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Attenuation of 7-ketocholesterol- and 7 β -hydroxycholesterol-induced oxiaoptophagy by nutrients, synthetic molecules and oils: potential for the prevention of age-related diseases

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Abstract: Age-related diseases for which there are no effective treatments include cardiovascular diseases; neurodegenerative diseases such as Alzheimer's disease; eye disorders such as cataract and age-related macular degeneration; and, more recently, Severe Acute Respiratory Syndrome (SARS-CoV-2). These diseases are associated with plasma and/or tissue increases in cholesterol derivatives mainly formed by auto-oxidation: 7-ketocholesterol, also known as 7-oxo-cholesterol, and 7 β -hydroxycholesterol. The formation of these oxysterols can be considered as a consequence of mitochondrial and peroxisomal dysfunction, leading to increased oxidative stress, which is accentuated with age. 7-ketocholesterol and 7 β -hydroxycholesterol cause a specific form of cytotoxic activity defined as oxiaoptophagy, including oxidative stress and induction of death by apoptosis associated with autophagic criteria. Oxiaoptophagy is associated with organelle dysfunction and in particular with mitochondrial and peroxisomal alterations involved in the induction of cell death and in the rupture of redox balance. As the criteria characterizing 7-ketocholesterol- and 7 β -hydroxycholesterol-induced cytotoxicity are often simultaneously observed in major age-related diseases (cardiovascular diseases, age-related macular degeneration, Alzheimer's disease) the involvement of these oxysterols in the pathophysiology of the latter seems increasingly likely. It is therefore important to better understand the signalling pathways associated with the toxicity of 7-ketocholesterol and 7 β -hydroxycholesterol in order to identify pharmacological targets, nutrients and synthetic molecules attenuating or inhibiting the cytotoxic activities of these oxysterols. Numerous natural cytoprotective compounds have been identified: vitamins, fatty acids, polyphenols, terpenes, vegetal pigments, antioxidants, mixtures of compounds (oils, plant extracts) and bacterial enzymes. However, few synthetic molecules are able to prevent 7-ketocholesterol- and/or 7 β -hydroxycholesterol-induced cytotoxicity: dimethyl fumarate, monomethyl fumarate, the tyrosine kinase inhibitor AG126, memantine, simvastatine, Trolox, dimethylsulfoxide, mangafodipir and mitochondrial permeability transition pore (MPTP) inhibitors. The effectiveness of these compounds, several of which are already in use in humans, makes it possible to consider using them for the treatment of certain age-related diseases associated with increased plasma and/or tissue levels of 7-ketocholesterol and/or 7 β -hydroxycholesterol.

Key words: age-related diseases, endoplasmic reticulum, 7-ketocholesterol, 7 β -hydroxycholesterol, lysosome, mitochondria, nutrients, oxysterol, oxiaoptophagy, peroxisome.

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1 Ageing and age-related diseases: potential roles of 7-ketocholesterol and 7 β -hydroxycholesterol

By the 2050s, according to estimates from the National Institute on Aging, the National Institute of Health, and the World Health Organization, the number of people over 65 years of age worldwide will be 1.5 billion out of a global population of 9.7 billion (National Institute on Aging, National Institute of Health, World Health Organization, Global health and aging. NIH publication n°11-7737, October 2011. <https://www.who.int/ageing/publications/global-health.pdf> (accessed 10 march 2021)). To take account of this major demographic change, it is essential to rethink the impact of ageing in terms of health, environment, infrastructure and institution, but also to anticipate the family, societal and economic consequences that this entails. In this context, a global effort is needed to better understand, prevent and treat age-related diseases in a world population where the proportion of people over 65 will be very high in the next few years.

Among the events contributing to ageing are dysfunctions of certain organelles, such as mitochondria and peroxisomes, whose metabolic functions are closely linked ((Terlecky et al., 2006) (Fransen et al., 2013) (Schrader et al., 2015) (Fransen et al., 2017) (Panov and Dikalov, 2020)). These dysfunctions cause an overproduction of reactive oxygen species (ROS) leading to oxidative stress, favouring lipid peroxidation, protein carbonylation and the formation of 8-hydroxyguanine ((Yin and Chen, 2005) (Wilson and Bohr, 2007)). These modifications have important consequences on cellular functions and can progressively lead to the death of the cells concerned. These changes can also promote ageing and mutagenicity, which can lead to cancer.

Depending on the subjects considered, their lifestyle, their environment and their genetic status, the increase in oxidative stress with age could ultimately result in age-related diseases: this hypothesis currently being widely explored and several elements are in its favour. In such a context, it has been shown that certain cholesterol oxidation derivatives mainly formed by cholesterol auto-oxidation (7-ketocholesterol (7KC) and 7 β -hydroxycholesterol (7 β -OHC)) are often associated with age-related diseases: cardiovascular pathologies, eye diseases (cataract, age-related macular degeneration) and dementia of the Alzheimer type ((Corsinovi et al., 2011) (Zarrouk et al., 2014) (Gargiulo et al., 2016) (Mutemberezi et al., 2016) (Samadi et al., 2020)). As cholesterol, these oxysterols belong to the sterol family: they are composed of a sterane nucleus, have a hydroxyl function in position 3, and have 27 carbon atoms. The physicochemical properties of these oxysterols make it possible to distinguish and quantify them in biological

fluids, cells and tissues (**Figure 1**). In these age-related diseases, increased levels of 7KC and 7 β -OHC are often observed in the biological fluids and tissues (arterial wall, retina, brain) of patients ((Girão et al., 1998) (Testa et al., 2018) (Zarrouk et al., 2020) (Anderson et al., 2020) (Brown et al., 2020)). The involvement of these oxysterols is also suspected in the frailty syndrome, which is characterized by cognitive and motor disorders in the most affected subjects ((Xue, 2011) (Yeolekar and Sukumaran, 2014)). More recently, significant plasma increases in the levels of 7KC and 7 β -OHC have been observed in COVID-19, whose severe or even fatal forms of SARS CoV-2 infection are mainly described in subjects over 65 years of age (Marcello et al., 2020). Elevated plasma levels of 7KC as well as of 7 β -OHC could be the consequence of an acute oxidative stress resulting from the immune response in COVID-19 patients. Based on these observations, increases of 7KC and, to a lesser extent, of 7 β -OHC seem to be a common denominator for certain frequent and often incurable age-related illnesses ((Zarrouk et al., 2014) (Testa et al., 2018)). A better understanding of the biological activities of these two oxysterols, by identifying their related signalling pathways, should therefore enable a better deciphering of the pathophysiology of these age-related diseases with a view to identifying natural or synthetic molecules to prevent, attenuate or treat them ((Brahmi et al., 2019) (Vejux et al., 2020)).

2. Biosynthesis and degradation of 7-ketocholesterol and 7 β -hydroxycholesterol

Oxysterols formed by the auto-oxidation of cholesterol can be detected both in the cells of different organs as well as in the blood, in oxidized Low Density Lipoproteins (LDLs) ((Hughes et al., 1994) (Colles et al., 2001) (Brown and Jessup, 2009)). The carbons of the A and B rings of the sterane nucleus are the most sensitive positions to radical attack, among them, carbons numbered 5, 6 and 7 (Anderson et al., 2020). There are two types of auto-oxidation, type I and II.

- Type I auto-oxidation concerns oxidation reactions involving reactive oxygen species (ROS) and reactive nitrogen species (RNS) (superoxide anion ($O_2^{\bullet-}$), hydroxyl radical (HO^{\bullet}), nitric oxide (NO), and peroxyxynitrite $ONOO^-$) which can be generated by cellular metabolism or by their decomposition into hydroxyl radicals by the dismutation of two superoxide anions into hydrogen peroxide ($2O_2^{\bullet-} + 2H^+ \rightarrow O_2 + H_2O_2$) 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 ((Iuliano, 2011) (Macho-González et al., 2020)). Most often, radical attacks by certain ROS or RNS cause the loss of hydrogen on carbon 7 because of the weak bond between the hydrogen and the carbon atoms

at this position. The dissociation energy of this bond is 88 kcal/mol (Zerbinati and Iuliano, 2017). As this local oxidation of C7 is rather stable, it can then easily react with molecular oxygen to form a peroxy radical (ROO•). Subsequently, by reacting with a hydrogen atom supplied by another molecule, the peroxy radical will form a cholesterol hydroperoxide (7 α - or 7 β -OOHC) ((Vejud et al., 2011) (Anderson et al., 2020)). As the hydroperoxide function is very unstable, hydroperoxide cholesterol breaks down into 7 α -OHC, 7 β -OHC or 7KC. These three C7-oxysterols are those formed mainly by auto-oxidation (Brown and Jessup, 2009). 7KC is the major oxysterol in OxLDLs and in tissues, and accounts for about 30% of total sterols (Brown et al., 1996).

- Type II auto-oxidation concerns non-radical attacks by oxygen singlets ($^1\Delta_gO_2$), hypochlorous acid (HOCl) or ozone (O₃) (Iuliano, 2011). The involvement of ozone is interesting given that it is linked to atmospheric pollution. Singlet oxygen can be formed by the reaction of hydrogen peroxide (H₂O₂) with HOCl, both produced during inflammatory reactions in the presence of myeloperoxidase enzyme. Such reaction leads to the formation of C5, C6 or C7 hydroperoxides, 5,6-epoxides (α/β) as well as secosterols as primary compounds in these reactions (Zerbinati and Iuliano, 2017). The 5 α/β -epoxycholesterols can be converted to cholestane-3 β ,5 α ,6 β -triol by the cholesterol epoxide hydrolase (ChEH) enzyme which is a component of the antiestrogen binding site (AEBS) ((Silvente-Poirot and Poirot, 2012) (de Medina et al., 2020)).

Among all the oxysterols formed by auto-oxidation, 7KC is certainly one of the most studied. Although its origin is mainly due to the auto-oxidation of cholesterol, it can also be formed enzymatically from 7 β -OHC. The hydroxysteroid dehydrogenases 11 β -HSD1 (HSD11B1 gene (OMIM:600713)) and 11 β -HSD2 (HSD11B2 gene (OMIM: 614232)) are involved respectively in the conversion of 7KC to 7 β -OHC and 7 β -OHC to 7KC, respectively ((Mitić et al., 2013a) (Mitić et al., 2013b) (Beck et al., 2019a) (Anderson et al., 2020)). However, these enzymes metabolize many other substrates (Griffiths et al., 2019). The conversion of 7KC to 7 β -OHC by 11 β -HSD1 can occur in many tissues and is well established in the arterial wall (Mitić et al., 2013a) but little is known about its tissue distribution and expression (Dammann et al., 2019). In human embryonic kidney cells (HEK-293), hexose-6-phosphate dehydrogenase (H6PDH) directly determines the reaction direction of 11 β -HSD1 (Atanasov et al., 2004). In contrast, the conversion of 7 β -OHC to 7KC by 11 β -HSD2 was not found in mouse aortic rings (Mitić et al., 2013a). Of note, the oxysterol synthase 11 β -HSD2 participates in the production of Smoothened-

activating oxysterols and promotes Hedgehog activation (Raleigh et al., 2018). In patients with cerebrotendinous xanthomatosis or with Smith-Lemli-Opitz syndrome, 7KC can also be formed from 7-dehydrocholesterol (7DHC; a direct precursor in cholesterol synthesis) by the enzyme cholesterol 7- α -hydroxylase (CYP7A1) ((Björkhem et al., 2014) (Mutemberezi et al., 2016) (Vejux et al., 2020)). Under normal physiological conditions, the CYP7A1 enzyme located in hepatocytes forms 7 α -hydroxycholesterol from the cholesterol ((Mast et al., 2005) (Griffiths and Wang, 2020)). The biosynthesis of 7KC and 7 β -OHC is summarized in **Figure 2**.

Overall, 7KC is detected wherever there are large quantities of cholesterol in the body: in the plasma at LDL level or fixed to albumin, but also in the cell membranes of different tissues ((Brown and Jessup, 2009) (Olkkonen and Hynynen, 2009)). Both 7KC and 7 β -OHC can nevertheless react with different molecules (sulfate, fatty acids) via the hydroxyl group localized on C3 in the ring A, which leads to inhibition of their toxicity ((Vejux et al., 2020) (Sanchez et al., 2020)). The enzyme sulfotransferase 2B1b (SULT 2B1b) is involved in the sulfonation of 7KC and probably of 7 β -OHC (Fuda et al., 2007). As for the esterification of 7KC, in ARPE19 retinal epithelial cells, a combined action of cytosolic phospholipase A2 alpha (CPLA2 a) and sterol-O-acyltransferase (SOAT1) has been reported (Lee et al., 2015). In addition, Acyl-coenzyme A transferases (ACATs, also abbreviated as SOATs), which convert cholesterol into cholesteryl esters, can also use certain steroids and oxysterols as substrates: oxysterols are also substrates for SOAT1 and SOAT2 (Rogers et al., 2015). The lecithin cholesterol acyl-transferase (LCAT) also efficiently esterifies oxysterols in the plasma (Brown and Jessup, 2009). 7KC can also be taken up by the enzyme cholesterol 27-hydroxylase (CYP27A1) to form 27-hydroxycholesterol-7KC which significantly reduced the toxicity of 7KC in retinal pigmentary epithelial cells ((Lee et al., 2006) (Brown and Jessup, 2009) (Heo et al., 2011) (Mutemberezi et al., 2016)). Using recombinant enzymes, the formation of 7-keto,25-hydroxycholesterol (7KC25-OHC) from 7KC by cholesterol 25-hydroxylase and further stereospecific oxoreduction to 7 β ,25-dihydroxycholesterol (7 β -OHC25-OHC) by human and mouse 11 β -HSD1 has also been demonstrated and additionally, experiments using human 11 β -HSD2 showed the oxidation of 7 β -OHC25-OHC to 7KC25-OHC (Beck et al., 2019b). Currently, as several studies reported that 7KC and 7 β -OHC accumulate in certain tissues and organs (cells of the arterial wall (Hodis et al., 1991); retina ((Rodriguez et al., 2014) (Zhang et al., 2021)); cortical brain area (Testa et al., 2016)) over time, this supports the hypothesis that these oxysterols are involved in some age-

related diseases. It has also been reported that smoking which increases mortality from all causes and has a crucial role in atherosclerotic cardiovascular diseases (Gallucci et al., 2020) is associated with high 7KC-plasma levels (Seet et al., 2011). It is therefore important to know the biological activities of 7KC and 7 β -OHC, and of their metabolites which are still not well known (Wang and Griffiths, 2018), as well as the related signalling pathways, in order to identify therapeutic targets for the treatment of age-related diseases.

3. Organelle dysfunction and signalling pathways associated with 7-ketocholesterol- and 7 β -hydroxycholesterol-induced oxiaoptophagy

3.1. Effects of 7-ketocholesterol and 7 β -hydroxycholesterol on organelles

It is well established that 7KC and 7 β -OHC modify ion flows at the plasma membrane level, alter plasma membrane properties, stimulate oxidative stress, trigger several signalling pathways that can lead to cell death and stimulate inflammation ((Martinet et al., 2008) (Nury et al., 2020b) (Vejux et al., 2020)). They also directly or indirectly affect organelles and their function. The accumulation of 7KC in lysosomes is well established, and it is likely that 7KC and 7 β -OHC interact with the membranes of mitochondria and peroxisomes, which would modify their activities ((Leoni et al., 2017) (Dias et al., 2019) (Nury et al., 2020a)). Thus, 7KC and 7 β -OHC have been shown to disrupt mitochondrial, peroxisomal and lysosomal functions and to trigger endoplasmic reticulum stress ((Luchetti et al., 2017) (Vejux et al., 2020)).

3.1.1. Mitochondria

Mitochondria are central organelles in cell metabolism. They are the site of the β -oxidation of long chain fatty acids (C14-C20) and are the source of energy production via the biosynthesis of adenosine triphosphate (ATP), involving the oxidative phosphorylation and the Tricarboxylic Acid Cycle (TCA; also named Krebs / Citric Acid Cycle). In order to produce ATP through oxidative phosphorylation, the required electrons come from electron carriers such as NADH and FADH₂ generated by the TCA cycle (Aon et al., 2014). The mitochondria also represent the main source of basal intracellular ROS which are produced during oxidative phosphorylation and it is considered that 1-5% of the dioxygen (O₂) consumed by the respiratory chain is incompletely reduced at the mitochondrial level (Wei et al., 2001) leading, to O₂^{•-} and H₂O₂ formation, which can contribute to induce oxidative process and favor ageing process and/or the development of

age related diseases, mainly neurodegenerative diseases ((Cenini et al., 2019) (Zhang et al., 2018) (Yeung et al., 2021)). In addition, it is now well established that mitochondria play a key role in the equilibrium between life and death, since several of their components are involved in different types of cell death signalling pathways especially during apoptosis and necroptosis (Galluzzi and Kroemer, 2008). Since the origin of 7KC and 7 β -OHC is mainly due to the presence of ROS and formation by autoxidation ((Iuliano, 2011) (Zerbinati and Iuliano, 2017)), it cannot be excluded that mitochondria play an important role in their production, particularly when mitochondrial metabolism is disturbed. Indeed, it has been shown on different cell lines that 7KC and 7 β -OHC induce a loss of $\Delta\Psi_m$ and disturb mitochondrial metabolism (Vejux et al., 2020). In 158N oligodendrocytes, these alterations are characterized by a decrease in mitochondrial activity, which translates into a decrease in $\Delta\Psi_m$ accompanied by a reduction in NAD and ATP; in addition, lactate levels are increased while the levels of pyruvate, citrate, fumarate and succinate, which are TCA cycle intermediates, are decreased (Leoni et al., 2017). In 7KC-treated cells, alterations in mitochondrial activity can lead in first to mitochondrial hyperpolarization (Zahm et al., 2003), considered as an early and reversible event regulated by NO during activation of T lymphocytes (Nagy et al., 2007), and subsequently to mitochondrial depolarization (loss of $\Delta\Psi_m$), which contributes to activation of cell death by apoptosis via Cytochrome c release; activation of a cascade of caspases involving caspase-3, -7, -8 and -9; decreased Bcl-2 level; and PARP cleavage leading to internucleosomal DNA fragmentation associated with the presence of cells with condensed and/or fragmented nuclei ((Han et al., 2007) (Vejux et al., 2020)). 7KC and 7 β -OHC-induced mitochondrial dysfunction can also be associated with ROS overproduction at the mitochondrial level and in whole cells as shown by staining with MitoSOX Red and dihydroethidium, respectively (Sghaier et al., 2019a). According to Fu *et al.*, in mouse model C57BL/6 aortic endothelial cells, 7KC increases the presence of miR144 which decreases the expression of isocitrate dehydrogenase 2 (IDH2) (Fu et al., 2014). In addition, the close metabolic interactions between mitochondria and other organelles (endoplasmic reticulum (ER), peroxisome) can be disrupted in the presence of 7KC and 7 β -OHC, which would amplify the toxic effects of these oxysterols and have pathophysiological consequences ((Lismont et al., 2015) (Keenan et al., 2020) (Vejux et al., 2020)).

3.1.2. Peroxisome

The peroxisome is present in the cytoplasm of all eukaryotic cells except reticulocytes and, in contrast to mitochondria, does not contain DNA. It is delimited by a simple lipid membrane and most often has a spheroidal aspect of 0.1 to 1.5 μm in diameter ((Islinger et al., 2012) (Ribeiro et al., 2012) (Smith and Aitchison, 2013)). The peroxisome was discovered in 1954 by the Swedish doctoral student Johannes Rhodin, who first described it in his PhD Thesis as a 'microbody' when he observed this cytoplasmic structure in mouse kidney cells ((Gabaldón, 2010) (Nordgren et al., 2013) (Vamecq et al., 2014)). It was only in 1956 that the designation of 'peroxisome' was definitively attributed to this organelle following the discovery of its first function by Christian de Duve: the degradation of hydrogen peroxide (H_2O_2) by catalase into 2 molecules of H_2O and one molecule of O_2 (De Duve and Baudhuin, 1966). Subsequently, many biological functions of the peroxisome were identified and it is now well established that the peroxisome, which is functionally and often spatially tightly connected with the mitochondria ((Lismont et al., 2015) (Fransen et al., 2017)), is involved in lipid metabolism (degradation of branched chain fatty acids and very long chain fatty acids, biosynthesis of docosahexaenoic acid (DHA, C22:6 n-3), plasmalogens, cholesterol and bile acids) and in the control of redox homeostasis ((Nordgren et al., 2013) (Faust and Kovacs, 2014) (Wanders, 2014) (Fransen et al., 2020) (He et al., 2021)). The number, size and morphology of the peroxisomes present in the cells are highly variable, depending on the cell type and metabolic status (energy requirements, redox status, inflammation) ((Trompier et al., 2014) (Nury et al., 2020a)). When nerve cells (158N, BV-2 and N2-a) are exposed to 7KC, several effects are observed at the peroxisomal level: decrease in peroxisomal mass revealed by flow cytometry after immunofluorescence staining with an antibody directed against the peroxisomal transporter ABCD3 used as a peroxisomal mass marker; decrease in the expression of mRNAs of the peroxisomal membrane transporters (ABCD1, ABCD2) but also of the peroxisomal enzymes involved in the β -oxidation of very long chain fatty acids (ACOX1, MFP2) ((Debbabi et al., 2016) (Badreddine et al., 2017) (Nury et al., 2018) (Yammine et al., 2020)). In murine microglial BV-2 cells, 7KC also induces a decrease in the expression of PEX14, which is a peroxin involved in peroxisome biogenesis (Fujiki et al., 2020), and of ACOX1, while catalase activity is increased (Nury et al., 2017). In the context of X-linked adrenoleukodystrophy (X-ALD), which is a peroxisomal genetic disease characterized by a mutation of the ABCD1 gene leading to increased levels of very long chain fatty acids (VLCFAs including C24:0 and C26:0) in the plasma and tissues (Kemp et al., 2012), elevated

plasma levels of 7KC as well as other markers of oxidative stress (9/13-hydroxyoctadecadienoic acids (HODEs), malondialdehyde (MDA), 7 β -OHC) have been measured ((Nury et al., 2017) (Deon et al., 2016)); it is assumed that 7KC amplifies the side effects of X-ALD at the peroxisomal level but also on other organelles ((Nury et al., 2017) (Nury et al., 2018)). The effects of 7KC and 7 β -OHC on the peroxisome also decrease peroxisomal β -oxidation resulting in an accumulation of VLCFAs which are also known to be cytotoxic on several cell types ((Zarrouk et al., 2012) (Nury et al., 2018) (Doria et al., 2019) (Sghaier et al., 2019a)).

3.1.3. Lysosome

Lysosome is a small intracytoplasmic organelle about 0.1 to 1.2 μm in diameter, delimited by a simple lipid membrane; the number of lysosomes in the cell is variable (Hamer et al., 2012). Proton pumps are present at the lysosomal membrane, actively accumulate protons (H^+) and maintain an intraluminal pH of between 3.5 and 5. In addition, the lysosome contains several proteolytic and hydrolytic enzymes (proteases, lipases, glucosidases, nucleases) that are active at acidic pH, enabling it to play a role in the degradation and recycling of extra- and intra-cellular components (Trivedi et al., 2020). The lysosome is involved in the digestion of a wide variety of exogenous components (heterophagy: including endocytosis and phagocytosis) but also of endogenous materials (autophagy, corresponding to the controlled degradation of endogenous cell structures) (Inpanathan and Botelho, 2019). Thus, during the autophagic process, lysosomes fuse with autophagosomes to form autolysosomes (also called autophagolysosomes) capable of recycling dysfunctional organelles (mitochondria, peroxisome, endoplasmic reticulum) in the case of macroautophagy, cytosolic components in the case of microautophagy, and misfolded proteins in the case of chaperone mediated autophagy (Klionsky et al., 2021). Lysosomes are physiologically involved in the normal process of renewal of organelles via autophagy and are consequently involved in ageing control ((Barja, 2019) (Warraich et al., 2020)). Currently, it is well established that 7KC induces lysosomal toxicity via different pathways ((Yuan et al., 2000) (Anderson et al., 2020)) and induces lysosomal damage in numerous cell types from different species (Vejuj et al., 2020). 7KC can induce an increase in lysosome membrane permeability due to an increase in non-esterified cholesterol and induce a decrease in lysosomal pH ((Li et al., 2011) (Sudo et al., 2015)). In addition, 7KC-induced lysosomal membrane changes can prevent its fusion with endosomes and/or autophagic vesicles. 7KC can also modify lysosomal enzyme activities. Thus, in vascular smooth muscle cells, 7KC reduces the expression and proteolytic

activity of cathepsins B and D (Sudo et al., 2015). In the presence of 7KC, even if the lysosomes are able to fuse with the autophagosomes, the degradative activity of autolysosomes can be reduced. This results in dysfunctional proteins and/or organelles remaining in the cytoplasm and disrupting the normal metabolism of the cell. Thus, mitochondria overproducing ROS, which are eliminated by autophagy under normal conditions, would no longer be eliminated in the presence of 7KC ((Butler and Bahr, 2006) (Li et al., 2012) (Luchetti et al., 2015)).

3.1.4. Endoplasmic reticulum

The endoplasmic reticulum (ER) is a cellular organelle linked to the nuclear membrane. It consists of the smooth ER and the rough ER which is associated with the ribosomes. In eukaryotic cells, the smooth ER is involved in drug detoxification and lipid synthesis (phospholipids, steroids, sterols and especially cholesterol), while the rough ER is involved in protein synthesis; both the rough and smooth ER are involved in Ca^{2+} storage (Ricciardi and Gnudi, 2020). Various genetic and environmental factors such as ischemia, hypoxia, oxidative stress, ageing and genetic factors can contribute to induce ER stress, and the response to this stress is called the "unfolded protein response" (UPR). The function of UPR is to increase the capacity to eliminate abnormal proteins. During prolonged or overly intense ER stress, this UPR response can lead to cell death by apoptosis via the C/EBP-Homologous Protein (CHOP). Deregulation of the UPR response is implicated in several diseases such as diabetes and inflammatory diseases, as well as age-related pathologies including cardiovascular and neurodegenerative disorders (Navas-Madroñal et al., 2019). 7KC and 7 β -OHC are among the inducers of the ER stress and the effects of 7KC are rather well known. In MC3T3-E1 osteoblastic cells, it has been shown that 7KC induced an ER stress characterized by an increase in the levels of CHOP and 78-kDa glucose-regulated protein (GRP78) transcripts markers (Sato et al., 2017). CHOP is a transcription factor involved in the regulation of pro- and anti-apoptotic genes and GRP78 is an ER light chaperone protein involved in protein folding. In 7KC-treated ARPE-19 human retinal cells, the ER stress response seems to be mediated by kinases activated through the TLR4 receptor; the ER stress markers (CHOP and GRP78 proteins) are increased and the NF κ B pathway appears to be involved (Huang et al., 2014). Furthermore, in human aortic smooth muscle cells, 7KC-induced apoptosis is associated with an early activation of ER stress, as assessed by the expression of the cell death effector CHOP and of the GRP78 chaperone via

the activation of endoribonuclease inositol-requiring enzyme 1 (IRE-1): all hallmarks of the UPR (Pedruzzi et al., 2004). In vascular smooth muscle cells, 7KC induces an increase of the following ER stress markers: activating transcription factors 4 and 6 (ATF4, ATF6), CHOP, heat shock protein family A (Hsp70) member 5 (HSPA5), IRE-1, Suppressor/Enhancer of Lin-12-like (SEL1L) and cysteine-rich with epidermal growth factor (EGF)-like domains 2 (CREDL2) (Navas-Madroñal et al., 2019). In J774A1 murine macrophages, 7 β -OHC activates ER stress involving CHOP and IRE-1 α and the latter helps to activate the signalling pathway TNF Receptor-associated Factor 2 (TRAF2)-apoptosis signal-regulating kinase 1 (ASK1)-c-Jun N-terminal kinase1/2 (JNK1/2) involved in the activation of apoptosis (Park et al., 2016). In addition, in U937 monocytic cells and ARPE-19 cells, 7KC and 7 β -OHC also induce the cytoplasmic formation of multilamellar structures, called myelin figures, which are now considered a sign of reticulophagy (autophagy of the ER) ((Vejud and Lizard, 2009) (Vejud et al., 2020)).

In addition to its detoxification and synthetic functions, the ER also plays a key role in the uptake and release of Ca²⁺, a key second messenger. Cytosolic Ca²⁺ is a fundamental regulator of cell physiology, with cell-death displaying a U-shaped dependency on the concentration of this ion (Plattner and Verkhratsky, 2016). Oxysterols modulate Ca²⁺ signalling by a variety of mechanisms, some of which are dependent on the ER (Mackrill, 2011). For example, in U937 human monocytes, 7 β -OHC decreased the amplitude of signals elicited by thapsigargin, an inhibitor of the SR/ER Ca²⁺-ATPase pumps (Lordan et al., 2009). This suggests that 7 β -OHC reduces the quantity of Ca²⁺ stored in the ER. In A7r5 rat smooth muscle cells, both 7 β -OHC and 7KC reduce Ca²⁺ signals elicited by hormones acting on G-protein coupled receptors, such as bradykinin or arginine vasopressin. These decreases are potentially due to reductions in ER Ca²⁺ storage and also in the levels of inositol 1,4,5-trisphosphate receptor proteins, responsible for release of Ca²⁺ from this organelle (Hammoud et al., 2013). However, in 158N oligodendrocytes, both 7KC and 7 β -OHC are cytotoxic, but neither exerts significant changes in cytoplasmic Ca²⁺ concentration (Ragot et al., 2013); similarly in human neuronal SK-N-BE cells, no changes in Ca²⁺ were observed by fluorescent video-microscopy, whereas microscopic observation of Von Kossa stained cells revealed intracellular deposits of Ca²⁺ in 7KC- and 7 β -OHC treated cells (Zarrouk et al., 2015).

3.2. 7-ketocholesterol- and 7 β -hydroxycholesterol-induced oxiaoptophagy: characteristics and associated signalling pathways

Understanding of the signalling pathways involved in oxiaoptophagy, the notion of which was introduced in 2003 ((Monier et al., 2003) (Nury et al., 2020b)), has evolved considerably. This type of death induced by certain oxysterols is associated with a) oxidative stress characterized by ROS overproduction; up and down regulation of the activity and/or expression of several antioxidant enzymes (catalase, superoxide dismutase (SOD), glutathione peroxidase (GPx)); lipid peroxidation (formation of conjugated dienes (CDs) and malondialdehyde (MDA)); and protein carbonylation (formation of carbonylated proteins (CPs)); b) organelle dysfunction (mitochondria, ER, lysosome, peroxisome); c) induction of apoptosis leading to internucleosomal DNA fragmentation associated with activation of the mitochondrial pathway; and d) autophagic criteria including activation of LC3-I into LC3-II. At the moment, the notion of oxiaoptophagy (OXIdative stress + APOPTOsis + autoPHAGY) is not limited to 7KC but also concerns other cytotoxic oxysterols such as 7 β -OHC and 24(S)-hydroxycholesterol (Nury et al., 2015). Schematic representations of 7KC- and 7 β -OHC-induced oxiaoptophagy are summarized in **Figure 3** and **Figure 4**, respectively. In the human mammary gland / breast cancer cell line (MDA-MB-231), 7KC-induced apoptosis affects the smoothed (SMO) and Sonic Hedgehog (SHh) expression supporting that the Hedgehog signalling pathway might be also involved in the cell death process promoted by this oxysterol (Levy et al., 2019). In addition, it is important to note that 7KC and 7 β -OHC trigger inflammation: they favour cytokine secretion and also enhance expression of adhesion molecules (Vejux et al., 2020). A better understanding of the contribution of 7KC and 7 β -OHC in the inflammation associated with age-related chronic diseases should lead to new therapeutic perspectives (Anand, 2020).

Currently, 7KC-induced oxiaoptophagy has been demonstrated in U937 human monocytes U937, 158N murine oligodendrocytes, BV-2 murine microglial cells, N2a murine neuronal cells and bone marrow mesenchymal stem cells from patients with acute myeloid leukemia ((Monier et al., 2003) (Nury et al., 2014) (Nury et al., 2017) (Paz et al., 2019) (Yamine et al., 2020)). 7KC accumulates in lipid rafts, alters membrane fluidity and favours externalization of phosphatidylserine ((Ragot et al., 2011) (Lemaire-Ewing et al., 2012)). It can thus disrupt membrane signals such as Ca²⁺, Na⁺ and K⁺ fluxes involved in cell death and modifies the activities of several ionic transporters including P2X7, Na⁺-K⁺-ATPase and Kv3.1 ((Duran et al.,

2010) (Mackrill, 2011) (Olivier et al., 2016) (Bezine et al., 2018b) (Bezine et al., 2018a)). 7KC inhibits the PI3-K/PKB/Akt pathway, leading to GSK3 β activation which contributes to the drop in $\Delta\Psi_m$ via Mcl-1 and induces apoptosis in several cell types ((Rusiñol et al., 2004) (Vejux and Lizard, 2009) (Jang and Lee, 2011) (Ragot et al., 2011) (Ragot et al., 2013) (Chang et al., 2016)). On the other hand, 7KC induces an increase in oxidative stress associated with ROS overproduction which favours mitochondrial, peroxisomal and lysosomal dysfunction in 158N, BV-2 and N2a nerve cells ((Vejux et al., 2020) (Yammine et al., 2020)). In human aortic smooth muscle cells, the overproduction of ROS involves NADPH-oxidase (Nox4) and triggers ER stress (Pedruzzi et al., 2004) and autophagy induction involves Nox4 and Atg4B (He et al., 2013). On human neutrophil, 7KC-induced ROS overproduction involves the cellular membrane translocation of the NADPH oxidase cytosolic components, p47phox and p67phox (Alba et al., 2016). The involvement of NADPH oxidase in the overproduction of ROS by 7KC and 7 β -OHC was initially suggested by Rosenblat and Aviram using Apolipoprotein E deficient mice (Rosenblat and Aviram, 2002). On murine MIN6 pancreatic cells, 7KC-induced cell death was associated with a rupture of redox homeostasis, mitochondrial and lysosomal dysfunctions (Boumhras et al., 2014). An increase in inflammation including cytokine secretion (IL-1 β , IL-8) and over-expression of adhesion molecules (ICAM-1, VCAM-1, E-selectin) can also be observed via activation of the TLR4 membrane receptor ((Huang et al., 2014) (Vejux et al., 2020)). The induction of IL-1 β production could induce the NLRP3 inflammasome ((Li et al., 2014) (Koka et al., 2017)).

Unlike 7KC, 7 β -OHC does not accumulate in lipid rafts (Ragot et al., 2013). At present, in the case of 7 β -OHC, oxiaoptophagy has only been demonstrated in 158N cells (Nury et al., 2015). 7 β -OHC favours an intracellular accumulation of Ca²⁺, and inhibits the PI3-K/PKB/Akt signalling pathway; this oxysterol is also a potent inducer of oxidative stress (ROS overproduction; dysregulation of the activity of anti-oxidant enzymes (i.e. catalase, SOD and GPx); enhanced levels of CDs, MDA and CPs) ((Li et al., 2012) (Zarrouk et al., 2015) (Nury et al., 2020b)). In addition, it induces dysfunction in several organelles, including morphological, topographical and functional changes of mitochondria, peroxisomes, and lysosomes ((Sghaier et al., 2019a) (Sghaier et al., 2019b) (Nury et al., 2020a)). The loss of $\Delta\Psi_m$ resulting from mitochondrial dysfunction contributes to activation of apoptosis ((Sghaier et al., 2019a) (Sghaier et al., 2019b)). Moreover, 7 β -OHC-induced cell death is associated with autophagic criteria:

presence of large cytoplasmic vacuoles revealed by staining with monodansylcadaverine and activation of LC3-I into LC3-II ((Sghaier et al., 2019a) (Sghaier et al., 2019b)). As 7 β -OHC and 7KC are two potent inducers of oxiaoptophagy some signalling pathways are therefore similar. However, as 7 β -OHC is a stronger inducer of apoptosis than 7KC, this suggests some differences between these two oxysterols. It should be noted that activation of the PKC/P38/MEK/ERK signalling pathway is a link between apoptosis and inflammation induced by 7 β -OHC (Prunet et al., 2006). In human macrophages, 7 β -OHC regulates IL-8 expression independently of TLR 1, 2, 4, or 6 signalling (Erridge et al., 2007).

4. Inhibition of 7-ketocholesterol- and 7 β -hydroxycholesterol-induced cytotoxicity with nutrients and synthetic molecules

High oxysterol levels, of 7KC but also of 7 β -OHC, have been detected in frequent age-related diseases including cardiovascular diseases, certain neurodegenerative diseases (Alzheimer's disease) and eye diseases (cataract, age-related macular degeneration) as well as in certain rare diseases (X-ALD, Niemann Pick's disease, Smith-Lemli-Opitz syndrome) or chronic inflammatory bowel diseases ((Anderson et al., 2020) (Brown et al., 2020) (Vejux et al., 2020) (Alhouayek et al., 2021)). A better understanding of the signalling pathways associated with 7KC- and 7 β -OHC-induced cytotoxicity (oxidative stress, cell death induction), including oxiaoptophagy, makes it possible to envisage the search for natural or synthetic molecules, as well as mixtures of molecules, to prevent, attenuate and/or cure diseases in which 7KC and 7 β -OHC are potentially involved. Currently, different types of molecules opposing the oxiaoptophagy induced by 7KC and 7 β -OHC have been identified ((Cilla et al., 2017) (Brahmi et al., 2019)). These molecules include vitamins, fatty acids, phospholipids, terpenes, phenols, plant pigments, antioxidants, oils and plant extracts and synthetic molecules (dimethyl fumarate (DMF) and its major metabolite, monomethylfumarate (MMF)) as well as memantine and simvastatine ((Vejux et al., 2020) (Neekhara et al., 2020)).

4.1. Cytoprotective molecules against 7KC

The compounds able to counteract 7KC-induced cell death are listed in **Table 1** indicating the concentrations as well as the cell lines used.

4.1.1. Natural compounds preventing 7KC-induced cytotoxicity

α -tocopherol is a component of Vitamin E which is constituted of 4 tocopherols and 4 tocotrienols; α -tocopherol is one of the most efficient cytoprotective molecules (Rimbach et al., 2002). α -tocopherol has cytoprotective effect on several cell types of different species (human monocytic U937 cells; rat smooth muscle A7r5 cells; murine oligodendrocytic 158N cells; murine microglial BV-2 cells and murine neuronal N2-a cells) ((Lizard et al., 2000) (Miguet-Alfonsi et al., 2002) (Royer et al., 2009) (Vejux and Lizard, 2009) (Debbabi et al., 2016) (Debbabi et al., 2017) (Yammine et al., 2020)) suggesting a highly conserved cytoprotective mechanism. α -tocopherol opposes the accumulation of 7KC, but not of 7 β -OHC, in lipid rafts and prevents organelle dysfunction (mitochondria, peroxisome and lysosome) with consequent inhibition of ROS overproduction, inhibition of apoptosis and normalization of autophagy ((Brahmi et al., 2019) (Vejux et al., 2020)).

Cytoprotective molecules also include many other nutrients that are abundant in the Mediterranean diet such as ω 3, ω 6 and ω 9 fatty acids (α -linoleic acid (C18:2 n-6); eicosapentaenoic acid (C20:5 n-3); docosahexaenoic acid (DHA; C22:6 n-3); oleic acid (C18:1 n-9); and sterculic acid (a C19 cyclopropene fatty acid)). These fatty acids are efficient in protecting murine and human nerve cells (158N, BV-2, N2-a, and SK-N-BE), as well as human retinal epithelial ARPE-19 cells, against 7KC- and 7 β -OHC-induced cytotoxicity ((Huang et al., 2012) (Biasi et al., 2014) (Badreddine et al., 2017) (Brahmi et al., 2019) (Yammine et al., 2020)). In 158N cells, DHA enhances α -tocopherol protective effects (Nury et al., 2015). The vegetal pigment, indicaxanthine isolated from cactus pear (*Opuntia ficus-indica* L. Mill) fruit pulp (yellow cultivar) also prevents 7KC-induced apoptosis in human monocytic THP-1 cells (Tesoriere et al., 2013) and prevents eryptosis of human erythrocytes induced by a mixture of oxysterols consisting of 7KC, 7 α -hydroxycholesterol, 7 β -OH, cholestan-3 β ,5 α ,6 β -triol, 5 α ,6 α -epoxycholesterol and 5 β ,6 β -epoxy-cholesterol (Tesoriere et al., 2015).

Several phenolic compounds, including polyphenols, most of which are present in significant level in the Mediterranean diet, have shown cytoprotective activities with respect to 7KC. These include epicatechin, epigallocatechin gallate (EGCG), apigenin, quercetin, dihydroquercetin (taxifolin), tyrosol, hydroxytyrosol and ferrulic acid active in ARPE-19 retinal epithelial cells ((Dugas et al., 2010) (Kohno et al., 2020)), nerve cells (N2a, 158N, SH-SY-5Y, SK-N-BE) (Yammine et al., 2020), monocyte macrophages J774A.1 (Leonarduzzi et al., 2006), human M1 and M2 macrophages (Buttari et al., 2014), ISO-HAS human angiosarcoma (Yamagata et al.,

2013), Caco-2 human colorectal adenocarcinoma ((Deiana et al., 2010) (Atzeri et al., 2016)) and PC12 rat pheochromocytoma (Kim et al., 2017). Theobromine, which is present in dark chocolate, as well as cocoa bean shell extracts with different polyphenol contents, also prevents oxysterol-induced cell damage in Caco-2 cells ((Rossin et al., 2019) (Iaia et al., 2020)).

The phospholipid bis(monoacylglycero)phosphate (BMP) is a structural isomer of phosphatidylglycerol that exhibits an unusual sn1:sn1' stereoconfiguration based on the position of the phosphate moiety of its two glycerol units (Hullin-Matsuda et al., 2009). BMP prevents the formation of 7KC in murine macrophagic RAW264.7 cells (Arnal-Levron et al., 2019). It has recently been suggested that BMP could be useful in the prevention of COVID-19 infection associated with respiratory complications that can lead to death, especially in people over 65 years of age (Luquain-Costaz et al., 2020). A terpene (lycopene) has also been reported to prevent 7KC-induced cell death in THP-1 cells ((Palozza et al., 2010) (Palozza et al., 2011)). The ability of 7KC to trigger a rupture of redox homeostasis associated with ROS overproduction has led to the evaluation of the capacity of certain antioxidants for protection against these effects. Reduced glutathione (GSH) was shown to be effective in U937 cells (Lizard et al., 1998), N-acetyl cysteine (NAC) in U937 cells and MC3T3-E1 murine pre-osteoblasts ((Lizard et al., 2000) (Sato et al., 2017)) and ergothioneine on human cerebral endothelial microvascular hCMEC/D3 cells (Koh et al., 2020).

Furthermore, among dietary components that also have cytoprotective activities against 7KC, we can include oils used in the traditional Mediterranean cuisine (olive oil, argan oil and milk thistle seed oil). Such oils are rich in oleic acid, tocopherols and also contains polyphenols (Zarrouk et al., 2019a); Xuezhikang (red yeast rice extract) (Shen et al., 2017); methanolic extracts of *Clinacanthus nutans* (Kuo et al., 2020) and ethanolic mint leaf extracts (Brahmi et al., 2018) also have cytoprotective properties. It has also been reported that wine extracts from Sardinian grape varieties attenuate membrane oxidative damage in Caco-2 cells (Deiana et al., 2012), that red wine polyphenolic compounds prevent LDL oxidation (Deckert et al., 2002) and that red and white wines inhibit cholesterol oxidation (Tian et al., 2011).

4.1.2. Synthetic compounds preventing 7KC-induced cytotoxicity

Currently, in 158N cells, only five synthetic molecules have been shown to be effective in preventing 7KC toxicity. These are dimethyl fumarate (DMF) used in the treatment of multiple sclerosis in its relapsing-remitting form, which is believed to act by activating the Nrf2 pathway,

and its major metabolite, monomethylfumarate (MMF), (Zarrouk et al., 2017) as well as AG126, a tyrosine kinase inhibitor (Kim and Lee, 2010). In ARPE-19 cells, memantine (a non-competitive inhibitor of N-methyl-D-aspartate (NMDA) receptor used in the treatment of Alzheimer's disease) as well as simvastatine (an inhibitor of the enzyme hydroxymethylglutaryl-CoA reductase (HMG-CoA) used in the treatment of hypercholesterolemia) strongly attenuate 7KC-induced apoptosis as shown by an important decrease of caspase 3/7 activity (Neekhra et al., 2020).

However, some molecules may exhibit a cytoprotective effects in some cells but are ineffective in others. These are γ -tocopherol and α -tocotrienol, Vitamin C, and Biotin (also named Vitamin H, B7 or B8) evaluated either in human U937 monocytic cells (Lizard et al., 2000), rat A7r5 aortic smooth muscle cells (Royer et al., 2009) or murine 158N oligodendrocytes (Ragot et al., 2013). This is also the case of resveratrol evaluated in ARPE-19 retinal epithelial cells and 158N cells ((Dugas et al., 2010) (Ragot et al., 2011)). As for Nigella seed oil, it has no cytoprotective effect against 7KC on 158N cells (Meddeb et al., 2018) but protects C2C12 murine myoblasts from cell death induced by this oxysterol. On the other hand, some molecules are also currently considered totally ineffective in preventing 7KC toxicity regardless of the type of cells considered. In BV-2 murine microglial cells, no cytoprotective effect of elaidic acid (the trans-isomer of oleic acid) was observed (Debbabi et al., 2017). Similarly, phenolic compounds (ellagic acid, ferrulic acid), used at supraphysiological concentrations (50 μ M), did not show cytoprotection in 158N cells. Similarly, Trolox (6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid, a water-soluble analog of vitamin E), evaluated in BV-2 cells (Debbabi et al., 2016), and melatonin, evaluated in U937 cells (Lizard et al., 2000) as well as fingolimod (2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol; glatiramer acetate; FTY720; used at 30 and 500 nM) evaluated in 158N and N2a cells failed to show any cytoprotective effect.

As 7KC accumulates in the lysosome, a strategy based on the use of bacterial enzymes targeting this organelle has been described to inactivate this oxysterol ((Mathieu et al., 2008) (Mathieu et al., 2009) (Mathieu et al., 2010) (Mathieu et al., 2012) (Ghosh and Khare, 2016) (Ghosh and Khare, 2017) (Perveen et al., 2018)). The use of bacterial enzymes to reduce the cellular accumulation of 7KC has emerged as a concept for medical bioremediation ((Rittmann and Schloendorn, 2007) (Schloendorn et al., 2009)).

One can also imagine promoting the development of an appropriate intestinal microbiota in order to 1) degrade the dietary 7KC before it is absorbed in the intestine and then transported by the plasma chylomicrons in the entero-hepatic circuit and/or 2) promote the *in situ* production of molecules from the microbiota which could inhibit the oxysterol synthesis and/or activity of intestinal oxysterol transporters such as ABCA1 and ABCG1.

4.2. Cytoprotective molecules against 7 β -OHC

Compounds that prevent 7 β -OHC-induced cell death are shown in **Table 2** indicating the concentrations as well as the cell lines used.

4.2.1. Natural compounds preventing 7 β -OHC-induced cytotoxicity

Several molecules or mixtures of molecules active against 7KC are also cytoprotective against 7 β -OHC. This is the case for α -tocopherol (but not γ -tocopherol) ((Lyons et al., 2001) (O'Sullivan et al., 2003) (Ragot et al., 2013)), DHA ((Zarrouk et al., 2015) (Nury et al., 2015)), resveratrol (Dugas et al., 2010), EGCG (Mascia et al., 2010) as well as red wine extracts (Naito et al., 2004). Similarly, as it has been shown on 7KC, the combination (α -tocopherol + DHA) has a greater cytoprotective effect on 7 β -OHC than α -tocopherol and DHA used alone (Nury et al., 2015). Molecules, such as α -tocopherol and DHA, also prevent the toxicity induced by 24(S)-hydroxycholesterol (24(S)-OHC), and so are of great interest in preventing diseases where concomitant increases in 7KC, 7 β -OHC and 24(S)-OHC are observed, as is the case in certain neurodegenerative diseases such as X-ALD and at an early stage of Alzheimer's disease ((Testa et al., 2016) (Nury et al., 2017) (Zarrouk et al., 2020)). These nutrients (α -tocopherol, DHA) are also of interest for the prevention of cardiovascular diseases where simultaneous increases of 7KC and 7 β -OHC are observed in plasma and in atheromatous plaques (Testa et al., 2018). As α -tocopherol and DHA are compounds found in significant amounts in the Mediterranean diet and have important dietary roles (Román et al., 2019), this reinforces the interest of adequate nutrition to prevent common age-related diseases including cardiovascular and neurodegenerative diseases. On the other hand, some molecules are active against 7 β -OHC but not against 7KC. This is the case for biotin (Sghaier et al., 2019b). Finally, other molecules, including those extracted from plants or marine sources, are cytoprotective in different cell types (monocytes, endothelial cells, nerve cells), but their effects against 7KC toxicity have not been evaluated to date. These are plant extracts such as *Carpobrotus edulis* ethanol-water extract (Zarrouk et al.,

2019b) and anthocyanin-rich Aronox extract from *Aronia melanocarpa* E (Zapolska-Downar et al., 2008), sea urchin egg oil (Zarrouk et al., 2018), and mitochondrial permeability transition pore (MPTP) inhibitors (bongerik acid, cyclosporin A) (Ryan et al., 2005). However, no cytoprotective effects against 7 β -OHC-induced cell death have been found with certain phenolic compounds (ellagic acid, apigenin) ((Lordan et al., 2008) (Ragot et al., 2013)), and terpenoids (lycopene, astaxanthin) (Lordan et al., 2008).

4.2.2. Synthetic compounds preventing 7 β -OHC-induced cytotoxicity

DMF and its major metabolite MMF strongly attenuate 7 β -OHC-induced cytotoxicity in 158N cells (Sghaier et al., 2019a). Some molecules are also active against 7 β -OHC but not against 7KC. This is the case for Trolox (3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-carboxylic acid: a hydrophilic analogue of Vitamin E) (Ryan et al., 2004). Other molecules, are cytoprotective in different cell types (monocytes, endothelial cells, nerve cells), but their effects against 7KC toxicity have not been evaluated to date. These are dimethylsulfoxide (DMSO), which prevents 7 β -OHC-induced apoptosis in U937 cells by preserving lysosomes and mitochondria (Laskar et al., 2010b), and mangafodipir (a contrast agent used in magnetic resonance imaging of the liver) (Laskar et al., 2010a), as well as mitochondrial permeability transition pore (MPTP) inhibitors (ADP analogues; but not carboxyatractyloside) (Ryan et al., 2005). No cytoprotective effects against 7 β -OHC-induced cell death have been found with Ebselen, an organo-selenium drug molecule known for its anti-oxidant properties (Ryan et al., 2004).

5. Conclusion and perspectives

The list of natural molecules (fatty acids, polyphenols, tocopherols, vitamins) and synthetic molecules, as well as vegetable and animal oils, plant extracts and exogenous enzymes that prevent 7KC- and 7 β -OHC-induced cytotoxicity (cell death, oxidative stress) makes it worth developing either functional foods or drugs that will be effective in attenuating and/or curing age-related diseases in which the levels of these oxysterols are increased. It is interesting to note that several of these natural cytoprotective molecules are abundant in the Mediterranean diet ((Román et al., 2019) (Shannon et al., 2021)) as well as in the Okinawan diet (Willcox et al., 2014). It is expected that several technological developments, including genome mining and engineering strategies, will contribute to open new opportunities in order identifying new cytoprotective

molecules (Atanasov et al., 2021). In addition to the *in vitro* models used (primary cultures, cell lines, mixed cultures, organoids), appropriate *in vivo* models should take into account the bioavailability and metabolism of the administered products, and the incidence of the microbiota if the cytoprotective compounds are administered orally (food supplements, functional foods) (Tarasiuk and Fichna, 2019). The galenic aspect will also have to be worked on by considering the design of micro- and nano-encapsulation and functionalized nanoparticles which could possibly lead to a targeted therapy ((Ghosh et al., 2018) (Sallem et al., 2019) (Singh et al., 2020)). Finally, mixtures of molecules could also be produced to seek synergistic effects and increase cytoprotection.

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Author contributions: All authors have participated in the manuscript preparation and several of them have contributed to studies cited in references allowing a better characterization of the toxicity of 7KC and 7 β -OHC. This review is a follow-up to the review published in Ageing Research Review by Zarrouk A *et al.* in 2014 (Zarrouk et al., 2014). Yammine A, Ghzaïel I and Sassi K are currently PhD students in the laboratory Bio-peroxIL (Dijon, France) and are working on oxysterols cytotoxicity. Nury T defended his PhD Thesis on oxiaoptophagy in December 2020. Zarrouk A obtained her PhD Thesis in the laboratory Bio-peroxIL in 2013 and did post-doctoral stays in the laboratories of Dr Mackrill JJ (University College of Cork, Cork, Ireland) and Dr Pais de Barros JP (Inserm / Université de Bourgogne, Dijon, France) in the field of oxysterols and age-related diseases. Dr Brahmi F did several post-doctoral stays in the laboratory Bio-peroxIL to study the impact of natural compounds on oxysterol-induced cytotoxicity. Dr Samadi M, Mrs Rup-Jacques S (MS) and Dr Vervandier-Fasseur D are chemists; they provided oxysterols and polyphenols. Bergas V (MS) is analytical biochemist specialized in the analysis of lipids. Dr Ghosh S contributes to lot of studies on bioremediation to prevent 7KC-induced cell death. Dr Majeed M, Dr Pande A and Prof. Atanasov A provided lot of natural compounds. Prof. Hammami S, Prof. Hammami M, Prof. Nasser B, Dr Andreoletti P, Prof. Cherkaoui-Malki M, Dr Zarrouk A and Dr Vejux A have contributed to the supervision of several students working either on oxysterols, the effects of natural substances and/or their impact on organelles. Dr Lizard G initiated oxysterols research at the University of Burgundy (Dijon, France) in 1994; he heads the

Bio-peroxIL laboratory. Fourteen PhD theses have been carried out under his direction on this theme and three are currently in progress. The manuscript has been written by Dr Lizard G with the active contribution of all co-authors. The correction of English was done by Dr Mackrill JJ.

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Figures legends

Figure 1: Physico-chemical characteristics of 7-ketocholesterol and 7 β -hydroxycholesterol versus cholesterol. Values of m/z top peaks (cholesterol and 7KC) are from NIST/EPA/NIH Mass Spectral Library, Version 2.2 (2014). The value of m/z top peak (7 β -OHC) is from Dr J.P. Pais de Barros laboratory; the m/z values (cholesterol and 7KC) obtained in Dr J.P. Pais de Barros laboratory are the same than NIST values.

Figure 2: 7-ketocholesterol and 7 β -hydroxycholesterol synthesis pathways. 7-ketocholesterol (7KC) and 7 β -hydroxycholesterol (7 β -OHC) are mainly formed by the auto-oxidation of cholesterol (ROS / RNS; Fenton reaction: $\text{H}_2\text{O}_2 + \text{Me}^{n+} \rightarrow \text{HO}\cdot + \text{OH}^- + \text{Me}^{(n+1)+}$, where Me is a transition metal such as copper, iron, or aluminum; the Haber-Weiss reaction ($\text{O}_2^{\bullet-} + \text{H}_2\text{O}_2 \rightarrow \text{OH}\cdot + \text{OH}^- + \text{O}_2$) which can be written in two sequential sub-reactions: (1) $\text{O}_2^{\bullet-} + \text{Fe}^{3+} \rightarrow \text{O}_2 + \text{Fe}^{2+}$, and (2) $\text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \text{HO}\cdot + \text{OH}^-$; the second reaction is commonly referred to as the Fenton reaction). Under certain conditions, these two oxysterols can be formed enzymatically: interconversion of 7KC to 7 β -OHC by the enzyme 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD1; OMIM 600713); interconversion of 7 β -OHC to 7KC by the enzyme 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2; OMIM 614232). In Smith-Lemli-Opitz syndrome or in patients with cerebrotendinous xanthomatosis, the enzyme cholesterol 7 α -hydroxylase, CYP7A1 (OMIM 118455), is an oxidoreductase which also contributes to the

formation of 7KC from 7-dehydrocholesterol. CYP7A1 also permits the formation of 7 α -hydroxycholesterol from cholesterol (Mast et al., 2005). In food, by heating, cholesterol side chain oxidation can also provide 20-hydroxycholesterol and 25-hydroxycholesterol (25-OHC). This later can also be formed by the enzyme 25-hydroxylase (OMIM 604551). In addition, hydration of 5,6-epoxycholesterol can also give cholestane-3 β ,5 α ,6 β -triol ((Vejux et al., 2011) (Mutemberezi et al., 2016)).

Figure 3: Cell signalization associated with 7-ketocholesterol-induced oxiaoptophagy and inflammation.

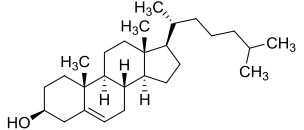
The concept of oxiaoptophagy was introduced in 2003 in U937 cells treated with 7KC (Monier et al., 2003) and further confirmed by Nury *et al.* (Nury et al., 2020b)). In 2009, based on results mainly obtained on vascular wall cells, retinal epithelial cells and monocytic cells, the signalling pathways induced by 7KC were poorly characterized, but the importance of the mitochondrial pathway was well established (Vejux and Lizard, 2009). Shortly thereafter, it was described in A7r5 aortic smooth muscle cells and 158N oligodendrocytes that the ability of 7KC to induce apoptosis was associated with its accumulation in lipid rafts ((Royer et al., 2009) (Ragot et al., 2013)). An important characteristic of 7KC is its ability to increase the production of ROS in all cells studied and to favor lipid peroxidation, protein carbonylation and formation of 8-hydroxyguanine ((Brahmi et al., 2019) (Vejux et al., 2020)); in human aortic smooth muscle cells, an activation of NADPH-oxidase (Nox4) has been demonstrated (Pedruzzi et al., 2004). Upon treatment with 7KC, an activation of NADPH-oxidase is also suspected in other cell types. This increase of oxidative stress is associated with an increase of plasma membrane permeability, an externalization of phosphatidylserine and an inactivation of the PIP2/PIP3/PDK1/PKB(Akt) signalling pathway with consequent activation of GSK3 β which contributes to mitochondrial depolarization involved in apoptosis (Vejux et al., 2009). Since 2010, the relationships between oxidative stress, apoptosis and autophagy have been extensively studied and much information has been obtained on the effects of 7KC on organelles, particularly on the peroxisome, and on the contribution of organelles to 7KC-induced cell death. The effects of 7KC on the lysosome led to interest in autophagy and to show activation of LC3-I into LC3-II which is a criterion for autophagy (Nury et al., 2014). Furthermore, the presence of myelin figures in the cytoplasm of 7KC-induced apoptotic cells (Vejux et al., 2007) is now considered as a sign of reticulophagy.

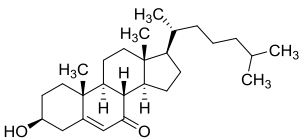
Pexophagy has also been described (Nury et al., 2018) and mitophagy is likely on the basis of transmission electron microscopy observations. During 7KC-induced cell death, autophagy is considered to be survival autophagy ((Yuan et al., 2016) (Yammine et al., 2020)). Furthermore, the study of peroxisomes has shown that 7KC reduces peroxisomal mass, modifies their topography and induces several morphological and functional dysfunctions of the latter. These peroxisomal dysfunctions could contribute to the amplification of oxidative stress and contribute to cell death due to important functional interactions between the mitochondria and the peroxisome, the activity of one influencing that of the other (Lismont et al., 2015). Thus, under the influence of 7KC, the observed decrease in the mRNA levels of peroxisomal transporters and enzymes involved in β -oxidation as well as of β -oxidation activity favors the accumulation of very long chain fatty acids ($C \geq 22$) known to activate the ROS overproduction (Baarine et al., 2012). In addition, 7KC also has pro-inflammatory properties by inducing the secretion of pro-inflammatory cytokines (IL-1 β ; IL-8). It is also reported that 7KC interacts with the microsomal antiestrogen binding site (AEBS) and inhibits its cholesterol epoxide hydrolase (ChEH) activity (de Medina et al., 2010). In addition, 7KC binds and inhibits the transactivation of the aryl carbon receptor (AhR) (Savouret et al., 2001). The part taken by these receptors (AEBS, AhR) in oxiaoptophagy is as yet unknown. The figure presented is based on that published by Brahmī F *et al.* (Brahmī et al., 2019) and Vejux A. *et al.* (Vejux et al., 2020) and includes new data.

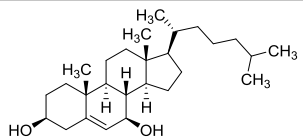
Figure 4: Cell signalling associated with 7 β -hydroxycholesterol-induced oxiaoptophagy and inflammation. The signalling pathways associated with oxiaoptophagy and 7 β -OHC-induced inflammation are often common to those induced by 7KC; they are less well known because 7 β -OHC is less studied than 7KC (Vejux et al., 2020). Unlike 7KC, 7 β -OHC does not accumulate in lipid rafts. However, the latter induces alterations of plasma membrane (externalization of phosphatidylserine) and inactivates the PIP2/PIP3/PDK1/PKB(Akt) signalling pathway with consequent activation of GSK3 β which contributes to mitochondrial depolarization involved in apoptosis. 7 β -OHC is also a powerful oxidative stress activator by promoting the overproduction of ROS and lipid peroxidation. Several data support that the rupture of redox homeostasis favors organelle dysfunctions (lysosome, mitochondria, peroxisome) which participates in the activation of apoptosis and autophagy, which would initially be survival

autophagy. Autophagy is characterized by an increased ratio [(LC3-II)/(LC3-I)] whatever the cell considered and on C6 rat glioma cells increased levels of autophagic proteins (mTOR, Beclin, free Atg12, Atg12-Atg15) involved in the autophagosome formation has been observed (Sassi et al., 2019). In addition, 7 β -OHC also has pro-inflammatory properties by inducing the secretion of pro-inflammatory cytokines (IL-1 β ; IL-8). The figure presented is based on that published by Vejux A. *et al.* (Vejux et al., 2020) and includes new data.

Figure 1: NURY T et al.

Name	Cholesterol
Synonyms	Cholesterin; cholesten-5-en-3beta-ol
Structure	 The chemical structure of cholesterol is shown, featuring a four-ring steroid nucleus with a hydroxyl group at C3, methyl groups at C10 and C13, and a branched hydrocarbon side chain at C17.
Cholesterol formula	C ₂₇ H ₄₆ O
PubChem CID	5997
Molecular Weight	386.7 g/mol
Water solubility	0.025 to 0.095 mg/L at 30°C (Around ?)
Melting point	148.5°C
Spectral information	129
GC-MS (mode EI); spectra of sterols derivatized as O-trimethylsilyl ethers * m/z top peak	

Name	7-ketocholesterol
Synonyms	7-oxocholesterol; 5-cholesten-3β-ol-7-one; 3β-hydroxy-5-cholesten-7-one
Structure	 The chemical structure of 7-ketocholesterol is shown, which is identical to cholesterol except for the presence of a ketone group at C7.
7-ketocholesterol formula	C ₂₇ H ₄₄ O ₂
PubChem CID	91474
Molecular Weight	400.6 g/mol
Water solubility	0.004 mg/L (Around 10 ⁻⁸ M)
Melting point	168-172° C
Spectral information	75
GC-MS (mode EI); spectra of sterols derivatized as O-trimethylsilyl ethers * m/z top peak	

Name	7β-hydroxycholesterol
Synonyms	5-cholestene-3beta, 7beta-diol
Structure	 The chemical structure of 7β-hydroxycholesterol is shown, which is identical to cholesterol except for the presence of a hydroxyl group at C7.
7β-hydroxycholesterol formula	C ₂₇ H ₄₆ O ₂
PubChem CID	473141
Molecular Weight	402.7 g/mol
Water solubility	0.48 mg/L (Around ?) (Source : https://hmdb.ca/metabolites/HMDB0006119)
Melting point	177-178° C
Spectral information	456
GC-MS (mode EI); spectra of sterols derivatized as O-trimethylsilyl ethers * m/z top peak	

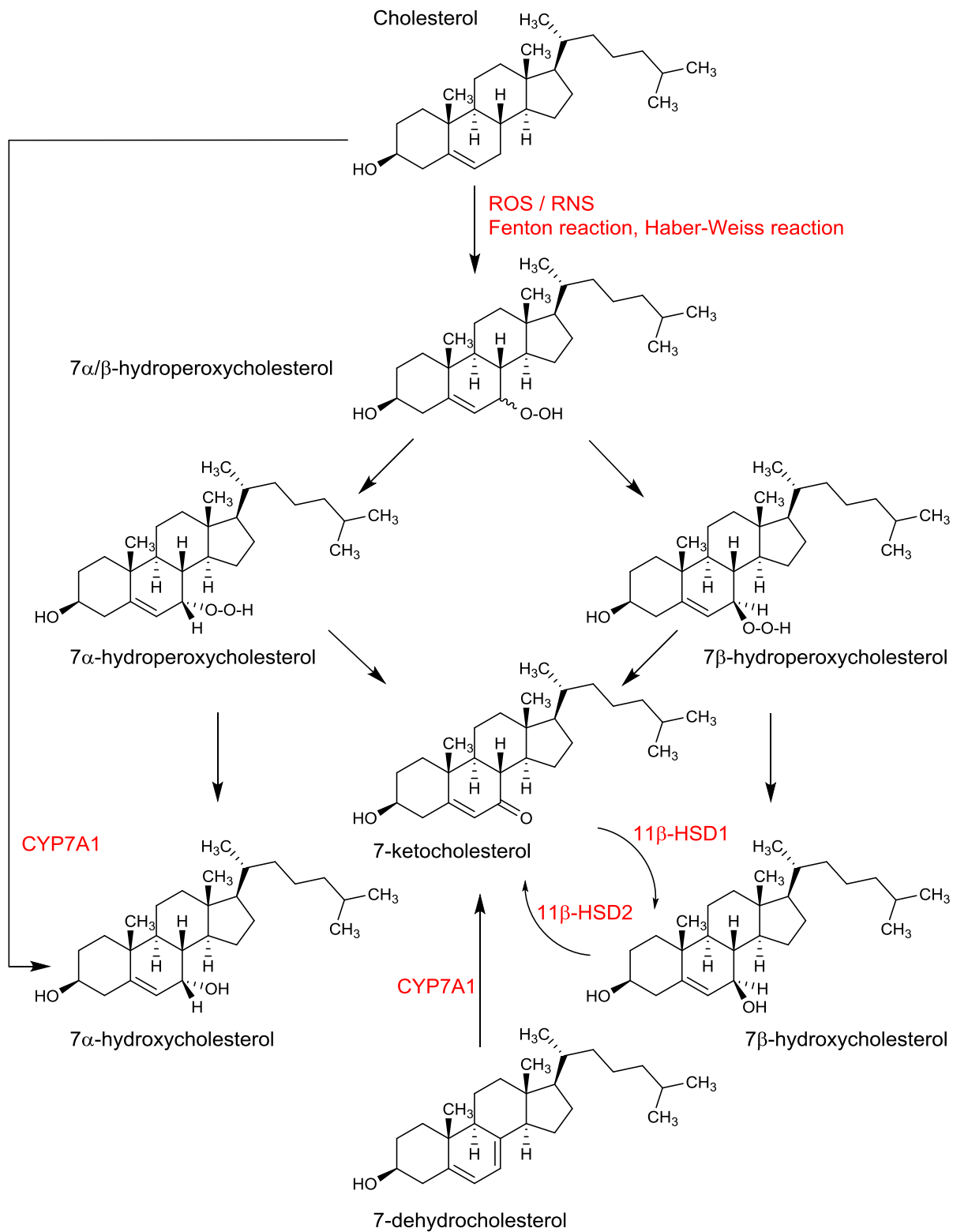


Figure 2 : NURY T et al.

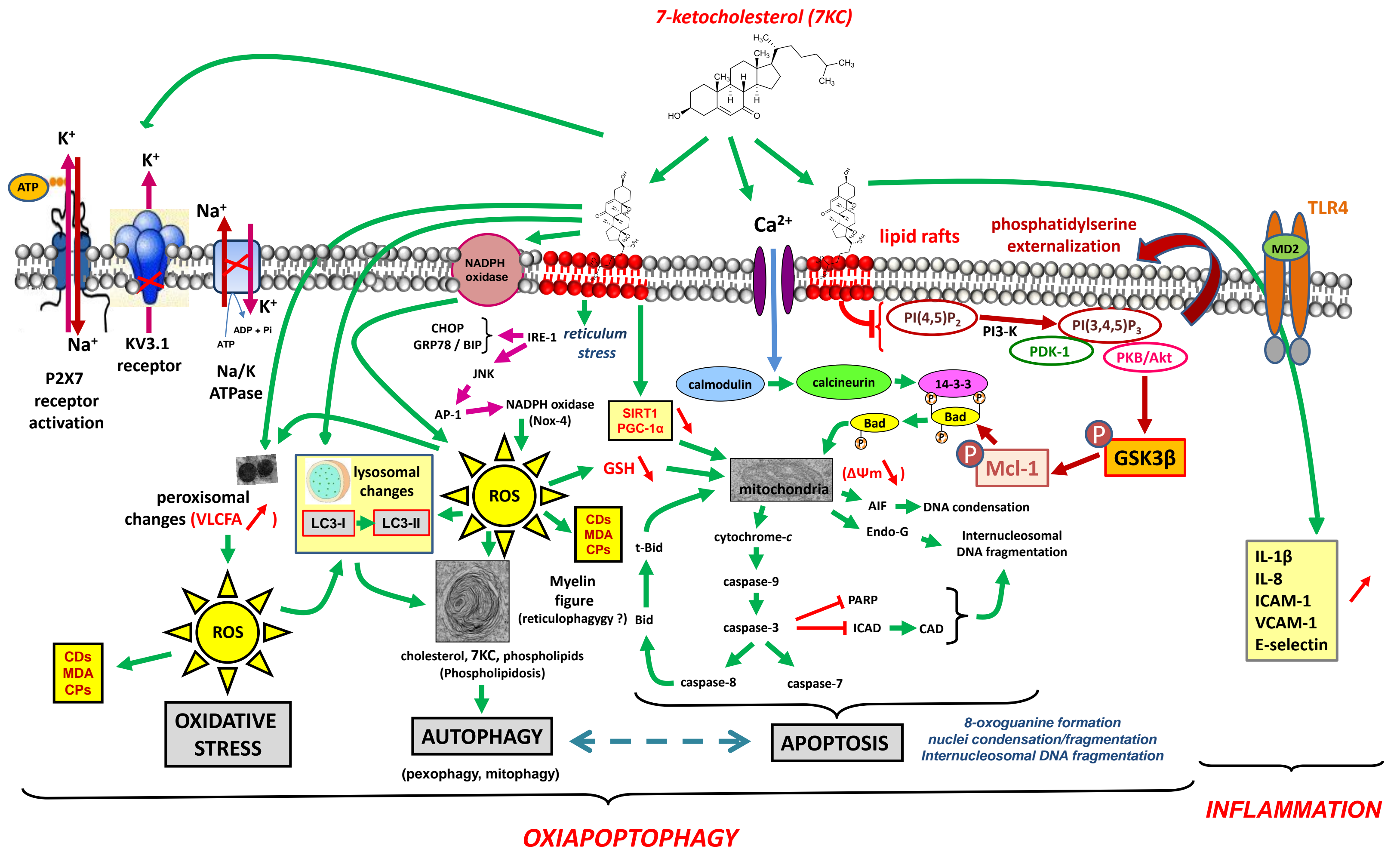


Figure 3 : NURY T et al.

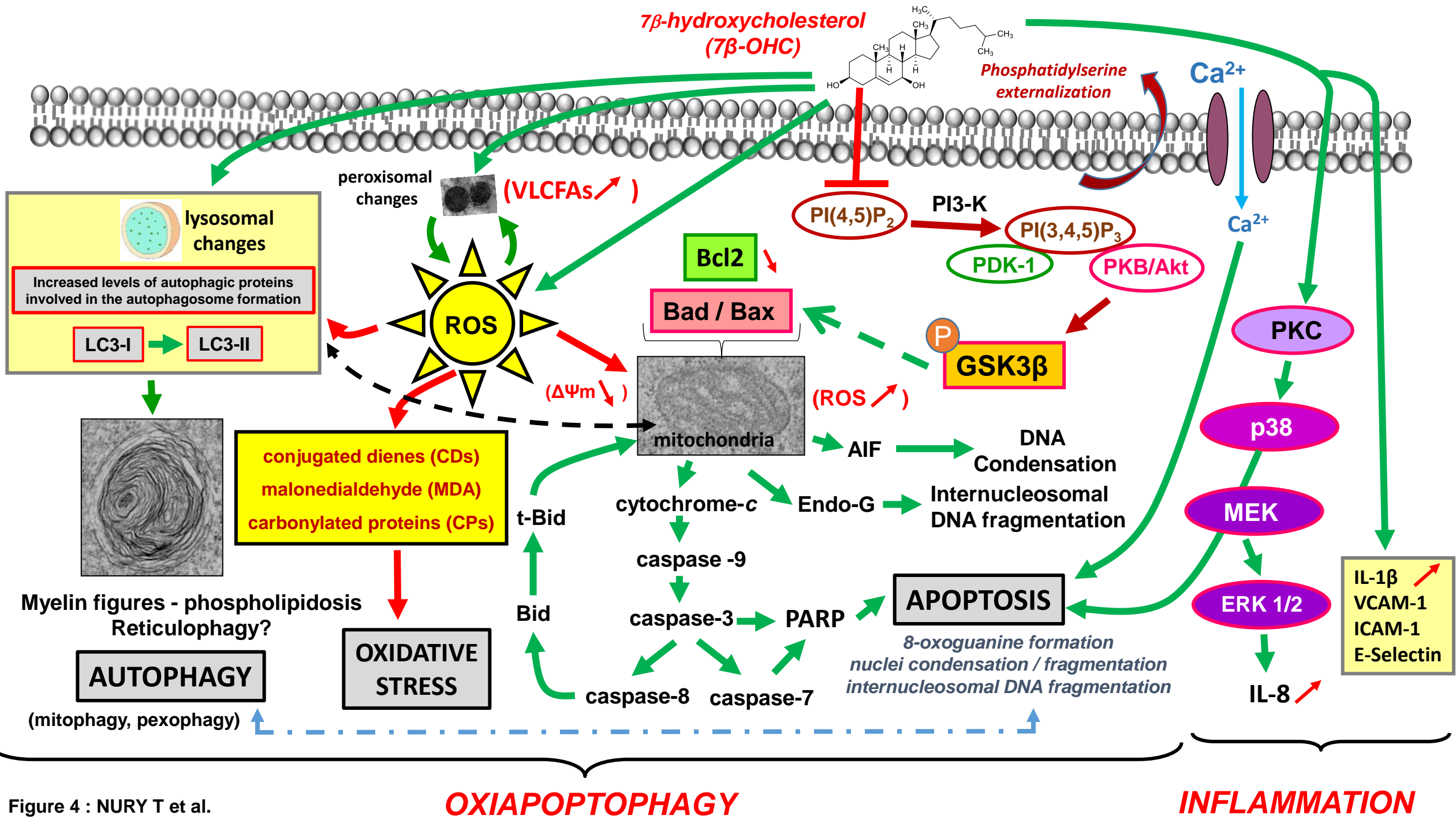


Figure 4 : NURY T et al.

Family of compounds	Cytoprotective compounds	Concentrations	Cells	7KC concentrations	References
Tocopherols	α-tocopherol	100 - 400 μM	U937 cells ; 158N cells ; rat aortic smooth muscle cells (A7R5) ; murine neuroblastoma cells (N2a) ; murine microglial cells (BV-2)	25 - 50 μM	(Lizard et al., 2000), (Miguet-Alfonsi et al., 2002), (Vejux and Lizard, 2009), (Royer et al., 2009), (Debbabi et al., 2016), (Debbabi et al., 2017), (Yammine et al., 2020)
	γ-tocopherol	400 μM	BV-2 cells	50 μM	(Debbabi et al., 2016)
Fatty acids	ALA (C18:3 n-3)	50 μM	N2a cells	50 μM	(Yammine et al., 2020)
	EPA (C20:5 n-3)	50 μM	N2a cells	50 μM	(Yammine et al., 2020)
	DHA (C22:6 n-3)	50 μM	BV-2 cells ; 158N cells; N2a cells ; SK-NB-E cells	25 - 50 μM	(Nury et al., 2015) (Zarrouk et al., 2015) (Nury et al., 2017) (Debbabi et al., 2017) (Yammine et al., 2020)
	Oleic acid (C18:1 n-9)	100 - 200 μM	158N cells ; BV-2 cells ; N2a cells	50 μM	(Debbabi et al., 2016) (Badreddine et al., 2017) (Debbabi et al., 2017) (Yammine et al., 2020)
	Sterculic acid	1 μM	ARPE-19 cells	12 μM	(Huang et al., 2012) (Huang et al., 2014)
Terpenes	Lycopene	0.5 - 2 μM	Human monocyte cells (THP-1)	10 - 25 μM	(Palozza et al., 2010) (Palozza et al., 2011)
Polyphenols	Epicatechin	5 - 10 μM	Murine Monocyte / Macrophage (J774A,1)	20 μM	(Leonarduzzi et al., 2006)
	Epigallocatechin-3-gallate (EGCG)	30 - 50 μM	Human angiosarcoma cells (ISO-HAS)	50 μM	(Yamagata et al., 2013)
	Resveratrol	1.5 - 30 μM	N2a cells ; human monocytes; ARPE-19 cells	15 - 150 μM	(Dugas et al., 2010) (Buttari et al., 2014) (Yammine et al., 2020)
	Apigenin	1.5 - 6.25 μM	N2a cells	50 μM	(Yammine et al., 2020)
	Quercetin	1.5 - 6.25 μM	N2a cells	50 μM	(Yammine et al., 2020)
	Hydroxytyrosol	2.5 - 10 μM	Caco-2 cells	187,5 μM	(Deiana et al., 2010) (Atzeri et al., 2016)

Polyphenols	Tyrosol	2.5 - 10 μ M	Caco-2 cells	187,5 μ M	(Deiana et al., 2010) (Atzeri et al., 2016)
	Homovanillic alcohol	5 - 25 μ M	Caco-2 cells	Prevention of oxysterol formation	(Deiana et al., 2010)
	Taxifoline (dihydroquercetin)	15 μ M	Rat pheochromocytoma cells (PC12) ; human neuroblastoma cells (SH-SY5Y)	125 μ M	(Kim et al., 2017)
Vegetal pigment	Indicaxanthin	1 - 5 μ M	Murine monocytes (THP-1) ; human erythrocytes	7 - 16 μ M	(Tesoriere et al., 2013) (Tesoriere et al., 2015)
Antioxidants	NAC	10 - 15 mM	U937 cells , murine osteoblasts (MC3T3-E1)	100 μ M	(Lizard et al., 1998) (Lizard et al., 2000) (Sato et al., 2017)
	GSH	10 - 15 mM	U937 cells	100 μ M	(Lizard et al., 1998) (Lizard et al., 2000)
	Ergothioneine	0.1 – 1 mM	Human brain endothelial cells (hCMEC/D3)	30 μ M	(Koh et al., 2020)
Synthetic molecules	- Tyrosine kinase inhibitor AG126 - DMF / MMF - Memantine - Simvastatine	1 – 10 μ M 25 - 50 μ M 1 μ M ; 1 mM 0.01 μ M ; 0.05 μ M	PC12 cells 158N cells ARPE-19 cells	100 μ M 25 - 50 μ M 75 μ M	(Kim and Lee, 2010) (Zarrouk et al., 2017) (Neekhara et al., 2020)
Mixtures of compounds, plant extracts, oil	α-tocopherol + DHA	400 μ M + 50 μ M	158N cells	50 μ M	(Nury et al., 2015)
	Red yeast rice extract	100 μ g/mL	Murine monocyte/macrophage (RAW 264.7)	70 μ M	(Shen et al., 2017)
	Olive oil	1 / 1000	158N cells	50 μ M	(Debbabi et al., 2016) (Debbabi et al., 2017) (Badreddine et al., 2017)
	Argan oil	2 / 1000	158N cells	50 μ M	(Badreddine et al., 2017)
	Milk thistle seed oil	3 / 1000	158N cells	50 μ M	(Meddeb et al., 2018)
	Ethanollic leaves mint extracts	25 – 400 μ g/mL	Mouse monocyte macrophage RAW 264.7	20 μ M	(Brahmi et al., 2018)
Bacterial enzymes	- Cholesterol oxydase (<i>Chromobacterium</i> DS-1) - bacteria <i>Rhodococcus erythropolis</i> MTCC 3951	-	Human fibroblasts	25 - 50 μ M	(Mathieu et al., 2012) (Ghosh and Khare, 2017)

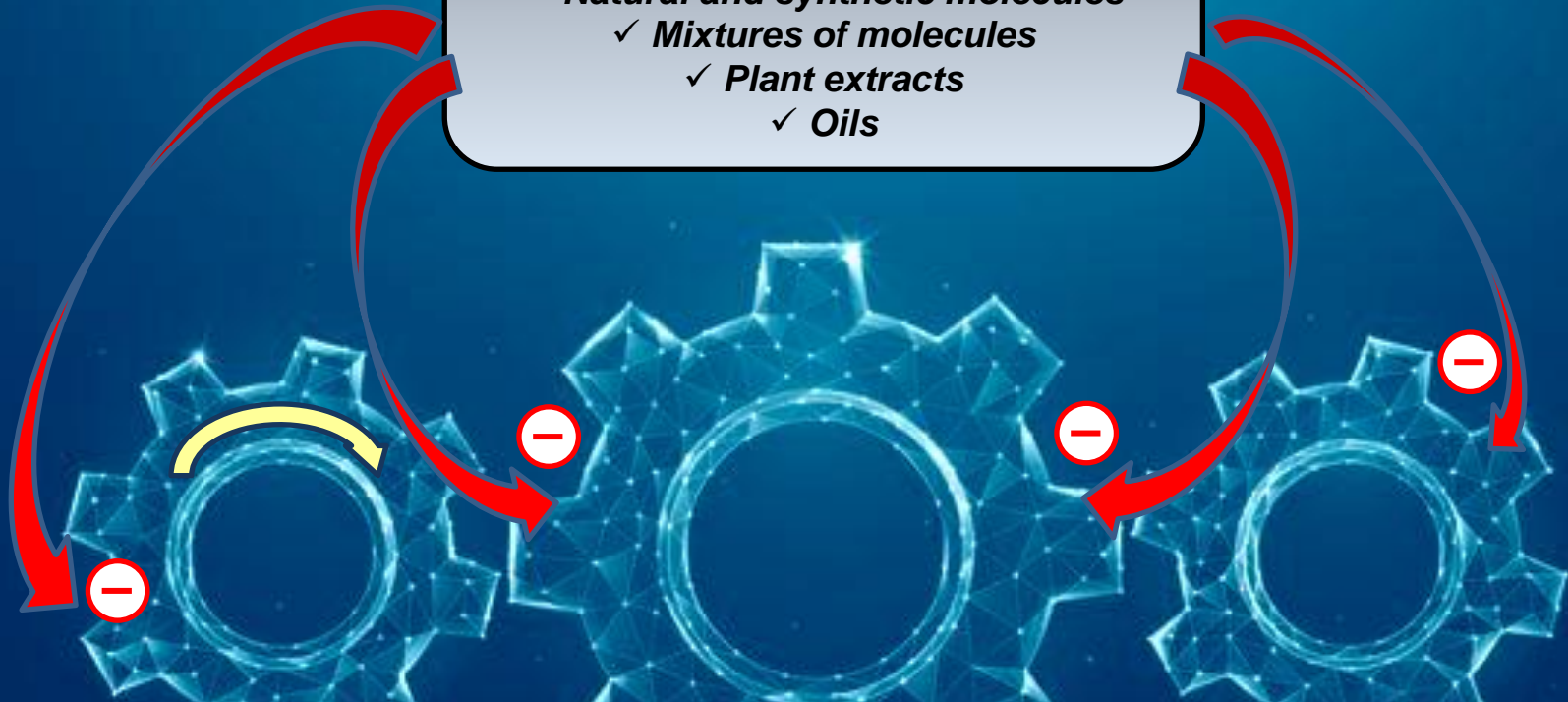
Table 1: List of compounds counteracting 7-ketocholesterol-induced cytotoxicity

Family of compounds	Cytoprotective compounds	Concentrations	Cells	7 β -OHC concentrations	References
Tocopherols	α-tocopherol	100 - 400 μ M 10 μ M	Murine oligodendrocytes (158N) Human monocytes (U937)	50 μ M 30 μ M	(Ragot et al., 2013) (Lyons et al., 2001)
Fatty acids	DHA	50 μ M	158N cells; Human neuroblastoma (SK-NB-E)	50 μ M	(Nury et al., 2015) (Zarrouk et al., 2015)
Polyphenols	Epigallocatechin-3-gallate (EGCG)	1 μ M	Human epithelial colonic cells (CaCo-2)	4.4 μ M	(Mascia et al., 2010)
	Resveratrol	1 μ M	Human retinal epithelial cells (ARPE-19)	75 μ M	(Dugas et al., 2010)
Synthetic molecules	DMF	25 μ M	158N cells; SK-NB-E cells	50 μ M	(Sghaier et al., 2019a)
	MMF	25 μ M	158N cells; SK-NB-E cells	50 μ M	(Sghaier et al., 2019a)
	Trolox	10 μ M	U937 cells	30 μ M	(Ryan et al., 2004)
	Dimethylsulfoxide	0.1%	U937 cells	28 μ M	(Laskar et al., 2010b)
	Mangafodipir	400 μ M	U937 cells	28 μ M	(Laskar et al., 2010a)
Vitamins	Biotin	100 nM - 400 μ M	158N cells; SK-NB-E cells	50 μ M	(Sghaier et al., 2019b)
Mixtures of compounds, plant extracts, oil	α-tocopherol + DHA	400 μ M + 50 μ M	158N cells; SK-NB-E cells	50 μ M	(Nury et al., 2015)
	Red wine extract	1 - 100 ng/mL	Human aortic endothelial cells (HAEC)	10 μ M	(Naito et al., 2004)
	<i>Carpobrotus edulis</i> ethanol-water extract	160 μ g/mL	158N cells	50 μ M	(Zarrouk et al., 2019b)
	Aronia melanocarpa E extract (Aronox)	50 μ g/mL	Human umbilical vein endothelial cells (HUVEC)	50 μ M	(Zapolska-Downar et al., 2008)
	Sea urchin egg oil	160 μ g/mL	158N cells; SK-NB-E cells	50 μ M	(Zarrouk et al., 2018)
MPTP inhibitors	Bongerik acid	5 μ M	U937 cells	30 μ M	(Ryan et al., 2005)
	Cyclosporin A	1 μ M	U937 cells	30 μ M	(Ryan et al., 2005)
	ADP analogue (Burzik et al., 2003)	5 mM	U937 cells	30 μ M	(Ryan et al., 2005)

Table 2: List of compounds counteracting 7 β -hydroxycholesterol-induced cytotoxicity

CYTOPROTECTIVE COMPOUNDS

- ✓ *Natural and synthetic molecules*
- ✓ *Mixtures of molecules*
- ✓ *Plant extracts*
- ✓ *Oils*



7-ketocholesterol
7 β -hydroxycholesterol

Oxysterol
levels

age

CELL DAMAGES

- OXIdative stress
- APOPTOsis
- autoPHAGY

OXIAPOPTOPHAGY

AGE-RELATED DISEASES

Cardiovascular diseases

Eye diseases
*age-related
macular degeneration,
*Cataract

Neurodegenerative diseases
*Alzheimer's disease

