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The colourless carotenoids phytoene and phytofluene: From dietary sources to their usefulness for the functional foods and nutricosmetics industries

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ABSTRACT

Carotenoids are dietary compounds of great interest in food science, nutrition and health due to the fact that some of them can be converted into retinoids exhibiting vitamin A activity, their role as natural colorants and a growing body of evidence indicating that they may provide health benefits. This is not all as some carotenoids accumulate in human skin where, besides promoting health by protecting against UV damage, they can provide cosmetic benefits by contributing to improved skin colour or improving other skin characteristics. Of the over 800 carotenoids described, only very few of them are colourless. Two of these, phytoene and phytofluene, are attracting much attention recently as they are taken with the diet, they are bioavailable and there are studies of diverse nature indicating that they could be beneficial for health. However, they have not been as extensively studied as the other major bioavailable carotenoids, namely lutein, zeaxanthin, β-cryptoxanthin, β-carotene and lycopene. The aim of this review is to summarize much of the research carried out on these carotenoids, highlighting their potential in the context of functional foods and the related area of nutricosmetics.

1. Introduction

The linear carotenes phytoene (7,8,11,12,7′,8′,11′,12′-octahydro-ψ,ψ-carotene, PT) and phytofluene (7,8,11,12,7′,8′-hexahydro-ψ,ψ-carotene, PTF) (Fig. 1) are rarities within the carotenoids as they lack one of the distinctive characteristics of this group of isoprenoids, visible colour. As can be observed in Fig. 1, phytoene (PT) and phytofluene (PTF) have 9 and 10 double bonds, respectively, although the number of conjugated double bonds (c.d.b.) is much lower as compared to coloured carotenoids. Thus, whilst coloured carotenoids have at least 7 (c.d.b.) (Meléndez-Martínez et al., 2007), phytoene and phytofluene have 3 and 5 (c.d.b.) respectively. Thus, unlike coloured carotenoids, which have absorption maxima in the visible region, PT and PTF absorb maximally in the ultraviolet region. More specifically, their λ_{max} in petroleum ether are 286 and 348 nm, respectively (Rodriguez-Amaya, 2001). These wavelengths are far from 450 nm, a wavelength typically used to detect carotenoids in HPLC-DAD, meaning they may go undetected in many published studies − possibly one of the reasons for the scarcity of data on phytoene and phytofluene levels in foods and animal fluids and tissues as compared to other major dietary and bioavailable carotenoids like lutein, zeaxanthin, β-cryptoxanthin, β-carotene (BCAR) and lycopene (LYC).

Despite being rarities among carotenoids, PT and PTF are very important for a series of reasons and are attracting much interest recently from diverse point of views. For instance, some recent studies provide new data concerning their antioxidant capacity, their geometrical isomerization and methodologies to analyze different isomers that may be present in humans (Meléndez-Martínez et al., 2013b,2014; Stinco et al., 2016b). Similarly, they are precursors of the coloured carotenoids, hence their relevance in studies dealing with the biosynthesis of these carotenoids. They are present in foods like tomatoes, some citrus, carrots, being also bioavailable. Thus, they circulate in blood and are present in diverse tissues including the skin (Khachik et al., 2002). Furthermore, a number of studies indicate that they may be related to the reduction of the risk of developing certain cancers, such as skin, prostate, leukemia, breast and endometrial cancer, and atherosclerosis (reviewed in (Meléndez-Martínez et al., 2015)).

In this context, the goal of this review is to summarize much of the

Abbreviations: ABA, abscisic acid; ABTS, 2,2-azinobis-3-ethylbenzothiazoline-6-sulfonic acid; ARE, antioxidant response element; BCAR, β-carotene; BHT, butylated hydroxytoluene; CD, control diet; CD36, cluster of differentiation 36; c.d.b., conjugated double bonds; COX-1, cyclooxygenase 1; COX-2, cyclooxygenase 2 enzymes; CVD, cardiovascular disease; GGPP, geranylgeranyl pyrophosphate; HFD, high fat diet; IL, interleukin; LDL, low density lipoprotein; LYC, lycopene; MED, minimum erythemal dose; MeOH, methanol; MTBE, methyl-tert-butyl ether; Nrf2, nuclear factor E2-related factor; PSY, phytoene synthase; PDS, phytoene desaturase; PPARγ, peroxisome proliferator-activated receptor gamma; PT, phytoene; PTF, phytofluene; TE, tomato extract; UVR, UV radiation

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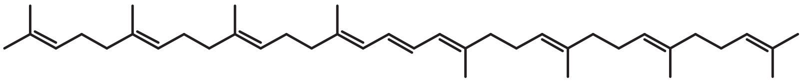
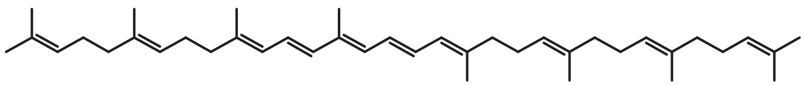


(All-*E*)-phytoene



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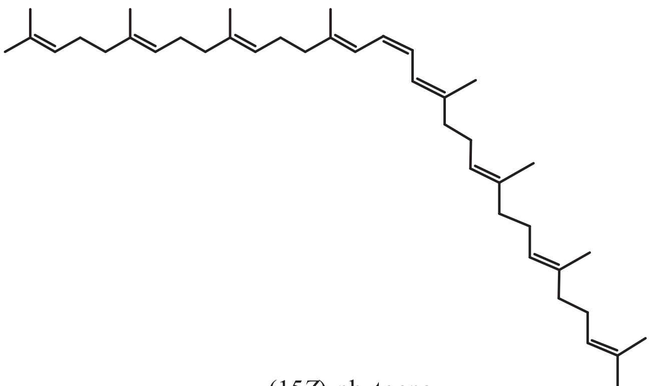

(15*Z*)-phytoene

Fig. 1. Representation of the chemical structures of the (all-*E*)-isomers of phytoene and phytofluene and (15*Z*)-phytoene.

research carried out regarding these carotenoids in the context of food science, nutrition and health; highlighting their potential in the context of functional foods and nutricosmetics. Nutricosmetics is at the intersection between food, nutrition, health and cosmetics that include products somewhat related to functional foods and nutraceuticals commonly referred to as "beauty foods", "beauty pills" or "oral cosmetics" that promote "beauty from within", this being a key concept in this context (Anunciato and da Rocha Filho, 2012; Madhere and Simpson, 2010). There is no standard definition for "functional foods", although there is a widely accepted working definition provided by the European Comission Concerted Action "Functional Food Science in Europe" (FUFOSE): 1) "A food that beneficially affects one or more target functions in the body beyond adequate nutritional effects in a way that is relevant to either an improved state of health and well-being and/or reduction of risk of disease"; 2) "not a pill, a capsule or any form of dietary supplement"; 3) "consumed as part of a normal food pattern" (Howlett, 2008). As far as nutricosmetics is concerned, the usefulness of PT and PTF as components of products to promote "beauty from within" is also discussed, since the interest on dietary compounds that can promote both skin appearance and health is an expanding field (Madhere and Simpson, 2010).

2. Biosynthesis

Carotenoids are members of the isoprenoid family (Bouvier et al., 2005). The typical first commited step in the biosynthesis of carotenoids is the condensation of two molecules of geranylgeranyl pyrophosphate (GGPP, a compound with 20 atoms of carbon) to form phytoene (Fraser and Bramley, 2004). This is typically in the form of the (15Z) isomer (Than et al., 1972).

Carotenoids are biosynthesized by all photosynthetic organisms (cyanobacteria, algae and plants) as well as some bacteria and fungi that do not have the ability to carry out photosynthesis. Traditionally it has been considered that animals cannot synthesize carotenoids *de novo* and that they incorportate them through the diet. On the other hand, animals can *modify* carotenoids. Thus, mammals possess at least two different kinds of oxygenase enzymes able to cleave carotenoids to give retinoids, apocarotenoids and other oxidized derivatives (Lietz et al., 2012; Sui et al., 2013). However, it has been demonstrated recently that some animals, specifically arthropods, can biosynthesize carotenoids. One example would be some types of aphids (Moran and Jarvik, 2010).

The formation of phytoene from GGPP is catalyzed by phytoene synthase (PS), whereas phytoene desaturase (PDS) introduces new double bonds to form phytofluene and then other more unsaturated compounds (reviewed in (Fraser and Bramley, 2004; Sandmann, 2009)). Depending on the carotenogenic organism, there are certain differences in the biosynthesis of colourless carotenoids. For instance, there can be differences across organisms in relation to the number of genes codifying for PS and PDS, number of isozymes, the number of desaturation steps carried out by specific phytoene desaturases and so on (Meléndez-Martínez et al., 2015). As an example, the desaturation of carotenes (a key target site for bleaching herbicides) is thought to be very different in bacteria and fungi compared to oxygenic photosynthetic organisms, since bleaching compounds that are effective in inhibiting desaturases in the latter do not work in the former (Sandmann, 2009). Recently, the bleaching chemical norflurazon has been used to produce ^{14}C-labelled phytoene in tomato cell cultures as a preliminary step to produce a sufficient quantity of this compound to expand our knowledge on the fate and actions of this carotenoid in humans (Campbell et al., 2006a).

Genes codifying PS have been identified in a number of plant crops, like maize (Li et al., 2009), rice (Chaudhary et al., 2010; Welsch et al., 2008), wheat (Howitt et al., 2009), tomato (Bartley and Scolnik, 1993; Fray and Grierson, 1993), melon (Karvouni et al., 1995) and others. Similarly, genes encoding PDS have been identified in red pepper (Hugueney et al., 1992), maize (Li et al., 1996), soybean (Bartley et al., 1991) and tomato (Pecker et al., 1992), among others. According to Cazzonelli and Pogson (Cazzonelli and Pogson, 2010), the existence in