

Invited Commentary

Phytosterols: to be or not to be toxic; that is the question

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Plant sterols (phytosterols) are membrane constituents of all plants with a structure analogous to that of cholesterol. Thus, phytosterols have either an additional methyl or ethyl group on the carbon-24 position or an additional double bond in the side chain⁽¹⁾. Noteworthy, in patients with the rare inherited disease of phytosterolaemia characterized by a hyperabsorption and diminished biliary secretion of cholesterol and phytosterols as well as by tendon and tuberous xanthoma, elevated plasma concentrations of phytosterols (campesterol, sitosterol) have been shown to constitute a risk factor for premature atherosclerosis⁽²⁾. However, whether plasma concentrations of campesterol and sitosterol are risk factors for CVD in subjects without phytosterolaemia is not clearly established, and still remains controversial⁽³⁾. Thus, whereas some benefits are attributed to phytosterols found in fruits, vegetables, vegetable oils, seeds and nuts⁽⁴⁾, especially their ability in decreasing cholesterol concentrations through various ATP-binding cassette transporters present at the intestinal level^(5,6), the potential effects of phytosterols, and of their oxide derivatives⁽⁷⁾, on other metabolic processes remain to be elucidated⁽⁸⁾. Therefore, the article by Rubis *et al.*⁽⁹⁾, published in the current issue of the *British Journal of Nutrition*, concerning the *in vitro* effects of rape seed oil extract components (a mixture of various phytosterols containing mainly campesterol, sitosterol and stigmasterol derivatives), of β -sitosterol, and of 5 α ,6 α -epoxycholesterol on the proliferation and viability of the human abdominal aorta endothelial cells, HAAE-2, is of great interest. In agreement, with previous investigations⁽¹⁰⁾, strong cytotoxic effects of β -sitosterol were shown, whereas a low cytotoxicity and no side-effects were observed with 5 α ,6 α -epoxycholesterol and the seed oil extract, respectively. Although absorption of plant sterols is low compared with cholesterol⁽¹¹⁾, these data show that some phytosterols, in isolation, can have more or less pronounced cytotoxic effects on normal cells. These observations are in agreement with those obtained with high concentrations of β -sitosterol (up to 0.7 mM) on human umbilical vein endothelial cells where cell contraction and increased release of intracellular lactate dehydrogenase in the culture medium was reported⁽¹²⁾. Interestingly, these observations suggest

that very high concentrations of certain phytosterols (mainly β -sitosterol) in foodstuffs might impair vascular reactivity, and interfere with the vascular tone. As it has been well established (1) that atherosclerosis is associated with abnormalities of vascular function characterized both by an increase in the response to specific vasoconstrictor agents⁽¹³⁾, and by a marked attenuation of endothelium-dependent relaxation⁽¹⁴⁾, and (2) that alteration of vascular reactivity occurs at an early stage of the atherosclerotic process^(13,15), it seems very important to identify precisely the effects of certain phytosterols on the endothelium. However, only concentrations of the oil extract that contain high, non-physiological concentrations of β -sitosterols resulted in a significant growth inhibition. Therefore, as previously reported and as well described with oxysterol mixtures⁽¹⁶⁾, these data indicate that some phytosterols may quench the inherent toxic effects of others, and may therefore counteract the proatherogenic signals involved in the initiation and the development of atherosclerotic lesions. Thus, as the involvement of phytosterols in atherogenesis cannot be excluded, a better knowledge of the biological activities of these molecules present in high amounts in various foodstuffs remains an important and essential source of investigation necessary to avoid important side-effects, and to identify adequate phytosterol mixtures capable of bringing benefit to human health.

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