Chapter 54
Nutraceutical Intervention of Phytosterols in Cardiovascular Aging

Charu Gupta
https://orcid.org/0000-0001-6023-8289
Amity University, India

Dhan Prakash
Amity University, India

Sneh Gupta
RGPG College, India

ABSTRACT

Phytosterols and phytostanols are a large group of compounds that are found exclusively in plants. They are structurally and functionally related to cholesterol but differ from cholesterol in the structure of the side chain. Phytosterols lower total and low-density lipoprotein (LDL) blood cholesterol by preventing cholesterol absorption from the intestine, so they have been known as blood cholesterol-lowering agents. Phytosterols are naturally found in fruits, vegetables, nuts, and mainly oils. Dietary phytosterol intakes normally range from 160-400 mg/day with variations depending on food culture and major food sources. Dairy foods remain a food of choice for use as delivery vehicle for many functional ingredients including phytosterols and there are many dairy products available in the global markets which are enriched with phytosterols. The use of phytosterols in commonly consumed dairy products may soon provide an effective tool against CVD and its introduction to our food products is worth anticipating in the near future as nutraceuticals for healthy ageing.

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INTRODUCTION

Cardiovascular diseases were collectively the number one cause of death in the United States in 2007, accounting for one third of deaths (Xu, Kochanek, Murphy, & Tejada-Vera, 2010). Most of these deaths were attributable to ischemic heart diseases, in which a portion of the muscle in the heart does not receive adequate blood flow. A major cause of ischemia is atherosclerosis, which is characterized by inflammation and lipid accumulation in the lumen of arteries, which decreases blood flow by narrowing the artery and can eventually lead to thrombosis, thereby completely blocking the artery with a blood clot. The Framingham Heart Study is often credited with being the first to systematically investigate the links between blood cholesterol concentrations as a risk factor for cardiovascular diseases, and particularly the effects of low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and total cholesterol (Castelli, 1988). The Framingham Heart Study, a long-term observational study, is now observing the third generation of participants from residents in Framingham, MA. The data from this study have allowed a number of prediction models of cardiovascular disease risk associated with a variety of risk factors, and has worked to separate environmental, genetic, and other effects through epidemiological modeling. In one such model, cholesterol concentrations were determined to be such a significant risk factor for coronary heart disease that all other risk factors, such as diabetes, smoking, and blood pressure, were converted into either cholesterol or LDL-C risk points, which were then compared to categories on a risk chart (Wilson, D'Agostino, Levy, Belanger, Silbershatz, & Kannel, 1998). Clearly, LDL-C concentrations are an important risk factor for heart disease.

Cholesterol in the body mainly comes from two sources- endogenous synthesis and dietary consumption. Dietary cholesterol contributes a relatively minor proportion of the cholesterol in the system, with an average of only 276 mg of cholesterol consumed per day (Agricultural Research Service USDA, 2010). In addition, dietary cholesterol minimally affects blood cholesterol, with estimates of only a 0.022-0.027 mg/dL difference in blood cholesterol for every 1 mg of dietary cholesterol consumed (McNamara, 2000). To put this into perspective, an individual with high cholesterol (>240 mg/dL) would need to consume an additional 100 mg of cholesterol per 6 day to increase their blood cholesterol by about 1%. Although dietary cholesterol alone seems to have little effect on blood cholesterol, dietary cholesterol is not the only source of cholesterol in the intestinal lumen. The gall-bladder secretes approximately 1000 mg of cholesterol per day into the small intestine. Of the total cholesterol in the intestinal lumen, approximately 50% is absorbed, making inhibition of intestinal cholesterol absorption, not just decreasing dietary cholesterol, an important target for lowering blood cholesterol concentrations (McNamara, 2000).

Cardiovascular diseases (CVDs) inflict a huge burden in terms of mortality and morbidity, contributing to disability and decline of quality of life (Niccoli & Partridge, 2012; North & Sinclair, 2012). In addition, aging itself produces numerous changes in human heart, at structural, molecular, and functional levels. The most important age-related alterations are left ventricular (LV) hypertrophy, fibrosis, denervation, and maladaptive remodeling that frequently lead to diastolic dysfunction (Rengo, Pagano, Vitale, Formisano, Komici, & Petraglia, 2016). Vascular aging is characterized by impaired endothelial function, chronic vascular inflammation, and augmented arterial stiffness (Ungvari, Kaley, de Cabo, Sonntag, & Csiszar, 2010). Endothelial dysfunction is mainly related to increased production of reactive oxygen species (ROS) partially due to an increased activity of NAD(P)H oxidases (NOX) (Csiszar, Ungvari, Edwards, Kaminski, Wolin… & Koller, 2002). Moreover, increased age-related oxidative stress and decreased production of nitric oxide (NO) constitute critical factors for the alteration of cardiovas-