Phytosterols as potential allies in the battle against cancer

Regularly, our body produces cancer cells that, fortunately, are quickly eliminated by our patrolling immune system (known as innate immunity). The relationship between a healthy immune system and the appearance of diseases emphasizes the need to know how to maintain this balance to prevent the onset of diseases, but also, once the disease is present, how to deal with it effectively, so it affects our quality of life as little as possible.

Phytosterols, known plant compounds that help us fight the presence of bad cholesterol in our body, have surprised us by providing other possible health benefits. One of them is helping to strengthen the immune system, thus achieving preventive action against cancer. This document summarizes what has been so far described regarding the healing anti-cancer activity of phytosterols.

Epidemiological Correlations between Phytosterol Consumption and Low Cancer Incidence

The first observations that allowed us to deduce the probable anti-cancer activity of phytosterols came from correlations obtained in epidemiological studies, these were generally associated with a high consumption of plant-based foods particularly rich in phytosterols[1,2]. To begin with, vegetarian populations exhibit lower cancer rates than the general population [3,4,5,6]. A specific example of this, is the diminished risk of colorectal cancer detected in the "Adventist Health Study-1". This is associated with the ovo-lacto-vegetarian diet promoted within this community in comparison with non-vegetarians[7]. Additionally, the low incidence of colon, breast and prostate cancer as observed in Asian countries, suffered a dramatical increase after relocation and acquisition of Western dietary habits which ischaracterized by a higher consumption of animal products. This was the case of the Japanese immigrant population of Los Angeles, USA[8]. Other studies state that the female population who consume a diet rich in phytosterols have a diminished risk of breast cancer, as is the case of Japanese women who eat many soy-based products, rich in phytosterols[9] . Especially interesting are the results derived from the meta-analysis of 11 observational clinical studies in which the dietary consumption of 500 mg /day of total phytosterols or more specifically 10 mg /day of campesterol (one of the main types of phytosterol, present in mixtures of phytosterols obtained from pine or soy) is associated with a 13% lower cancer risk. These studies' dose response analysis showed an inverse and linear relationship between total cancer risk and the intake of up to 50 mg daily of phytosterols, specifically campesterol; but not of other phytosterols[10].

Therapeutic Use of Phytosterols

In the previous section, we highlighted a possible association between the consumption of foods rich in phytosterols and a low risk of cancer. Despite this, clinical trials to test the efficacy of phytosterols have only focused on benign prostatic hyperplasia, that is, an uncontrolled but not cancerous proliferation of the tissue.

The clinical evidence derived from four clinical studies conducted between 1985 and 1995 with products based on β-sitosterol indicates that in treatments that lasted between 1 to 6 months and included a total of 519 patients with symptomatic benign hyperplasia, the administration of β-sitosterol significantly improved urinary flow parameters and reduced symptoms and discomfort, but not prostate size[11].
Interestingly, the beneficial effect lasted 18 months after treatment, showing that its use could be very promising for this type of ailment, which affects at least 50% of the population over 60 years of age, and almost 90% of the population over 70 years old. The low doses used are striking, ranging between 60 and 195 mg / day, compared to the recommended 2 g daily to reduce LDL cholesterol (bad cholesterol).

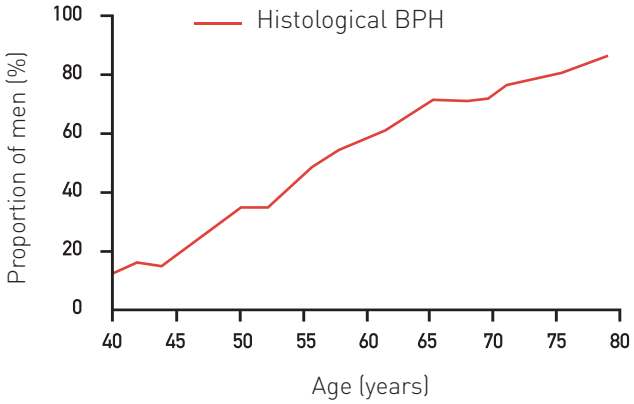

Figure 1: Incidence of benign prostatic hyperplasia in the United States (adapted from Health Press 2010)

What Basic Studies Show

Basic studies in cell models or in animals allow us to delve into why a pathology is generated and where and how a compound exerts a corrective action. Cancer is a disease with multiple possible origins and routes that allow its survival in the body. Hence, it is also possible to attack it through different targets. The following section briefly summarizes the possible therapeutic action of phytosterols based on the diversity of cancer types and their particular mechanisms.

The emergence and maintenance of some prostate and breast cancers depend on sex hormones. Among the approaches for pharmacological treatment, some aim to block the synthesis of hormones to deprive tumor cells of this stimulus. Specifically, the conversion of testosterone to other steroids is associated with the development of hyperplasia and prostate cancer[12,13], which happens due to the action of enzymes present in the liver (5α-reductase) and the prostate (5α-aromatase)[14].

As in the prostate, in the breast there are also certain types of tumors that depend on the availability of estrogens. In this case, the activity of phytosterols is less clear and requires that their concentrations in plasma reach values up to 10 times those found in the 2 g daily doses currently authorized and recommended for hypocholesterolemic applications. On the one hand, it has been reported that it can mimic, albeit weakly, the action of estrogens on its receptor[13,14]. . This is an undesired effect that could explain why the administration of phytosterols (when given in very high doses) has estrogenic effects in rodents[15,16]. On the other hand, there is also experimental evidence that may prove that phytosterols have an antiestrogenic role, since they prevent the transformation of cholesterol into estrogens [17,18], and also prevent the proliferation of breast tumor cells when transplanted into female mice that have been manipulated to promote tumor growth[19]. Therefore, the participation of phytosterols in pro or anti breast cancer processes is not well defined and requires further analysis.

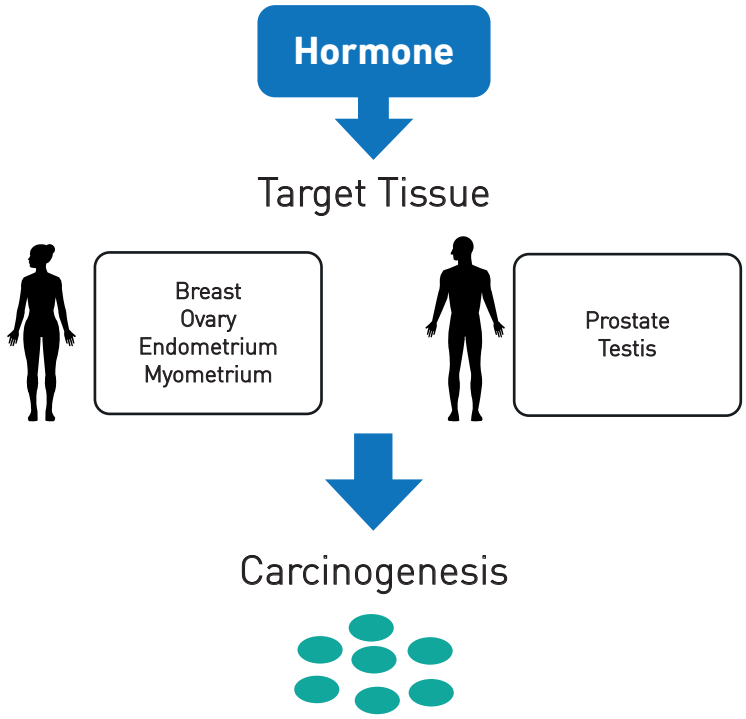

Figure 2: Types of hormone-dependent cancers

Another way to control the advance of cancer by phytosterols is by inhibition of tumor proliferation. Phytosterol supplementation has significantly inhibited both the percentage of animals that develop tumors and the number of tumors per animal in cell proliferation models in the intestinal tract[20,21]. Furthermore, phytosterols have regularized the normal characteristics of the intestinal epithelium[22,23].

Metastasis is the ability of certain types of cancer cells to migrate from a tumor and colonize and grow in another organ. Trials in cell cultures that study the different stages of metastasis separately, have shown that by imitating the concentration of phytosterols reached by a two gram daily consumption, the invasion of breast cancer cells is inhibited; thus demonstrating additional mechanisms by which phytosterols contribute to restricting the growth of this type of tumors and reduce metastasis rate[24].

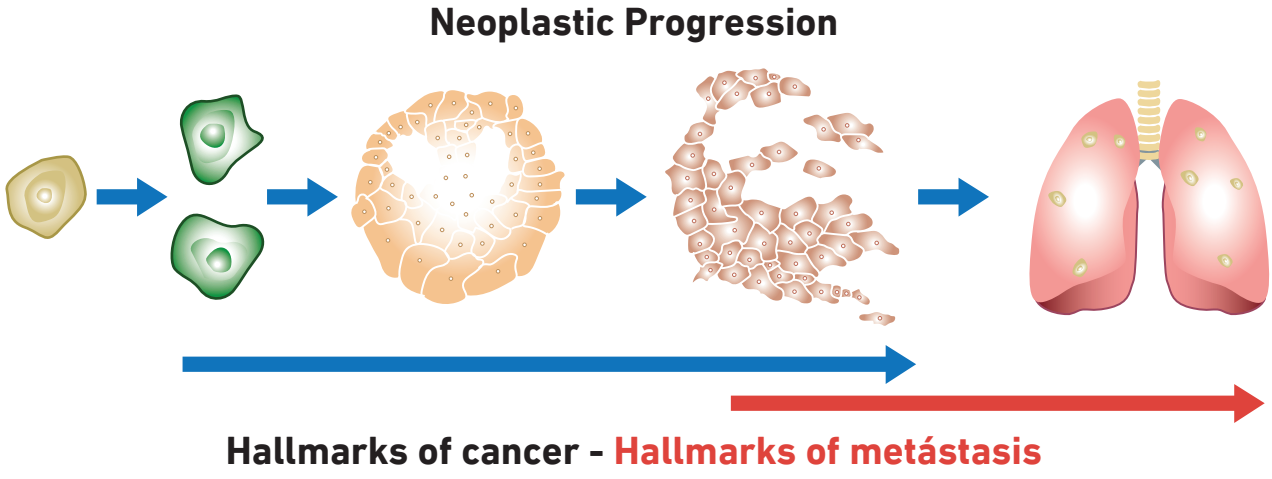

Figure 3: Neoplastic progression, proliferation and metastasis

The molecules involved

On the previous section we have seen that there are three possible mechanisms involved: one is interfering in the signaling of sex hormones in tumors whose survival depends on these molecules, the other is interfering in the invasiveness of a tumor type, and the last one is decreasing the multiplication of tumor cells[2]. Phytosterols may inhibit the multiplication or proliferation of tumor cells by the following actions, either in a single or a concerted way:

- Activation of the immune system for better recognition and elimination of tumors[1],
- Blocking the routes of activation of tumor proliferation[25],
- Activation of selective death of tumor cells (apoptosis).

Activation of selective death of tumor cells (apoptosis)[26], prostate[25], colon[27], fibrosarcoma[28], or stomach[29] have shown that phytosterols stimulate apoptosis.

Phytosterols, as lipids with a molecular structure very similar to cholesterol, most probably localize and use the same metabolic routes as cholesterol and its derivatives. Congruently, they can place themselves in cell membranes and change the entire functionality of the cell. By inserting themselves into the membrane instead of cholesterol, for example, they modify the fluidity of the plasma membrane, the composition of its specialized regions, and thereby alter contact interactions, enzyme and / or receptor activity, or the signals that are generated in the membrane to and from the cells. Of particular interest is the increase in the generation of ceramides from the plasma membrane, ceramides being a bioactive lipid that promotes apoptosis[30]. Their production in tumor cells is stimulated by treatments such as radio and chemotherapies[31],[32] as well as from culturing colon[33], breast[34] and prostate[35] tumor cells with phytosterols in concentrations that mimic those reached in plasma through the intake of two grams per day. This means that phytosterols could improve the anti-neoplastic effects of traditional treatments, reducing their known harmful effects.

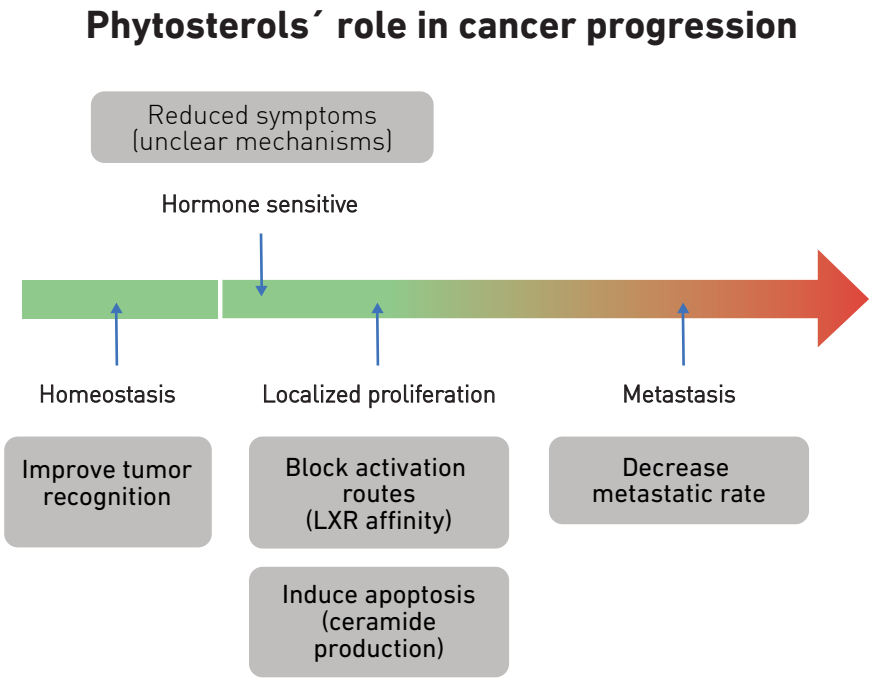

Figure 4: Role of Phytosterols in a simplified schematic of cancer progression

Phytosterols use cholesterol pathways and its endogenous derivatives not only in the cell membrane but also in the cytoplasm. Cholesterol controls its availability through the interaction of its endogenous derivatives (oxy-cholesterol) with cytosolic receptors, called LXR. Together they activate the expression of genes that control cholesterol metabolism and thus maintain a balanced level (feedback mechanism). But, in addition, these same LXR-type receptors are used by synthetic drugs with anti-proliferative activity in various cell types derived from tumors[36,37,38]. . These same anti-proliferative pathways may be common for phytosterols since they have been shown to have a high affinity with LXR receptors both in vitro and in vivo[39], evidencing their anti-proliferative therapeutic potential.

Conclusions

Cumulative evidence indicates that phytosterols may play an important role in the prevention and treatment of cancer through an interaction with common mechanisms employed by the body's natural ligands for cholesterol and its metabolic derivatives. Unlike pharmacological treatments, phytosterols are products that have been shown to be safe after intensive consumption and could be considered not as an alternative but as an ally of treatments currently in use.

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