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Review article

Phytosterols as a natural anticancer agent: Current status and future perspective

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ABSTRACT

Phytosterols are naturally occurring compounds in plants, structurally similar to cholesterol. The human diet is quite abundant in sitosterol and campesterol. Phytosterols are known to have various bioactive properties including reducing intestinal cholesterol absorption which alleviates blood LDL-cholesterol and cardiovascular problems. It is indicated that phytosterol rich diets may reduce cancer risk by 20%. Phytosterols may also affect host systems, enabling antitumor responses by improving immune response recognition of cancer, affecting the hormone dependent endocrine tumor growth, and by sterol biosynthesis modulation. Moreover, phytosterols have also exhibited properties that directly inhibit tumor growth, including reduced cell cycle progression, apoptosis induction, and tumor metastasis inhibition. The objective of this review is to summarize the current knowledge on occurrences, chemistry, pharmacokinetics and potential anticancer properties of phytosterols *in vitro* and *in vivo*. In conclusion, anticancer effects of phytosterols have strongly been suggested and support their dietary inclusion to prevent and treat cancers.

Contents

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1. Introduction

1.1. Study background of phytosterols

Phytosterols are plant sterols having similar structural and biological functions to cholesterol [1,2]. They have shown protection against various chronic ailments [3] like cardiovascular diseases [2,4] hepatoprotective [5] diabetes [6] and cancer [2,7–12]. With regard to cancer prevention, it has been claimed that phytosterol rich diet may reduce the cancer risk by 20% [9,13–15]. Phytosterols are cell membrane structural components involved in regulation of membrane fluidity, permeability and membrane-associated metabolism [16,17]. Phytosterols are byproducts of isoprenoid biosynthesis pathway via squalene from acetyl coenzyme-A [14]. Its synthesis is a complex chemical cascade involving more than 30 enzymes catalyzed reactions like cholesterol biosynthesis within the plant cell membranes [18,19]. Phytosterols are families of more than 200 different compounds that originate in a variety of vegetation and aquatic flora [20]. Plant based foods stuff chiefly nuts, seeds, vegetable oils, cereals and legumes are the richest source of phytosterols [3,21–23]. Campesterol, beta-sitosterol and stigmasterol are the most common phytosterols [24], both structurally resembling cholesterol except for an additional hydrocarbon chain at the C-24 position [4,23]. Human body derives phytosterols solely through ingestion of plant origin diets as the cell does not synthesize phytosterols endogenously [25,26]. Serum phytosterol levels in humans range from 7 to 41 μmol/L (2.9–17.0 mg/L) [27]. The present review summarizes the recent updates relating to the phytosterol sources, its structures, and metabolism in human body as well as anticancer effects. Finally it reviews the experimental and clinical evidence advocating their anticancer properties and discusses the cellular and signal transduction processes that dietary phytosterols experience within human tissues accounting for their chemotherapeutic properties.

1.2. Occurrence and dietary intake of phytosterols

In all higher plants, cholesterol and the C-24 alkyl plant sterols occur as free esters of β-D-glucosides also known as sterolins and their 6-O'-esters in small but readily identifiable amounts as primary essential biosynthetic products [1,2]. Considerable amounts of phytosterols are found in the lipid-rich and fiber-rich fractions of all plant foods. Good sources of plant sterols are vegetable oils and products made from oils like spreads and margarine [19]. Other foods which contribute to the daily intake of plant sterols are cereal grains, cereal based products, nuts, legumes, vegetables and fruits [28–32]. Plant stanols (saturated sterols) are also present in some foods but at a much lower concentrations. They are found in some cereal grains like rye, corn and wheat as well as in non-hydrogenated vegetable oils [19]. Plant stanols may be found in coniferous trees such as pine and spruce. The daily dietary intake of plant stanols is about 25 mg/day [15] compared to sterols ranging from 150 to 400 mg/day which include 65% of intake as β-sitosterol, 30% as campesterol and 5% as stigmasterol [33,34].

1.3. Chemistry of phytosterols

The most common phytosterols in the human diet are β-sitosterol, campesterol and stigmasterol. The concentrations of these phytosterols vary among food groups but a typical distribution of phytosterols in common plant foods as reported in the Food Chemical Codex monograph for sterols consists of 50–65% β-sitosterol, 10–40% campesterol, and 0–35% stigmasterol [35]. The chemical differences among the common 4-desmethyl sterols are due to number of carbon atoms in the carbon-17 branch chain (either 8 or 10) and because of the presence or absence of a double bond at particular position [36]. All phytosterols contain one double bond at carbon-5 position and saturation of this double bond occurs either enzymatically *in vivo* or through hydrogenation.

Both β-sitostanol and campestanol are the two most common stanols. The major types of free phytosterols and phytostanols are presented in Table 1. In some preparations, they are esterified with vegetable oil fatty acids like esters of sitostanol (sitostanyl oleate) and esters of campesterol (campesteryl oleate).

1.4. Pharmacokinetics of phytosterols

Dietary sterols are absorbed by all investigational animals and most of them (including dog, pig, mouse, rat and sheep) contain about 10–20 times more sitosterol in their serum and tissues than humans (~5 μM) [36–41]. In a healthy human, the sitosterol to cholesterol ratio on a molar basis is about 1 to 800–1000 [41–44]. Despite the structural similarity between cholesterol and the major phytosterols, their absorption by mammalian intestine is low. In general, the absorption rates are 0.5% for β-sitosterol, 1.9% for campesterol, 0.04% for sitostanol and 0.16% for campestanol, compared to 56% for cholesterol [34,45]. The low absorption of phytosterols as compared to cholesterol is due to their rapid re-secretion from the intestinal cells back into the gut lumen via the ATP-binding cassette (ABC) transporters ABC G5 and ABC G8 [46]. Phytosterols are absorbed under similar conditions needed for cholesterol absorption. Like cholesterol, they are also taken up from dietary mixed micelles, which typically contain mixtures of free cholesterol, mono- and di-glycerides, fatty acids, phospholipids and