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Oxysterols, age-related-diseases and nutritherapy: Focus on 7-ketocholesterol and 7β-hydroxycholesterol

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ABSTRACT

Age-related diseases are often associated with a disruption of RedOx balance that can lead to lipid peroxidation with the formation of oxysterols, especially those oxidized on carbon-7: 7-ketocholesterol (also known as 7-oxocholesterol) and 7β-hydroxycholesterol. Like cholesterol, these oxysterols have 27 carbons, they are composed of a sterane nucleus and have a hydroxyl function in position 3. The oxysterols 7-ketocholesterol and 7β-hydroxycholesterol are mainly formed by cholesterol autoxidation and are biomarkers of oxidative stress. These two oxysterols are frequently found at increased levels in the biological fluids (plasma, cerebrospinal fluid), tissues and/or organs (arterial wall, retina, brain) of patients with age-related diseases, especially cardiovascular diseases, neurodegenerative diseases (mainly Alzheimer's disease), ocular diseases (cataract, age-related macular degeneration), and sarcopenia. Depending on the cell type considered, 7-ketocholesterol and 7β-hydroxycholesterol induce either caspase- dependent or -independent types of cell death associated with mitochondrial and peroxisomal dysfunctions, autophagy and oxidative stress. The caspase dependent type of cell death associated with oxidative stress and autophagy is defined as oxiapoptophagy. These two oxysterols are also inducers of inflammation. These biological features associated with the toxicity of 7-ketocholesterol, and 7β-hydroxycholesterol are often observed in patients with age-related diseases, suggesting an involvement of these oxysterols in the pathophysiology of these disorders. The cytotoxic effects of 7-ketocholesterol and 7β-hydroxycholesterol are counteracted on different cell models by representative nutrients of the Mediterranean diet: ω3 and ω9 fatty acids, polyphenols, and tocopherols. There are also evidences, mainly in cardiovascular diseases, of the benefits of α-tocopherol and phenolic compounds. These *in vitro* and *in vivo* observations on 7-ketocholesterol and 7β-hydroxycholesterol, which are frequently increased in age-related diseases, reinforce

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the interest of nutritherapeutic treatments to prevent and/or cure age-related diseases currently without effective therapies.

1. Cholesterol and cholesterol autoxidation products: formation and inactivation of 7-ketocholesterol and 7β-hydroxycholesterol

Oxysterols are molecules obtained by the oxidation of cholesterol; they can be formed endogenously (by autoxidation, via specific enzymes or by both processes), and/or provided through the diet such as dairy, egg, and meat products [1]. Like cholesterol, oxysterols consist of a sterane nucleus, and an aliphatic side chain connected to the nucleus at carbon-17 (https://lipidmaps.org/resources/lipidweb/index.php?page=lipids/simple/chol-der/index.htm). Oxidation of cholesterol can take place by the addition of oxygen to the sterane nucleus and/or the side chain either by autoxidation (type I or II autoxidation) [2,3], or by enzymes, most commonly Cytochrome P450 enzymes [1,4]. Type I autoxidation concerns oxidation reactions involving reactive oxygen species (ROS) and/or reactive nitrogen species (RNS) (superoxide anion ($O_2^{\bullet -}$), hydroxyl radical ($HO^{\bullet}$), nitric oxide (NO), and peroxynitrite ($ONOO^-$). ROS and RNS can be generated by cellular metabolism, or by their decomposition into hydroxyl radicals by the dismutation of two superoxide anions into hydrogen, or by the Fenton reaction ($H_2O_2 + Me^{n+} \rightarrow HO^{\bullet} + OH^- + Me^{(n+1)+}$) where Me is a transition metal such as copper, iron, or aluminum; type II autoxidation concerns non-radical attacks by oxygen singlet ($^1\Delta_gO_2$ or $^1O_2$), hypochlorous acid (HOCl; corresponding oxyanion: hypochlorite (ClO^-) or ozone (O_3) [2,5]. Oxysterols resulting from oxidation on the sterane nucleus and/or on the side chain can be increased or decreased in several severe diseases: age-related diseases (cardiovascular, brain and ocular diseases, sarcopenia) [6], metabolic diseases (type 2 diabetes, metabolic syndrome) [7,8], and genetic diseases (X-linked adrenoleukodystrophy (X-ALD), Niemann Pick disease) [9,10]. Several oxysterols, especially those oxidized on the side chain, interact with cellular receptors [11]. They can be ligands or activators of the following receptors: (i) nuclear receptors, such as liver X receptors (LXRs) α or β [12] and retinoic acid receptor-related orphan receptor α and γ (RORα [NR1F1] and RORγ [NR1F3]) [13], (ii) cytoplasmic receptors such as SREBP (sterol regulatory element binding transcription protein) [14], NPC1 (NPC intracellular cholesterol transporter 1 / Nieman-Pick type C1) [15], FXR (NR1H4, farnesoid X receptor alpha) [16], oxysterols binding proteins (OSBPs), OSBPs-related proteins (ORPs) [17,18] and cholesterol epoxide hydrolase (ChEH) (also named anti-estrogen binding site (AEBS); ChEH is an hetero-oligomeric complex comprising 3beta-hydroxysterol-delta(8)-delta(7)-isomerase (D8D7I) and 3beta-hydroxysterol-delta(7)-reductase (DHCR7)) [19] as well as (iii) membrane receptors such as receptor tyrosine kinases [20] and the Epstein–Barr virus-induced gene 2 receptor (EBI2, also known as GPR183) [21–23]. Among the oxysterols involved in age-related diseases, there are, among others, those which are formed mainly by autoxidation on the carbon 7, such as 7-ketocholesterol (7KC) and 7β-hydroxycholesterol (7β-OHC). It is important to underline that 7KC can also be formed enzymatically from 7β-OHC by the hydroxysteroid dehydrogenase type 2 (11β-HSD2; HSD11B2 gene, OMIM 614232) which is mainly expressed in the kidney, colon, and placenta [24]. In addition, in patients with cerebrotendinous xanthomatosis or with Smith Lemli Opitz (SLO) syndrome, 7KC can be formed from 7-dehydrocholesterol (a direct precursor in cholesterol biosynthesis belonging to the Kandutsch–Russel pathway) [25] by the enzyme cholesterol-7α-hydroxylase (CYP7A1) [26,27]. In addition, the enzyme hydroxysteroid dehydrogenase type 1 (11β-HSD1; HSD11B1 gene, OMIM 600713) reduces 7KC to 7β-OHC [28]. Noteworthy, during lipid peroxidation, which affects all lipids, cholesterol is less susceptible to free radical attacks than polyunsaturated fatty acids in body fluids, while the opposite occurs at the cellular level [29]. The preferential site of oxidation of cholesterol by highly reactive species is at C7 because a relatively weak carbon–hydrogen bond. Therefore, increased levels of 7KC and 7β-OHC in the body fluids, as well as tissues and organs affected by the diseases is a sign of strong oxidative stress; however, in contrast to plasma oxidation, cellular cholesterol is more susceptible to oxidation than cellular linoleates [29]. The detailed mechanisms leading to the formation of 7KC but also 7β-OHC, and the associated metabolites, have been described by several authors [2,3,30,31]. The major oxysterol metabolite routes for 7KC and 7β-OHC inactivation are esterification, sulfation, oxidation, and reduction. These different aspects of biogenesis and inactivation of 7KC and 7β-OHC are summarized in Fig. 1. Metal ions (Me^{n+}) which are involved in the Fenton reaction, where Me is a transition metal (copper, iron, or aluminum) also contribute to the biogenesis of 7KC and 7β-OHC via $HO^{\bullet}$ production, not only in the body but also during the processing of industrial meat [32].

Currently, several data support that 7KC and 7β-OHC, as well as their metabolites and degradation products, can constitute suitable biomarkers for several pathologies especially age-related diseases and in the ageing process [8,33,34]. They could be also of interest as biomarkers in some “civilization” diseases (diabetes, metabolic syndrome) [35] and in food industry involved in the production of more or less highly processed foods to evaluate food quality: indeed, long term storage as well as the industrial methods used to prepare food can influence autoxidation and have detrimental consequences on food qualities [36].

2. Required precautions and available methods for the identification and quantification of 7-ketocholesterol and 7β-hydroxycholesterol

To evaluate the part taken by 7KC and 7β-OHC in cell and tissue samples, reliable and sensitive analytical methods are required. These methods need important expertise, and several cautions must be taken both for sample collection and storage, as well as during the pre-analytical and analytical steps to avoid artefactual results. The analysis of 7KC and 7β-OHC encounters numerous challenges due most often to their low concentrations in biological fluids and tissues, typically in the nanomolar range, with cholesterol coexisting at concentrations 10^4–10^6 times higher in the same samples. Concentrations in the micromolar ranges have however been observed in advance stages of patients with the most aggressive forms of X-linked adrenoleukodystrophies (X-ALD) [9] as well as in patients with acid SMase-deficient Niemann-Pick disease [37]. High amounts of these oxysterols can also be observed in brain lesions of patients with Alzheimer’s disease [38] and in the biological fluids (cerebrospinal fluid, plasma, serum) [39,40]. In addition, it is important to underline that after fat-rich meals, very high levels of 7KC can be found in the plasma [41,42] suggesting that regular consumption of fat could progressively favor the accumulation of this oxysterol in various tissues and gradually trigger important dysfunctions, since 7KC has strong pro-oxidant and inflammatory activities [6,43]. 7KC concentration is also strongly increased in the plasma of patients with chronic artery disease (CAD), and it is reproducibly detected in more than 90 % of patients with CAD [44]. In addition, multiple regression analysis revealed that 7KC was an independent variable for CAD progression [45]. It is important to underline that presence of high concentrations of cholesterol not only disrupts chromatography and contaminates instruments, but also poses the risk of autoxidation during sample preparation, leading to the artifactual formation of oxysterols such as 7KC and 7β-OHC. Therefore, care must be taken for accurate identification and quantification of 7KC and 7β-OHC. Several chromatography-based analytical methods have been developed to avoid this problem [1–4]. New analytical methods

available on tissues samples including antibody - based methods [5], as well as mass spectrometry imaging of oxysterols and cholesterol have been applied for this purpose [46,47], with advantages and limitations.

Thorough understanding of the fundamental levels of 7KC and 7β-OHC is closely tied to the experimental conditions employed throughout the analytical process. This encompasses various stages such as sample collection, extraction, fractionation, separation, detection, and quantification [6]. Notably, the strategies applied in sample preparation such as the type of sample collection tubes used, the number of freeze-thaw cycles, presence of antioxidant compounds and storage conditions significantly contribute to variability, impacting the stability of samples, as well as the overall recovery and profile of 7KC and 7β-OHC.

Oxysterol analysis has been successfully performed using mass spectrometry (MS) methods coupled with gas or liquid chromatographic separation. Over the years, research has been advanced to tackle common analytical challenges of oxysterol analysis with the development of high-sensitive mass spectrometers. Different approaches such as chemical derivatisation to improve the ionisation characteristics of the 7KC and 7β-OHC for subsequent MS detection have been successfully applied in literature [7]. Derivatisation is often employed to enhance the volatility of oxysterols for efficient separation. However, this method requires a multi-step sample preparation process, making it time-consuming and prone to potential errors.

Various liquid chromatography methods, including reverse-phase and normal-phase chromatography, have been developed for separating 7KC and 7β-OHC [4]. Tandem mass spectrometry (MS/MS) enhances specificity by providing structural information through fragmentation patterns [8]. Another widely used method in MS is the multiple reaction monitoring (MRM) method that allows to selectively detect and quantify 7KC and 7β-OHC based on the screening of specified precursor-to-fragment ion transitions [2]. Since this method uses targeted approach, it is not possible to screen for unknown oxysterols.

MS methods are superior to high-performance liquid chromatography (HPLC) coupled with UV or fluorescence detection. However, HPLC methods remains a valuable option, as this provides a fast, simple technique to separate, identify, and quantify most of the oxysterols [9], particularly for laboratories without access to advanced mass spectrometers.

ELISA assays offer a high-throughput and cost-effective alternative for screening many molecules. However, its specificity can be a concern for oxysterols, as the antibodies used may cross-react with structurally similar sterol compounds. For localization studies, immunohistochemistry allows researchers to visualize the distribution of 7KC within tissues. This technique provides valuable insights into the spatial distribution of 7KC in cells and tissue [5]. However, the methods must be used with care and adapted to the types of cells and tissue samples studied. Currently, the potential of mass spectrometry imaging (MSI) to study cholesterol, its precursors, and its metabolites, including oxysterols, in human biopsies is a major challenge [47].

Despite the advancements in oxysterol analysis, challenges persist, such as the need for stable isotope-labelled internal standards for accurate quantification and the isomer interference during separation of 7α-hydroxycholesterol and 7β-OHC. Future research may focus on refining existing methods, exploring novel techniques, and developing standardized protocols to ensure reproducibility and comparability across studies [48,49]. The identification and quantification of 7KC and 7β-OHC are pivotal for unravelling their roles in health and disease. Researchers must carefully select and validate analytical methods based on the specific requirements of their investigations, balancing sensitivity, specificity, and practical considerations. Continued advancements in analytical techniques will undoubtedly contribute to a deeper understanding of the complex roles played by these oxysterols in cellular processes and disease pathogenesis including age-related diseases and ageing process [49,50].

3. Identification of 7-ketocholesterol and 7β-hydroxycholesterol in patients with age-related diseases

A more or less pronounced oxidative stress is a common feature of age-related diseases [51–53]. Consequently, several biomarkers of

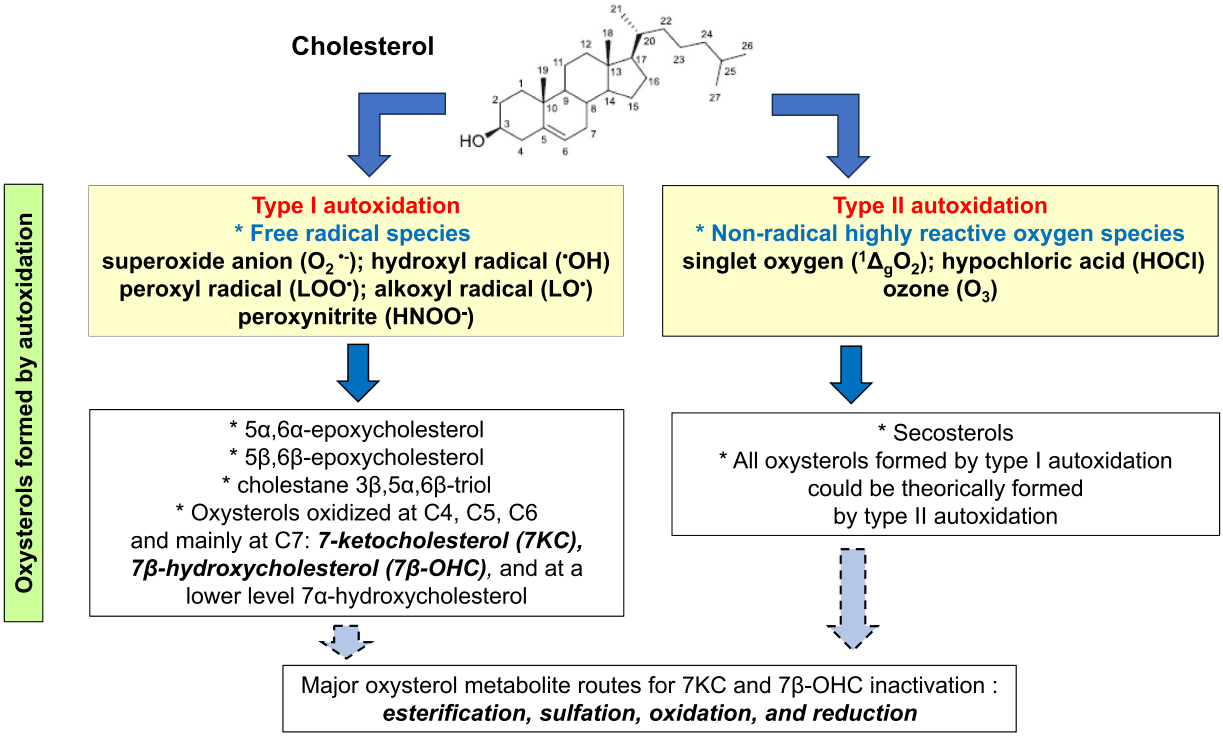

Fig. 1. Oxysterols formed by autoxidation. Details about the formation of 7-ketocholesterol (7KC) and 7β-hydroxycholesterol (7β-OHC) are given in the following references: Iuliano in 2011, and Zerbinati & Iuliano in 2017 [2,3]; Anderson *et al.* in 2020 [30] and Ghzaiel *et al.* in 2022 [31].

oxidative stress have been observed in these diseases, including lipid peroxidation biomarkers which reflect fatty acid oxidation (increased level of malondialdehyde (MDA) [54], 4-hydroxynonenal (4-HNE) [55], F(2)-isoprostanes [56], 9-hydroxy-10,12-octadecadienoic acid and 9-hydroxy-10,12-octadecadienoic acid (HODEs) [57], cholesterol autoxidation products (oxysterols: 7KC and 7β-OHC), and enhanced levels of carbonylated proteins [58] and/or advanced glycation end products (AGEs) [59]. Overall, oxysterols, formed either by autoxidation and enzymatically, could be useful as biomarkers of aging to evaluate biological aging compared to chronological aging [33,34]. Whereas chronological age corresponds how old we are, biological age is how old our cells are depending on internal and external factors [60]. As a result, there is not necessarily a correlation between chronological and biological age, and thus we can appear younger or older than our age. Some biomarkers of oxidative stress, especially 7KC and 7β-OHC, are most often described in biological fluids (cerebrospinal fluid, plasma) and in the cells and/or tissues of organs (atheroma plaques, heart, arteries and blood vessels, lens, retina, brain) affected by the disease [6,61]. In cardiovascular diseases, enhanced levels of 7KC and 7β-OHC have been described both in the plasma and atheroma plaques where apoptotic cells can be simultaneously detected [8,62]. It has been clearly established that the cytotoxic components of oxidized low-density lipoproteins (LDL) were 7KC and 7β-OHC [63]. The role of 7KC and 7β-OHC is also widely suspected in vascular aging [64,65]. In age related macular degeneration and cataract enhanced levels of 7KC are found in drusen at the retinal level [66] and in the lens [67] respectively. In Alzheimer's disease enhanced levels of 7KC and 7β-OHC have been observed in brain lesions [68], and in the cerebrospinal fluid and plasma [39,69]. In sarcopenia, significant increased levels of 7β-OHC have been identified [70,71]. In breast cancer, which is the most common cancer in young and post-menopausal women, a significant increase in the level of 7KC was observed in the samples following tumor removal and the start of therapy compared to the sampling before [72]. *In vitro* data suggest that 7KC could modulate the efficiency of chemotherapeutic treatment (doxorubicin, tamoxifen) in breast cancer cells: 7-KC stimulates the efflux function of P-glycoprotein and reduced intracellular doxorubicin accumulation in MCF-7 human breast cancer cells (estrogen receptor (ER) positive cells); 7KC slightly decreases the efficacy of tamoxifen in MCF-7 cells, while an increased effect of tamoxifen and higher caspase 3/7 activity was observed in the human breast cancer BT-20 cell line (ER negative cells) [73,74]. Some authors suggested that 7KC and derivatives, due to its biological activities (stimulation of immune response, cell death induction) could be used as anti-tumoral drugs [75,76]. In severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection often observed in patients over 65 years old, enhanced levels of 7KC and 7β-OHC were reported, and the contribution of these oxysterols in the pathophysiology of this infectious disease still remains not well understood [70,77]. However, accumulation of oxysterols, including 7KC, in the erythrocytes of COVID-19 patients has been proposed as a biomarker for case severity [78]. Altogether, data on the potential involvement of 7KC and 7β-OHC in frequent age-related disorders is questionable since these oxysterols favor oxidative stress, inflammation and cell death which are hallmarks of several age-related diseases. The biological characteristics of these oxysterols also open new perspectives with therapeutic applications in several human diseases including age-related diseases, infectious and inflammatory diseases, and cancers [79,80].

3.1. *Biological activities of 7-ketocholesterol and 7β-hydroxycholesterol*

The biological activities of 7KC and 7β-OHC were initially described on cells of the vascular wall (endothelial cells and smooth muscle cells) and human monocytic U937 cells in the context of cardiovascular diseases [81–83] and cancer [84,85], respectively. Subsequently, the biological activities of 7KC and 7β-OHC were studied on retinal epithelial cells, nerve cells, skeletal muscle cells and bone cells, since enhanced levels of these oxysterols were found in patients with cardiovascular diseases, age-related macular degeneration, Alzheimer's disease, sarcopenia and osteoporosis [86]. Noteworthy, 7KC and 7β-OHC are strong inducers of cell death, and the mode of cell death induced can be caspase-dependent or -independent, depending on the cell type considered. However, this cell death is always associated with an increased production of reactive oxygen species (ROS) and a rupture of RedOx homeostasis, as well as with organelle dysfunctions (mitochondria, peroxisome and/or lysosome) [86] (Fig. 2). In some cells, 7KC and 7β-OHC can also induce inflammatory processes leading to the secretion of inflammatory cytokines [62] stimulation of the expression of adhesion molecules [87–89] and activation of matrix metalloproteinase [90,91]. In several cell types from different species, 7KC and 7β-OHC induce a mode of cell death defined as oxiapoptophagy, described for the first time in human monocytic cells U937 in 2003 [92], which is considered as an hybrid cell death type [93], and could favor vascular diseases [94]. In U937 cells, oxiapoptophagy is associated with cytokine-dependent inflammation characterized by a secretion of MCP-1, MIP-1β, TNF-α, and/or IL-8 secretion, the latter involving the MEK / ERK1/2 signaling pathway [62]. This type of cell death, which includes the activation of oxidative stress, apoptosis induction, and is associated with autophagic criteria (oxiapoptophagy: OXIdative stress + APOPTOsis + autoPHAGY) [95] has been observed in the presence of 7KC and/or 7β-OHC on murine nerve cells (oligodendrocytes, glial cells, neuronal cells) [96–99], in bone marrow mesenchymal stem cell from patients with acute myeloid leukemia [100] and in the murine osteoblastic MC3T3-E1 cell line [101]. Noteworthy, this type of cell death can also be induced by other oxysterols. Thus, oxiapoptophagy has been described on 158 N oligodendrocytes in the presence of 24S-hydroxycholesterol [102], in myeloma cell in the presence of 5,6-epoxycholesterol [103], with 25-hydroxycholesterol in murine L929 fibroblasts [104], and with 7α, 25-dihydroxycholesterol in murine chondrocytes both *in vitro* and *in vivo* [105]. The detailed signaling pathways associated with 7KC- and 7β-OHC-induced oxiapoptophagy are well described by Vejux *et al.* [86] and Nury *et al.* [5] which makes it possible i) to consider identifying pharmacological targets and ii) to search for natural or synthetic molecules as well as mixtures of molecules (such as edible oils) to oppose the toxicity of these compounds [5,106]. Currently, there is also preliminary data supporting that oxiapoptophagy can be induced by natural molecules, which are not sterols. In C6 rat glioma cells, 7β-OHC induces a mode of cell death by autophagy (lethal autophagy) associated with oxidative stress and organelle dysfunctions [107]. In other cells, such as human fibroblasts, 7KC and 7β-OHC induces a mode of cell death considered as necrosis [82] and in human retinal ARPE-19 cells, both caspase-dependent and -independent modes of cell death have been reported [108–111] with a simultaneous induction of IL-8 secretion [109]. In the immortalized mouse myoblast C2C12 cell line, 7KC and / or 7β-OHC induce a caspase-independent mode of cell death associated with ROS overproduction, mitochondrial and peroxisomal changes [70,71] evocating ferroptosis [112,113] with a simultaneous secretion of IL-6, IL-8, and TNF-α [71]. Fig. 3 summarizes the main cytotoxic effects of 7β-OHC (50 μM; 24 h of treatment) [70,71] observed on C2C12 cells. The 7β-OHC-induced cell death, was measured by flow cytometry after staining with fluorescein diacetate (FDA); it was associated with loss of transmembrane mitochondrial potential (ΔΨm), measured using 3, 3′-dihexyloxacarbocyanine iodide (DiOC6(3)); overproduction of reactive oxygen species (ROS) was evaluated on whole cells and at the mitochondrial level after staining with dihydroethidine (DHE) and MitoSOX red, respectively, and peroxisomal changes was evaluated by transmission electron microscopy. Whereas few peroxisomes were observed in untreated C2C12 cells, several peroxisomes localized in vacuolar structures, evocating pexophagy [114,115], were detected in 7β-OHC-treated cells. Under treatment with 7KC and 7β-OHC, whatever the type of cells used and the type of cell death induced, an overproduction of ROS is always observed, associated with mitochondrial and peroxisomal dysfunctions.

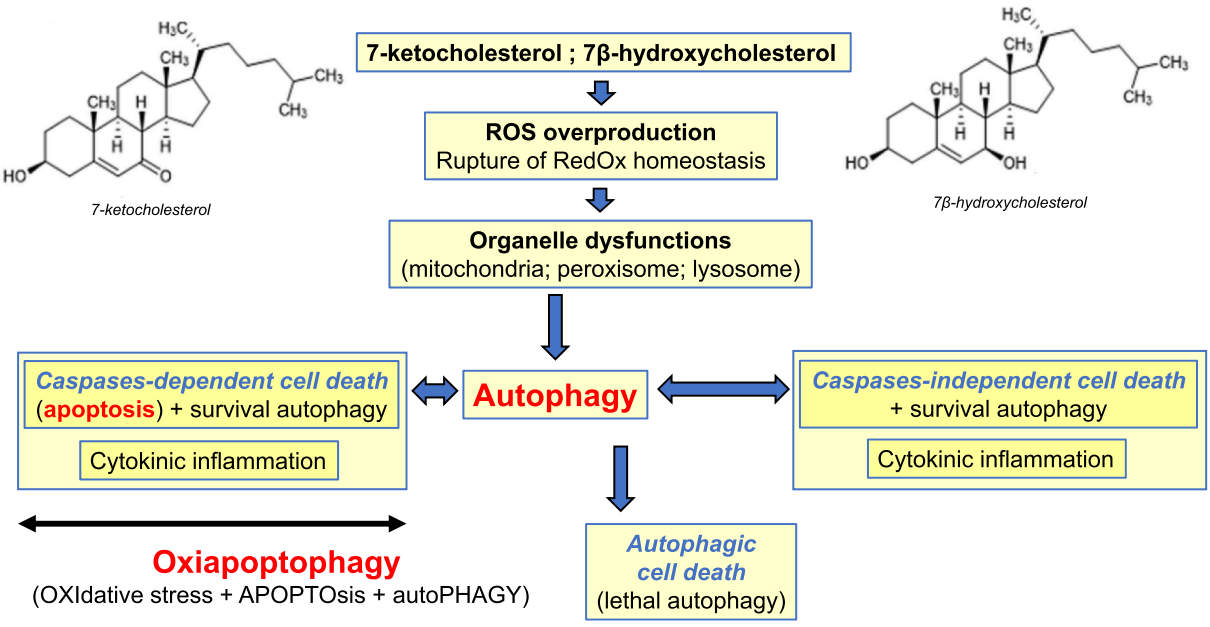

Fig. 2. Caspase-dependent and -independent mode of cell death induced by 7-ketocholesterol and 7β-hydroxycholesterol. Various types of cell death have often been described as caspase-dependent and -independent [182]. 7KC and 7β-OHC are strong inducers of cell death, and the mode of cell death induced is always associated with an increase production of reactive oxygen species (ROS) and a rupture of RedOx homeostasis, as well as with organelle dysfunctions (mitochondria, peroxisome and/or lysosome). The signalling pathways associated with 7KC- and 7β-OHC-induced oxiapoptophagy (a caspase-dependent mode of cell death associated with oxidative stress, apoptosis and autophagy) are well described by Vejux *et al.* and Nury *et al.* [95,183]. Oxiapoptophagy is currently considered as an hybrid cell death type [93].

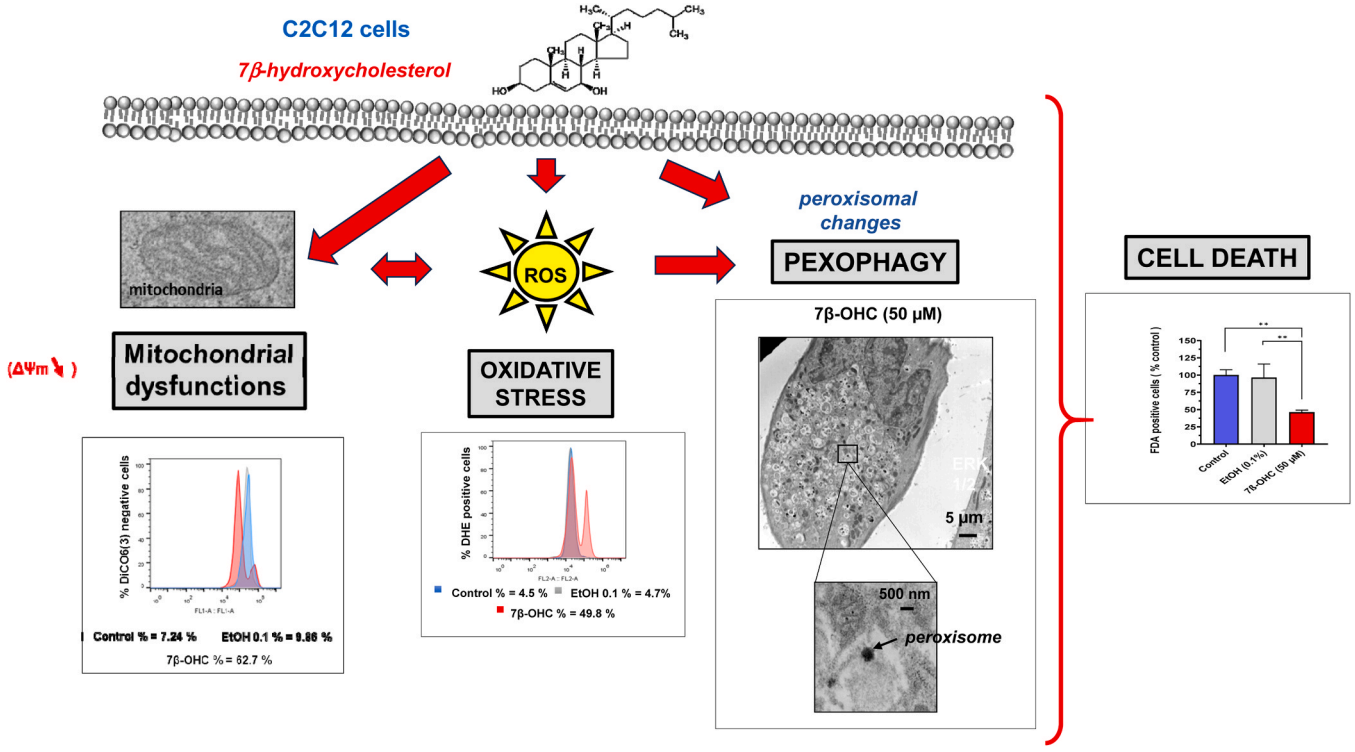

Fig. 3. Main characteristics of 7β-hydroxycholesterol-induced cell death in the immortalized mouse myoblast C2C12 cell line. 7β-OHC -induced cell death in C2C12 cells, which is not an apoptotic mode of cell death, is associated with an increase of depolarized mitochondria, overproduction of ROS at both whole-cell and mitochondrial levels, and the presence of altered peroxisomes leading to a particular type of autophagy: pexophagy. This figure illustrates the main cytotoxic effects of 7β-OHC and 7KC observed whatever the type of cell used and the type of cell death induced: ROS overproduction, mitochondrial and peroxisomal dysfunctions.

3.2. Prevention of 7-ketocholesterol- and 7β-hydroxycholesterol-induced cytotoxic effects with major nutrients of the Mediterranean diet and edible oils: in vitro studies

To prevent 7KC- and 7β-OHC-induced cytotoxic effects (oxidative stress, inflammation, and cell death induction), several strategies can be used. Currently, three strategies are possible consisting of either i) promoting the degradation of 7KC with bacterial enzymes [116], ii) selectively removing 7KC from the cells with UDP-003, which belongs to a new class of cyclodextrin dimers [117] or iii) acting on the signaling pathways involved in the cytotoxicity of this oxysterol [5]. For this latter strategy, molecules or mixtures of molecules (edible oils), which are efficient on 7KC, are also most often efficient on 7β-OHC [5,86,106]. Interestingly, among natural molecules and edible oils counteracting 7KC- and 7β-OHC-induced cytotoxic effects, several of them are representative nutrients of Mediterranean diet known for its benefits on human health, to prevent cardiovascular diseases, and to favor ageing in good health [118,119].

Up to now, only a few synthetic molecules attenuate 7KC- and 7β-OHC-induced cytotoxic effects. These are dimethyl fumarate (DMF), also known under the name of Tecfidera which is commercialized by Biogen and used in the treatment of remitting-relapsing multiple sclerosis, and one of its metabolites, monomethyl fumarate (MMF) [120,121]. Interestingly, sulfo-N-succinimidyl oleate (SSO, a synthetic derivative of oleic acid (C18:1 n-9)) (SSO) has been shown to prevent 7KC-induced oxidative stress and cell death on 158 N and ARPE-19 cells, without lipid droplet formation induction as observed in the presence of fatty acids and edible oils [122].

Among natural molecules ω3 and ω9 fatty acids such as docosahexaenoic acid (DHA, C22:6 n-3) present in high amount in some fishes (sardine, mackerel, tuna) present in Mediterranean cuisine [123] and fish oils [124], as well as oleic acid (C18:1 n-9) present in high amount in several Mediterranean oils, especially olive and argan oils [125,126], strongly attenuate 7KC- and 7β-OHC-induced cytotoxic effects [5]. Alpha-tocopherol (a component of vitamin E comprising four tocopherols (α-, β-, γ-, and δ-tocopherol) and four tocotrienols (α-, β-, γ-, and δ-tocotrienol)) [127] is also present in several edible oils associated with the Mediterranean diet, and can be considered as a strong inhibitor of 7KC- and 7β-OHC-induced cell death: it is efficient whatever the cell type considered and the type of cell death induced [5,86,128–131]. In 7KC-treated cells, α-tocopherol prevents the accumulation of 7KC in lipid rafts [132,133]. However, whereas 7β-OHC does not accumulate in lipid rafts, α-tocopherol also prevents its cytotoxicity [133]. Besides its accumulation in lipid raft and its antioxidant role, α-tocopherol has also important effects on cell signaling and gene expression which could explain its cytoprotective activity [134]. There is also evidence that several polyphenols found in high amount in the Mediterranean diet (*trans* resveratrol, quercetin, apigenin) [135] attenuate 7KC-induced oxiapoptophagy on neuronal N2a cells, Human Monocyte-Derived M1 and M2 Macrophages or ARPE-19 cells [99,109,136]. Other nutrients present in the Mediterranean diet as γ-tocopherol, sterculic acid, lycopene, epicatechin, epigallocatechin-3-gallate, hydroxytyrosol, and tyrosol are also potent inhibitors of 7KC- and 7β-OHC-induced cytotoxic effects [5,35,137–144]. Protective effects of biotin (also known as Vitamin B8, identified in seeds and oleaginous fruits) have only been observed on 7β-OHC-treated cells [145]. However, epidemiological studies revealed that isolated bioactive phytochemicals (polyphenols, tocopherols) are not as effective as fruits and vegetables containing these substances whereas they are of interest for the functional food industry [146].

As several Mediterranean oils are a mixture of nutrients (fatty acids, polyphenols, tocopherols), which counteract 7KC- and/or 7β-OHC-induced cytotoxic effects, the cytoprotective activities of these edible oils (olive and argan oils, *Pistacia lentiscus* seed oil, pomegranate seed oil, and milk thistle seed oil) were evaluated *in vitro* in 7KC- and/or 7β-OHC-treated cells.

In a recent study conducted by Ghzaiel *et al.* [147], it was proven that with Tunisian *Pistacia lentiscus* seed oil (PLSO) (100 μg/mL), the 7β-OHC-induced cytotoxic effects in murine C2C12 myoblasts were strongly attenuated. The cytoprotection was comparable to that seen with 400 μM of α-tocopherol, which was utilized as a positive control. This cytoprotective effect was characterized by decreased oxidative stress (reduction in ROS overproduction in whole cells and at the mitochondrial level; decrease in the formation of lipid and protein oxidation products; and normalization of antioxidant enzyme activities: glutathione peroxidase (GPx) and superoxide dismutase (SOD)), as well as prevention of cell death and organelle dysfunctions (restoration of cell adhesion, cell viability, and plasma membrane integrity; prevention of mitochondrial and peroxisomal damages). These findings demonstrate that PLSO comprises a combination of bioactive compounds that counteract the cytotoxic effects of 7 β-OHC on C2C12 myoblasts and has antioxidant qualities comparable to α-tocopherol used at high concentration. The cytoprotective properties of Mediterranean oils against the toxicity induced by 7KC (25 μM; 50 μM) and 7β-OHC (12.5 μM; 25 μM) were also confirmed by Ksila *et al.* [148] in N2a murine neuronal cells when using pomegranate seed oil (100–200 μg/mL). Additionally, it was observed that argan oil and milk thistle seed oil prevented ROS overproduction induced by 7KC (25 μM) in murine oligodendrocytes (158 N) (measured by flow cytometry after staining with DHE) and improved plasma membrane permeability to propidium iodide (PI), which is a cell death criterion [149,150]. It is widely known that 7KC causes oxidative stress, cell death, and organelle malfunction (mitochondria, lysosomes, endoplasmic reticulum, and peroxisomes), which are the hallmarks of neurodegeneration. It was proven that the 7KC-induced adverse effects are significantly reduced by olive oil which is frequently utilized in the Mediterranean diet for cooking. The cytoprotective effects obtained with this oil on 158 N oligodendrocytes and BV-2 microglial cells further support its potential to protect against neurodegenerative illnesses. Indeed, on 158 N and BV-2 cells, 7KC (25 μM)-induced loss of plasma membrane esterase activity measured after staining with FDA, which is also a cell death criterion, is prevented by olive and argan oil [151,152]. These data support that olive oil could be a helpful supplement to pharmaceutical treatments or to prevent central nervous system (CNS) dysfunction [153]. Based on animal models and clinical investigations, some polyphenols of olive oil, such as hydroxytyrosol, may induce their protective effects through the potentiation of neurotrophins, which are molecules known to favor neuron growth, proliferation, survival and differentiation, and which also have antioxidant properties [154,155].

In a fibroblast model of patients with Smith-Lemli-Opitz syndrome (SLOS, an inborn error of cholesterol biosynthesis characterized by diminished cholesterol and increased 7-dehydrocholesterol (7-DHC) levels), a mix of antioxidants showed a decrease in 7-DHC-derived oxysterol, 3β,5α-dihydroxycholest-7-en-6-one levels but also a normalization of the changes observed in gene expression [156]. The antioxidant mix was composed of vitamin A, coenzyme Q10, vitamin C, and vitamin E. According to the results of this study, the effects of the antioxidant mix were mainly due to vitamin E [156].

There are also several studies supporting that the cytoprotective effects of edible oils could be due to tocopherols (α- and γ-tocopherol), and oleic acid (C18:1 n-9), which strongly reduce 7KC- and 7β-OHC-induced cytotoxicity [109,137,157,158]. Interestingly, some of them could cross the blood-brain barrier. This is well established for tocopherols, long-chain fatty acids (carbon chain of 13–22 carbons) as well as polyphenols [159–161]. Bioactive compounds counteracting 7KC and 7β-OHC-induced cytotoxicity are listed respectively in Table 1 and Table 2.

3.3. Prevention of age-related diseases associated with increased levels of 7-ketocholesterol and 7β-hydroxycholesterol: in vivo arguments in favor of nutritherapy on animal models

Numerous evidences of the contribution of 7KC and 7β-OHC in age-

Table 1
Bioactive compounds counteracting 7-ketocholesterol-induced cytotoxicity (oxidative stress, inflammation and/or cell death induction).

Oxyterol	Cytoprotective compounds (nutrients and edible oils)		Cells	7KC concentrations	References
7-ketocholesterol (7KC)	Tocopherols	α-tocopherol; 100–400 μM	U937 cells; A7r5 cells; 158 N cells; N2a cells; BV−2 cells	25–50 μM	[39,111, 113, 114–116; 140]
		γ-tocopherol; 400 μM	BV−2 cells	50 μM	[114]
	Fatty acids	ALA (C18:3 n−3); 50 μM	N2a cells	50 μM	[111]
		EPA (C20:5 n−3); 50 μM	N2a cells	50 μM	[111]
		OA (C18:1 n−9); 100–200 μM	158 N cells; BV−2 cells N2a cells	50 μM	[111,114,133,140]
		Sterculic acid; 1 μM	ARPE−19 cells	12 μM	[123,124]
	Polyphenols	Epicatechin; 5–10 μM	J774A,1 cells	20 μM	[125]
		Epigallocatechin−3- gallate (30–50 μM)	Human angiosarcoma cells (ISO-HAS)	50 μM	[126]
		Resveratrol; 1.5–30 μM	N2a cells; Human Monocyte-Derived M1 and M2 Macrophages; ARPE−19 cells	15–150 μM	[93,103,120]
		Apigenin; 1.5–6.25 μM	N2a cells	50 μM	[93]
		Quercetin; 1.5–6.25 μM	N2a cells	50 μM	[93]
		Hydroxytyrosol; 2.5–10 μM	Caco−2 cells	1875 μM	[127,128]
		Tyrosol; 2.5–10 μM	Caco−2 cells	1875 μM	[127,128]
	Edible oils	Olive oil; 0.1 %	158 N cells	50 μM	[114; 133, 140]
		Argan oil; 0.2 %	158 N cells	50 μM	[133]
		Milk Thistle seed oil; 0.3 %	158 N cells	50 μM	[134]
		Pomegranate seed oil (100–200 μg/mL)	N2a cells	25 μM; 50 μM	[132]

ALA: Alpha Linoleic Acid; **EPA**: Eicosapentaenoic acid; **OA**: Oleic Acid.
Nerve cells: murine neuroblast N2a cells; rat oligodendrocyte 158 N cells; murine microglial BV-2 cells; ***human colorectal adenocarcinoma cells***: CaCo-2; ***Human angiosarcoma cells***: ISO-HAS; ***Pro-Monocytic cells***: human monocytes derived from M1 and M2 macrophages; human pro-monocytic leukemia cells U937; murine macrophages J774A,1; ***Rat smooth muscle cells*** A7r5; ***Human retinal pigment epithelial cells***: ARPE-19.

related diseases are reported in cardiovascular diseases, ocular diseases and sarcopenia. In this context, convincing data are described on various animal models [162]. Dietary 7-ketocholesterol exacerbates myocardial ischemia–reperfusion injury in mice through monocyte/macrophage-mediated inflammation [86,163] and in humans [68,164,165]. In cardiovascular diseases, several compounds representative of the Mediterranean diet known to counteract 7KC- and 7β-OHC-induced *in vitro* cytotoxic effects, can also preserve a normal vascular status. Thus, phytosterols (β-sitosterol, stigmasterol), which are abundant in several vegetables, are beneficial in improving lipoprotein profile and aortic function in hamster [166]. Less 7KC- and 7β-OHC were also identified in the meat from chicken fed α-tocopherol- and β-carotene-supplemented diets supporting a potential benefits of these nutrients in sarcopenia[167]. Although studies have shown that people who eat diets rich in vitamin E are less likely to suffer from cardiovascular diseases, other studies on vitamin E supplements are rather contradictory [168,169]. In a model of hamsters fed hypercholesterolemic diets, it was shown that antioxidant supplementation (selenium, α-tocopherol) led to a drop in plasma cholesterol concentrations, a reduction in lipid peroxidation in tissues, and an increase in liver oxysterol concentrations (inhibition of free radical-mediated oxysterol catabolism) [170]. In a mouse model of SLOS (Dhcr7-heterozygous), pregnant females were fed a vitamin E-enriched diet. This supplementation reduced the formation of oxysterols in the brain and liver of the newborn Dhcr7-knockout pups [156]. Currently, several benefits of *trans* resveratrol have been shown to be effective in the prevention and / or treatment of patients with age-related macular degeneration or cataract [171]. The PREDIMED ("PREvención con DIeta MEDiterránea") study has also shown that the incidence of major cardiovascular events was lower among the patients assigned to a Mediterranean diet supplemented with extra-virgin olive oil or nuts than among those assigned to a reduced-fat diet [172]. Red wine polyphenolic compounds also preserve a normal vascular reactivity by acting at different stages of the cascade that leads to lipid oxidation, endothelium dysfunctions and vasospasm [173]. Extended lifespan was also observed in obese mice fed a diet supplemented with a polyphenol-rich plant extract (PRPE) [174] which also favors the differentiation of myocytes in myotubes supporting also potential benefits in patients with sarcopenia [175]. Altogether, these in vivo data support benefits of nutritherapy with representative compounds of the Mediterranean diet to prevent and / or cure age-related diseases associated with increased levels of 7KC and 7β-OHC.

3.4. Prevention of age-related diseases associated with increased levels of 7-ketocholesterol and 7β-hydroxycholesterol: in vivo arguments in favor of nutritherapy based on human studies

Clinical studies have been carried out to assess the effects of various dietary compounds on oxysterol-induced toxicity. These studies were mainly carried out in the context of cardiovascular diseases identified very early on as involving oxysterols. Most clinical studies focus on the involvement of oxysterols in pathology, notably cardiovascular pathology, but also in neurodegenerative diseases such as Alzheimer's disease. Few studies on nutritherapy applied to oxysterols have published results, but their number is increasing. Some are still in the recruitment phase, while others have completed their recruitment very recently. Here are a few interesting studies: Cholesterol and Antioxidant Treatment in Patients With SLOS (ClinicalTrials.gov ID NCT01773278) and Evaluation of Consuming Olive Extract on Total Cholesterol Levels (OLICOL) (ClinicalTrials.gov ID NCT06490133).

In healthy subjects, the changes in lipid species relevant to cardiovascular disease (fatty acids, sterols, and oxysterols) were studied after drinking 400 mL coffee a day for 8 weeks [176]. Two coffees were tested containing 787 mg or 407 mg of chlorogenic acid. In the "coffee" group, subjects saw their levels of oxysterols and free fatty acids fall, while in the control group there was an increase [176]. At the same time, the

Table 2
Bioactive compounds counteracting 7β-hydroxycholesterol-induced cytotoxicity.

Oxyterol	Cytoprotective compounds (nutrients and edible oils)		Cells	7 β-OHC concentrations	References
7β-hydroxycholesterol (7β-OHC)	Tocopherols	α-tocopherol; 10–400 μM	158 N cells; U937 cells	50 μM 30 μM	[112,117]
	Polyphenols	Epigallocatechin−3-gallate; 1 μM	CaCo−2 cells	4.4 μM	[122]
		Resveratrol; 1 μM	ARPE- 19 cells	75 μM	[103]
	Edible oils	Pomegranate seed oil; 100 μg/mL; 200 μg/mL	N2a cells	12.5 μM; 25 μM	[132]
		Pistacia lentiscus L. seed oil; 100 μg/mL	C2C12 cells	50 μM	[131]

Human Retinal Pigment Epithelial Cells: ARPE-19, Nerve Cells: N2a (mouse neuroblasts); 158 N (rat oligodendrocytes), Human Pro-Monocytic Cells: U937, Epithelial Intestinal Cells: CaCo-2; Mouse Myoblasts: C2C12.

antioxidants in coffee were tested on a foam cell model (human THP-1 monocytic cells treated with oxidized LDL) and a decrease in the presence of oxysterols and arachidonic acid was observed [176]. In 68 postmenopausal women with hypercholesterolemia, Korean red ginseng consumption (2 g once a day) improves cholesterol metabolism by decreasing cholesterol and 7-hydroxycholesterol levels [177]. However, further studies are needed to corroborate these results. The effect of vitamin E supplementation was tested in candidates for carotid endarterectomy for whom plasma levels of 7β-OHC, 7KC, cholesterol, and vitamin E were measured [178]. In parallel with an increase in plasma vitamin E levels, this supplementation showed a decrease in 7β-OHC levels. This improvement in oxidative status via the drop in 7β-OHC was only observed in plasma, with no difference observed in the content of oxysterol and vitamin E in plaques. Twenty healthy Italian subjects were recruited to study the bioavailability of vitamin E in relation to dietary intake and the effect on plasma lipid peroxide-scavenging activity and on 7β-OHC and 7KC as markers of oxidative stress [179]. Vitamin E was administered either with food or directly on an empty stomach. Plasma vitamin E levels increased significantly with food intake. The lipid peroxide–scavenging activity of plasma increased significantly in the group where vitamin E was given with food. A reduction in 7β-OHC and 7KC levels was observed, but without statistical differences [179]. The authors emphasize that oxysterol levels were initially low, probably related to the Mediterranean diet. In view of these results, the authors therefore recommend using vitamin E added to meals for greater effectiveness. Altogether, the clinical studies presented tend to demonstrate that nutritherapy can be a possible way to help slow the progression of cardiovascular diseases associated with increased levels of 7β-OHC and/or 7KC, but that it is important to consider the form of this nutritional intake.

4. Conclusion

Oxysterols, 7KC and 7β-OHC, are often present at an increased level in biological fluids, tissues and/or organs of patients affected by age-related diseases: cardiovascular diseases, ocular diseases (age-related macular degeneration, cataract), neurodegenerative diseases (Alzheimer's disease in particular), and sarcopenia. In the light of these considerations, 7KC and 7β-OHC may be considered as biomarkers of these diseases specially to evaluate the local and / or systemic oxidative stress level. However, there is still a need to better define how to optimize the use of 7KC and 7β-OHC alone or in combination with other biomarkers in terms of diagnosis, prognosis, and evaluation of treatments efficiencies. In addition, a better knowledge of the cytotoxic activities of 7KC and 7β-OHC will provide a better understanding of the associated signaling pathways, enabling pharmacological targets to be identified for better treatment of the diseases. Interestingly, the ability of several nutrients from the Mediterranean diet (fatty acids, polyphenols and tocopherols) to counteract 7KC- and 7β-OHC-induced cytotoxic effects brings additional arguments supporting the importance of nutrients to prevent age-related diseases. The marked cytoprotective activities observed with ω3 and ω9 fatty acids, polyphenols and α-tocopherol highlight a new concept relying on oxysterols, nutrition and age-related diseases. Consequently, diet or functional foods rich in nutrients (ω3 and ω9 fatty acids, polyphenols and α-tocopherol) that counteract the toxicity of 7KC and 7β-OHC could therefore reduce the incidence of age-related diseases, the frequency of which is increasing as life expectancy is longer. As well as being of scientific and medical interest, the use of nutritherapy to prevent and / or cure 7KC- and 7β-OHC-induced age-related diseases can be considered of economic and social interest.

CRediT authorship contribution statement

El Midaoui Adil: Writing – original draft. **Meziane Smail**: Investigation. **Atanasov Atanas G.**: Writing – original draft. **Hammami Sonia**: Writing – original draft. **Ksila Mohamed**: Investigation. **Zarrouk Amira**: Investigation. **Nury Thomas**: Investigation. **Brahmi Fatiha**: Investigation. **Mackrill John J**: Writing – original draft. **Ghzaiel Imen**: Writing – original draft, Investigation. **Dias Irundika H K**: Writting - original draft. **Rezig Leila**: Writing – original draft. **Vejux Anne**: Writing – original draft, Supervision, Conceptualization, Investigation. **Latruffe Norbert**: Writting - original draft. **Jouanny Pierre:** Writting - original draft. **Lizard Gérard**: Writing – original draft, Conceptualization, Investigation.

Declaration of Competing Interest

The authors have no conflict of interest to declare.

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Data availability

No data was used for the research described in the article.

References

[1] V. Mutemberezi, O. Guillemot-Legris, G.G. Muccioli, Oxysterols: from cholesterol metabolites to key mediators, Prog. Lipid Res 64 (2016) 152–169, https://doi.org/10.1016/j.plipres.2016.09.002.

[2] L. Iuliano, Pathways of cholesterol oxidation via non-enzymatic mechanisms, Chem. Phys. Lipids 164 (2011) 457–468, https://doi.org/10.1016/j.chemphyslip.2011.06.006.

[3] C. Zerbinati, L. Iuliano, Cholesterol and related sterols autoxidation, Free Radic. Biol. Med 111 (2017) 151–155, https://doi.org/10.1016/j.freeradbiomed.2017.04.013.

[4] F.A. de Freitas, D. Levy, A. Zarrouk, G. Lizard, S.P. Bydlowski, Impact of oxysterols on cell death, proliferation, and differentiation induction: current status, Cells 10 (2021) 2301, https://doi.org/10.3390/cells10092301.

[5] T. Nury, A. Yammine, I. Ghzaiel, K. Sassi, A. Zarrouk, F. Brahmi, M. Samadi, S. Rup-Jacques, D. Vervandier-Fasseur, J.P. Pais de Barros, V. Bergas, S. Ghosh, M. Majeed, A. Pande, A. Atanasov, S. Hammami, M. Hammami, J. Mackrill, B. Nasser, P. Andreoletti, M. Cherkaoui-Malki, A. Vejux, G. Lizard, Attenuation of 7-ketocholesterol- and 7β-hydroxycholesterol-induced oxiapoptophagy by nutrients, synthetic molecules and oils: potential for the prevention of age-related diseases, Ageing Res Rev. 68 (2021) 101324, https://doi.org/10.1016/j.arr.2021.101324.

[6] A. Zarrouk, A. Vejux, J. Mackrill, Y. O'Callaghan, M. Hammami, N. O'Brien, G. Lizard, Involvement of oxysterols in age-related diseases and ageing processes, Ageing Res Rev. 18 (2014) 148–162, https://doi.org/10.1016/j.arr.2014.09.006.

[7] A. Samadi, A. Gurlek, S.N. Sendur, S. Karahan, F. Akbiyik, I. Lay, Oxysterol species: reliable markers of oxidative stress in diabetes mellitus, J. Endocrinol. Invest 42 (2019) 7–17, https://doi.org/10.1007/s40618-018-0873-5.

[8] I.H.K. Dias, H. Shokr, Oxysterols as biomarkers of aging and disease, Adv. Exp. Med Biol. 1440 (2024) 307–336, https://doi.org/10.1007/978-3-031-43883-7_16.

[9] T. Nury, A. Zarrouk, K. Ragot, M. Debbabi, J.-M. Riedinger, A. Vejux, P. Aubourg, G. Lizard, 7-Ketocholesterol is increased in the plasma of X-ALD patients and induces peroxisomal modifications in microglial cells: Potential roles of 7-keto-cholesterol in the pathophysiology of X-ALD, J. Steroid Biochem. Mol. Biol. 169 (2017) 123–136, https://doi.org/10.1016/j.jsbmb.2016.03.037.

[10] S. Boenzi, F. Deodato, R. Taurisano, B.M. Goffredo, C. Rizzo, C. Dionisi-Vici, Evaluation of plasma cholestane-3β,5α,6β-triol and 7-ketocholesterol in inherited disorders related to cholesterol metabolism, J. Lipid Res 57 (2016) 361–367, https://doi.org/10.1194/jlr.M061978.

[11] G. Lizard, J.J. Mackrill, T. Willinger, Implication of oxysterols in infectious and non-communicable inflammatory diseases, Cells 12 (2023) 241, https://doi.org/10.3390/cells12020241.

[12] E. Viennois, A.J.C. Pommier, K. Mouzat, A. Oumeddour, F.-Z.El Hajjaji, J. Dufour, F. Caira, D.H. Volle, S. Baron, J.-M.A. Lobaccaro, Targeting liver X receptors in human health: deadlock or promising trail? Expert Opin. Ther. Targets 15 (2011) 219–232, https://doi.org/10.1517/14728222.2011.547853.

[13] Y. Wang, N. Kumar, C. Crumbley, P.R. Griffin, T.P. Burris, A second class of nuclear receptors for oxysterols: regulation of RORalpha and RORgamma activity by 24S-hydroxycholesterol (cerebrosterol), Biochim Biophys. Acta 1801 (2010) 917–923, https://doi.org/10.1016/j.bbalip.2010.02.012.

[14] R. Sato, Sterol metabolism and SREBP activation, Arch. Biochem Biophys. 501 (2010) 177–181, https://doi.org/10.1016/j.abb.2010.06.004.

[15] X.-H. Yu, N. Jiang, P.-B. Yao, X.-L. Zheng, F.S. Cayabyab, C.-K. Tang, NPC1, intracellular cholesterol trafficking and atherosclerosis, Clin. Chim. Acta 429 (2014) 69–75, https://doi.org/10.1016/j.cca.2013.11.026.

[16] U. Kovač, C. Skubic, L. Bohinc, D. Rozman, T. Režen, Oxysterols and gastrointestinal cancers around the clock, Front Endocrinol. (Lausanne) 10 (2019) 483, https://doi.org/10.3389/fendo.2019.00483.

[17] V.M. Olkkonen, E. Ikonen, Cholesterol transport in the late endocytic pathway: roles of ORP family proteins, J. Steroid Biochem Mol. Biol. 216 (2022) 106040, https://doi.org/10.1016/j.jsbmb.2021.106040.

[18] I. Arora, M. Sharma, L.Y. Sun, T.O. Tollefsbol, The epigenetic link between polyphenols, aging and age-related diseases, Genes (Basel) 11 (2020) 1094, https://doi.org/10.3390/genes11091094.

[19] S. Silvente-Poirot, M. Poirot, Cholesterol epoxide hydrolase and cancer, Curr. Opin. Pharm. 12 (2012) 696–703, https://doi.org/10.1016/j.coph.2012.07.007.

[20] Y.J. Kim, C.S. Lee, Tyrosine kinase inhibitor AG126 reduces 7-ketocholesterol-induced cell death by suppressing mitochondria-mediated apoptotic process, Neurochem. Res 35 (2010) 603–612, https://doi.org/10.1007/s11064-009-0105-7.

[21] S. Hannedouche, J. Zhang, T. Yi, W. Shen, D. Nguyen, J.P. Pereira, D. Guerini, B. U. Baumgarten, S. Roggo, B. Wen, R. Knochenmuss, S. Noël, F. Gessier, L. M. Kelly, M. Vanek, S. Laurent, I. Preuss, C. Miault, I. Christen, R. Karuna, W. Li, D.-I. Koo, T. Suply, C. Schmedt, E.C. Peters, R. Falchetto, A. Katopodis, C. Spanka, M.-O. Roy, M. Detheux, Y.A. Chen, P.G. Schultz, C.Y. Cho, K. Seuwen, J.G. Cyster, A.W. Sailer, Oxysterols direct immune cell migration via EBI2, Nature 475 (2011) 524–527, https://doi.org/10.1038/nature10280.

[22] C. Liu, X.V. Yang, J. Wu, C. Kuei, N.S. Mani, L. Zhang, J. Yu, S.W. Sutton, N. Qin, H. Banie, L. Karlsson, S. Sun, T.W. Lovenberg, Oxysterols direct B-cell migration through EBI2, Nature 475 (2011) 519–523, https://doi.org/10.1038/nature10226.

[23] J. Emgård, H. Kammoun, B. García-Cassani, J. Chesné, S.M. Parigi, J.-M. Jacob, H.-W. Cheng, E. Evren, S. Das, P. Czarnewski, N. Sleiers, F. Melo-Gonzalez, E. Kvedaraite, M. Svensson, E. Scandella, M.R. Hepworth, S. Huber, B. Ludewig, L. Peduto, E.J. Villablanca, H. Veiga-Fernandes, J.P. Pereira, R.A. Flavell, T. Willinger, Oxysterol sensing through the receptor GPR183 promotes the lymphoid-tissue-inducing function of innate lymphoid cells and colonic inflammation, Immunity 48 (2018) 120–132.e8, https://doi.org/10.1016/j.immuni.2017.11.020.

[24] P. Ferrari, The role of 11β-hydroxysteroid dehydrogenase type 2 in human hypertension, Biochim Biophys. Acta 1802 (2010) 1178–1187, https://doi.org/10.1016/j.bbadis.2009.10.017.

[25] A.M. Petrov, M.R. Kasimov, A.L. Zefirov, Brain Cholesterol metabolism and its defects: linkage to neurodegenerative diseases and synaptic dysfunction, Acta Nat. 8 (2016) 58–73.

[26] I. Björkhem, U. Diczfalusy, A. Lövgren-Sandblom, L. Starck, M. Jonsson, K. Tallman, H. Schirmer, L.B. Ousager, P.J. Crick, Y. Wang, W.J. Griffiths, F. P. Guengerich, On the formation of 7-ketocholesterol from 7-dehydrocholesterol in patients with CTX and SLO, J. Lipid Res 55 (2014) 1165–1172, https://doi.org/10.1194/jlr.P048603.

[27] W. Liu, L. Xu, C.R. Lamberson, L.S. Merkens, R.D. Steiner, E.R. Elias, D. Haas, N. A. Porter, Assays of plasma dehydrocholesteryl esters and oxysterols from Smith-Lemli-Opitz syndrome patients, J. Lipid Res 54 (2013) 244–253, https://doi.org/10.1194/jlr.M031732.

[28] R.A.S. Schweizer, M. Zürcher, Z. Balazs, B. Dick, A. Odermatt, Rapid hepatic metabolism of 7-ketocholesterol by 11beta-hydroxysteroid dehydrogenase type 1: species-specific differences between the rat, human, and hamster enzyme, J. Biol. Chem. 279 (2004) 18415–18424, https://doi.org/10.1074/jbc.M313615200.

[29] Y. Saito, N. Noguchi, 7-Hydroxycholestrol as a possible biomarker of cellular lipid peroxidation: difference between cellular and plasma lipid peroxidation, Biochem Biophys. Res Commun. 446 (2014) 741–744, https://doi.org/10.1016/j.bbrc.2013.12.083.

[30] A. Anderson, A. Campo, E. Fulton, A. Corwin, W.G. Jerome, M.S. O'Connor, 7-Ketocholesterol in disease and aging, Redox Biol. 29 (2020) 101380, https://doi.org/10.1016/j.redox.2019.101380.

[31] I. Ghzaiel, K. Sassi, A. Zarrouk, S. Ghosh, I.H.K. Dias, T. Nury, M. Ksila, S. Essadek, M.T. Joutey, F. Brahmi, W. Mihoubi, S. Rup-Jacques, M. Samadi, L. Rezig, S. Meziane, T. Ghrairi, O. Masmoudi-Kouki, S. Hammami, B. Nasser, M. Hammami, Y. Wang, W.J. Griffiths, A. Vejux, G. Lizard, Sources of 7-keto-cholesterol, metabolism and inactivation strategies: food and biomedical applications, Redox Exp. Med. (2022) (2022) R40–R56, https://doi.org/10.1530/REM-22-0005.

[32] A. Macho-González, A. Garcimartín, M.E. López-Oliva, S. Bastida, J. Benedí, G. Ros, G. Nieto, F.J. Sánchez-Muniz, Can meat and meat-products induce oxidative stress? Antioxid. (Basel) 9 (2020) 638, https://doi.org/10.3390/antiox9070638.

[33] P. de Medina, S. Silvente-Poirot, M. Poirot, Oxysterols are potential physiological regulators of ageing, Ageing Res Rev. 77 (2022) 101615, https://doi.org/10.1016/j.arr.2022.101615.

[34] S. Vigne, C. Pot, Implication of oxysterols and phytosterols in aging and human diseases, Adv. Exp. Med Biol. 1440 (2024) 231–260, https://doi.org/10.1007/978-3-031-43883-7_12.

[35] L. Rezig, I. Ghzaiel, M. Ksila, A. Yammine, T. Nury, A. Zarrouk, M. Samadi, M. Chouaibi, A. Vejux, G. Lizard, Cytoprotective activities of representative nutrients from the mediterranean diet and of mediterranean oils against 7-keto-cholesterol- and 7β-hydroxycholesterol-induced cytotoxicity: Application to age-related diseases and civilization diseases, Steroids 187 (2022) 109093, https://doi.org/10.1016/j.steroids.2022.109093.

[36] F. Canzoneri, V. Leoni, G. Rosso, D. Risso, R. Menta, G. Poli, Oxysterols as reliable markers of quality and safety in cholesterol containing food ingredients and products, Front Nutr. 9 (2022) 853460, https://doi.org/10.3389/fnut.2022.853460.

[37] N. Lin, H. Zhang, W. Qiu, J. Ye, L. Han, Y. Wang, X. Gu, Determination of 7-ketocholesterol in plasma by LC-MS for rapid diagnosis of acid SMase-deficient Niemann-Pick disease, J. Lipid Res 55 (2014) 338–343, https://doi.org/10.1194/jlr.D044024.

[38] G. Testa, E. Staurenghi, C. Zerbinati, S. Gargiulo, L. Iuliano, G. Giaccone, F. Fantò, G. Poli, G. Leonarduzzi, P. Gamba, Changes in brain oxysterols at different stages of Alzheimer's disease: their involvement in neuroinflammation, Redox Biol. 10 (2016) 24–33, https://doi.org/10.1016/j.redox.2016.09.001.

[39] A. Zarrouk, S. Hammouda, I. Ghzaiel, S. Hammami, W. Khamlaoui, S.H. Ahmed, G. Lizard, M. Hammami, Association between oxidative stress and altered cholesterol metabolism in alzheimer's disease patients, Curr. Alzheimer Res 17 (2020) 823–834, https://doi.org/10.2174/1567205017666201203123046.

[40] J. Ha, G.E. Kwon, Y. Son, S.A. Jang, S.Y. Cho, S.J. Park, H. Kim, J. Lee, J. Lee, D. Seo, M. Lee, D.Y. Lee, M.H. Choi, E. Kim, Cholesterol profiling reveals 7β-hydroxycholesterol as a pathologically relevant peripheral biomarker of Alzheimer's disease, Psychiatry Clin. Neurosci. 78 (2024) 473–481, https://doi.org/10.1111/pcn.13706.

[41] J. Linseisen, G. Wolfram, Absorption of cholesterol oxidation products from ordinary foodstuff in humans, Ann. Nutr. Metab. 42 (1998) 221–230, https://doi.org/10.1159/000012737.

[42] M. Brzeska, K. Szymczyk, A. Szterk, Current knowledge about oxysterols: a review, J. Food Sci. 81 (2016) R2299–R2308, https://doi.org/10.1111/1750-3841.13423.

[43] A. Vejux, G. Lizard, Cytotoxic effects of oxysterols associated with human diseases: Induction of cell death (apoptosis and/or oncosis), oxidative and inflammatory activities, and phospholipidosis, Mol. Asp. Med 30 (2009) 153–170, https://doi.org/10.1016/j.mam.2009.02.006.
[44] J. Song, D. Wang, H. Chen, X. Huang, Y. Zhong, N. Jiang, C. Chen, M. Xia, Association of plasma 7-ketocholesterol with cardiovascular outcomes and total mortality in patients with coronary artery disease, Circ. Res 120 (2017) 1622–1631, https://doi.org/10.1161/CIRCRESAHA.117.311049.
[45] T. Hitsumoto, M. Takahashi, T. Iizuka, K. Shirai, Clinical significance of serum 7-ketocholesterol concentrations in the progression of coronary atherosclerosis, J. Atheroscler. Thromb. 16 (2009) 363–370, https://doi.org/10.5551/jat.no703.
[46] E. Yutuc, R. Angelini, M. Baumert, N. Mast, I. Pikuleva, J. Newton, M.R. Clench, D.O.F. Skibinski, O.W. Howell, Y. Wang, W.J. Griffiths, Localization of sterols and oxysterols in mouse brain reveals distinct spatial cholesterol metabolism, Proc. Natl. Acad. Sci. USA 117 (2020) 5749–5760, https://doi.org/10.1073/pnas.1917421117.
[47] W.J. Griffiths, E. Yutuc, Y. Wang, Mass spectrometry imaging of cholesterol and oxysterols, Adv. Exp. Med Biol. 1440 (2024) 73–87, https://doi.org/10.1007/978-3-031-43883-7_5.
[48] W.J. Griffiths, Y. Wang, Oxysterol research: a brief review, Biochem Soc. Trans. 47 (2019) 517–526, https://doi.org/10.1042/BST20180135.
[49] W.J. Griffiths, P.J. Crick, Y. Wang, Methods for oxysterol analysis: past, present and future, Biochem Pharm. 86 (2013) 3–14, https://doi.org/10.1016/j.bcp.2013.01.027.
[50] B. Sottero, D. Rossin, E. Staurenghi, P. Gamba, G. Poli, G. Testa, Omics analysis of oxysterols to better understand their pathophysiological role, Free Radic. Biol. Med 144 (2019) 55–71, https://doi.org/10.1016/j.freeradbiomed.2019.05.026.
[51] K. Jomova, R. Raptova, S.Y. Alomar, S.H. Alwasel, E. Nepovimova, K. Kuca, M. Valko, Reactive oxygen species, toxicity, oxidative stress, and antioxidants: chronic diseases and aging, Arch. Toxicol. 97 (2023) 2499–2574, https://doi.org/10.1007/s00204-023-03562-9.
[52] V.P. Reddy, Oxidative stress in health and disease, Biomedicines 11 (2023) 2925, https://doi.org/10.3390/biomedicines11112925.
[53] B. Lee, N.A. Afshari, P.X. Shaw, Oxidative stress and antioxidants in cataract development, Curr. Opin. Ophthalmol. 35 (2024) 57–63, https://doi.org/10.1097/ICU.0000000000001009.
[54] V. Schneider, A. Vejux, T. Nury, G. Dupont, J.P. Pais de Barros, D. Lakomy, G. Lizard, T. Moreau, Neurodegeneration, oxidative stress and lipid metabolism plasma biomarkers to differentiate Parkinson's disease from atypical parkinsonian syndromes, Rev. Neurol. (Paris) 179 (2023) 961–966, https://doi.org/10.1016/j.neurol.2022.12.015.
[55] Y. Li, T. Zhao, J. Li, M. Xia, Y. Li, X. Wang, C. Liu, T. Zheng, R. Chen, D. Kan, Y. Xie, J. Song, Y. Feng, T. Yu, P. Sun, Oxidative stress and 4-hydroxy-2-nonenal (4-HNE): implications in the pathogenesis and treatment of aging-related diseases, J. Immunol. Res 2022 (2022) 2233906, https://doi.org/10.1155/2022/2233906.
[56] S. Basu, F2-isoprostanes in human health and diseases: from molecular mechanisms to clinical implications, Antioxid. Redox Signal 10 (2008) 1405–1434, https://doi.org/10.1089/ars.2007.1956.
[57] Y. Yoshida, A. Umeno, Y. Akazawa, M. Shichiri, K. Murotomi, M. Horie, Chemistry of lipid peroxidation products and their use as biomarkers in early detection of diseases, J. Oleo Sci. 64 (2015) 347–356, https://doi.org/10.5650/jos.ess14281.
[58] O. Dilek, Current probes for imaging carbonylation in cellular systems and their relevance to progression of diseases, Technol. Cancer Res Treat. 21 (2022) 15330338221137303, https://doi.org/10.1177/15330338221137303.
[59] N. Nass, B. Bartling, A. Navarrete Santos, R.J. Scheubel, J. Börgermann, R. E. Silber, A. Simm, Advanced glycation end products, diabetes and ageing, Z. Gerontol. Geriatr. 40 (2007) 349–356, https://doi.org/10.1007/s00391-007-0484-9.
[60] M.R. Hamczyk, R.M. Nevado, A. Barettino, V. Fuster, V. Andrés, Biological versus chronological aging: JACC focus seminar, J. Am. Coll. Cardiol. 75 (2020) 919–930, https://doi.org/10.1016/j.jacc.2019.11.062.
[61] A. Samadi, S. Sabuncuoglu, M. Samadi, S.Y. Isikhan, S. Chirumbolo, M. Peana, I. Lay, A. Yalcinkaya, G. Bjørklund, A comprehensive review on oxysterols and related diseases, Curr. Med Chem. 28 (2021) 110–136, https://doi.org/10.2174/0929867327666200316142659.
[62] C. Prunet, T. Montange, A. Véjux, A. Laubriet, J.-F. Rohmer, J.-M. Riedinger, A. Athias, S. Lemaire-Ewing, D. Néel, J.-M. Petit, E. Steinmetz, R. Brenot, P. Gambert, G. Lizard, Multiplexed flow cytometric analyses of pro- and anti-inflammatory cytokines in the culture media of oxysterol-treated human monocytic cells and in the sera of atherosclerotic patients, Cytom. A 69 (2006) 359–373, https://doi.org/10.1002/cyto.a.20272.
[63] H. Hughes, B. Mathews, M.L. Lenz, J.R. Guyton, Cytotoxicity of oxidized LDL to porcine aortic smooth muscle cells is associated with the oxysterols 7-ketocholesterol and 7-hydroxycholesterol, Arterioscler. Thromb. 14 (1994) 1177–1185, https://doi.org/10.1161/01.atv.14.7.1177.
[64] S. Gargiulo, P. Gamba, G. Testa, G. Leonarduzzi, G. Poli, The role of oxysterols in vascular ageing, J. Physiol. 594 (2016) 2095–2113, https://doi.org/10.1113/JP271168.
[65] C. Luquain-Costaz, I. Delton, Oxysterols in vascular cells and role in atherosclerosis, Adv. Exp. Med Biol. 1440 (2024) 213–229, https://doi.org/10.1007/978-3-031-43883-7_11.
[66] I.R. Rodriguez, M.E. Clark, J.W. Lee, C.A. Curcio, 7-ketocholesterol accumulates in ocular tissues as a consequence of aging and is present in high levels in drusen, Exp. Eye Res 128 (2014) 151–155, https://doi.org/10.1016/j.exer.2014.09.009.
[67] A. Vejux, M. Samadi, G. Lizard, Contribution of cholesterol and oxysterols in the physiopathology of cataract: implication for the development of pharmacological treatments, J. Ophthalmol. 2011 (2011) 471947, https://doi.org/10.1155/2011/471947.
[68] G. Testa, D. Rossin, G. Poli, F. Biasi, G. Leonarduzzi, Implication of oxysterols in chronic inflammatory human diseases, Biochimie 153 (2018) 220–231.
[69] D. Lopergolo, S. Bianchi, G.N. Gallus, S. Locci, B. Pucci, V. Leoni, D. Gasparini, E. Tardelli, A. Chincarini, S. Sestini, F.M. Santorelli, H. Zetterberg, N. De Stefano, A. Mignarri, Familial alzheimer's disease associated with heterozygous NPC1 mutation, J. Med Genet 61 (2024) 332–339, https://doi.org/10.1136/jmg-2023-109219.
[70] I. Ghzaiel, K. Sassi, A. Zarrouk, T. Nury, M. Ksila, V. Leoni, B. Bouhaouala-Zahar, S. Hammami, M. Hammami, J.J. Mackrill, M. Samadi, T. Ghrairi, A. Vejux, G. Lizard, 7-Ketocholesterol: Effects on viral infections and hypothetical contribution in COVID-19, J. Steroid Biochem Mol. Biol. 212 (2021) 105939, https://doi.org/10.1016/j.jsbmb.2021.105939.
[71] I. Ghzaiel, A. Zarrouk, V. Pires, J.-P.P. de Barros, S. Hammami, M. Ksila, M. Hammami, T. Ghrairi, P. Jouanny, A. Vejux, G. Lizard, 7β-Hydroxycholesterol and 7-ketocholesterol: New oxidative stress biomarkers of sarcopenia inducing cytotoxic effects on myoblasts and myotubes, J. Steroid Biochem Mol. Biol. 232 (2023) 106345, https://doi.org/10.1016/j.jsbmb.2023.106345.
[72] P. Soucek, D. Vrana, Y.-F. Ueng, S. Wei, R. Kozevnikovova, F.P. Guengerich, Selective changes in cholesterol metabolite levels in plasma of breast cancer patients after tumor removal, Clin. Chem. Lab Med 56 (2018) e78–e81, https://doi.org/10.1515/cclm-2017-0409.
[73] C.-W. Wang, C.-C. Huang, P.-H. Chou, Y.-P. Chang, S. Wei, F.P. Guengerich, Y.-C. Chou, S.-F. Wang, P.-S. Lai, P. Souček, Y.-F. Ueng, 7-ketocholesterol and 27-hydroxycholesterol decreased doxorubicin sensitivity in breast cancer cells: estrogenic activity and mTOR pathway, Oncotarget 8 (2017) 66033–66050, https://doi.org/10.18632/oncotarget.19789.
[74] A. Spalenkova, M. Ehrlichova, S. Wei, F. Peter Guengerich, P. Soucek, Effects of 7-ketocholesterol on tamoxifen efficacy in breast carcinoma cell line models in vitro, J. Steroid Biochem Mol. Biol. 232 (2023) 106354, https://doi.org/10.1016/j.jsbmb.2023.106354.
[75] D. Levy, T. Correa de Melo, B.Y. Ohira, M.L. Fidelis, J.L.M. Ruiz, A. Rodrigues, S. P. Bydlowski, Oxysterols selectively promote short-term apoptosis in tumor cell lines, Biochem Biophys. Res Commun. 505 (2018) 1043–1049, https://doi.org/10.1016/j.bbrc.2018.10.008.
[76] D. Levy, T.C. de Melo, B.A. Oliveira, J.L. Paz, F.A. de Freitas, C.O. Reichert, A. Rodrigues, S.P. Bydlowski, 7-Ketocholesterol and cholestane-triol increase expression of SMO and LXRα signaling pathways in a human breast cancer cell line, Biochem Biophys. Rep. 19 (2019) 100604, https://doi.org/10.1016/j.bbrep.2018.12.008.
[77] A. Marcello, A. Civra, R. Milan Bonotto, L. Nascimento Alves, S. Rajasekharan, C. Giacobone, C. Caccia, R. Cavalli, M. Adami, P. Brambilla, D. Lembo, G. Poli, V. Leoni, The cholesterol metabolite 27-hydroxycholesterol inhibits SARS-CoV-2 and is markedly decreased in COVID-19 patients, Redox Biol. 36 (2020) 101682, https://doi.org/10.1016/j.redox.2020.101682.
[78] A. Khedr, M.T. Khayat, A.N. Khayyat, H.Z. Asfour, R.A. Alsilmi, A.K. Kammoun, Accumulation of oxysterols in the erythrocytes of COVID-19 patients as a biomarker for case severity, Respir. Res 24 (2023) 206, https://doi.org/10.1186/s12931-023-02515-1.
[79] M. Ksila, I. Ghzaiel, K. Sassi, A. Zarrouk, V. Leoni, G. Poli, L. Rezig, V. Pires, S. Meziane, A.G. Atanasov, S. Hammami, M. Hammami, O. Masmoudi-Kouki, O. Hamdi, P. Jouanny, M. Samadi, A. Vejux, T. Ghrairi, G. Lizard, Therapeutic applications of oxysterols and derivatives in age-related diseases, infectious and inflammatory diseases, and cancers, Adv. Exp. Med Biol. 1440 (2024) 379–400, https://doi.org/10.1007/978-3-031-43883-7_19.
[80] A.J. Brown, L.J. Sharpe, M.J. Rogers, Oxysterols: from physiological tuners to pharmacological opportunities, Br. J. Pharm. (2020), https://doi.org/10.1111/bph.15073.
[81] G. Lizard, V. Deckert, L. Dubrez, M. Moisant, P. Gambert, L. Lagrost, Induction of apoptosis in endothelial cells treated with cholesterol oxides, Am. J. Pathol. 148 (1996) 1625–1638.
[82] G. Lizard, S. Monier, C. Cordelet, L. Gesquière, V. Deckert, S. Gueldry, L. Lagrost, P. Gambert, Characterization and comparison of the mode of cell death, apoptosis versus necrosis, induced by 7beta-hydroxycholesterol and 7-ketocholesterol in the cells of the vascular wall, Arterioscler. Thromb. Vasc. Biol. 19 (1999) 1190–1200, https://doi.org/10.1161/01.atv.19.5.1190.
[83] A. Vejux, L. Malvitte, G. Lizard, Side effects of oxysterols: cytotoxicity, oxidation, inflammation, and phospholipidosis, Braz. J. Med Biol. Res 41 (2008) 545–556, https://doi.org/10.1590/s0100-879x2008000700001.
[84] K. Aupeix, D. Weltin, J.E. Mejia, M. Christ, J. Marchal, J.M. Freyssinet, P. Bischoff, Oxysterol-induced apoptosis in human monocytic cell lines, Immunobiology 194 (1995) 415–428, https://doi.org/10.1016/S0171-2985(11)80108-7.
[85] P.L. Bischoff, V. Holl, D. Coelho, P. Dufour, D. Weltin, B. Luu, Apoptosis at the interface of immunosuppressive and anticancer activities: the examples of two classes of chemical inducers, oxysterols and alkylating agents, Curr. Med Chem. 7 (2000) 693–713, https://doi.org/10.2174/0929867003374769.
[86] A. Vejux, D. Abed-Vieillard, K. Hajji, A. Zarrouk, J.J. Mackrill, S. Ghosh, T. Nury, A. Yammine, M. Zaibi, W. Mihoubi, H. Bouchab, B. Nasser, Y. Grosjean, G. Lizard, 7-Ketocholesterol and 7β-hydroxycholesterol: In vitro and animal models used to characterize their activities and to identify molecules preventing their toxicity, Biochem Pharm. 173 (2020) 113648, https://doi.org/10.1016/j.bcp.2019.113648.

[87] S. Lemaire, G. Lizard, S. Monier, C. Miguet, S. Gueldry, F. Volot, P. Gambert, D. Néel, Different patterns of IL-1beta secretion, adhesion molecule expression and apoptosis induction in human endothelial cells treated with 7alpha-, 7beta-hydroxycholesterol, or 7-ketocholesterol, FEBS Lett. 440 (1998) 434–439, https://doi.org/10.1016/s0014-5793(98)01496-3.

[88] S. Gargiulo, P. Gamba, G. Testa, B. Sottero, M. Maina, T. Guina, F. Biasi, G. Poli, G. Leonarduzzi, Molecular signaling involved in oxysterol-induced β1-integrin over-expression in human macrophages, Int J. Mol. Sci. 13 (2012) 14278–14293, https://doi.org/10.3390/ijms131114278.

[89] M. Tani, Y. Kamata, M. Deushi, M. Osaka, M. Yoshida, 7-Ketocholesterol enhances leukocyte adhesion to endothelial cells via p38MAPK pathway, PLoS One 13 (2018) e0200499, https://doi.org/10.1371/journal.pone.0200499.

[90] G. Poli, F. Biasi, G. Leonarduzzi, Oxysterols in the pathogenesis of major chronic diseases, Redox Biol. 1 (2013) 125–130, https://doi.org/10.1016/j.redox.2012.12.001.

[91] M. Deiana, S. Calfapietra, A. Incani, A. Atzeri, D. Rossin, R. Loi, B. Sottero, N. Iaia, G. Poli, F. Biasi, Derangement of intestinal epithelial cell monolayer by dietary cholesterol oxidation products, Free Radic. Biol. Med 113 (2017) 539–550, https://doi.org/10.1016/j.freeradbiomed.2017.10.390.

[92] S. Monier, M. Samadi, C. Prunet, M. Denance, A. Laubriet, A. Athias, Impairment of the cytotoxic and oxidative activities of 7 beta-hydroxycholesterol and 7-ketocholesterol by esterification with oleate, Biochem Biophys. Res Commun. 303 (2003) 814–824.

[93] S. Dehghan, N. Kheshtchin, S. Hassannezhad, M. Soleimani, Cell death classification: A new insight based on molecular mechanisms, Exp. Cell Res 433 (2023) 113860, https://doi.org/10.1016/j.yexcr.2023.113860.

[94] S. Saberianpour, A. Karimi, M.H. Saeed Modaghegh, M. Ahmadi, Different types of cell death in vascular diseases, Mol. Biol. Rep. 48 (2021) 4687–4702, https://doi.org/10.1007/s11033-021-06402-0.

[95] T. Nury, A. Zarrouk, A. Yammine, J.J. Mackrill, A. Vejux, G. Lizard, Oxiapoptophagy: A type of cell death induced by some oxysterols, Br. J. Pharm. 178 (2021) 3115–3123, https://doi.org/10.1111/bph.15173.

[96] T. Nury, A. Zarrouk, A. Vejux, M. Doria, J.M. Riedinger, R. Delage-Mourroux, Induction of oxiapoptophagy, a mixed mode of cell death associated with oxidative stress, apoptosis and autophagy, on 7-ketocholesterol-treated 158N murine oligodendrocytes: impairment by alpha-tocopherol, Biochem Biophys. Res Commun. 446 (2014) 714–719.

[97] T. Nury, A. Zarrouk, J.J. Mackrill, M. Samadi, P. Durand, J.-M. Riedinger, M. Doria, A. Vejux, E. Limagne, D. Delmas, M. Prost, T. Moreau, M. Hammami, R. Delage-Mourroux, N.M. O'Brien, G. Lizard, Induction of oxiapoptophagy on 158N murine oligodendrocytes treated by 7-ketocholesterol-, 7β-hydroxycholesterol-, or 24(S)-hydroxycholesterol: protective effects of α-tocopherol and docosahexaenoic acid (DHA; C22:6 n-3), Steroids 99 (2015) 194–203, https://doi.org/10.1016/j.steroids.2015.02.003.

[98] T. Nury, A. Zarrouk, K. Ragot, M. Debbabi, J.-M. Riedinger, A. Vejux, P. Aubourg, G. Lizard, 7-Ketocholesterol is increased in the plasma of X-ALD patients and induces peroxisomal modifications in microglial cells: potential roles of 7-keto-cholesterol in the pathophysiology of X-ALD, J. Steroid Biochem Mol. Biol. 169 (2017) 123–136, https://doi.org/10.1016/j.jsbmb.2016.03.037.

[99] A. Yammine, A. Zarrouk, T. Nury, A. Vejux, N. Latruffe, D. Vervandier-Fasseur, M. Samadi, J.J. Mackrill, H. Greige-Gerges, L. Auezova, G. Lizard, Prevention by dietary polyphenols (resveratrol, quercetin, apigenin) against 7-ketocholesterol-induced oxiapoptophagy in neuronal N2a cells: potential interest for the treatment of neurodegenerative and age-related diseases, E2346, Cells 9 (2020), https://doi.org/10.3390/cells9112346.

[100] J.L. Paz, D. Levy, B.A. Oliveira, T.C. de Melo, F.A. de Freitas, C.O. Reichert, A. Rodrigues, J. Pereira, S.P. Bydlowski, 7-ketocholesterol promotes oxiapoptophagy in bone marrow mesenchymal stem cell from patients with acute myeloid leukemia, E482, Cells 8 (2019), https://doi.org/10.3390/cells8050482.

[101] J. Ouyang, Y. Xiao, Q. Ren, J. Huang, Q. Zhou, S. Zhang, L. Li, W. Shi, Z. Chen, L. Wu, 7-ketocholesterol induces oxiapoptophagy and inhibits osteogenic differentiation in MC3T3-E1 cells, Cells 11 (2022) 2882, https://doi.org/10.3390/cells11182882.

[102] T. Nury, A. Zarrouk, J.J. Mackrill, M. Samadi, P. Durand, J.-M. Riedinger, M. Doria, A. Vejux, E. Limagne, D. Delmas, M. Prost, T. Moreau, M. Hammami, R. Delage-Mourroux, N.M. O'Brien, G. Lizard, Induction of oxiapoptophagy on 158N murine oligodendrocytes treated by 7-ketocholesterol-, 7β-hydroxycholesterol-, or 24(S)-hydroxycholesterol: protective effects of α-tocopherol and docosahexaenoic acid (DHA; C22:6 n-3), Steroids 99 (2015) 194–203, https://doi.org/10.1016/j.steroids.2015.02.003.

[103] O. Jaouadi, I. Limam, M. Abdelkarim, E. Berred, A. Chahbi, M. Caillot, B. Sola, F. Ben Aissa-Fennira, 5,6-epoxycholesterol isomers induce oxiapoptophagy in myeloma cells, Cancers (Basel) 13 (2021) 3747, https://doi.org/10.3390/cancers13153747.

[104] J.-S. Kim, H. Lim, J.-Y. Seo, K.-R. Kang, S.-K. Yu, C.S. Kim, D.K. Kim, H.-J. Kim, Y.-S. Seo, G.-J. Lee, J.-S. You, J.-S. Oh, GPR183 regulates 7α,25-dihydroxycholesterol-induced oxiapoptophagy in L929 mouse fibroblast cell, Molecules 27 (2022) 4798, https://doi.org/10.3390/molecules27154798.

[105] J.-S. You, H. Lim, J.-Y. Seo, K.-R. Kang, D.K. Kim, J.-S. Oh, Y.-S. Seo, G.-J. Lee, J.-S. Kim, H.-J. Kim, S.-K. Yu, J.-S. Kim, 25-Hydroxycholesterol-Induced Oxiapoptophagy in L929 Mouse Fibroblast Cell Line, Molecules 27 (2021) 199, https://doi.org/10.3390/molecules27010199.

[106] F. Brahmi, A. Vejux, R. Sghaier, A. Zarrouk, T. Nury, W. Meddeb, L. Rezig, A. Namsi, K. Sassi, A. Yammine, I. Badreddine, D. Vervandier-Fasseur, K. Madani, L. Boulekbache-Makhlouf, B. Nasser, G. Lizard, Prevention of 7-ketocholesterol-induced side effects by natural compounds, Crit. Rev. Food Sci. Nutr. 59 (2019) 3179–3198, https://doi.org/10.1080/10408398.2018.1491828.

[107] K. Sassi, T. Nury, A. Zarrouk, R. Sghaier, A. Khalafi-Nezhad, A. Vejux, M. Samadi, F.B. Aissa-Fennira, G. Lizard, Induction of a non-apoptotic mode of cell death associated with autophagic characteristics with steroidal maleic anhydrides and 7β-hydroxycholesterol on glioma cells, J. Steroid Biochem Mol. Biol. 191 (2019) 105371, https://doi.org/10.1016/j.jsbmb.2019.04.020.

[108] L. Malvitte, T. Montange, A. Vejux, C. Joffre, A. Bron, C. Creuzot-Garcher, G. Lizard, Activation of a caspase-3-independent mode of cell death associated with lysosomal destabilization in cultured human retinal pigment epithelial cells (ARPE-19) exposed to 7beta-hydroxycholesterol, Curr. Eye Res. 33 (2008) 769–781, https://doi.org/10.1080/02713680802337397.

[109] B. Dugas, S. Charbonnier, M. Baarine, K. Ragot, D. Delmas, F. Ménétrier, J. Lherminier, L. Malvitte, T. Khalfaoui, A. Bron, C. Creuzot-Garcher, N. Latruffe, G. Lizard, Effects of oxysterols on cell viability, inflammatory cytokines, VEGF, and reactive oxygen species production on human retinal cells: cytoprotective effects and prevention of VEGF secretion by resveratrol, Eur. J. Nutr. 49 (2010) 435–446, https://doi.org/10.1007/s00394-010-0102-2.

[110] S. Luthra, B. Fardin, J. Dong, D. Hertzog, S. Kamjoo, S. Gebremariam, V. Butani, R. Narayanan, J.K. Mungcal, B.D. Kuppermann, M.C. Kenney, Activation of caspase-8 and caspase-12 pathways by 7-ketocholesterol in human retinal pigment epithelial cells, Invest Ophthalmol. Vis. Sci. 47 (2006) 5569–5575, https://doi.org/10.1167/iovs.06-0333.

[111] A. Neekhra, S. Luthra, M. Chwa, G. Seigel, A.L. Gramajo, B.D. Kuppermann, M. C. Kenney, Caspase-8, -12, and -3 activation by 7-ketocholesterol in retinal neurosensory cells, Invest Ophthalmol. Vis. Sci. 48 (2007) 1362–1367, https://doi.org/10.1167/iovs.06-0900.

[112] M. Mazhar, A.U. Din, H. Ali, G. Yang, W. Ren, L. Wang, X. Fan, S. Yang, Implication of ferroptosis in aging, Cell Death Discov. 7 (2021) 149, https://doi.org/10.1038/s41420-021-00553-6.

[113] R.-P. Zhou, Y. Chen, X. Wei, B. Yu, Z.-G. Xiong, C. Lu, W. Hu, Novel insights into ferroptosis: implications for age-related diseases, Theranostics 10 (2020) 11976–11997, https://doi.org/10.7150/thno.50663.

[114] I. Ghzaiel, A. Zarrouk, S. Essadek, L. Martine, S. Hammouda, A. Yammine, M. Ksila, T. Nury, W. Meddeb, M. Tahri Joutey, W. Mihoubi, C. Caccia, V. Leoni, M. Samadi, N. Acar, P. Andreoletti, S. Hammami, T. Ghrairi, A. Vejux, M. Hammami, G. Lizard, Protective effects of milk thistle (Sylibum marianum) seed oil and α-tocopherol against 7β-hydroxycholesterol-induced peroxisomal alterations in murine C2C12 myoblasts: Nutritional insights associated with the concept of pexotherapy, Steroids 183 (2022) 109032, https://doi.org/10.1016/j.steroids.2022.109032.

[115] I. Ghzaiel, S. Maaloul, M. Ksila, A. Namsi, A. Yammine, M. Debbabi, A. Badreddine, W. Meddeb, V. Pires, T. Nury, F. Ménétrier, L. Avoscan, A. Zarrouk, M. Baarine, O. Masmoudi-Kouki, T. Ghrairi, R. Abdellaoui, B. Nasser, S. Hammami, M. Hammami, M. Samadi, A. Vejux, G. Lizard, In vitro evaluation of the effects of 7-ketocholesterol and 7β-hydroxycholesterol on the peroxisomal status: prevention of peroxisomal damages and concept of pexotherapy, Adv. Exp. Med Biol. 1440 (2024) 437–452, https://doi.org/10.1007/978-3-031-43883-7_21.

[116] S. Ghosh, I. Ghzaiel, A. Vejux, S. Meaney, S. Nag, G. Lizard, G. Tripathi, F. Naez, S. Paul, Impact of oxysterols in age-related disorders and strategies to alleviate adverse effects, Adv. Exp. Med Biol. 1440 (2024) 163–191, https://doi.org/10.1007/978-3-031-43883-7_9.

[117] P. Bhargava, D. Dinh, F. Teramayi, A. Silberg, N. Petler, A.M. Anderson, D. M. Clemens, M.S. O'Connor, Selective removal of 7KC by a novel atherosclerosis therapeutic candidate reverts foam cells to a macrophage-like phenotype, bioRxiv (2023) 2023.10.23.563623, https://doi.org/10.1101/2023.10.23.563623.

[118] D. Martini, Health benefits of mediterranean diet, Nutrients 11 (2019) 1802, https://doi.org/10.3390/nu11081802.

[119] L. Serra-Majem, L. Tomaino, S. Dernini, E.M. Berry, D. Lairon, J. Ngo de la Cruz, A. Bach-Faig, L.M. Donini, F.-X. Medina, R. Belahsen, S. Piscopo, R. Capone, J. Aranceta-Bartrina, C. La Vecchia, A. Trichopoulou, Updating the mediterranean diet pyramid towards sustainability: focus on environmental concerns, Int J. Environ. Res Public Health 17 (2020) 8758, https://doi.org/10.3390/ijerph17238758.

[120] R. Sghaier, T. Nury, V. Leoni, C. Caccia, J.-P. Pais De Barros, A. Cherif, A. Vejux, T. Moreau, K. Limem, M. Samadi, J.J. Mackrill, A.S. Masmoudi, G. Lizard, A. Zarrouk, Dimethyl fumarate and monomethyl fumarate attenuate oxidative stress and mitochondrial alterations leading to oxiapoptophagy in 158N murine oligodendrocytes treated with 7β-hydroxycholesterol, J. Steroid Biochem. Mol. Biol. 194 (2019) 105432, https://doi.org/10.1016/j.jsbmb.2019.105432.

[121] A. Zarrouk, T. Nury, E.-M. Karym, A. Vejux, R. Sghaier, C. Gondcaille, P. Andreoletti, D. Trompier, S. Savary, M. Cherkaoui-Malki, M. Debbabi, A. Fromont, J.-M. Riedinger, T. Moreau, G. Lizard, Attenuation of 7-ketocholesterol-induced overproduction of reactive oxygen species, apoptosis, and autophagy by dimethyl fumarate on 158N murine oligodendrocytes, J. Steroid Biochem. Mol. Biol. 169 (2017) 29–38, https://doi.org/10.1016/j.jsbmb.2016.02.024.

[122] T. Nury, I. Ghzaiel, A. Hichami, C. Caccia, V. Leoni, V. Pires, A.G. Atanasov, A. Zarrouk, G. Lizard, A. Vejux, Lipid droplets dependent or independent cytoprotective activities of unsaturated fatty acids, Lorenzo's oil and sulfo-N-succinimidyl oleate on 7-ketocholesterol-induced oxidative stress, organelle dysfunction and cell death on 158N and ARPE-19 cells: Cell targets and benefits of sulfo-N-succinimidyl oleate, Curr. Res. Biotechnol. 7 (2024) 100195, https://doi.org/10.1016/j.crbiot.2024.100195.

[123] R. Uauy-Dagach, A. Valenzuela, Marine oils as a source of omega-3 fatty acids in the diet: how to optimize the health benefits, Prog. Food Nutr. Sci. 16 (1992) 199–243.
[124] F. Chamorro, P. Otero, M. Carpena, M. Fraga-Corral, J. Echave, S. Seyyedi-Mansour, L. Cassani, M.A. Prieto, Health benefits of oily fish: illustrated with blue shark (prionace glauca), shortfin mako shark (isurus oxyrinchus), and swordfish (xiphias gladius), Nutrients 15 (2023) 4919, https://doi.org/10.3390/nu15234919.
[125] A. Zarrouk, L. Martine, S. Grégoire, T. Nury, W. Meddeb, E. Camus, A. Badreddine, P. Durand, A. Namsi, A. Yammine, B. Nasser, M. Mejri, L. Bretillon, J.J. Mackrill, M. Cherkaoui-Malki, M. Hammami, G. Lizard, Profile of fatty acids, tocopherols, phytosterols and polyphenols in mediterranean oils (argan oils, olive oils, milk thistle seed oils and nigella seed oil) and evaluation of their antioxidant and cytoprotective activities, Curr. Pharm. Des. 25 (2019) 1791–1805, https://doi.org/10.2174/1381612825666190705192902.
[126] A. Yammine, T. Nury, A. Vejux, N. Latruffe, D. Vervandier-Fasseur, M. Samadi, H. Greige-Gerges, L. Auezova, G. Lizard, Prevention of 7-ketocholesterol-induced overproduction of reactive oxygen species, mitochondrial dysfunction and cell death with major nutrients (polyphenols, ω3 and ω9 unsaturated fatty acids) of the mediterranean diet on N2a neuronal cells, E2296, Molecules 25 (2020), https://doi.org/10.3390/molecules25102296.
[127] G. Rimbach, A.M. Minihane, J. Majewicz, A. Fischer, J. Pallauf, F. Virgli, P. D. Weinberg, Regulation of cell signalling by vitamin E, Proc. Nutr. Soc. 61 (2002) 415–425, https://doi.org/10.1079/pns2002183.
[128] N.M. Lyons, J.A. Woods, N.M. O'Brien, alpha-Tocopherol, but not gamma-tocopherol inhibits 7 beta-hydroxycholesterol-induced apoptosis in human U937 cells, Free Radic. Res 35 (2001) 329–339, https://doi.org/10.1080/10715760100300861.
[129] C. Miguet-Alfonsi, C. Prunet, S. Monier, G. Bessède, S. Lemaire-Ewing, A. Berthier, F. Ménétrier, D. Néel, P. Gambert, G. Lizard, Analysis of oxidative processes and of myelin figures formation before and after the loss of mitochondrial transmembrane potential during 7beta-hydroxycholesterol and 7-ketocholesterol-induced apoptosis: comparison with various pro-apoptotic chemicals, Biochem. Pharm. 64 (2002) 527–541, https://doi.org/10.1016/s0006-2952(02)01110-3.
[130] M. Debbabi, T. Nury, A. Zarrouk, N. Mekahli, M. Bezine, R. Sghaier, S. Grégoire, L. Martine, P. Durand, E. Camus, A. Vejux, A. Jabrane, L. Bretillon, M. Prost, T. Moreau, S.B. Ammou, M. Hammami, G. Lizard, Protective effects of α-tocopherol, γ-tocopherol and oleic acid, three compounds of olive oils, and no effect of trolox, on 7-ketocholesterol-induced mitochondrial and peroxisomal dysfunction in microglial BV-2 cells, Int J. Mol. Sci. 17 (2016), https://doi.org/10.3390/ijms17121973.
[131] G. Lizard, C. Miguet, G. Besséde, S. Monier, S. Gueldry, D. Neel, P. Gambert, Impairment with various antioxidants of the loss of mitochondrial transmembrane potential and of the cytosolic release of cytochrome c occuring during 7-ketocholesterol-induced apoptosis, Free Radic. Biol. Med. 28 (2000) 743–753, https://doi.org/10.1016/s0891-5849(00)00163-5.
[132] M.C. Royer, S. Lemaire-Ewing, C. Desrumaux, S. Monier, J.P. Barros, A. Athias, 7-ketocholesterol incorporation into sphingolipid/cholesterol-enriched (lipid raft) domains is impaired by vitamin E: a specific role for alpha-tocopherol with consequences on cell death, J. Biol. Chem. 284 (2009) 15826–15834.
[133] K. Ragot, J.J. Mackrill, A. Zarrouk, T. Nury, V. Aires, A. Jacquin, A. Athias, J.-P. Pais de Barros, A. Véjux, J.-M. Riedinger, D. Delmas, G. Lizard, Absence of correlation between oxysterol accumulation in lipid raft microdomains, calcium increase, and apoptosis induction on 158N murine oligodendrocytes, Biochem Pharm. 86 (2013) 67–79, https://doi.org/10.1016/j.bcp.2013.02.028.
[134] G. Rimbach, J. Moehring, P. Huebbe, J.K. Lodge, Gene-regulatory activity of alpha-tocopherol, Molecules 15 (2010) 1746–1761, https://doi.org/10.3390/molecules15031746.
[135] C. Zhor, L. Wafaa, I. Ghzaiel, K. Kessas, A. Zarrouk, M. Ksila, T. Ghrairi, N. Latruffe, O. Masmoudi-Kouki, A. El Midaoui, D. Vervandier-Fasseur, M. Hammami, G. Lizard, A. Vejux, O. Kharoubi, Effects of polyphenols and their metabolites on age-related diseases, Biochem. Pharmacol. 214 (2023) 115674, https://doi.org/10.1016/j.bcp.2023.115674.
[136] B. Buttari, E. Profumo, L. Segoni, D. D'Arcangelo, S. Rossi, F. Facchiano, L. Saso, R. Businaro, L. Iuliano, R. Riganò, Resveratrol counteracts inflammation in human M1 and M2 macrophages upon challenge with 7-oxo-cholesterol: potential therapeutic implications in atherosclerosis, Oxid. Med Cell Longev. 2014 (2014) 257543, https://doi.org/10.1155/2014/257543.
[137] F. Brahmi, A. Vejux, R. Sghaier, A. Zarrouk, T. Nury, W. Meddeb, L. Rezig, A. Namsi, K. Sassi, A. Yammine, I. Badreddine, D. Vervandier-Fasseur, K. Madani, L. Boulekbache-Makhlouf, B. Nasser, G. Lizard, Prevention of 7-ketocholesterol-induced side effects by natural compounds, Crit. Rev. Food Sci. Nutr. 59 (2019) 3179–3198, https://doi.org/10.1080/10408398.2018.1491828.
[138] C. Mascia, M. Maina, E. Chiarpotto, G. Leonarduzzi, G. Poli, F. Biasi, Proinflammatory effect of cholesterol and its oxidation products on CaCo-2 human enterocyte-like cells: effective protection by epigallocatechin-3-gallate, Free Radic. Biol. Med 49 (2010) 2049–2057, https://doi.org/10.1016/j.freeradbiomed.2010.09.033.
[139] J.-D. Huang, J. Amaral, J.W. Lee, I.M. Larrayoz, I.R. Rodriguez, Sterculic acid antagonizes 7-ketocholesterol-mediated inflammation and inhibits choroidal neovascularization, Biochim Biophys. Acta 1821 (2012) 637–646, https://doi.org/10.1016/j.bbalip.2012.01.013.
[140] J.-D. Huang, J. Amaral, J.W. Lee, I.R. Rodriguez, 7-Ketocholesterol-induced inflammation signals mostly through the TLR4 receptor both in vitro and in vivo, PLoS One 9 (2014) e100985, https://doi.org/10.1371/journal.pone.0100985.
[141] G. Leonarduzzi, B. Vizio, B. Sottero, V. Verde, P. Gamba, C. Mascia, E. Chiarpotto, G. Poli, F. Biasi, Early involvement of ROS overproduction in apoptosis induced by 7-ketocholesterol, Antioxid. Redox Signal 8 (2006) 375–380, https://doi.org/10.1089/ars.2006.8.375.
[142] K. Yamagata, N. Tanaka, K. Suzuki, Epigallocatechin 3-gallate inhibits 7-keto-cholesterol-induced monocyte-endothelial cell adhesion, Micro Res 88 (2013) 25–31, https://doi.org/10.1016/j.mvr.2013.03.006.
[143] A. Atzeri, R. Lucas, A. Incani, P. Peñalver, A. Zafra-Gómez, M.P. Melis, R. Pizzala, J.C. Morales, M. Deiana, Hydroxytyrosol and tyrosol sulfate metabolites protect against the oxidized cholesterol pro-oxidant effect in Caco-2 human enterocyte-like cells, Food Funct. 7 (2016) 337–346, https://doi.org/10.1039/c5fo00074b.
[144] M. Deiana, G. Corona, A. Incani, D. Loru, A. Rosa, A. Atzeri, M. Paola Melis, M. Assunta Dessì, Protective effect of simple phenols from extravirgin olive oil against lipid peroxidation in intestinal Caco-2 cells, Food Chem. Toxicol. 48 (2010) 3008–3016, https://doi.org/10.1016/j.fct.2010.07.041.
[145] R. Sghaier, A. Zarrouk, T. Nury, I. Badreddine, N. O'Brien, J.J. Mackrill, A. Vejux, M. Samadi, B. Nasser, C. Caccia, V. Leoni, T. Moreau, M. Cherkaoui-Malki, A. Salhedine Masmoudi, G. Lizard, Biotin attenuation of oxidative stress, mitochondrial dysfunction, lipid metabolism alteration and 7β-hydroxycholesterol-induced cell death in 158N murine oligodendrocytes, Free Radic. Res. 53 (2019) 535–561, https://doi.org/10.1080/10715762.2019.1612891.
[146] I. Koss-Mikołajczyk, M. Baranowska, V. Todorovic, A. Albini, C. Sansone, P. Andreoletti, M. Cherkaoui-Malki, G. Lizard, D. Noonan, S. Sobajic, A. Bartoszek, Prophylaxis of non-communicable diseases: why fruits and vegetables may be better chemopreventive agents than dietary supplements based on isolated phytochemicals? Curr. Pharm. Des. 25 (2019) 1847–1860, https://doi.org/10.2174/1381612825666190702093301.
[147] I. Ghzaiel, A. Zarrouk, T. Nury, M. Libergoli, F. Florio, S. Hammouda, F. Ménétrier, L. Avoscan, A. Yammine, M. Samadi, N. Latruffe, S. Biressi, D. Levy, S.P. Bydlowski, S. Hammami, A. Vejux, M. Hammami, G. Lizard, Antioxidant properties and cytoprotective effect of pistacia lentiscus l. seed oil against 7β-hydroxycholesterol-induced toxicity in C2C12 myoblasts: reduction in oxidative stress, mitochondrial and peroxisomal dysfunctions and attenuation of cell death, Antioxid. (Basel) 10 (2021) 1772, https://doi.org/10.3390/antiox10111772.
[148] Evaluation des potentiels neurotrophiques d'huiles essentielles, de stilbènes et d'oxystérols sur des modèles cellulaires de neurodégénérescence in vitro - Laboratoire Bio-PeroxIL. Biochimie du Peroxysome, Inflammation et Métabolisme Lipidique, (n.d.). ⟨https://theses.hal.science/BOIPEROXIL/tel-04198423v1⟩ (accessed April 10, 2024).
[149] A. Badreddine, A. Zarrouk, E.M. Karym, M. Debbabi, T. Nury, W. Meddeb, R. Sghaier, M. Bezine, A. Vejux, L. Martine, S. Grégoire, L. Bretillon, E. Prost-Camus, P. Durand, M. Prost, T. Moreau, M. Cherkaoui-Malki, B. Nasser, G. Lizard, Argan oil-mediated attenuation of organelle dysfunction, oxidative stress and cell death induced by 7-ketocholesterol in murine oligodendrocytes 158N, Int. J. Mol. Sci. 18 (2017) 2220, https://doi.org/10.3390/ijms18102220.
[150] W. Meddeb, L. Rezig, A. Zarrouk, T. Nury, A. Vejux, M. Prost, L. Bretillon, M. Mejri, G. Lizard, Cytoprotective activities of milk thistle seed oil used in traditional tunisian medicine on 7-ketocholesterol and 24S-hydroxycholesterol-induced toxicity on 158N murine oligodendrocytes, E95, Antioxid. (Basel) 7 (2018), https://doi.org/10.3390/antiox7070095.
[151] G. Lizard, S. Fournel, L. Genestier, N. Dhedin, C. Chaput, M. Flacher, M. Mutin, G. Panaye, J.P. Revillard, Kinetics of plasma membrane and mitochondrial alterations in cells undergoing apoptosis, Cytometry 21 (1995) 275–283, https://doi.org/10.1002/cyto.990210308.
[152] J. Zheng, F. Yin, G. Jin, X. Zhang, L. Zhang, Z. Gong, X. Kang, H. Hu, In vitro neuroprotection of rat hippocampal neurons by manninotriose and astragaloside iv against corticosterone-induced toxicity, Molecules 23 (2018) 3339, https://doi.org/10.3390/molecules23123339.
[153] E. Sangiovanni, P. Brivio, M. Dell'Agli, F. Calabrese, Botanicals as modulators of neuroplasticity: focus on BDNF, Neural Plast. 2017 (2017) 5965371, https://doi.org/10.1155/2017/5965371.
[154] F. Moosavi, R. Hosseini, L. Saso, O. Firuzi, Modulation of neurotrophic signaling pathways by polyphenols, Drug Des. Devel Ther. 10 (2016) 23–42, https://doi.org/10.2147/DDDT.S96936.
[155] V. Carito, M. Ceccanti, L. Tarani, G. Ferraguti, G. N. Chaldakov, M. Fiore, Neurotrophins' modulation by olive polyphenols, Curr. Med Chem. 23 (2016) 3189–3197, https://doi.org/10.2174/0929867323666160627104022.
[156] Z. Korade, L. Xu, F.E. Harrison, R. Ahsen, S.E. Hart, O.M. Folkes, K. Mirnics, N. A. Porter, Antioxidant supplementation ameliorates molecular deficits in Smith-Lemli-Opitz syndrome, Biol. Psychiatry 75 (2014) 215–222, https://doi.org/10.1016/j.biopsych.2013.06.013.
[157] M. Debbabi, A. Zarrouk, M. Bezine, W. Meddeb, T. Nury, A. Badreddine, E. M. Karym, R. Sghaier, L. Bretillon, S. Guyot, M. Samadi, M. Cherkaoui-Malki, B. Nasser, M. Mejri, S. Ben-Hammou, M. Hammami, G. Lizard, Comparison of the effects of major fatty acids present in the Mediterranean diet (oleic acid, docosahexaenoic acid) and in hydrogenated oils (elaidic acid) on 7-ketocholesterol-induced oxiapoptophagy in microglial BV-2 cells, Chem. Phys. Lipids 207 (2017) 151–170, https://doi.org/10.1016/j.chemphyslip.2017.04.002.
[158] A. Cilla, A. Alegría, A. Attanzio, G. Garcia-Llatas, L. Tesoriere, M.A. Livrea, Dietary phytochemicals in the protection against oxysterol-induced damage, Chem. Phys. Lipids 207 (2017) 192–205.
[159] P. Lee, L.M. Ulatowski, Vitamin E: Mechanism of transport and regulation in the CNS, IUBMB Life 71 (2019) 424–429, https://doi.org/10.1002/iub.1993.

[160] E. Lei, K. Vacy, W.C. Boon, Fatty acids and their therapeutic potential in neurological disorders, Neurochem. Int 95 (2016) 75–84, https://doi.org/10.1016/j.neuint.2016.02.014.
[161] I. Figueira, R. Menezes, D. Macedo, I. Costa, C.N. Dos Santos, Polyphenols beyond barriers: a glimpse into the brain, Curr. Neuropharmacol. 15 (2017) 562–594, https://doi.org/10.2174/1570159X14666161026151545.
[162] A. Meynier, A. Andre, J. Lherminier, A. Grandgirard, L. Demaison, Dietary oxysterols induce in vivo toxicity of coronary endothelial and smooth muscle cells, Eur. J. Nutr. 44 (2005) 393–405, https://doi.org/10.1007/s00394-005-0539-x.
[163] T. Uchikawa, T. Matoba, T. Kawahara, I. Baba, S. Katsuki, J.-I. Koga, Y. Hashimoto, R. Yamasaki, I. Ichi, H. Akita, H. Tsutsui, Dietary 7-ketocholesterol exacerbates myocardial ischemia-reperfusion injury in mice through monocyte/macrophage-mediated inflammation, Sci. Rep. 12 (2022) 14902, https://doi.org/10.1038/s41598-022-19065-z.
[164] A.J. Brown, W. Jessup, Oxysterols and atherosclerosis, Atherosclerosis 142 (1999) 1–28.
[165] A. Zmysłowski, A. Szterk, Current knowledge on the mechanism of atherosclerosis and pro-atherosclerotic properties of oxysterols, Lipids Health Dis. 16 (2017) 188, https://doi.org/10.1186/s12944-017-0579-2.
[166] Y.T. Liang, W.T. Wong, L. Guan, X.Y. Tian, K.Y. Ma, Y. Huang, Z.-Y. Chen, Effect of phytosterols and their oxidation products on lipoprotein profiles and vascular function in hamster fed a high cholesterol diet, Atherosclerosis 219 (2011) 124–133, https://doi.org/10.1016/j.atherosclerosis.2011.06.004.
[167] C. Maraschiello, E. Esteve, J.A. García Regueiro, Cholesterol oxidation in meat from chickens fed alpha-tocopherol- and beta-carotene-supplemented diets with different unsaturation grades, Lipids 33 (1998) 705–713, https://doi.org/10.1007/s11745-998-0260-4.
[168] A.P. Spencer, D.S. Carson, M.A. Crouch, Vitamin E and coronary artery disease, Arch. Intern Med 159 (1999) 1313–1320, https://doi.org/10.1001/archinte.159.12.1313.
[169] M. Vardi, N.S. Levy, A.P. Levy, Vitamin E in the prevention of cardiovascular disease: the importance of proper patient selection, J. Lipid Res 54 (2013) 2307–2314, https://doi.org/10.1194/jlr.R026641.
[170] J. Poirier, K.A. Cockell, W.M.N. Ratnayake, K.A. Scoggan, N. Hidiroglou, C. Gagnon, H. Rocheleau, H. Gruber, P. Griffin, R. Madère, K. Trick, S. Kubow, Antioxidant supplements improve profiles of hepatic oxysterols and plasma lipids in butter-fed hamsters, Nutr. Metab. Insights 3 (2010) 1–14, https://doi.org/10.4137/NMI.S3911.
[171] A. Bryl, M. Falkowski, K. Zorena, M. Mrugacz, The role of resveratrol in eye diseases-a review of the literature, Nutrients 14 (2022) 2974, https://doi.org/10.3390/nu14142974.
[172] R.A.H. Stewart, Primary prevention of cardiovascular disease with a mediterranean diet supplemented with extra-virgin olive oil or nuts, N. Engl. J. Med 379 (2018) 1388, https://doi.org/10.1056/NEJMc1809971.
[173] V. Deckert, C. Desrumaux, A. Athias, L. Duverneuil, V. Palleau, P. Gambert, D. Masson, L. Lagrost, Prevention of LDL alpha-tocopherol consumption, cholesterol oxidation, and vascular endothelium dysfunction by polyphenolic compounds from red wine, Atherosclerosis 165 (2002) 41–50, https://doi.org/10.1016/s0021-9150(02)00189-2.
[174] V. Aires, J. Labbé, V. Deckert, J.-P. Pais de Barros, R. Boidot, M. Haumont, G. Maquart, N. Le Guern, D. Masson, E. Prost-Camus, M. Prost, L. Lagrost, Healthy adiposity and extended lifespan in obese mice fed a diet supplemented with a polyphenol-rich plant extract, Sci. Rep. 9 (2019) 9134, https://doi.org/10.1038/s41598-019-45600-6.
[175] J. Kaminski, M. Haumont, E. Prost-Camus, P. Durand, M. Prost, G. Lizard, N. Latruffe, Protection of C2C12 skeletal muscle cells toward oxidation by a polyphenol-rich plant extract, (2023). https://doi.org/10.1530/REM-23-0002.
[176] O.J. Lara-Guzmán, R. Álvarez, K. Muñoz-Durango, Changes in the plasma lipidome of healthy subjects after coffee consumption reveal potential cardiovascular benefits: a randomized controlled trial, Free Radic. Biol. Med. 176 (2021) 345–355, https://doi.org/10.1016/j.freeradbiomed.2021.10.012.
[177] Y.-J. Kwon, S.-N. Jang, K.-H. Liu, D.-H. Jung, Effect of Korean red ginseng on cholesterol metabolites in postmenopausal women with hypercholesterolemia: a pilot randomized controlled trial, Nutrients 12 (2020) 3423, https://doi.org/10.3390/nu12113423.
[178] F. Micheletta, S. Natoli, M. Misuraca, E. Sbarigia, U. Diczfalusy, L. Iuliano, Vitamin E supplementation in patients with carotid atherosclerosis, Arterioscler., Thromb., Vasc. Biol. 24 (2004) 136–140, https://doi.org/10.1161/01.ATV.0000104028.07929.72.
[179] L. Iuliano, F. Micheletta, M. Maranghi, G. Frati, U. Diczfalusy, F. Violi, Bioavailability of vitamin E as function of food intake in healthy subjects, e34–e37, Arterioscler., Thromb., Vasc. Biol. 21 (2001), https://doi.org/10.1161/hq1001.098465.
[180] G. Lizard, M. Poirot, L. Iuliano, European network for oxysterol research (ENOR): 10 th anniversary, J. Steroid Biochem Mol. Biol. 214 (2021) 105996, https://doi.org/10.1016/j.jsbmb.2021.105996.
[181] G. Lizard, M. Poirot, L. Iuliano, European Network for oxysterol research (ENOR): 10th ENOR symposium - Web meeting, Steroids 195 (2023) 109242, https://doi.org/10.1016/j.steroids.2023.109242.
[182] L. Galluzzi, I. Vitale, S.A. Aaronson, J.M. Abrams, D. Adam, P. Agostinis, E. S. Alnemri, L. Altucci, I. Amelio, D.W. Andrews, M. Annicchiarico-Petruzzelli, A. V. Antonov, E. Arama, E.H. Baehrecke, N.A. Barlev, N.G. Bazan, F. Bernassola, M. J.M. Bertrand, K. Bianchi, M.V. Blagosklonny, K. Blomgren, C. Borner, P. Boya, C. Brenner, M. Campanella, E. Candi, D. Carmona-Gutierrez, F. Cecconi, F.K.-M. Chan, N.S. Chandel, E.H. Cheng, J.E. Chipuk, J.A. Cidlowski, A. Ciechanover, G.M. Cohen, M. Conrad, J.R. Cubillos-Ruiz, P.E. Czabotar, V. D'Angiolella, T. M. Dawson, V.L. Dawson, V. De Laurenzi, R. De Maria, K.-M. Debatin, R. J. DeBerardinis, M. Deshmukh, N. Di Daniele, F. Di Virgilio, V.M. Dixit, S. J. Dixon, C.S. Duckett, B.D. Dynlacht, W.S. El-Deiry, J.W. Elrod, G.M. Fimia, S. Fulda, A.J. García-Sáez, A.D. Garg, C. Garrido, E. Gavathiotis, P. Golstein, E. Gottlieb, D.R. Green, L.A. Greene, H. Gronemeyer, A. Gross, G. Hajnoczky, J. M. Hardwick, I.S. Harris, M.O. Hengartner, C. Hetz, H. Ichijo, M. Jäättelä, B. Joseph, P.J. Jost, P.P. Juin, W.J. Kaiser, M. Karin, T. Kaufmann, O. Kepp, A. Kimchi, R.N. Kitsis, D.J. Klionsky, R.A. Knight, S. Kumar, S.W. Lee, J. J. Lemasters, B. Levine, A. Linkermann, S.A. Lipton, R.A. Lockshin, C. López-Otín, S.W. Lowe, T. Luedde, E. Lugli, M. MacFarlane, F. Madeo, M. Malewicz, W. Malorni, G. Manic, J.-C. Marine, S.J. Martin, J.-C. Martinou, J.P. Medema, P. Mehlen, P. Meier, S. Melino, E.A. Miao, J.D. Molkentin, U.M. Moll, C. Muñoz-Pinedo, S. Nagata, G. Nuñez, A. Oberst, M. Oren, M. Overholtzer, M. Pagano, T. Panaretakis, M. Pasparakis, J.M. Penninger, D.M. Pereira, S. Pervaiz, M. E. Peter, M. Piacentini, P. Pinton, J.H.M. Prehn, H. Puthalakath, G.A. Rabinovich, M. Rehm, R. Rizzuto, C.M.P. Rodrigues, D.C. Rubinsztein, T. Rudel, K.M. Ryan, E. Sayan, L. Scorrano, F. Shao, Y. Shi, J. Silke, H.-U. Simon, A. Sistigu, B. R. Stockwell, A. Strasser, G. Szabadkai, S.W.G. Tait, D. Tang, N. Tavernarakis, A. Thorburn, Y. Tsujimoto, B. Turk, T. Vanden Berghe, P. Vandenabeele, M. G. Vander Heiden, A. Villunger, H.W. Virgin, K.H. Vousden, D. Vucic, E. F. Wagner, H. Walczak, D. Wallach, Y. Wang, J.A. Wells, W. Wood, J. Yuan, Z. Zakeri, B. Zhivotovsky, L. Zitvogel, G. Melino, G. Kroemer, Molecular mechanisms of cell death: recommendations of the nomenclature committee on cell death 2018, Cell Death Differ. 25 (2018) 486–541, https://doi.org/10.1038/s41418-017-0012-4.
[183] A. Vejux, D. Abed-Vieillard, K. Hajji, A. Zarrouk, J.J. Mackrill, S. Ghosh, T. Nury, A. Yammine, M. Zaibi, W. Mihoubi, H. Bouchab, B. Nasser, Y. Grosjean, G. Lizard, 7-ketocholesterol and 7β-hydroxycholesterol: In vitro and animal models used to characterize their activities and to identify molecules preventing their toxicity, Biochem Pharm. 173 (2020) 113648, https://doi.org/10.1016/j.bcp.2019.113648.