3-OGlucoside from Lannea Kerstingii Engl. and K. Krause (Anacardiaceae). Nitte Univ J Health Sci (NUJHS) 6:4–8

Novotny L, Abdel-Hamid ME, Hunakova L (2017) Anticancer potential of β-sitosterol. Int J Clin Pharmacol Pharmacother 2:2–4

Nweze NE (2011) In vitro anti-trypanosomal activity of Morinda lucida leaves. Afr J Biotechnol 11:1812–1817

Padee P, Nualkaew S, Talubmook C, Sakuljaitrong S (2010) Hypoglycemic effect of a leaf extract of Pseuderanthemum palatiferum (Nees) Radlk. in normal and streptozotocin-induced diabetic rats. J Ethnopharmacol 132:491–496

Phillips KM, Ruggio DM, Ashraf-Khorassani M (2005) Phytosterol composition of nuts and seeds commonly consumed in the United States. J Agric Food Chem 53:9436–9445

Rahuman AA, Gopalakrishnan G, Venkatesan P, Geetha K (2008) Isolation and identification of mosquito larvicidal compound from Abutilon indicum (Linn.) sweet. Parasitol Res 102:981–988

Rao N, Mittal S, Sudhanshu ME (2013) Antioxidant potential and validation of bioactive B-Sitosterol in Eulophia campestris Wall. Adv Biores 4:136–142

Raport E (2008) Consumption of food and beverages with added plant sterols in the European Union. EFSA J 133:1–21

Ras RT, Geleijnse JM, Trautwein EA (2014) LDL-cholesterol-lowering effect of plant sterols and stanols across different dose ranges: a meta-analysis of randomised controlled studies. Br J Nutr 112:214–219

Retelny VS, Neuendorf A, Roth JL (2008) Nutrition protocols for the prevention of cardiovascular disease. Nutr Clin Pract 23:468–476

Ribeiro N, Streiff S, Heissler D, Elhabiri M, Albrecht-Gary AM, Atsumi M, Gotoh M, Desaubry L, Nakatani Y, Ourisson G (2007) Reinforcing effect of bi- and tri-cyclopolyprenols on 'primitive' membranes made of polyprenyl phosphates. Tetrahedron 63:3395–3407

Richter WO, Geiss HC, Sönnichsen AC, Schwandt P (1996) Treatment of severe hypercholesterolemia with a combination of beta-sitosterol and lovastatin. Curr Therap Res 57:497–505

Ryökkynen A, Käyhkö UR, Mustonen AM, Kukkonen JV, Nieminen P (2005) Multigenerational exposure to phytosterols in the mouse. Reprod Toxicol 19:535–540

Saeidnia S, Manayi A, Gohari AR, Abdollahi M (2014) The story of beta-sitosterol – a review. Europ J Med Plants 4:590–609

Santos A, Niero R, Yunes R, Pizzolatti M, Delle Monache F, Calixto J (1995) Antinociceptive properties of steroids isolated from Phyllanthus corcovadensis in mice. Planta Med 61:329–332

Schneider K, DiNovi M, Baines J, Schlatter J (2009) Phytosterols, phytostanols and their esters. Saf Eval Certain Food Addit 60:117–157

Shi C, Wu F, Zhu X, Xu J (2013) Incorporation of β-sitosterol into the membrane increases resistance to oxidative stress and lipid peroxidation via estrogen receptor-mediated PI3K/GSK3β signalling. Biochim Biophys Acta 1830:2538–2544

Singh K, Gupta RS (2016) Antifertility activity of β-sitosterol isolated from Barleria prionitis (l.) roots in male albino rats. Int J Pharm Pharm Sci 8:88–96

Subramaniam S, Keerthiraja M, Sivasubramanian A (2014) Synergistic antibacterial action of β-sitosterol-D-glucopyranoside isolated from Desmostachya bipinnata leaves with antibiotics against common human pathogens. Rev Bras Farm 24:44–50

Sugano M, Morioka H, Ikeda I (1977) A comparison of hypocholesterolemic activity of betasitosterol and beta-sitostanol in rats. J Nutr 107:2011–2019

Vivancos M, Moreno JJ (2005) β-Sitosterol modulates antioxidant enzyme response in RAW 264.7 macrophages. Free Radic Biol Med 39:91–97

Von Holtz RL, Fink CS, Awad AB (1998) Beta-sitosterol activates the sphingomyelin cycle and induces apoptosis in LNCaP human prostate cancer cells. Nutr Cancer 32:8–12

Yin Y, Liu X, Liu J, Cai E, Zhao Y, LiH ZL, LiP GY (2018) The effect of beta-sitosterol and its derivatives on depression by the modification of 5-HT, DA and GABA-ergic systems in mice. RSC Adv 8:671–680