Review

Cholesterol photosensitized oxidation in food and biological systems

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ABSTRACT

Lipid oxidation is one of the main chemical degradations occurring in biological systems and leads to the formation of compounds that are related to aging and various chronic and degenerative diseases. The extent of oxidation will depend on the presence of antioxidants/pro-oxidants, the unsaturation degree of fatty acids, and environmental conditions. Lipid oxidation can also affect other molecules that have double bonds in their chemical structures, such as cholesterol. Cholesterol oxidation products (COPs) have been studied in depth, because of their negative and controversial biological effects. The formation of COPs can be particularly favored in the presence of light and photosensitizers, since they generate excited singlet oxygen that rapidly reacts with the double bond by a non radical mechanism and without any induction period. The present review intends to provide an overall and critical picture of cholesterol photosensitized oxidation in food and biological systems, and its possible impact on human health and well-being.

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1. Introduction

Cholesterol is a monounsaturated molecule located in the cell membrane and it is involved in membrane permeability and fluidity. The A ring of the molecule is exposed to the outer side of the double phospholipid layer, with the hydroxyl group interacting with the polar head groups of the membrane phospholipids, while the side chain is situated among the alkyl chain of phospholipids [1,2]. Due to the presence of a double bond in position 5,6 of the B ring, cholesterol can oxidize, following similar oxidative pathways as monounsaturated fatty acids [3–5]. Cholesterol tends to oxidize first in an undamaged cell membrane and its oxidative instability could be further favored by the presence of a relatively large amount of polyunsaturated fatty acids (PUFA) in the cell membrane [6]. Cholesterol oxidation products (COPs) can be generated by autoxidation, photosensitized oxidation and enzymatic oxidation [2–7]; the types and concentrations of the single COPs produced

will depend on the oxidative mechanism they originate from, as well as on environmental conditions (temperature, light, water activity) and the presence of trace elements and biomolecules with prooxidant and/or antioxidant activities. COPs have been studied in depth in food [5,7–11], as they are likely to be involved in several chronic and degenerative diseases, disturbance of cell functionality and lipid metabolism [7,10,12,13]. While the role of photosensitized oxidation on the production of dietary COPs has been well documented [8–11,14–18], there is little information dealing with photosensitized oxidation of biological tissues that are daily exposed to light, such as skin, retina and lens.

This review intends to provide a picture on cholesterol photosensitized oxidation on food and biological tissues, in order to better understand its impact on food quality, biological tissue integrity and consumer health.

1.1. Cholesterol photosensitized oxidation

Cholesterol photooxidation reactions are classified as either type I (free radical mechanism) or type II (singlet oxygen mediated) [19,20]. Cholesterol photosensitized oxidation requires singlet oxygen ($^1O_2$) for the initiation phase to occur, being mainly generated when photosensitizers absorb light, become electronically excited and interact with triplet oxygen to convert it into reactive singlet oxygen. The latter is more reactive (32,000 times for monounsaturated structures and 1600 times for diunsaturated ones) than triplet oxygen [21], as it has higher redox potential and a lower energy of

activation. When cholesterol photosensitized oxidation takes place, $^1O_2$ attacks the steroid molecule by an *ene* addition mechanism on either side of the double bond [22]. In reactions mediated by $^1O_2$, 5α-hydroperoxycholesterol (5α-HPC), 6α-hydroperoxycholesterol (6α-HPC) and 6β-hydroperoxycholesterol (6β-HPC) are the only three hydroperoxides that are generated, 5α-HPC being the most abundant one [3,23] (Fig. 1). The latter can rearrange and give rise to both 7α-hydroperoxycholesterol (7α-HPC) and 7β-hydroperoxycholesterol (7β-HPC), which are usually present at different concentration levels as the α epimer is less favored from a thermodynamics standpoint [2,3,5]. Hydroperoxides are then rapidly converted into hydroxyl and keto derivatives by a dismutation reaction, giving rise to 7α-hydroxycholesterol (7α-HC) and 7β-hydroxycholesterol (7β-HC), together with 7-ketocholesterol (7-KC) (Fig. 1). As observed for hydroperoxides, 7α-HC is commonly found at lower concentrations levels than its corresponding epimer. Depending on the lighting conditions, it might be possible that 7-HCs and 7-KC are interconvertible [24]; this behavior could be also influenced by an oxidant environment. While the formation of such oxidation compounds occurs, hydroperoxides can also follow a bimolecular reaction pathway, which involves the interaction with a cholesterol molecule that generates 5α,6α-epoxycholesterol (α-EC) and 5β,6β-epoxycholesterol (β-EC) (Fig. 1). In presence of water and acidic conditions, the epoxy derivatives can undergo ring opening and, thus, produce cholestanetriol (CT, triol). The formation of side-chain COPs is also possible due the presence of tertiary atoms at C-20 and C-25 in the side chain of the cholesterol molecule [4]; although the oxidation mechanisms are similar to those of the ring structure, a lower extent of side-chain oxidation is usually observed [3]. It is important to consider that, in any case, the trend of photosensitized oxidation can be affected by the surrounding environment, which will impact the type and amount of the oxidation products that are generated.

2. Photosensitized cholesterol oxidation in food

Over the past 35 years, COPs have been studied in food systems, as they exhibit different negative biological effects at different concentrations [7,10,11,25], including atherogenesis, cytotoxicity, mutagenesis, apoptosis, carcinogenesis, selective estrogen receptor modulation and inhibition of cholesterol biosynthesis and membrane functions [7,10—13,26—30]. Among COPs, triol is considered as one of the most toxic oxidation products, even at low concentration levels [7,10,25]. Although dietary COPs might represent a risk for human health, no toxicity limit for such compounds has been specified yet, so the threshold of toxicological concern (TTC) for unclassified compounds (0.15 μg per person per day) [31] can be utilized as reference.

Table 1 reports the COPs content found in food subjected to photosensitized oxidation.

2.1. Egg and egg products

Eggs have a very high content of cholesterol (about 400 mg/100 g of edible portion) [32], so the formation of COPS has been widely studied in egg powders and egg products. The large consumption of industrialized egg-containing foods, such as bakery products and pasta, has favored the utilization of egg as powders [33], which are characterized by a better microbiological safety, a smaller volume as compared to unshelled or liquid eggs [34] and a low water content. The most common systems to produce egg powders are freeze-drying and spray-drying; the first provides the best ingredient overall quality but, due to its relatively high cost, spray-drying is most widely used at commercial level. The quality of the egg powder lipid fraction can be greatly influenced by processing and storage conditions [35,36]. One of the most critical chemical modifications that can occur is lipid oxidation, including cholesterol oxidation, due to the egg powders' large surface area. In fact, because of the high surface activity of sterols, they tend to migrate to the oil—water interface, where oxidative stress is high [1]; this behavior would suggest that cholesterol locates at the interface before water removal, remaining at the surface level of the egg powder and being thus directly exposed to air and consequently to oxidation. The large surface area will be further decisive when egg powder and egg-containing food are subjected to light
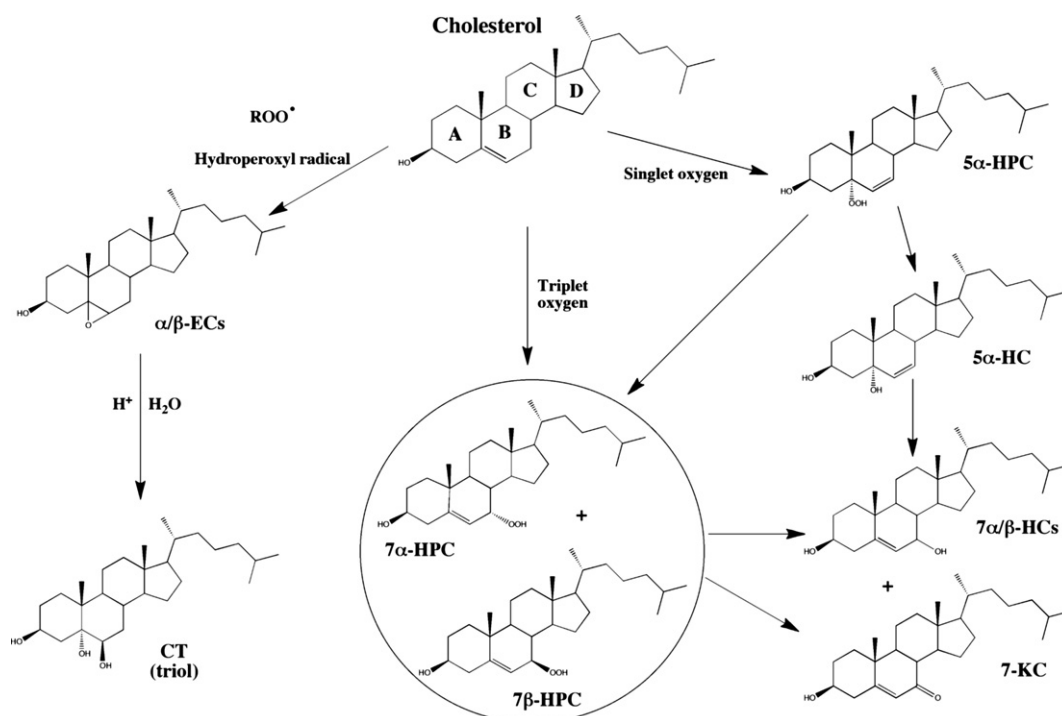

Fig. 1. Oxidation cholesterol pathways.