

Cholesterol Oxidation Products (COPs) in Ruminant Meat: A Biological and Pathological Approach: A Review

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ABSTRACT

After slaughter, meat tissues lose their antioxidant defenses, and more complex oxidative processes are initiated to form COPs—oxygenated derivatives of cholesterol. The oxysterol content in meat and meat products depends on factors such as temperature, heating time, storage time, packing conditions, and illumination. The composition and content of polyunsaturated fatty acids (PUFAs) and the age and the sex of the animal also influence the COP rate. The most common oxysterols present in meat and its products are 7-ketocholesterol, 20 α -hydroxycholesterol, 25-hydroxycholesterol and α , β - epoxycholesterol. Oxysterols participate in a number of biological activities, such as cholesterol metabolism, the regulation of membrane fluidity and intracellular signaling pathways, by the activation of specific mediators, such as LXR, SREBPs and OSBP/ORP. However, their role in inflammatory, apoptotic, mutagenic, carcinogenic, and toxic mechanisms can elucidate their effect on human health.

Keywords: Biological activities, Cholesterol, Human diseases, Oxysterols, Ruminant meat.

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INTRODUCTION

Meat lipids are composed primarily of triglycerides (85% of total lipids). They are also composed of phospholipids (12% of total lipids) and cholesterol (Ch; 3% of total lipids) (Bonnet *et al.*, 2010). The cholesterol level varies very little in muscles (Evrat-Goergel, 2005), which contains 40–80 mg of cholesterol per 100 g of fresh weight (Gandemer, 1992).

Cholesterol is the most important sterol in animal fats. It is not only a precursor of bile acids, steroid hormones (progesterone, oestradiol and testosterone), adrenal hormones (cortisol and aldosterone) and vitamin D, but also a major component of cell membranes, in which it is intercalated between phospholipids and decreases membrane permeability to water-soluble molecules (Pommier, 2010). The distribution of cholesterol in the membranes is variable. For example, erythrocyte and myelin membranes contain similar molar concentrations of cholesterol and phospholipids, whereas membranes of high metabolic organelles, such as the sarcoplasmic reticulum and the inner mitochondrial membrane contain less cholesterol (Cullis and Hope, 1991).

In the cell, cholesterol is used as part of the cell membrane, either for the renewal of the existing membrane or for the synthesis of new membranes during cell division. However, if the demand for cholesterol decreases, the excess cholesterol is converted to cholesterol esters, bile acids, steroid hormones, lipoproteins, or is transported to other cells (Dinh, 2010).

In addition, cholesterol is a reactive molecule that can suffer oxidation reactions, producing COPs or oxysterols. The COPs have received considerable attention in recent years due to their biological activities associated with human diseases.

In this review, we discuss the synthesis of oxysterols during the oxidation of cholesterol and the factors influenc-

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ing the formation of COPs in meat such as the heat, the packing condition, pH,

Finally, we present also the COPs metabolic pathways (absorption, elimination), and their most important biological activities and their impact on human health.

FORMATION OF COPs

COPs, or oxysterols, are a family of 27-carbon oxidation derivatives of cholesterol (from a biological source) that can originate exogenously, such as from the diet, or endogenously. Oxysterols are structurally identical to cholesterol, but have one or more additional oxygen-containing functional groups, such as alcohol, carbonyl, or epoxide (Brown and Jessup, 2009).

Cholesterol oxidation

Cholesterol oxidation products (COPs) can be formed by non-enzymatic oxidation (autoxidation) or enzymatic reactions (Leonarduzzi *et al.*, 2002; Smith and Murphy, 2008), as illustrated in Figure 1. Non-enzymatic oxidation affects the sterol ring, while enzymatic processes affect the side-chain of

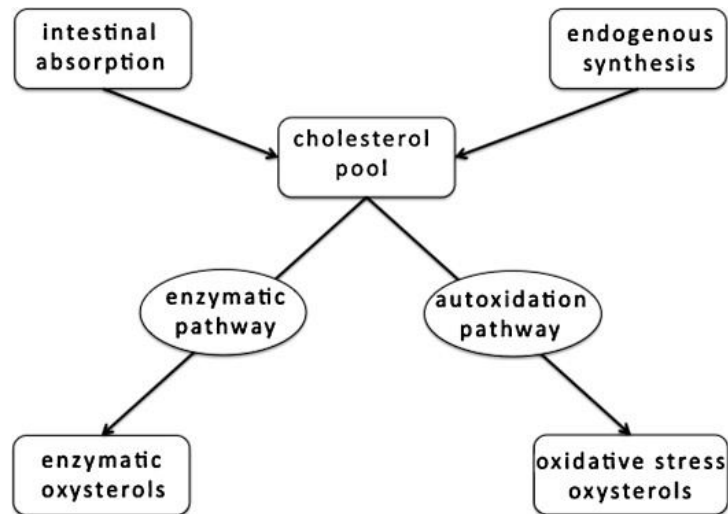


Figure 1 : Pathways of cholesterol oxidation (Iuliano, 2011)

sterol structures (Ryan *et al.*, 2005). Oxidation can occur on the sterol nucleus, in particular in positions 4, 5, 6 and 7, which are the most sensitive to oxidation. It can also occur in positions 24, 25 and 27 of the side chain. This leads to a large diversity of molecules, thus creating the family of oxysterols (Souidi *et al.*, 2004). The cholesterol oxidation rate can be 57–68% of the initial concentration (Otaegui-Arrazola *et al.*, 2010).

Autoxidation

By definition, autoxidation is a spontaneous reaction of molecular oxygen with lipids, leading to oxidative deterioration (Wasowicz *et al.*, 2004). It includes free radical-, lipid peroxide- and divalent cation-induced oxidative processes.

In a membrane environment, cholesterol is more easily attacked than polyunsaturated fatty acids (PUFAs) by reactive oxygen species (ROS). Cholesterol autoxidation frequently starts at the methylene group in the allylic position (C-7) by a free radical, producing a cholesteryl radical that reacts rapidly with dioxygen to produce a 7 α - or 7 β -peroxyl

radical. The formed radical stabilizes, abstracts a hydrogen from the allylic carbon of another lipid molecule, and forms primary COPs—isomers of 7-hydroperoxycholesterol. The seven hydroperoxycholesterols can further convert into 7 α -hydroxycholesterol (7 α -OHCh) and 7 β -hydroxycholesterol (7 β -OHCh) (Papuc *et al.*, 2017).

The main products of cholesterol autoxidation present in muscle tissue are 7-ketocholesterol (7-keto), 20 α -hydroxycholesterol, 25-hydroxycholesterol (25-OHCh) and α , β -epoxycholesterol (Orczewska-Dudek *et al.*, 2012). Figure 2 shows the structure of cholesterol and the main autoxidation products present in food muscle tissue. The oxysterols contained in cholesterol-rich foods such as meat, meat products, eggs, and dairy products are most likely generated through a non-enzymatic process during cooking, processing, and storage (Brown and Jessup, 2009).

Enzymatic oxidation of cholesterol

The enzymatic oxidation of cholesterol is performed by several enzymes that are mainly from the cytochrome P450

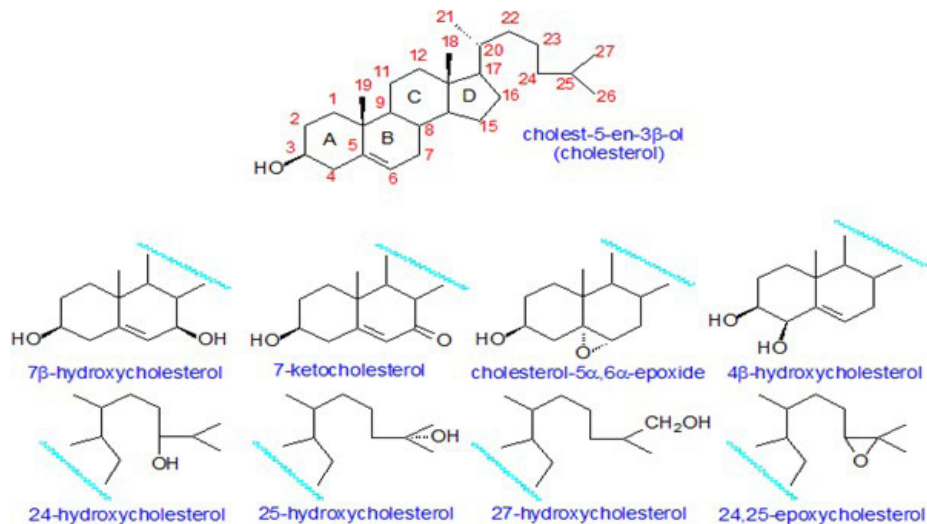


Figure 2: Non-enzymatic oxidation products of cholesterol



family of oxygenases, such as monooxygenase, dioxygenase, dehydrogenase, and oxidase. Enzymatic oxidation begins with the formation of specific hydroxycholesterol (OHCh) molecules, as shown in Table 1.

Because certain enzymes are specific to particular tissues, there is considerable variation in oxysterol distribution across organs. For example, a primary product of enzymatic oxidation is 7 α -OHCh, which is an important intermediate in the biosynthesis of bile acids and is produced in the liver by the action of cholesterol 7 α -hydroxylase (CYP7A1), which has a critical role in cholesterol homeostasis (Gill *et al.*, 2008). However, it is also formed by the non-enzymatic oxidation of cholesterol (Niki *et al.*, 2005). The enzymatic reaction is under strict regulatory control, and any circulating 7 α -OHCh represents leakage from the liver.

In contrast, 7 β -OHCh is produced in the brain by the action of the toxic β -amyloid peptide and its precursor to cholesterol. 24(S)-OHCh, termed cerebrosterol, is formed exclusively in the brain in humans, and there is a continuous flux of it from the brain to the circulation (Zhang and Liu, 2015). 22-OHCh is found preferentially in steroidogenic tissues, and 27-OHCh in macrophages and plasma (Alioui, 2016).

The free radical-mediated oxidation of cholesterol results in 7 α - and 7 β - hydroperoxycholesterol (7 α -OOHCh and 7 β -OOHCh), 7 α -OHCh, 7 β -OHCh, 5 α , 6 α - and 5 β , 6 β -epoxycholesterol, and 7-keto as the major products (Diczfalusy, 2004). Side-chain oxidation products such as 20-, 22-, 24-, 25- and 27-OHCh are formed by an enzymatic mechanism.

The conversion of 7-keto to 7 β -OHCh *in vivo* has been reported. The oxidation of 7-OHCh either by the 7 α -OHCh dehydrogenase enzyme or by non-enzymatic autoxidation produces 7- Keto. Singlet oxygen oxidizes cholesterol by a non-enzymatic and non-radical mechanism to produce 5 α -OHCh, with a lower quantity of 6-OHCh. 5-OHCh is a specific marker for singlet oxygen oxidation. 7 β -OHCh can be considered a marker for free radical-mediated oxidation (Niki *et al.*, 2005).

Photooxidation of cholesterol

In addition to the free radical mechanism, there is another mechanism of oxidation that occurs in the presence of a sensitizer and UV-light and leads to the formation of hydroperoxides (Wasowicz *et al.*, 2004). In the photooxidation

of cholesterol, single oxygen is formed from triplet oxygen by light in the presence of an active sensitizer, such as a natural pigment or synthetic colorant. Cholesterol can react with singlet oxygen in the presence of a photosensitizer, forming dominant hydroperoxide at C-5. A part of the hydroperoxide converts into 5 α -OHCh, and the remainder of the 5-hydroperoxide is further converted into stable 7-hydroperoxide and 6-hydroperoxide, which are present in small amounts. The 7-hydroperoxides can be converted into isomeric 7-OHCh and 7-keto at the same time as 5-OHCh is formed (Ubhayasekera, 2004).

COPs IN RUMINANT MEAT

The exogenous source of oxysterols is dietary intake (Otaegui-Arrazola *et al.*, 2010). After slaughter, meat tissues lose their antioxidant defenses, and more complex oxidative processes emerge (Papuc *et al.*, 2017) and promote the formation of oxidized sterols. Oxysterols absorbed from food have been shown to enter circulation (Brown and Jessup, 1999). However, an exact quantitative estimation of the levels of endogenous as opposed to exogenous oxysterols does not exist.

In lean meat, the mean lipid content is 10% of the weight, of which cholesterol is a small component, ranging from 50–89 mg (Paniangvait *et al.*, 1995) and assumed to be less than 100 mg/kg (Ahn *et al.*, 2001).

A number of studies have studied the oxidation of lipids in different types of meat. However, the majority of these studies did not consider the COP content of meat from ruminant species; instead, they considered non-ruminant species, such as turkey (Boselli *et al.*, 2005), poultry (Bonoli *et al.*, 2007) and pork (Rudzińska *et al.*, 2007; Thurner *et al.*, 2007). Several studies have considered the cholesterol oxidation of meat from ruminants, primarily beef (Verleyen *et al.*, 2003; Thurner *et al.*, 2007), and very few studies have considered lamb (Serra *et al.*, 2006; Samouris *et al.*, 2011). No studies have been conducted on COPs in raw goat meat, most likely because of this meat's low intramuscular cholesterol content relative to the meat of other ruminants.

Fresh meat and meat products contain zero or trace amounts of cholesterol oxides; in cooked meat; however, the oxysterol content ranges from 180 to 1900 μ g/g. The predominant oxidized cholesterol detected in ruminant meat is 7-ketocholesterol and 7-OHCh, followed by

Table 1: Enzymatic oxidation of cholesterol (Niki *et al.*, 2005)

Enzyme	Abbreviation	Principal product
Cytochrome P450 3A4	CYP3A4	4 β -OHCh
Cholesterol 7 α -hydroxylase	CYP7A1	7 α -OHCh
Cytochrome P450 scc	CYP11A1	20 α -OHCh,
Cholesterol 24-hydroxylase	CYP46	22-OHCh
Cholesterol 25-hydroxylase		24(S)-OHCh
Sterol 27-hydroxylase	CYP27A1	25-OHCh 27-OHCh

β -epoxycholesterol, α -epoxycholesterol, and cholestantriol (Hur *et al.*, 2007; Serra *et al.*, 2014). 7-keto occurs in relatively high concentrations in many foods (Pie *et al.*, 1991) and its amount varies depending on the type of biological matrix (Lercker and Rodriguez-Estrada, 2000). It has also been proposed as an indicator of cholesterol oxidation (Shazamawati *et al.*, 2013).

Lipid oxidation has been associated with quality deterioration related to the development of off-flavors and off-odors during storage (Kumar and Singhal, 1992). The excessive oxidation of cholesterol, however, affects the nutritional quality due to the implications of COPs in the modulation of lipid metabolic processes, such as linoleic acid desaturation and cholesterol metabolism (Boselli *et al.*, 2012). Moreover, unlike the oxidation products of PUFAs, COPs are not volatile compounds; as a result, cholesterol oxidation cannot be identified by foul-smelling compounds (Dutta, 2004).

FACTORS INFLUENCING OXYSTEROL CONCENTRATIONS IN MEAT

The oxidation of cholesterol in muscle meat is influenced by many factors, such as the processing temperature for heating and cooking, storage time, packaging conditions, (Paniangvait *et al.*, 1995), pH, illumination and irradiation (Boselli *et al.*, 2012). The oxysterols contained in cholesterol-rich foods such as meat, meat products, eggs, and dairy products are most likely generated in a nonenzymatic way during cooking, processing, and storage (Brown and Jessup, 2009). The factors influencing the oxidation of cholesterol are discussed below.

Heat

The main source of oxysterols in meat is heat processing, mainly overheating (Paniangvait *et al.*, 1995). Microwaving and oven grilling results in higher production of COPs in processed meat in comparison to other cooking methods (Khan *et al.*, 2015). Several studies have been devoted to this subject. Lee *et al.* (2001) studied the effects of various cooking and reheating methods on the total cholesterol and formation of COPs in beef loin, and observed a significant reduction in cholesterol and an increase in COPs.

In addition, Dominguez *et al.* (2014) have reported that

among various methods used for cooking foal meat, such as roasting, grilling, microwaving, and frying, microwaving produced the highest oxidation products. In addition, chicken and beef samples treated in the microwave (900 W-3 minutes; internal temperature of the samples at the end of the process: 100°C) formed more COPs than those fried in olive oil (180°C-6 minutes; internal temperature: 85-90°C) (Echarte *et al.*, 2003). Additionally, under drastic heating conditions such as 180°C for two hours in the presence of oxygen, there is a very high level of oxidation (Xu *et al.*, 2009).

Table 2 illustrates the effects of different cooking methods on cholesterol oxidation in beef hamburgers, demonstrating a higher content of 7-keto from the combination of roasting and microwave heating in comparison to other cooking treatments.

Storage and packaging

Additional studies have reported an increase in COP formation during storage. Hwang and Maerker (1993) reported that storing non-irradiated beef at 0-4°C for two weeks considerably increased the COP content. Bendeddouche *et al.* (2012) observed the same result when storing raw lamb *longissimus* dorsi muscle under refrigeration for 20 days. Lee *et al.* (2006) observed an increase in COP formation after cooking stored beef loin. The results indicate that even frozen storage of cooked meat does not prevent the development of COPs. Furthermore, Ferioli *et al.* (2008) reported that the COP content in raw and cooked minced beef increased six-fold after storage at 4°C for two weeks, with the COP content higher in cooked meat than in raw meat.

With respect to the effects of packaging, researchers have reported the presence of COPs in fresh meat and have suggested that the transparent films used in packaging meat do not prevent cholesterol oxidation because they are permeable to light and oxygen, and the cholesterol oxidation process in meat is promoted by hem protein photocatalysis (Lercker and Rodriguez-Estrada 2000). Lee *et al.* (2001) have also suggested that the vacuum storage of cooked meat products promotes increased COP formation post-storage.

pH

pH also affects the rate and abundance of COP formation. At a pH between 8.0 and 12.0, the production of α - and

Table 2: Effect of cooking treatments on the total 7-keto content and the ratio of total 7-keto to total cholesterol (Savage *et al.*, 2007)

Treatment	7-keto ($\mu\text{g/g}$ in lipids)*	7-keto / total cholesterol (%)*
Raw	25.2d	0.5b
Roasted	18.0b	0.5b
Microwave	19.6c	0.4a
Microwave and roasted	22.0e	0.5b
Barbecue	19.5c	0.4a
Boiling	16.4a	0.4a
Frying pan	18.6b	0.4a

*Mean values of three replications. (a_e): Means with different superscripts within the same category are significantly different ($p = 0.05$).



β -cholesterol epoxide is time-dependent with a ratio that is approximately constant. However, at pH between 5.5 and 3.0, this ratio progressively increases, since the β -isomer is more labile in acidic conditions than the α -isomer, being preferentially converted to cholesterol by hydrolysis (Vicente *et al.*, 2012).

Illumination

Various COPs are formed through the oxidation of cholesterol during illumination, and their quantity increases with an increased illumination time. In addition, COPs are more concentrated at the surface of the meat than throughout the rest of it during illumination. The COPs produced include free radicals formed by triplet sensitizer-reducing substrate interaction (Hwang and Maerker, 1993).

Irradiation

Hwang and Maerker (1993) have reported that the irradiation of raw beef and veal at ten kGy increased the COP content, and the increase in COPs in those meats during storage was greater in the irradiated meat than the non-irradiated meat. The same results have been reported for other meat species (Ahn *et al.*, 2001; Lee *et al.*, 2001).

The effects of storage and radiation have also been noted in some studies, in which COPs such as 7 α -OHCh, 7 β -OHCh, and 7-keto were detected in fresh raw meats at day zero at a level of 10.9 to 49.2 mg/g lipid. After seven days of storage, other COPs, such as epoxides, 20 α -OHCh and cholestane-triol, were formed in mainly aerobically packaged and irradiated raw meats (Nam *et al.*, 2001).

Lipid content and composition

The composition and content of fats in meat play an important role in the oxidation rates of lipids and cholesterol (Ahn *et al.*, 2001). As a general rule, the more unsaturated a fatty acid is, the faster and more intense the formation of COPs is (Vicente *et al.*, 2012). For example, Li *et al.* (1996) and Min *et al.* (2015) have reported that a high level of PUFAs leads to increased production of COPs. In addition, the synergistic decrease in the levels of cholesterol, and PUFAs provides evidence that cholesterol oxidation is promoted by the oxidation of PUFAs.

PUFA content varies considerably across animal species and decreases in the following order: fish > poultry > pork > beef > lamb. Therefore, the susceptibility to lipid oxidation and the consequent formation of COPs decreases in the same order (Hur *et al.*, 2007).

The environmental conditions promoting the production of COPs have not yet been determined. However, it is reasonable to suspect that the oxidation of cholesterol is accelerated in the presence of peroxidized lipids (Li *et al.*, 1996). Xu *et al.* (2011) have investigated the interactions of stearic, oleic, linoleic, and α -linolenic acids during the oxidation of cholesterol, and concluded that surrounding fatty acids affect cholesterol oxidation. They also reported that the fatty acids accelerated the oxidation of cholesterol for the first 60 minutes at 180° C, after which their pro-oxidant

activity became weaker, with the exception of α -linolenic acid, which exerted an inhibitory effect after 120 minutes.

Sex

Sex has not been widely considered a variable in food research, although the effect of sex on meat composition has occasionally been reported. For example, in a recent study conducted by Vladimiro *et al.* (2016) on eight Segureña lambs, samples of approximately 20 g of minced meat from lamb leg were used for cooking burger patties at 72° C. With the exception of 7 α -OHCh, male meat samples were characterized by high COP contents in comparison to female meat samples.

Age

Serra *et al.* (2014) reported that the cholesterol content of lamb muscles tended to decrease with the age of an animal, while the COP content significantly increased. Among COPs, 7-ketocholesterol and 7-OHCh were the most abundant, followed by epoxy-cholesterol and cholestane-triol.

METABOLISM OF COPs

Cholesterol oxidation products (COPs), or oxysterols, tend to be more polar than cholesterol and can be absorbed in the human intestinal tract and distributed to tissues by a mechanism similar to that of cholesterol absorption. The absorption of COPs is lower than that of cholesterol, likely due to the lower solubility of COPs in micelles, the lower susceptibility to esterification in enterocytes, and the cytotoxic effects in mucosal cells (Osada *et al.*, 1994). In addition, each type of COP is absorbed to different degrees; 7 β -OHCh, 7-keto, and 5 α , 6 α -epoxycholesterol are detected in greater amounts than 5 β , 6 β -epoxycholesterol, and 25-OHCh (Vine *et al.*, 1998). Notably, in contrast to 7 β -OHCh, 7-keto is slightly absorbed and rapidly metabolized by the liver (Schweizer *et al.*, 2004).

Oxysterols are able to pass through lipophilic membranes much faster than cholesterol (Linseisen and Wolfram, 1998). They can enter the blood circulation with dietary cholesterol and biliary cholesterol (endogenous cholesterol) as part of the chylomicron structure (Savage *et al.*, 2002; Shazamawati *et al.*, 2013) and lipoprotein, primarily low density lipoprotein (LDL) and, to a lesser degree, high density lipoprotein (HDL) (Staprans *et al.*, 2003). 7 α / β -OHCh and 7-keto are the most abundant oxysterols in lipoproteins (Linseisen and Wolfram, 1998; Vine *et al.*, 1998). Recent studies have shown that unesterified cholesterol oxides associate readily with serum albumin (Lin and Morel, 1995).

Due to their hydrophobicity, most oxysterols can only be eliminated from cells through specific membrane lipid transporters. Apart from the ATP-binding cassette (ABC) transporters, ABCG5 and ABCG8, which pump oxysterols back into the intestine, there are other ATP-binding cassette transporters involved in oxysterol excretion. ABCA1 and ABCG1 are mainly located in the macrophages and liver to

transport oxidized sterols and other molecules out of the cell (Brown and Jessup, 2009).

THE BIOLOGICAL EFFECT OF COPs

In the following section, the major biological roles of oxysterols are discussed, and other roles are summarised in Figure 3.

Oxysterol as a cholesterol modulator (metabolism and homeostasis)

Several oxysterols enzymatically generated from cholesterol are able to regulate the intracellular cholesterol content through the following mechanisms.

Sterol regulatory element binding proteins SREBPs

Oxysterols have been described as modulators of cholesterol metabolism through their influence on the sequestration of SREBPs in the endoplasmic reticulum (ER), thereby limiting the expression of genes involved in cholesterol synthesis. The insulin-induced gene (Insig), an oxysterol sensor, is another key regulator in the ER membrane. It can inhibit the function of the SREBP by trapping and retaining the SREBP cleavage activating protein (SCAP) complex in the ER. Thus, several oxysterols such as 22(R)-OHCh, 25-OHCh and 24(S), 25-epoxycholesterol are able to attenuate cholesterol biosynthesis and the expression and activity of the LDL receptor in a macrophage (Shao and Espenshade 2012).

Oxysterol binding protein (OSBP)/ OSBP- related proteins (ORP)

Oxysterols can also control the esterification of cholesterol and the activity of hydroxymethylglutaryl-CoA reductase (HMG-CoA), the rate-limiting enzyme in cholesterol synthesis (Brown and Jessup, 2009), through the OSBP and ORP (Kental

et al., 2015). In the human body, there are at least 12 OSBP/ORP proteins. OSBP, ORP1, and ORP2 are involved mainly in vesicle transport of cholesterol, particularly the transport between the ER and Golgi apparatus (Olkkonen, 2015).

liver X receptor (LXR)

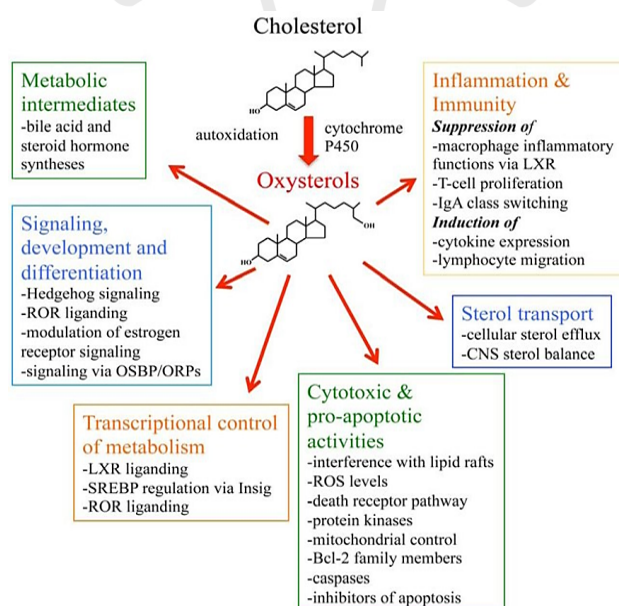
Oxysterols also have ligands of the nuclear LXR, whose essential role in the maintenance of cholesterol homeostasis, thus protecting cells from the toxic effects of cell cholesterol overload. The LXR regulates the expression of the proteins involved in the efflux and transport of cholesterol. The most potent of these oxysterol ligands are 22(R)-OHCh, 24(S)-OHCh and 24(S), 25-epoxycholesterol (Kuver, 2012).

Oxysterols in immune cell function

Oxysterols, acting through transcription factors such as LXRs, SREBPs and the Epstein-Barr virus-induced G-protein coupled receptor 2 (EBI2), have been implicated in regulating the differentiation and population expansion of cells of the innate and adaptive immune systems, their responses to inflammatory mediators. They have also been implicated in phagocytic functions of macrophages and in antiviral activities and immune cell migration (Spann and Glass, 2013). For example, the 7 α , 25-dihydroxycholesterol oxysterol is a potent and selective agonist of the G-protein-coupled receptor EBI2, which is required for humoral immune responses (Hannedouche *et al.*, 2011).

Oxysterols as developmental process regulators

The Hedgehog (Hh) signaling pathway is indispensable for normal patterning of multicellular embryos and also functions in postembryonic development and adult tissue homeostasis, including the regulation of stem cell physiology (Jacob and Lum, 2007). Corcoran and Scott (2006) have



ROR, retinoic acid receptor-related orphan receptor; Bcl-2, B-cell lymphoma 2; IgA, immunoglobulin A; CNS, central nervous system.

Figure 3: Schematic diagram summarising the major functions of oxysterols (Olkkonen *et al.*, 2012)



reported evidence that cholesterol or certain oxysterols are required for Sonic Hh pathway signal transduction and proliferation of medulloblastoma cells. Additionally, Dwyer *et al.*, (2007) have demonstrated that naturally occurring oxysterols exert osteoinductive effects through the activation of the Hh signaling pathway. Similarly, Kim *et al.* (2007) have provided evidence that the inhibition of bone marrow stromal cell differentiation into adipocytes by 20(S)-OHCh occurs through an Hh-dependent mechanism.

Oxysterols as oestrogen receptor function regulators

Oestrogen receptor- α/β (ER- α/β) is a member of a nuclear hormone superfamily, and mediates a number of physiological processes. Oestrogens exert protective effects on the blood vessel wall, regulating the cardiovascular system. 27-OHCh has been found to directly antagonize the transcriptional and non-transcriptional functions of the oestrogen receptors, resulting in a loss of the cardioprotective function of oestrogen. This oxysterol thus acts as an endogenous selective oestrogen receptor modulator based on its cell-type-specific proestrogenic activity (Chen, 2016).

Oxysterols as pro-apoptotic and cytotoxic factors

Apoptosis is genetically programmed cell death that has been conserved throughout evolution and used to maintain normal cell numbers in the organism, including during growth. It is a coordinated and active process characterized by specific morphological changes: chromatin condensation and nuclear fragmentation, membrane blebbing, and apoptotic body formation. Apoptosis is triggered through both an extrinsic, or death-receptor-mediated, pathway and an intrinsic, or mitochondrial, pathway. Both pathways appear to be activated by a variety of biologically relevant oxysterols that exert strong pro-apoptotic effects. Some findings support the involvement of death receptors in oxysterol-induced apoptosis. 27-OHCh and 22-OHCh induce tumor necrosis factor- α (TNF- α) in macrophagic cells (Gargiulo *et al.*, 2015), and upregulation of TNF receptors has been observed in human aortic smooth muscle cells after challenged with 7-keto (Lee *et al.*, 2005).

With respect to cytotoxic activities, several routes have been proposed for COPs: perturbation of intracellular calcium levels, intracellular ROS overproduction, mitochondrial and lysosomal membrane modifications, and polyamine metabolic perturbations (Sottero *et al.*, 2009).

IMPACT OF COPs ON HUMAN HEALTH

In recent years, considerable attention has been devoted to the study of cholesterol oxidation due to the biological activities of COPs associated with human diseases. Research has demonstrated that certain cholesterol oxides are cytotoxic, mutagenic, and carcinogenic (Otaegui Arrazola *et al.*, 2010). Moreover, they slow down deoxyribonucleic acid (DNA) and cholesterol biosynthesis and are calmodulin inhibitors, disturbing the activity of cell membranes (Derewiaka and Obiedziński, 2009).

Oxysterol and atherosclerosis

Atherosclerosis is a progressive disease of the arterial blood vessels and a principle contributor to the pathogenesis of myocardial and cerebral infarction. As such, it is the leading cause of human mortality. Many studies have detected oxysterols in human atherosclerotic plaque, especially 27-OHCh. Following 27-OHCh, 7-keto is the most abundant oxysterol in advanced atherosclerotic lesions, followed by 7 β -OHCh and 7 α -OHCh (Iuliano *et al.*, 2003). Together, these four oxysterols comprise 75–85% of the nine oxysterols detected in plaques.

The other oxysterols are 5,6-epoxycholesterol, 25-OHCh, and 24-OHCh. Although there is no direct evidence in humans that oxysterols contribute to the development of atherosclerosis, these oxysterols are thought to play an active role in plaque development due to their cytotoxicity (Shibata and Glass, 2010).

The most prevalent oxysterol in cardiovascular lesions is 27-OHCh, and it is considered a major factor responsible for triggering atherosclerosis (Dantas *et al.*, 2015). Levels of circulating 27-OHCh in health humans range from 150 to 730 nM; in atherosclerotic lesions, these levels are two orders of magnitude higher (Brown and Jessup, 1999). Moreover, evidence suggests that 27-OHCh promotes atherogenesis by upregulating the inflammatory pathways in vascular cells and increasing the accumulation of macrophages in the vascular wall (Kloudova *et al.*, 2017).

Another oxysterol, 7-keto, is one of the major oxygenated products found in oxidised low-density lipoproteins (oxLDLs) and in atherosclerotic plaque, where it is believed to play a role in arterial pathology (Philips *et al.*, 2001). It is also involved in atherosclerosis development, either by inducing apoptosis or by inhibiting reverse cholesterol transport (Sozen *et al.*, 2018). Levels of 7-keto are considerably increased in the plasma of patients with coronary artery disease (Pordal *et al.*, 2015).

Oxysterols, as quantitatively relevant components of oxLDLs, are likely to be candidate molecules in the pathogenesis of vascular aging (Kloudova *et al.*, 2017). They accumulate in the endothelium blood vessels, constituting one of the most important elements of atheroma (Jailal and Devaraj, 1996) due to their marked pro-oxidant, pro-inflammatory, and pro-apoptotic properties. They are also implicated in the age-related genesis of endothelium dysfunction, intimal thickening due to lipid accumulation and smooth muscle cell migration, and arterial stiffness due to increased collagen deposition and calcification (Gargiulo *et al.*, 2016), as shown in Figure 4.

Oxysterol and neurodegenerative disorders

Oxysterols also present interesting targets in various neurodegenerative disorders, such as multiple sclerosis, Huntington's disease, Parkinson's disease and Alzheimer's disease (Kulig *et al.*, 2016), specifically in the form of 24-OHCh, or cerebrosterol. Therefore, 24S-OHCh plasma levels can

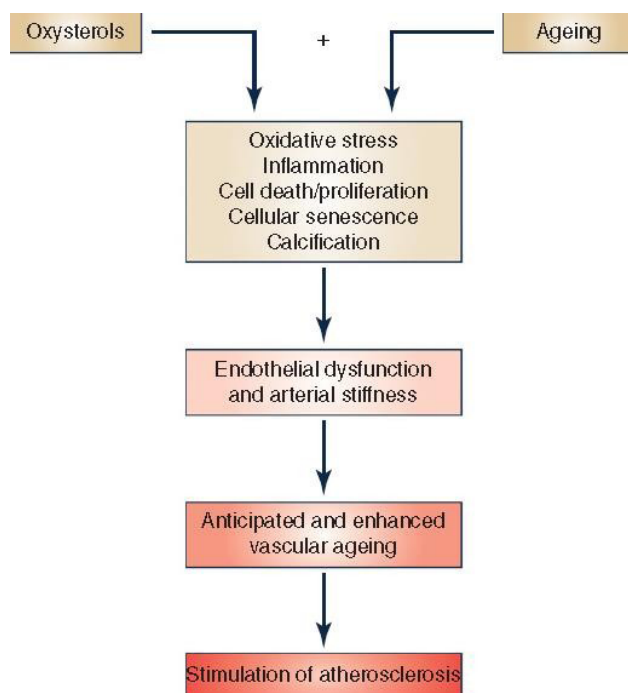


Figure 4: Role of oxysterols in atherosclerosis and vascular ageing (Gargiulo *et al.*, 2016)

potentially be used as an early biochemical marker for altered cholesterol homeostasis in the central nervous system (Lütjohann *et al.*, 2000). Another study has reported that 24-OHCh in concentrations of 10–50 μM induces apoptosis in T-lymphoma Jurkat cells and necroptosis in neuronal cells (Yamanaka *et al.*, 2015).

For example, Alzheimer's disease, the most common cause of dementia in the elderly, is characterized by a regional accumulation of senile plaques, neurofibrillary tangles, and extensive neuronal cell death. 24S-OHCh may be a major component of the mechanism that promotes the elimination of cerebral cholesterol (Lütjohann *et al.*, 2000); however, in too large of a quantity, it can be neurotoxic. An increase in the concentration of 24S-OHCh can be due to mutations in the gene coding for the enzyme that synthesizes it in the brain, CYP46A1 (Kolsch *et al.*, 2002). 24S-OHCh is one of the ligands of LXRs. At the cerebral level, this may explain the induction of target genes such as ABCA1, a membrane transporter involved in the cellular efflux of cholesterol that appears also to be involved in the secretion of beta peptides–protein constituents of senile plaques in Alzheimer's disease (Fukumoto *et al.*, 2002).

Oxysterol and cancer

The 27-OHCh oxysterol is the most abundant oxysterol in plasma, and its involvement has been demonstrated in the pathogenesis of several cancers, including breast and prostate cancer. For example, in breast cancer, oxysterols are important navigators that stimulate bone metastasis formation (Silva *et al.*, 2006). 27-OHCh has been found to accumulate in breast tissue and stimulate tumor growth via the oestrogen receptor. Although most tissues express CYP27A1, its highest levels are in macrophages. Therefore,

more attention has been given to the production of 27-OHCh in subendothelial macrophages as part of reverse cholesterol transport (Javitt, 2015).

In men, 27-OHCh may influence prostate carcinoma by stimulating the proliferation of prostatic cells, enhancing the expression of prostate-specific antigen, and increasing androgen receptor transcriptional activity (Raza *et al.*, 2016). However, its role in colorectal cancer has not been investigated. Warns *et al.* (2018) treated Caco2 and SW620, two well-characterized colon cancer cells, with low, physiological, and high concentrations of 27-OHCh, and found that 27-OHCh reduced cellular proliferation in these cells.

CONCLUSION

Cholesterol oxidation products (COPs) have crucial physiological functions, serving as metabolic intermediates, modulators of cell permeability, and regulators of cholesterol homeostasis and the expression of genes and receptors in cell signaling. Elucidating the role of oxysterol interactions with human receptors, such as oestrogen receptors and Insig, has opened new avenues for better understanding lipid metabolism, Alzheimer's disease, cancer, atherosclerosis, and other pathologies.

Additional studies on oxysterols are needed to facilitate the diagnosis, treatment, and prevention of these disorders. These studies should use genomic, proteomic, and metabolomic profiling of a series of blood samples and target tissues from patients with different pathologies. In addition, further research is needed to determine the most effective way to apply antioxidants to prevent the oxidation of cholesterol. This task is a challenge for biochemists, food chemists, food engineering engineers, and processing technologists.



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