Trends in Food Science & Technology 79 (2018) 148–159

Contents lists available at ScienceDirect

Trends in Food Science & Technology

journal homepage: www.elsevier.com/locate/tifs

Review

How do oxyphytosterols affect human health?

Mengmeng Wang, Baiyi Lu*

College of Biosystems Engineering and Food Science, Zhejiang University, National Engineering Laboratory of Intelligent Food Technology and Equipment, Key Laboratory for Agro-Products Postharvest Handling of Ministry of Agriculture, Key Laboratory for Agro-Products Nutritional Evaluation of Ministry of Agriculture, Zhejiang Key Laboratory for Agro-Food Processing, Fuli Institute of Food Science, Hangzhou 310058, PR China

ARTICLE INFO

Keywords:
Oxyphytosterols
Absorption
Distribution
Transport
Biological effects

ABSTRACT

Oxyphytosterols are similar to oxycholesterols in structure, and they exhibit pro-atherogenic properties. Recently, more interests were focused on the metabolism of oxyphytosterols for their increasing intake from phytosterol-enriched food. In this review, we discussed the origin, absorption, distribution, and transport of oxyphytosterols in vivo and their biological effects in humans. The two dominant oxyphytosterols in human plasma are 7-keto-sitosterol and 7-keto-campesterol, but their origins are unclear. It is suggested that oxysitosterols are formed to eliminate sitosterol from tissue to the blood stream. Aside from the pro-atherogenic, oxyphytosterols also exhibit pro-inflammatory properties and antiviral activity against equine herpesvirus 1. Further research is needed to investigate the physiological and pathological role of oxyphytosterols in humans.

1. Introduction

Phytosterols are a class of natural organic molecules in plants and similar to cholesterol in structure; they have been used as health supplements in functional foods over the past 20 years because of their cholesterol-lowering effect (Abumweis, Barake, & Jones, 2008; Katan, Grundy, Jones, Law, Miettinen, & Paoletti, 2003; Piironen, Lindsay, Miettinen, Toivo, & Lampi, 2000). However, phytosterols are prone to oxidation in foods (Barriuso, Ansorena, & Astiasaran, 2017), and the increased consumption of phytosterol-enriched food leads to increased oxyphytosterol intake (Lin, Knol, & Trautwein, 2016; Renzo Bortolomeazzi, Francesca Cordaro, Lorena Pizzale, & Conte, 2003; Scholz, Guth, Engel, & Steinberg, 2015). Oxyphytosterols have been found to have cytotoxic and potentially pro-inflammatory effects (Alemany, Laparra, Barberá, & Alegría, 2013; Gao, Chen, Zhang, Cheng, Xu, Wu, et al., 2015), which may contribute to increased cardiovascular disease (CVD) risk (Baumgartner et al., 2015).

Nowadays, considerable interests have been focused on the physiological roles of oxyphytosterols because of their important biological effects. Oxycholesterols are the oxidation products of cholesterol. Studies showed that oxycholesterols play important roles in cholesterol homeostasis (Gill, Chow, & Brown, 2008) and in the immune system (Spann & Glass, 2013; Traversari & Russo, 2012), act as activators of the Hedgehog signaling pathway (Corcoran & Scott, 2006; Dwyer et al., 2007) and ligands for several receptors (Umetani & Shaul, 2011; Wang, Kumar, Solt, Richardson, Helvering, Crumbley, et al., 2010), and are involved in the development of several diseases, such as neurodegenerative diseases (Bjorkhem, Cedazo-Minguez, Leoni, & Meaney, 2009; Leoni, Long, Mills, Di Donato, Paulsen, & group, 2013) and atherosclerosis (Brown & Jessup, 1999; Umetani, Ghosh, Ishikawa, Umetani, Ahmed, Mineo, et al., 2014). Oxyphytosterols are similar to oxycholesterols in structure and had been reported qualitatively to exhibit similar toxic effects to oxycholesterols at high concentrations to elicit comparable levels of toxicity (Ryan, Chopra, McCarthy, Maguire, & O'Brien, 2005). Oxyphytosterols and oxycholesterols may both come from dietary intake or endogenous formation by oxidation of their parent sterols. The endogenous formation of oxycholesterols is related to enzymes, such as cytochrome P450 (Lund, Guileyardo, & Russell, 1999; Shinkyo, Xu, Tallman, Cheng, Porter, & Guengerich, 2011). Different from oxycholesterols, the endogenous formation of oxyphytosterols is still unclear. However, recently, an increasing number of studies reported the origin, absorption, distribution, transport, and biological effects of oxyphytosterols. This review aims to provide an overview of the studies investigating the absorption and distribution of oxyphytosterols in humans, discuss their potential transport mechanisms and biological effects, and attempt to identify knowledge gaps and questions for further research.

2. Analytical methods

Given the molecular structure and epimers of the oxyphytosterols, they are difficult to quantify. Gas chromatography-mass spectrometry

* Corresponding author.
E-mail address: bylu@zju.edu.cn (B. Lu).

https://doi.org/10.1016/j.tifs.2018.07.002
Received 27 April 2018; Received in revised form 8 July 2018; Accepted 11 July 2018
Available online 26 July 2018
0924-2244/

(GC–MS) in SIM mode can satisfy the needs for its high selectivity. The occurrence of oxyphytosterols in foods, such as vegetable oils (Bortolomeazzi, Cordaro, Lorena Pizzale, & Conte, 2003), French fries (Dutta, 1997), infant foods (Garcíallatas, Cercaci, Rodriguezestrada, Lagarda, Farré, & Lercker, 2008), and dark chocolates (Botelho et al., 2014), has been reviewed by Scholz (Scholz, Guth, Engel, & Steinberg, 2015). However, in biological samples, the oxyphytosterols have a low level (parts ng/mL or parts pg/mL), which made the detection difficult. For oxycholesterols, many methods have been employed to generate the analytical data in biological samples, including GC–MS, LC–MS/MS, LC–ESI–MS/MS, and LC–MS^n, which have been summarized by Giffiths (Griffiths, Crick, & Wang, 2013). Recently, UPLC–IM–TOFMS(Kylli, Hankemeier, & Kostiainen, 2017) and HPLC–APCI–MS/MS(Gorassini, Verardo, Fregolent, & Bortolomeazzi, 2017) had been applied to detect oxycholesterols. However, due to the lack of basic or acidic groups in the oxyphytosterols, the main method for oxyphytosterol measurements in biological samples is still GC–MS.

In 2011 and 2012, Husche and Menéndez-Carreño validated the use of GC–MS and GC × GC/TOF–MS for analyzing oxyphytosterols in serum (Husche, Weingärtner, Pettersson, Vanmierlo, Böhm, Laufs, et al., 2011; Menéndez-Carreño, Steenbergen, & Janssen, 2012). Table 1 summarizes the methods and validation parameters. As shown from Table 1, the pre-treatments were similar, including oxyphytosterol extraction and saponification, isolation by silica SPE cartridges, and derivatization to TMS. However, the limit of detection (LOD) and limit of quantification (LOQ) differed between the two methods, which calls for a standardization of oxyphytosterol analyses. Taken together, the LOD and LOQ of 7-keto-oxyphytosterols were higher than those of 7β-OH- and 7α-OH-oxyphytosterols.

3. Origin of oxyphytosterols in the human body

There are two main origins of oxyphytosterols in human plasma and tissues: from the absorption of oxyphytosterols in the diet or from the oxyphytosterols generated in vivo by the oxidation of plant sterols (Baumgartner, Mensink, Husche, Lutjohann, & Plat, 2013). Though the oxyphytosterols in vivo had been reported, the origin of oxyphytosterols is still not clear. Some researchers suggested that the presence of oxyphytosterols may come from the diet, for the oxyphytosterol concentration in the plasma was not increased after intake of 3.0 g/day of plant sterols in humans which may because that no more oxyphytosterols was generated in vivo (Baumgartner et al., 2013; Baumgartner et al., 2017a). The concentration of oxysitosterols in plasma is four to five times higher than that of oxycampesterols, but its ratio in the diet is approximately two times higher than that of oxycampesterols, suggesting a high absorption or additional generation of oxysitosterols in vivo (Baumgartner et al., 2013). However, other studies indicated the endogenous synthesis of oxyphytosterols. For example, elevated oxyphytosterols have been reported in the plasma of phytosterolemic patients even though these patients had very low plant sterol intake (Salen, Horak, Rothkopf, Cohen, Speck, & Tint, 1985), possibly indicating that oxyphytosterols in plasma result from endogenous oxidation of circulating serum plant sterol. Moreover, high oxyphytosterol intake does not change the concentration of oxyphytosterols in vivo, which suggests that the oxyphytosterols in vivo are not related to the dietary intake (Baumgartner et al., 2013). Recently, Baumgartner et al. reported that the plasma oxyphytosterol concentrations were higher in IGT or DM2 subjects than in healthy subjects and were not lower with 4-week vitamin E or lipoic acid supplementation (Baumgartner, Mensink, Haenen, Bast, Binder, Bekers, et al., 2017b), which indicated that oxyphytosterols may be related to health status.

3.1. Dietary exposure of oxyphytosterols

Several studies estimated the dietary exposure of oxyphytosterols (Lin, Knol, & Trautwein, 2016; Scholz, Guth, Engel, & Steinberg, 2015). The content of oxyphytosterls were reported in vegetable oils (2.7–67.5 mg/kg) (Bortolomeazzi, Cordaro, Pizzale, & Conte, 2003), French Fries (0.8–3.4 mg/kg) (Dutta, 1997), potato crisps (1.1–1.2 mg/kg) (Tabee, Jägerstad, & Dutta, 2007), milk (0.2–6.4 mg/kg) (Menéndez-Carreño, Ansorena, & Astiasarán, 2008; Soupas, Huikko, Lampi, & Piironen, 2005) and spread (13.3 mg/kg) (Conchillo et al., 2005). Scholz et al. reported that the daily intake of oxyphytosterols ranges from 1.2 mg/day to 2.9 mg/day for nonheated food and 3.5 mg/day to 4.2 mg/day for heated food; in the worst case, the dietary exposures are 13 and 130 mg/day at oxidation rates of 0.1% and 1%, respectively (Scholz, Guth, Engel, & Steinberg, 2015). Lin et al. revealed the oxyphytosterol intake from foods added with different chemical forms of phytosterols (Lin, Knol, & Trautwein, 2016). According to Lin et al.'s report, the estimated upper oxyphytosterol intake is 47.7 mg/day for foods with added plant sterol esters and 78.3 mg/day for foods with added free plant sterols. The absorption rate of oxyphytosterols in humans is lacking, but animal studies indicated a higher absorption of oxyphytosterols than that of non-oxidized phytosterols (Grandgirard, Sergiel, Nour, Demaison-Meloche, & Ginìes, 1999; Tomoyori, Kawata, Higuchi, Ichi, Sato, Sato, et al., 2004). For mice and hamsters, three studies all reported increased oxyphytosterols in plasma and other tissues after intake of diet containing added oxyphytosterol for 2–9 weeks (Bang, Arakawa, Takada, Sato, & Imaizumi, 2008; Grandgirard, Sergiel, Nour, Demaison-Meloche, & Ginìes, 1999; Tomoyori et al., 2004). Interestingly, different from the result of humans, the highest oxyphytosterols present in mice and hamsters are not 7-keto-oxyphytosterols but 7β-OH- and 7α-OH-oxyphytosterols even though 7-keto-oxyphytosterol has the highest concentration in the diet, which indicates that oxyphytosterol metabolism may differ in humans and mice.

3.2. Endogenous formation of oxyphytosterols

Theoretically, the endogenous synthesis of oxyphytosterols includes enzymatic and non-enzymatic oxidation. The enzymatic oxidation of cholesterols in humans has been well documented. The endogenous synthesis and metabolism of oxycholesterols have been reviewed (Luu, Sharpe, Capell-Hattam, Gelissen, & Brown, 2016; Mutemberezi, Guillemot-Legris, & Muccioli, 2016). The main enzymes are cytochrome P450s(Luu, Sharpe, Capell-Hattam, Gelissen, & Brown, 2016), and the oxycholesterols are not only the metabolic intermediates of cholesterols but also the full fledge bioactive lipids (Mutemberezi, Guillemot-Legris, & Muccioli, 2016). However, studies on the enzymes for the oxidation of phytosterols in humans are limited. Animal studies proved the rate of side chain hydroxylation of β-sitosterol was far lower than that of cholesterol, but the rate of campesterols was similar to that of cholesterol (Aringer, Eneroth, & Nordstrom, 1976).

For the microbial formation of oxycholesterols, Baumgartner et al. investigated the effects of microbiota on oxyphytosterol formation (Baumgartner, Mensink, Smet, et al., 2017a). They selected 13 healthy subjects to take 3.0 g/day plant stanols for 3 weeks, followed by a 4-week washout period. By analyzing the plasma oxyphytosterols and the composition and diversity of microbes, they did not find any correlations between oxyphytosterols and bacteria. However, they found correlations between several specific bacterial groups and plasma plant sterol.

4. Absorption of oxyphytosterols

The absorption of oxyphytosterols has been reported in rodent models and in humans. In mesenteric duct-cannulated adult male rats, Grandgirard et al. reported that the mean lymphatic absorption rates from intestine of 7-keto- and epoxy-derivatives of sitosterol and campesterol were 1.4% and 4.7%, which were higher than that of sitosterol (1.2%) but lower than that of campesterol (7.0%) (Grandgirard, Sergiel, Nour, Demaison-Meloche, & Ginìes, 1999). However, Tomoyori et al. reported that lymphatic recoveries of oxycampesterols (15.9%) and