

# PHYTOSTEROLS IN HUMAN HEALTH: FRIENDS OR FOES?

## FITOESTEROLES EN LA SALUD HUMANA: ¿AMIGOS O ENEMIGOS?

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### ABSTRACT

Phytosterols are steroids present in photosynthetic organisms and are frequent molecules present in the human diet. There is evidence showing the consumption of phytosterols can prevent cardiovascular problems, mainly by decreasing blood absorption of cholesterol present in our diet. In addition, there are research results pointing to an anticancer effect of PS. However, as presented in this article, recommendations to increase phytosterol consumption should be followed with precaution and medical guidance.

### RESUMEN

Fitoesteroles son esteroides presentes en organismos fotosintéticos y son moléculas presentes frecuentemente en la dieta humana. Hay evidencia que señala que el consumo de fitoesteroles puede prevenir problemas cardiovasculares, principalmente disminuyendo la absorción del colesterol presente en nuestra dieta. Además, se han encontrado estudios que indican que los fitoesteroles tienen un efecto anticancerígeno. No obstante, la recomendación de incrementar la ingesta de fitoesteroles debería tomarse con cautela y bajo seguimiento médico puesto que se han reportado efectos adversos.



## PHYTOSTEROLS, WHAT ARE THEY?

Both plant sterols and stanols are plant steroid molecules with a similar structure and function to cholesterol in humans that are collectively known as phytosterols (PS). The common structure among plant and animal sterols is a cyclopentanoperhydrophenanthrene ring. Additional biochemical modifications have been described for plant sterols and stanols compared to cholesterol. Thus, an additional ethyl and methyl group are found in  $\beta$ -sitosterol/stigmasterol and campesterol at C-24 of their sterol side chain, respectively. Besides, plant stanols do not present unsaturated bonds while plant sterols do.

In plants, functions of PS within the plant cell occur in a similar way as cholesterol in animal cells (Clouse, 2002), such as being part of the cell membrane and as substrates for elaboration of hormones. Metabolism in each part of a plant influences the relative amount of PS and key enzymes that are involved in PS biosynthesis have been identified (Zhang *et al.*, 2020). In addition to normal physiology, infection of plants can modify their sterol contents. Thus, the infection of tomato (*Solanum lycopersicum*) with the root-knot nematode *Meloidogyne incognita* changes the  $\beta$ -sitosterol-to-stigmasterol ratio significantly (Cabianca *et al.*, 2021).

In summary, PS are functional molecules in plants that are regulated by their metabolism and in response to biotic and abiotic factors. This may influence the specific content of a particular PS in the plant or part of the plant consumed in a diet.

## DISTRIBUTION IN MICROORGANISMS, ALGAE AND PLANTS

Due to their chemical structure, plant sterols and stanols are present in the insaponifiable part of plant fats and are highly concentrated in plant oils. PS co-exist in plants along with cholesterol as part of cell structure and metabolism, while PS are not synthesized in animal cells (Sonawane *et al.*, 2016). Also, in some cases, high levels of cholesterol have been found in plants, like in *Perilla frutescens* (Oh *et al.*, 2021).

PS are principally found in wheat germs,

vegetable oils, nuts, and seeds. Among PS,  $\beta$ -sitosterol, campesterol and stigmasterol are the most common sterols present in the human diet. Plant stanols are less abundant in nature compared to plant sterols. This was evidenced by using gas liquid chromatography to evaluate phytosterol contents in vegetables commonly consumed where pea, cauliflower, broccoli, romaine lettuce, cowpea and scallion had around 50 to 20 mg per 100 g of edible piece (Han *et al.*, 2008). In addition to vegetables, microalgae have been considered as a great source of PS (Le Goff *et al.*, 2019).

## ENTEROCYTE UPTAKE AND BLOOD ABSORPTION

PS, as well as cholesterol, are quickly uptaken by the enterocyte (Igel *et al.*, 2003). Due to its structural similarity to cholesterol, PS can be uptaken by enterocytes through the Niemann-Pick C1-like 1 (NPC1L1) multi-pass transporter (Hu *et al.*, 2021). Between these two types of molecules, plant sterol is better absorbed than stanol (Igel *et al.*, 2003), suggesting that their chemical structure play an important role. Unesterified cholesterol also utilizes the NPC1L1 transporter to cross the plasma membrane of the intestinal cell. Thus, ingested PS compete with cholesterol to enter the intestinal cell. As a consequence, this absorption displacement causes unesterified cholesterol to pass to the colon for excretion. Then, a high concentration of PS in the diet reduces cholesterol absorption. In fact, a clinical assay showed that PS reduced the blood absorption of cholesterol present in a meal (Amiot *et al.*, 2013).

Inside the enterocyte, cholesterol is esterified by acyl CoA:cholesterol acyltransferase 2 (ACAT2) to direct its exit via chylomicron towards the bloodstream. On the contrary, chemical differences in PS compared to cholesterol interfere with ACAT2 esterification, increasing their intracellular accumulation which in turn activates the plasma membrane transporters ABCG5 and ABCG8 that pumps out unesterified cholesterol and PS back to the intestinal lumen (Nguyen *et al.*, 2012). Normally, almost all PS are then eliminated from the enterocyte. However, when there is no correct functioning



of ABCG5/ABCG8 transporters, PS are found in high levels present in blood, a condition termed sitosterolemia (Othman *et al.*, 2013). This condition also points to the fact that PS can be incorporated as part of lipoproteins in the blood. It has been demonstrated, in mice, that plant sterols, but not stanols, are absorbed towards the blood (Igel *et al.*, 2003).

In addition to preventing cholesterol absorption, PS may perturb cholesterol absorption by other mechanisms. Thus, a 2-week ad-libitum diet of cholesterol plus  $\beta$ -sitosterol prevented the mRNA upregulation of NPC1L1 in small intestine cells in hamsters (Liu *et al.*, 2015), explaining how PS could reduce hypercholesterolemia.

Most of the PS in edible plants are present in the esterified form (Wang *et al.*, 2018). Therefore, to be uptaken by enterocyte, esterified PS has to be digested to free PS in the same way as diet esterified cholesterol is processed, by the action of cholesterol esterase in the small intestine. In vitro, it has been shown that pancreatic cholesterol esterase is able to hydrolyze esterified plant sterol and stanol suggesting that this process could happen in vivo to ensure plant sterol absorption (Brown *et al.*, 2010).

PS level in blood in healthy subjects has been reported. The ingestion of PS in adults with a strict plant-based diet is around 500 mg a day and the ratio  $\beta$ -sitosterol/cholesterol is significantly higher in them compared to non-vegetarian subjects (Jaceldo-Siegl *et al.*, 2017). Therefore, the amount of PS in the diet (over that of cholesterol) promotes the blood absorption of these plant sterols.

## PS AND CARDIOVASCULAR DISEASES

It has been extensively demonstrated that PS ingestion reduces serum cholesterol and atherogenic lesions in animal models genetically prone to develop atherosclerosis. The supplementation of a mixture of PS reduced the appearance of atheromas in apolipoprotein E-knockout mice by increasing HDL-cholesterol and decreasing hepatic lipase (Moghadasian *et al.*, 1999). In another study, the addition of plant stanols dramatically reduced the extent and severity of atheromas in the apoE\*3-Leiden transgenic mice by diminishing VLDL-, IDL- and LDL-cholesterol (Volger *et al.*, 2001).

To further prove the significance of PS in cardiovascular diseases, clinical trials using PS in food have been tested. After a period of 3 weeks ingesting PS containing fat-free milk, healthy subjects reduced their LDL- and non-HDL-cholesterol (San Mauro-Martín *et al.*, 2016). Recently, a clinical study in Brazil showed that regular consumption of phytosterols (>390 mg/day) was associated with lower total and LDL-cholesterol in healthy people, with no changes in markers of subclinical atherosclerosis (Pereira *et al.*, 2021).

However, in some studies, the expected protective effect against dyslipidemia was not observed. In a Brazilian study, administration of PS for 8 weeks to children and adolescents with dyslipidemia did not reduce LDL-cholesterol (Tavares *et al.*, 2021). This difference in results might be a consequence of the genetic variability among the participants in each study or the degree of development of the disease of the subjects.

## PS AND CANCER

A case-control study in Uruguay, hospitalized subjects were interviewed to fill a questionnaire to list their food consumption. It was shown that PS reduced the risk of adenocarcinoma of the lung in men (Mendilaharsu *et al.*, 1998). The same group also showed that PS, among other plant molecules, reduced the risk of breast cancer (Ronco *et al.*, 1999). In a retrospective study, PS consumption was also found to reduce the risk of endometrial cancer among women in western New York (McCann *et al.*, 2000). Also,



PS ( $\beta$ -sitosterol, campesterol and campestanol) were found in an inverse association with colorectal cancer risk within Chinese subjects (Huang *et al.*, 2017)

*In vitro* studies have confirmed the previous epidemiological results. Thus,  $\beta$ -sitosterol promotes the expression and activates the extrinsic death receptor FAS signaling in breast cancer cells (Awad *et al.*, 2007). In another study,  $\gamma$ -sitosterol induced G2/M arrest in MCF7 and A549 human cancer cells (Sundarraj *et al.*, 2012). Another PS, campesterol, was shown to inhibit proliferation and cell cycle progression of ovarian cancer cells (Bae *et al.*, 2021). In the same manner, stigmasterol was observed to inhibit cell migration and induce G2/M cell cycle arrest in human gastric cancer cell lines (Li *et al.*, 2018).

### CONCERNS OF PS IN DIET

Normally, cholesterol and fatty acids in a meal contribute to the uptake of lipophilic vitamins by enterocytes. Therefore, there is a concern that PS may reduce the absorption of lipid soluble vitamins. *In vitro*, this assumption was tested using the colon adenocarcinoma Caco-2 cells (Fahy *et al.*, 2004) where  $\beta$ -sitosterol interfered with  $\beta$ -carotene uptake by these colon cells. If a diet rich in PS is followed, it is recommended that at least one fruit or vegetable high in  $\beta$ -carotene (such as carrot, pumpkin, squash, broccoli, spinach, apricot, mango or rock melon) is eaten daily. In general, to avoid this problem a diet rich in fruit, vegetables and unsaturated-containing foods should improve the absorption of fat soluble vitamins.

To be highlighted, there are recent studies supporting the idea that PS could be proatherogenic. In a case-control study, high levels of PS:cholesterol in women were associated with increased cardiovascular risk (Rajaratnam *et al.*, 2000). In men, an increased risk of major coronary events was determined due to a high sitosterol/cholesterol ratio (Assmann *et al.*, 2006).

On the other hand, some studies have failed to demonstrate an association of PS consumption and cardiovascular disease (Pinedo *et al.*, 2007;

Windler *et al.*, 2009).

Therefore, PS consumption may decrease cardiovascular disease associated with high blood cholesterol. However, a close evaluation of PS-treated subjects is recommended since the PS treatment may not be effective or could cause major problems. This might be due to genetic background differences.

### CONCLUSIONS

There is abundant evidence to consider PS, as a food component or supplements, for alleviating cardiovascular problems (mainly regulating cholesterol levels) and inhibiting cancer progression. However, a medical follow-up is recommended to avoid possible side effects such as increasing the risk of atherosclerosis.

### ACKNOWLEDGMENTS

F. Ma was supported by the Central Public-interest Scientific Institution Basal Research Fund for the Chinese Academy of Tropical Agricultural Sciences (No. 1630092019002).

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