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Review

Antioxidants Maintain Cellular Redox Homeostasis by Elimination of Reactive Oxygen Species

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Antioxidants • Reactive oxygen species • Cytochrome P450 enzymes • Autophagy • Apoptosis • Necrosis

Abstract
Reactive oxygen species (ROS) are produced by living cells as normal cellular metabolic byproduct. Under excessive stress conditions, cells will produce numerous ROS, and the living organisms eventually evolve series of response mechanisms to adapt to the ROS exposure as well as utilize it as the signaling molecules. ROS molecules would trigger oxidative stress in a feedback mechanism involving many biological processes, such as apoptosis, necrosis and autophagy. Growing evidences have suggested that ROS play a critical role as the signaling molecules throughout the entire cell death pathway. Overwhelming production of ROS can destroy organelles structure and bio-molecules, which lead to inflammatory response that is a known underpinning mechanism for the development of diabetes and cancer. Cytochrome P450 enzymes (CYP) are regarded as the markers of oxidative stress, can transform toxic metabolites into ROS, such as superoxide anion, hydrogen peroxide and hydroxyl radical which might cause injury of cells. Accordingly, cells have evolved a balanced system to neutralize the extra ROS, namely antioxidant systems that consist of enzymatic antioxidants such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidases (GPxs), thioredoxin (Trx) as well as the non-enzymatic antioxidants which collectively reduce oxidative state. Herein, we review the recent novel findings of cellular processes induced by ROS, and summarize the roles of cellular endogenous antioxidant systems as well as natural anti-oxidative compounds in several human diseases caused by ROS in order to illustrate the vital role of antioxidants in prevention against oxidative stress.

Introduction

Generally, endogenous and physiological reactive oxygen species (ROS) are mainly generated in the oxidative reaction process of mitochondrial respiratory chain as byproducts

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of normal cellular metabolism [1]. ROS have comprehensive influence in cell physiology. Moderate amounts of ROS have positive effects including killing of invading pathogens, wound healing and repairing processes [2]. Briefly, the source of cytosol ROS include mitochondria and cytochrome P450 enzymes (CYP) system. Mitochondrial ROS is the very important potential ROS pool and sealed in the double membranes of mitochondria. The high oxygen and metabolic level will elevate the ROS production, and increasing mitochondrial membrane permeability will directly lead to the release of ROS to the cytosol. However, in certain conditions, such as the invasion of xenobiotic substance, the xenobiotic metabolic process in responses to the exposure to toxic compounds by the CYP can be another crucial important source of ROS. Excessive ROS exposure will disrupt the redox homeostasis, lead to the oxidative stress and ROS-mediated damage of the important organelles and biomolecules such as DNA and proteins as well as the injuries implicated in carcinogenesis [3], diabetes [4, 5], neurodegeneration [6, 7] and aging [8, 9]. Oxidative stress is considered to be an important factor to promote cell death in response to a variety of signals and pathophysiological situations. For instance, apoptotic response induced by the transforming growth factor β in fetal hepatocytes is mediated by ROS [10]. ROS are also the necrosis inducer [11] and activator of autophagy [12], which are the switches of cell survival and death. Cells harbor the comprehensive defense system against excessive ROS exposure. In addition to ROS, reactive nitrogen species (RNS) such as nitric oxide (NO), nitrogen dioxide (NO_2-), peroxynitrite (OONO-), dinitrogen trioxide (N_2O_3), and nitrous acid (HNO_2) also contribute to the oxidative stress [13]. NO is produced by three different isoforms of nitric oxide synthases (NOs), which catalyze L-arginine to L-citrulline by releasing the NO. Interestingly, NO as a small molecule has been proved to function in activation of AMP-activated protein kinase (AMPK) which is the powerful kinase in regulate energy and metabolic homeostasis [14]. Cellular NO interacts with ROS to cause the production of several RNS that are implicated in oxidative and nitrosative damage. Drugs as well as endogenous antioxidants such as superoxide dismutase (SOD), peroxidase, glutathione (GSH) and vitamin E have been discovered to eliminate the ROS. Due to CYP monoxygenases are a major source of ROS during ischemia/reperfusion [15]. Therapeutics that can inhibit the CYP activity has the potentials in protecting cells against from ROS-induced damage [16, 17]. Inhibition of ROS-induced cell injury by natural antioxidant or the synthetic compounds should be investigated for the better understanding their potentials in the treatment of diseases which originated from the excessive ROS exposure.

Generation of ROS and Oxidative Stress

In aerobic organisms, oxygen is essential for efficient energy production, but paradoxically, overwhelming of cellular energy metabolism and oxygen consumption are coupled with the generation of ROS which produce chronic toxic stress in cells. Thus, a reduction in metabolic rate reduces the formation of ROS, which may produce beneficial effect [18]. The metabolism of toxic compounds such as alcohol might accelerate the production of the toxic byproducts including ROS. ROS will attack the liver cells with its active metabolites, and the excessive production of ROS in liver is the main etiological factor for alcohol poisoning with severe depletion of endogenous antioxidants such as GSH. Therefore, replenishing the reducing power is the main antidote for alcohol poisoning treatment [19].

The metabolism of toxic compounds in the cellular enzymatic system is not totally efficient and sometimes the metabolic processes lead to the production of the byproducts including ROS which are more toxic than their parental compounds. For example, the metabolism of the toxic environmental contaminant benzo-a-pyrene produced by the CYP will lead to its metabolic activation into highly reactive byproducts which are carcinogenic. Therefore, exogenous toxicants are potential sources of ROS produced by CYP metabolism. The CYP enzymes are a super-family of monooxygenases and many of which are responsible for the detoxification of xenobiotics. Notably, CYP families appear to be the major members

of the first pass metabolic enzymes in the phase I reaction for the metabolism of the xenobiotics such as drugs and carcinogens as well as endogenous substrates such as steroids and hormones. Upon encountering substrates, CYP binds to the target compound via the combination of one molecule of oxygen to form an oxy complex. The oxy complex reduced to peroxy complex that accepts two protons and produces water through intermediate reaction. CYP transform the drugs, the following ROS generation result in nicotinamide adenine dinucleotide phosphate (NADPH) consumption by the CYP molecules [20]. The electron-transfer chain of microsome continues to deplete NADPH and promote the production of ROS even without any substrates. These overwhelming amounts of ROS give feedback to CYP gene repression [21]. Besides, many enzymes such as lipooxygenase and xanthine oxidase can also contribute to the ROS production. These ROS particularly superoxide radical get protonated to form perhydroxyl radical that plays a significant role in lipid peroxidation and membrane destabilization [22].

CYP are a very large gene family containing 57 CYP genes which are classified into 18 families and 44 subfamilies. However, only the 1, 2, and 3 CYP families are involved in phase I drug metabolism. CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5 are the CYP isoforms which function in the metabolism of therapeutic agents [23]. The production of ROS arises from the release of superoxide anion radical due to the decay of the one-electron-reduced ternary complex and the protonation of the CYP with the formation of hydrogen peroxide [24]. CYP2E1 has been demonstrated to be activated under diverse pathophysiological conditions including diabetes, obesity, starvation, cancer, alcohol liver disease, and non-alcoholic hepatic steatosis [25]. CYP2E1 as the powerful enzyme plays a role in oxidative stress in addition to carcinogenesis and chemical toxicity [26], as well as alcohol-mediated liver injury [27]. Moreover, the mitochondria-targeted CYP2E1 directly promotes the alcohol-mediated oxidative stress, mitochondrial DNA damage, and mitochondrial dysfunction in cells as well as the induction of oxidative stress in livers of ethanol-fed rats [28]. Besides the oxidative stress induced by CYP2E1, the induction of non-alcoholic steatohepatitis by CYP2E1 have been studied. As a member of the oxido-reductase cytochrome family, CYP2E1 is also involved in the oxidization of xenobiotics and fatty acids [29, 30]. CYP2E1 expression was increased in some condition such as in obesity and fatty liver diseases, which is appear to be correlated with the severity of non-alcoholic fatty liver disease [31].

Many xenobiotic receptors are involved in the activation of CYP gene expression and these receptors include the aryl hydrocarbon receptor (AhR), pregnant X receptor (PXR) and constitutive androstane receptor (CAR) [32]. The expression of the CYP1 gene family (1A1, 1A2 and 1B1) is transcriptionally regulated by AhR while the CYP2 (2A6, 2B6 and 2C8/9) as well as CYP3 (3A4) families are regulated by the PXR and CAR [33]. AhR is a ligand-dependent transcription factor to mediate the biotransformation and carcinogenic/teratogenic effects of environmental toxins [33]. In most conditions, AhR is retained in the cytosol and formed complexes with the chaperone proteins, heat-shock protein 90kDa (HSP90), aryl hydrocarbon receptor interacting protein (AIP), and p23 in the absence of a ligand. Ligand binding to AhR results in transformation of the AhR and releases it from complex and translocate into the nucleus where it forms complex with the aryl hydrocarbon receptor nuclear translocator (ARNT). The AhR-ARNT complex interacts with the core DNA sequences located in the regulatory regions of CYP genes, notably the CYP1A1 and the heterodimer function as the transcription factor triggering a cascade of transcriptional activities and leading to the gene activation. The CYP2B1 is mainly regulated by CAR, however, it has also been found to be regulated by the PXR, and the CYP3As are mainly regulated by the PXR have been found to be regulated by the CAR [34, 35]. Studies have indicated that there are cross-talk between the PXR and CAR-regulated gene expression and the cross-talk mainly mediated by the reciprocal bindings of the PXR-RXR and CAR-RXR complexes in the regulatory region of the genes [34].

In mitochondria, oxidative phosphorylation process as consuming O_2 is the major source of ATP production. ATP production process couples with the ATP synthase activity through the electron transporting chain (ETC). However, during the electrons passing through

the ETC, electrons can escape and be captured by O_2 to form the ROS. The ETC complexes comprise four different members: NADH: ubiquinone oxidoreductase (complex I), succinate dehydrogenase (complex II), ubiquinol: cytochrome c oxidoreductase (complex III) and cytochrome c oxidase (complex IV) [36]. The initiation process of electron transferring process from the tricarboxylic acid (TCA) cycle is delivering two electrons from NADH or succinate to complexes I and II, respectively, and the electrons are delivered to the CoEnzyme Q (CoQ) pool, a lipophilic electron carrier existing as oxidized ubiquinone and reduced ubiquinol. The electrons donated from complex I and II finally go into the CoQ pool and then passed through complex III to cytochrome c. At last, the electrons reduce oxygen to water by the complex IV. In the ETC process, protons are pumped into the intermembrane space by complexes I, III and IV to form a proton gradient across the mitochondrial inner membrane which is necessary for the catalysis of the ATP synthase. However, in addition to its proton gradient building function, the electrons escape from ETC continuously generates ROS [37]. When the electrons are donated to complex III, a free radical, ubisemiquinone, is transiently created. ETC sites that are implicated in ROS generation include complexes I, II, III and ubisemiquinone. Complex IV delivers electrons to O_2 which could generate ROS. Complex V does not participate in electron transport, and there is no evidence that it directly generates ROS. Whereas, the alteration of complex V activity can makes changes in the membrane potential, then affects ROS generation from the ETC [38].

ROS Signaling Transduction and Cellular Process

ROS are reactive molecules, as the primary source of cellular oxidative stress molecules can oxidize DNA, proteins, and lipids. At physiological levels, ROS are also the important signaling molecules which transmit signals for normal physiological processes. However, excessive ROS promote the activation of autophagy, apoptosis and necrosis (Fig. 1).

ROS Induce Autophagy

Autophagy is a highly regulated cellular degradation system which degrades damaged organelles, protein aggregates and invading microorganisms through lysosomes. Dysfunction of autophagy has been implicated in a broad spectrum of human diseases including cancers, neurodegeneration, infectious diseases, metabolic diseases and aging [39]. Autophagy can be activated under stress conditions such as starvation, endoplasmic reticulum (ER) stress, and organelles damage and pathogen infection. ROS have become a very important factor to activate autophagy. Accumulation of H_2O_2 in the cell will become the source of oxidative stress. ATG4 is an essential autophagy gene involving in the autophagic pathway. This gene has been identified as a direct target for oxidation by H_2O_2 during starvation. Accumulation of H_2O_2 can oxidize the activity of the ATG4 [40]. Oxidized ATG4 promotes lipidation of LC3/ATG8 for autophagy initiation [41]. The ROS-dependent of LC3-PE accumulates on the autophagosomal membranes, followed by promoting the first steps in autophagosome formation.

ROS can regulate autophagy indirectly through the activation of mitogen activated protein kinase (MAPK) family such as JNK1c-Jun-N-terminal kinase (JNK), p38 and Extracellular Signal-regulated Kinase (ERK) [42]. The MAPK family members are activated in a 3-tier kinase cascade comprising of MAPK kinase kinase (MAPKKK), MAPK kinase (MAPKK) and MAPK [43]. The persistent activation of JNK can trigger a robust increase of cellular ROS production to cause DNA damage. Finally p53 pathway becomes activated by sensing the cellular redox stress. As a transcription factor, p53 transactivates several autophagy inducers which may activate JNK and Sestrin2 which binds to the complex TSC1/TSC2 to induce phosphorylation and activation of TSC2 finally induce autophagy [44]. Another pathway that plays a role in the ROS-mediated autophagy is the regulation of Akt/

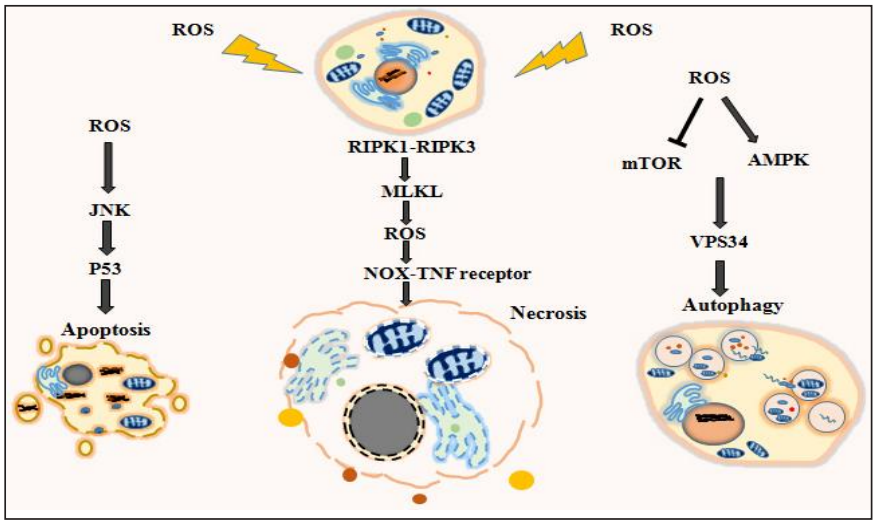

Fig. 1. High amount of reactive oxygen species (ROS) production can induce autophagy, apoptosis and necrosis in cells. Oxidative stress induced by ROS can inhibit the mTOR activity, while it can activate AMP-activated protein kinase (AMPK) to stimulate vacuolar protein sorting 34 (Vps34) complex activity which is required for initiation of autophagy. ROS can also activate apoptosis though the C-Jun-N-terminal kinase (JNK)/P53 pathway. ROS can injure the mitochondria membrane to release apoptotic factors. Receptor-interacting serine/threonine protein kinase 3 (RIP3) and the kinase activity of RIP1 are essential for stable formation of the RIP1-RIP3 complex, which critically controls downstream ROS production. Moreover, ROS is required for the Receptor-interacting serine/threonine protein kinase 3 (RIP1) mediated necrosis.

mTOR (mechanistic target of rapamycin) and AMPK signaling systems. The Akt/mTOR is a well-known kinase whose activity is modulated by ROS which oxidize the phosphatase and tensin homologue (PTEN) [45]. The activation of autophagy is triggered by inhibiting mTOR [46] and the activation of AMPK by regulating vacuolar protein sorting 34 (VPS34) complex activities [47].

ROS Trigger Apoptosis

Cell apoptosis initiation originates from extracellular or intracellular signals via the death receptors and the mitochondria-mediated pathways. Upon cell apoptosis initiation, the ROS increases through disrupting intracellular redox homeostasis, and irreversible oxidative modifications of lipid, protein, or DNA, which in turn can activates oxidative stress-induced apoptotic signaling [48]. ROS has been found to trigger the apoptosis of cancer cells via tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) [49-51] and up-regulate CD95 and TRAIL death receptors by activation of nuclear factor kappa B (NF-κB) [52]. In addition, ROS-induced activation of JNK can also induce the apoptotic signaling [53, 54]. JNK is a member of the MAPK family. Increasing evidence indicates a crucial role of JNK in mitochondrial dysfunction with subsequent initiation of apoptosis. Shikonin, a natural naphthoquinone derivative, induces apoptosis in various cancer cells, treatment of K562 cells with shikonin resulted in profound induction of apoptosis followed by rapid production of ROS and marked activation of JNK and p38 which lead to the activation of the apoptosis pathway [55]. Activation of ROS/JNK can also elevate and sustain p53 activity leading to robust outcome of apoptosis in cancer cells [56]. The redox-sensitive MAPK kinase and apoptosis signal-regulating kinase 1 (ASK1) are the upstream of ROS/JNK. ASK1 activity is inhibited by interactions with redox proteins (Grx and thioredoxin (Trx1)). ROS mediate Trx1 dissociation from the ASK1-Trx1 complex, and recruit tumor necrosis factor receptor-associated factors to the complex. Activated ASK1 signals down-regulate JNK activation and induces apoptosis either via mitochondrial signaling or via transcription of AP-1-dependent proapoptotic genes [57]. Additionally, ROS-mediated disruption of the mitochondrial ASK1/ASK2/Trx2 complex induces cytochrome c release [58]. When the ER stress occurs, ROS can

be elevated to induce the neighboring mitochondria for accentuating the onset of intrinsic apoptosis [59]. Flavone, as the antioxidant can protect myocardial ischemia/reperfusion injury anti-apotosis effect [60].

Necrosis Induced by ROS

Necrosis is a type of cell death that is different from apoptotic cell death. The programmed necrosis induced by TNF has been termed necroptosis [61]. Receptor-interacting serine/threonine protein kinase 3 (RIP3) is a protein kinase, which can cause cell death in many cell lines due to its high expression [62-64]. Programmed necrosis is controlled by the action of two serine/threonine kinases, RIP1 and RIP3. The phosphorylation of RIP1 and RIP3 is critical for assembly of the necrosome, an amyloid-like complex that initiates transmission of the pro-necrotic signal [65]. Depletion of RIP3 in cells reduces ROS concentration in necrosis-induced cells and increasing RIP3 levels increase ROS production in contrast. The effects of RIP3 in necrosis induction carried out through increasing energy metabolism-associated ROS production [66]. Study proves the phosphorylation of RIP1 and RIP3 stabilizes their association within the pronecrotic complex, activates the pronecrotic kinase activity, and triggers ROS production [67]. The enhanced production of mitochondrial ROS due to RIP1 phosphorylation-dependent activation can be regulated by the interaction between signal transducer and activator of transcription 3 (STAT3) and the mitochondrial electron transport chain complex I subunit GRIM-19. STAT3 interacts with GRIM-19, which brings about the accumulation of STAT3 and GRIM-19 in the mitochondria, where they induce an increase of ROS production and cell death by necroptosis [68]. Moreover, direct interactions between RIP3 and the enzymes glutamate-ammonia ligase (GLUL), glutamate dehydrogenase 1 (GLUD1) and glycogen phosphorylase (PYGL) increase energy metabolism and mitochondrial ROS production [11]. During necrosis induction, cell surface NADPH oxidase NOX enzyme complexes can interact with the TNF receptor which is also responsible for death-inducing ROS during necrosis [61]. Among the ROS-induced necrosis, mixed lineage kinase domain-like (MLKL) have been identified as a key RIP3 downstream component of TNF-induced necrosis. MLKL is also involved in generation of ROS and the late-phase activation of JNK during TNF-induced necrosis [69-71].

Ferroptosis Induced by ROS

Ferroptosis is a type of iron-dependent, oxidative cell death which can be triggered by structurally diverse small molecules (e.g. erastin, sulfasalazine and RSL3). Ferroptosis results from antioxidant system dysfunction leading to the loss of cellular redox homeostasis. The ferroptosis is distinct from apoptosis [72, 73]. The classic features of apoptosis, such as mitochondrial cytochrome c release, caspase activation, and chromatin fragmentation, are not observed in RSL induced cell death. However, ferroptosis is featured by association with increased levels of intracellular ROS and inhibition effect by iron chelation or genetic inhibition [74]. The increases of ROS lead to cell detachment and ferroptosis. However, ROS accumulation and ferroptosis were suppressed by treatment with the iron chelator deferoxamine [75]. SLC7A11 is a component of a plasma membrane transporter that mediates Na^+ independent cellular uptake of extracellular cystine in exchange for intracellular glutamate [76]. The p53-mediated transcriptional repression of SLC7A11 is critical for ROS-induced ferroptosis. The p53 inhibits cystine uptake and sensitizes cells to ferroptosis [77]. Last year, scientists found that the p53-mediated activation of spermine N 1-acetyltransferase 1 (SAT1) contributes significantly to ferroptotic responses. SAT1 is a rate-limiting enzyme in polyamine catabolism critically involved in the conversion of spermidine and spermine back to putrescine. Surprisingly, activation of SAT1 expression induces lipid peroxidation and sensitizes cells to undergo ferroptosis upon ROS-induced stress [78].

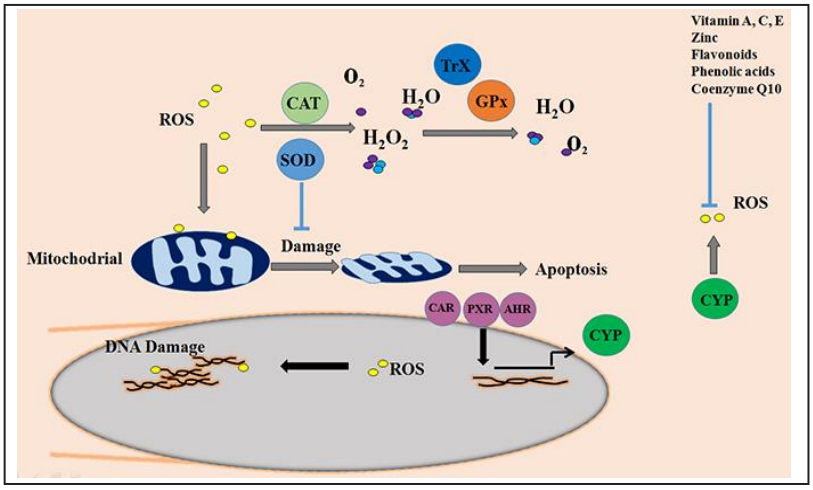

Fig. 2. Robust production of reactive oxygen species (ROS) can damage mitochondria and DNA. ROS production has been linked to cytochrome P450 enzymes (CYP) activity which is mediated by xenoreceptors aryl hydrocarbon receptor (AhR), pregnant X receptor (PXR), and the constitutive androstane receptor (CAR). Anti-oxidant system consist of (1) enzymatic antioxidants such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and thioredoxin (Trx) as well as the non-enzymatic antioxidants. The enzymatic antioxidants can directly or indirectly catalyze the ROS to protect the cells. Non-enzymatic antioxidants can neutralize the oxidative effect by promotion of anti-oxidative enzyme or directly processing oxidative chain reaction.

Endogenous Antioxidant System

Antioxidants can counteract free radicals and neutralize oxidants. The general endogenous antioxidant system consist of (1) enzymatic antioxidants like SOD, catalase (CAT) and glutathione peroxidase (GPx), and Trx; (2) hydrophilic antioxidants such as urate, ascorbate, glutathione and flavonoids; (3) lipophilic radical antioxidants such as tocopherol, carotenoid and ubiquinol. Antioxidants can be also classified according to their source including endogenous synthesis such as enzymes, and small molecules as well as exogenous diets such as phenolics, flavonoids, phenolic acids, carotenoids, vitamins and minerals [79] (Fig. 2).

Enzymatic Antioxidants

Enzymatic antioxidants consist of SOD, CAT, GPx and Trx system. The enzymatic antioxidants have more effective protective effects against active and massive oxidative attack due to the ability to decompose ROS [80]. Therefore, this set of antioxidants play important roles in disease conditions including acute hyperoxia injury, radiation injury, lung transplantation and inflammation.

SOD and CAT are the best antioxidants *in vivo*. SODs found in human can be classified into: cytosolic CuZn-SOD, mitochondrial Mn-SOD and extracellular SOD. The SOD can catalyze superoxide into oxygen and hydrogen peroxide [81]. SOD seems to be the first line of defense against oxygen-derived free radicals and can be rapidly induced in some conditions when exposed to the oxidative stress [82]. CAT can neutralize the hydrogen peroxide through decomposing it into molecular oxygen and water.

It is now well established that the mitochondria are the major producers of ROS and also the main targets of ROS. Massive accumulated ROS and free radicals in mitochondria lead to elevated expression of Mn-SOD to inhibit oxidative damage in mitochondria. The accumulation of ROS can induce mitochondrial permeability transition and disrupt the mitochondrial membrane stability [83]. Disruption of mitochondrial outer membrane will cause the release of cytochrome c and other pro-apoptotic factors, such as serine protease

OMI/HtrA2, Smac/Diablo, endonuclease G, and apoptosis inducing factor (AIF), ultimately triggering caspase activation and cell death [84]. A study of kidney transplant patients shows apparent roles of SOD in protecting the allograft from ischemia-reperfusion injury [85].

GPxs belong to a family of phylogenetically related enzymes [86]. The GPx family consists of three evolutionary groups: GPx1/GPx2, GPx3/GPx5/GPx6 and GPx4/GPx7/GPx8 [87]. GPxs can use GSH as a reductant to catalyze H_2O_2 or organic hydroperoxides into water or the corresponding alcohols, respectively [88]. Members of GPxs have anti-oxidative function at different cellular components, GPx1 is present ubiquitously in the cytosol and mitochondria, GPx2 in the cytosol and nucleus, and GPx3 in the plasma, GPx4 is membrane-associated and appears to protect membranes from oxidative challenge [89]. Study found that the loss of GPx1 increased production of H_2O_2 in mouse embryonic fibroblasts and muscles of GPx1 KO mice [90]. GPxs can regulate the concentration of hydroperoxide mediators therefore affect the several pathways of physiological importance has been shown for GPx1 in insulin signaling and GPx4 in cell survival/proliferation and GPx5 in spermatogenesis [86].

The Trx antioxidant system, composed by NADPH, thioredoxin reductase (TrxR), and Trx, is very important in against oxidative stress as endogenous antioxidant system. Trx antioxidants have function in DNA and protein repairing by reducing ribonucleotide reductase as well as methionine sulfoxide reductases. In addition, Trx systems have been found to be involved in response to the immune response [91]. Homodimeric TrxR is a member of the pyridine nucleotide-disulfide oxidoreductase family which includes TrxR, glutathione reductase (GR), TryR, alkyl hydroperoxide reductase, lipoamide dehydrogenase, and mercuric reductase [92]. Trx and TrxR are the dimeric FAD-containing enzyme that catalyzes the NADPH-dependent reduction of the active-site disulfide in oxidized Trx (Trx-S_2) to give a dithiol in reduced Trx [Trx-$(SH)_2$] [93]. Trx-$(SH)_2$ is a hydrogen donor for ribonucleotide reductase and a disulfide reductase regulating thiol redox [94]. Trx systems in cells can use the thiol and selenol groups to maintain redox level. Trx and its binding proteins (ASK1 and TBP2) appear to control apoptosis or metabolic states such as carbohydrate and lipid metabolism [95]. Both GSH system and Trx system can defense oxidative stress via the efficient removal of various ROS [96]. Cytosolic Trx1 and mitochondrial Trx2 are the major disulfide reeducates that affect cell proliferation and viability. The reduced/dithiol form of Trxs binds to ASK1 and inhibits its activity to induce apoptosis. When Trx is oxidized, it dissociates from ASK1 and apoptosis is induced [97]. Another important gene which can directly regulate antioxidant proteins expression is factor nuclear erythroid 2-related factor 2 (NRF2), a transcription factor. A small amount of oxidative stress will trigger NRF2 activation to induce of cytoprotective gene expression (cysteine uptake transporter, heme oxygenase 1) that is essential for cytoprotection and cell survival [98]. At a normal condition, NRF2 interacts with Kelch-like ECH-associated protein 1 (KEAP1). Once sensing the elevated ROS signals, ROS can oxidize redox-sensitive cysteine residues on KEAP1 in NRF2-KEAP1 complex, lead to KEAP1 release from NRF2. The free NRF2 will next translocates to the nucleus, and forms the heterodimerizes with the small MAF protein to bind to antioxidant-responsive elements (AREs) within the regulatory regions of multiple antioxidant genes which regulates their expression [99, 100].

Non-enzymatic Antioxidants

Vitamin A or retinol is a carotenoid produced in the liver and resulted from the breakdown of β-carotene. Vitamin A can directly bind peroxyl radicals before they propagate peroxidation to lipids [101]. CoQ10 can neutralize the oxidative effect of lipid peroxyl radicals and regenerate vitamin E [102]. Vitamin C is effective in scavenging the superoxide radical anion, hydrogen peroxide, hydroxyl radical, singlet oxygen and reactive nitrogen oxide [103]. Vitamin E has 8 isoforms which halts lipid peroxidation by donating its phenolic hydrogen to the peroxyl radicals forming tocopheroxyl radicals which are un-reactive and unable to continue the oxidative chain reaction [104]. Vitamin E can be regenerated through vitamin C

to sustain their antioxidant potential.

Minerals are a small proportion of dietary antioxidants. The most important minerals which have the anti-oxidative function are selenium and zinc. Minerals are the components of antioxidant enzymes which are important for activity maintenance of enzymes [105]. Zinc is an inhibitor of NADPH oxidases which catalyze the production of the singlet oxygen radical from oxygen by using NADPH as an electron donor. Zinc is also a component of superoxide dismutase which is an important antioxidant enzyme that converts the singlet oxygen radical into hydrogen peroxide. Zinc induces the production of metallothionein that is a scavenger of the hydroxyl radical. Zinc also acts as an effective anti-inflammatory and antioxidant agent which inhibits TNF-α-induced NF-κB activation [106].

Except for the vitamins and minerals, many metabolites such as uric acid, biblirubin, and melatonin exist antioxidative function. Studies report that uric acid can prevent peroxynitrite-induced protein nitrosylation, lipid and protein peroxidation and an inactivation of tetrahydrobiopterin, which results in scavenging free radical and chelating transitional metal ions [107]. The uric acid is also considered as the antioxidant to protect central nervous system (CNS) [108]. However, even though the uric acid can prevent the oxidative stress, as the metabolite of purines, its level is usually higher in obesity and diabetes patients which will be a danger sign for the metabolic disease. Bilirubin, the primary form (unconjugated form) of bilirubin circulating in healthy individuals, has antioxidant properties [109]. Recent studies report bilirubin treatment can increase the nuclear accumulation of NRF2 proteins and activation of NRF2 which will up-regulate heme-oxygenase-1 (HO-1) expression in HepG2 cells and primary mouse hepatocytes [110]. Melatonin is a tryptophan metabolite. Studies demonstrate one melatonin molecule has the capacity to scavenge up to 10 molecules of ROS. Melatonin improves the activities of several respiratory chain complexes, thereby reducing electron leakage and free-radical generation [111]. Except for the melatonin itself, its metabolites (N1-acetyl-N2-formyl-5-methoxykynuramine (AFMK), N-acetyl-5-methoxyknuramine (AMK)) have been found to protect cells from the ROS [112].

Flavonoids consist of flavonols, anthocyanins, isoflavonoids, flavanones and flavones. The antioxidant activity of flavonoids depends on the arrangement of functional groups base on structure. Both the configuration and total number of hydroxyl groups substantially influence the mechanism of the antioxidant activity [113]. The B ring hydroxyl configuration is the most significant determinant of ROS scavenging [114]. Phenolic acids are composed of hydroxycinnamic and hydroxybenzoic acids. They are ubiquitous in plant materials and sometimes present as esters and glycosides. They have antioxidant activity as the chelators and free radical scavengers with special impact over hydroxyl and peroxyl radicals, superoxide anions and peroxynitrites [115]. Carotenoids are a group of natural pigments that are synthesized by plants. The main antioxidant property of carotenoids is that the exciting carotenoids dissipate the newly acquired energy through a series of rotational and vibrational interactions with the solvent, thus returning to the unexcited state and allowing them to quench more radical species. This can occur while the carotenoids have conjugated double bonds. The only free radicals that completely destroy these pigments are peroxyl radicals. Carotenoids are relatively un-reactive but may also decay and form non-radical compounds that may terminate free radical attacks by binding to these radicals [116].

ROS and diseases

Oxidative Stress and Neurodegenerative Diseases

Neurodegenerative diseases include Parkinson's disease (PD), Alzheimer's disease (AD), multiple sclerosis and amyotrophic lateral sclerosis. In these diseases, the nerve cells from brain and spinal cord are suffered from mitochondrial dysfunctions as well as excitotoxicity and finally apoptosis, which lead to either functional loss or sensory dysfunctions. Since the brains have a high metabolic rate and relatively reduced capacity for cellular regeneration, nerve cells in brain area are particularly susceptible damaged by ROS shown in Fig. 3. The

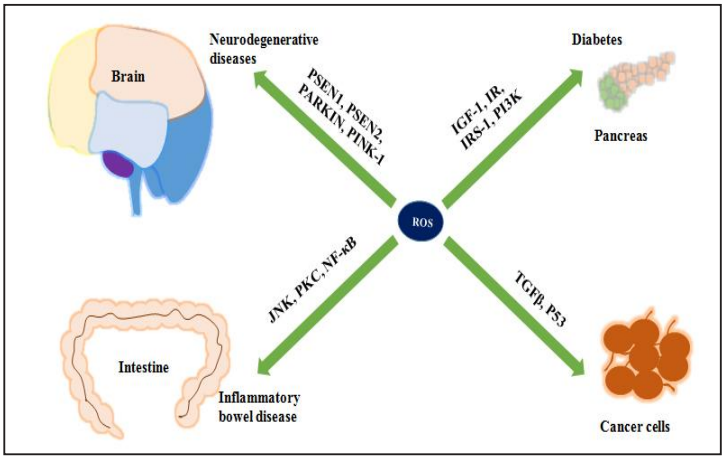

Fig. 3. Oxidative stress caused by reactive oxygen species (ROS) accumulate in different organ will persistently destroy the cells, which may lead to diseases. In brain, ROS will damage the nerve cells which cause neurodegenerative diseases associated with dysfunction of Alzheimer's disease related presenilin-1 and 2 genes (PSEN1 and PSEN2) as well as Parkinson's disease related genes (PARKIN and PINK-1); In gut, ROS will trigger C-Jun-N-terminal kinase (JNK), protein kinase C (PKC), and Nuclear factor kappa B (NF-κB) to damage the gut barrier as well as the microbial balance, which lead to the inflammatory bowel disease; ROS will also cause the DNA damage through p53 and dysregulation of transforming growth factor β (TGFβ) in the normal cell which disrupt cell cycle control and may cause cancer; In pancreas, ROS will inhibit insulin or insulin-like growth factor (IGF)-1, insulin receptor (IR), insulin receptor substrate (IRS)-1 and phosphatidylinositol-3 kinase (PI3K)/Akt kinases and cause the β-cells damage, which decrease the insulin secretion and may cause the diabetes.

neuronal biochemical composition contain large amount of unsaturated lipids, which are metabolized in peroxidation and oxidative modification. Because brain is not particularly enriched in antioxidant defenses, the brain is highly susceptible to ROS [117, 118] and in general the neural cells are more susceptible to oxidative damage as compared to other body tissues. Damage within specific brain region caused by ROS has been reported in the case of PD, AD and amyotrophic lateral sclerosis. For example, lipid peroxidation markers have been identified in the cortex and hippocampus of AD as well as spinal fluid from patients with amyotrophic lateral sclerosis [119]. It has been found that the protein oxidation marker increased in the hippocampus of AD patients [120] and motor neurons of PD patients [121] DJ-1 functions in reducing oxidative stress and transcriptional regulation. Dysfunction of DJ-1 might result in the onset of PD. DJ-1 has general cytoprotective function and antioxidant properties which regulates the extent of stroke-induced damage and neurodegeneration in AD. Indeed, several disease-causing gene mutations in AD related genes (PSEN1, PSEN2) and PD related genes (PARKIN, PINK-1) as well as AD susceptibility gene polymorphism (APOE4) are associated with the increases in oxidative damage and/or vulnerability of oxidative insults [122].

In clinical treatment, many natural and synthetic drugs have been tested. The puerarin is an extract of kudzu roots. Puerarin has been reported to possess neuroprotective function [123]. In dopaminergic neuronal degeneration rat model, puerarin treatment attenuates the disease as reduction of oxidative stress. As predicted, glutathione and catalase, KEAP1 and NEF-2 was elevated. The puerarin activated the NRF2/ARE pathway to clear the ROS may protect the neuron [124].

Gastrodin, is a main component extracted from the rhizome of Gastrodia elata, was found to have neuroprotective effects in PD models, study shows that the heme oxidase 1, superoxide dismutase, glutathione levels as well as NRF2 nuclear translocation were increased in 1-methyl-4-phenyl-1, 2,3, 6-tetrahydropyridine-intoxicated mice treated with gastrodin [125]. Another study demonstrates gastrodin can improved learning and memory abilities of Tg2576 transgenic mice and attenuated intracellular ROS level. Study found the expression levels of BACE1 (sporadic AD relevant protein), activated PKR (pPKRThr446) and activated eIF2α (peIF2αSer51) were elevated in the brains of mice and H_2O_2-stimulated cells [126].

Sulphoraphane is an isothiocyanate and sulphoxythiocarbamate that has anti-oxidative properties as an alternative candidate for AD therapy [127]. Study shows sulforaphane can ameliorated the cognitive function of Aβ-induced AD mouse models [128] and decreased locomotor activity in mice with AD-like lesions [129]. Furthermore, sulforaphane protected the brain from Aβ-induced oxidative cell death via activation of NRF2 signaling cascade [130] which induces cytoprotective proteins including HO-1 in the CNS [131]. Sulforaphane significantly attenuated the levels of microRNA-146a which is selectively upregulated in the temporal cortex and hippocampus of AD brains. Sulforaphane can also reduce STAT-1 activation as well as NLR family, pyrin domain-containing3 (NLRP3) inflammasome activation [132].

Oxidative Stress and IBD

In general, Inflammatory Bowel Disease (IBD) comprises of the chronic relapsing inflammatory disorders, i.e. Crohn's disease and ulcerative colitis. The precise etiology of IBD is still unknown. However, it is widely accepted that IBD is caused by the combinatory factors including genetics, gut microbiota, the host immune system and environmental factors. These factors interact with an outcome of disruption of intestinal homeostasis resulting in dysregulated inflammatory responses of the gut. Since inflammation is tightly associated with the formation of reactive intermediates, including reactive oxygen and nitrogen species, the oxidative stress become the potential mechanism underlying the pathophysiology of IBD. The host produces ROS as an evolutionarily conserved response to microbes or infections. However, chronic and excessive ROS production activates host inflammatory pathways and results in oxidative stress [133]. During IBD development, oxidative stress contributes to chronic inflammation and dysbiosis, control of oxidative stress may help to maintain the intestinal homeostasis [134, 135]. ROS can induce inflammation by triggering JNK, protein kinase C, growth factor tyrosine kinase receptor, and extracellular signal-regulated kinase signaling pathways. Several inflammatory transcription factors including NF-κB are redox sensitive and trigger cellular inflammation [136]. In IBD patients, chronic oxidative stress leads to a tissue destruction and disrupts the microbial balance. Studies have found some beneficial microbes function through fermentation and microbial metabolic products help to prevent the gut damage [137, 138]. However, the human clinical trials showed the variables results about the microbes function in IBD, the causal effect of the microbiotia with the development of IBD is still under active investigation shown in Fig. 3 [138, 139].

Coumarins comprise a large class of cinnamic acid-derived phenolic compounds found particularly in edible plants from different botanical families. Coumarins have antioxidant properties which can be used as antioxidant additives [140]. Study demonstrates that coumarin derivatives promote differential effects on the macroscopic and clinical parameters of the intestinal inflammatory process. Coumarin derivatives (fraxetin, esculin and daphnetin) reduced the incidence of diarrhoea, while the latter two additionally reduced the damage score and colonic weight [141].

Berberine is the principal component of many popular medicinal plants. Study finds the berberine functions as antioxidant through directly scavenging of ROS/RNS and suppression of ROS/RNS production [142]. Cells treated with berberine will induce expression of antioxidant related gene such as antioxidant defense (reduced-glutathione and superoxide dismutase) and oxidant-sensitive proteins (HO-1 and NRF2) [143].

Curcumin belongs to polyphenol, is the major representative of curcuminoids and the main chemical constituents of the spice turmeric as well as curry powder. Curcumin has two phenolic O-H groups and one methylene CH2 group that are capable of H bond-dissociation enthalpy, while trolox has only one phenolic O-H. Therefore, the presence of two identical OH groups as well as methylene CH2 group in curcumin can easily undergo successive oxidations compared to trolox [144]. Study demonstrates that curcumin shows important antioxidant effects as decrease of ROS/RON production, as well as increase of antioxidant enzymes [145].

Oxidative Stress and Cancer

In many types of cancer, an increased oxidative stress has been observed as common feature compared with normal cells. ROS have multiple cellular functions in tumor cells depending on the radical form, concentration and cellular location. ROS induced DNA and protein damage can contribute to cancer initiation through cellular signaling pathways which are associated with tumor cell proliferation, survival and tumor progression shown in Fig. 3. Cancer cells have higher metabolism level than normal cells; they can continuously produce and maintain higher ROS concentrations to maintain their high proliferation rate. The produced ROS can cause oxidative damage of DNA, which in turn to generate mutations in DNA that enhances both the processes of aging and carcinogenesis [146, 147]. IκB kinase β (IKKβ), an NF-κB activator, links ROS with carcinogenesis. Study demonstrates IKKβ is involved in chemically induced liver cancer with enhancing ROS production, JNK activation, and hepatocyte death in the IKKβ liver specific KO mice. Oral administration of an antioxidant successfully blocks JNK activation and compensatory cell proliferation in carcinogenesis mice [148]. In another case, TAK1 is an intracellular hub molecule that regulates NF-κB, TAK1 mutations were identified in patients with diffuse, large B-cell lymphoma and prostate cancer in humans [149]. Moreover, ROS can activate the MAPK pathways which the activation of ERK, JNK, and p38 MAPK signaling proteins were involved in apoptosis via ROS generation. Studies have demonstrated the MAPK pathways, plays a pivotal role in cell survival and the enhanced protection of cancer cells from apoptosis during tumorigenesis [150]. Modulation of MAPK by Antioxidant is also involved in the therapy such as heart failure model [151].

Study demonstrated that the high production of ROS was contingent on impaired TGFβ signaling, which leads to the suppression of the antioxidant enzyme GPx1 [152]. ROS can cause DNA damage, which may excite the p53 in normal cells and consequently activate stress responses as well as DNA repairing. Many studies have found the defect of p53 in cancer cells. Depletion of the p53, ROS-mediated DNA damage would accumulate owing to compromised DNA repair function. It would severely promote the genomic instability and lead to an activation of oncogenes and decrease in antioxidants, thus, increase in ROS levels, leading to more DNA damage and genetic instability. These processes form a vicious cycle which can effectively amplify oxidative stress and promote genomic instability as well as cancer development [153]. Because the increase of ROS in cancer cells may play an important role in the initiation and progression of cancer, such intrinsic oxidative stress has been regarded as an adverse event. However, excessive levels of ROS production can also be toxic to the cancer cells. Cancer cells with increased oxidative stress are likely to be more vulnerable to damage by further ROS insults induced by exogenous agents. Therefore, manipulating ROS levels by redox modulation is a way to selectively inhibit cancer cells proliferation [154, 155].

Green tea (Camellia sinensis) is rich in catechins, of which epigallocatechin-3-gallate (EGCG) is the most abundant. Studies in animal models of carcinogenesis have shown that green tea and EGCG can inhibit cancer cell proliferation. Tea polyphenols are strong radical scavengers because of the presence of the dihydroxy and trihydroxy groups. Treatment of mice with EGCG increases gene expression of γ-glutamyltransferase, glutamate cysteine ligase, and hemeoxygenase-1 in an NRF2-antioxidant response element-dependent manner [156]. Recently, treatment of human prostate cancer LNCaP cells with EGCG activates p53 through acetylation at the Lys373 and Lys382 residues along with consequent increase in GSTP1 (a p53 downstream protein expression in time-dependent manner) [157]. Except for the EGCG, berberine is another anti-cancer drug extracted from traditional Chinese herbal medicines such as berberis amurensis [158]. Studies found berberine can binds to oligonucleotides and stabilizes DNA triplexes or G-quadruplexes, inhibits telomerase and topoisomerase to inhibit many kinds of tumors growth. Berberine has ability to scavenge ROS, inhibit lipid peroxidation and reduce the concentration of metal ions in lipid peroxidation [159].

Oxidative Stress and Diabetes

Accumulating evidence has proven that mitochondrial ROS overproduction is causally related to diabetes and diabetic complications. ROS play an important role in the development of insulin resistance in the type II diabetes (T2DM) and decrease in the pancreatic β cell functions shown in Fig. 3 [160, 161]. Studies showed that high glucose activates various enzyme in mitochondrial, including NADPH oxidase, NO synthases and xanthine oxidase [162-164]. In diabetes, oxidation stress will cause β-cell's glucotoxicity and lipotoxicity [165], which result in an increased toxicity to β-cell by primary pathogenic process of diabetes: hyperglycemia and hyperlipidemia. Studies *in vitro* and *in vivo* have suggested that both high concentration of glucose and lipids are indeed harmful to the β-cells [166]. High glucose can lead to the oxidative stress which will affect insulin mRNA expression and insulin synthesis. In contrast, antioxidants reagent can rescue the expression of insulin promoter and insulin mRNA in cultured cells [167]. Under normal condition, cells need a bulk of cell signaling pathway such as insulin or insulin-like growth factor (IGF)-1, insulin receptor (IR), insulin receptor substrate (IRS)-1 and phosphatidylinositol-3 kinase (PI3K)/Akt or ERK kinases to maintain the normal physiological status. When ROS production exceeds the normal physiological levels, those signaling pathway will be adversely affected, which resulting in lower level of insulin secretion even insulin resistance [168]. A large number of evidence suggested that oxidative stress plays an important role in the pathogenesis of diabetes, and the pancreas in general has low ROS detoxification capacity therefore is sensitive to ROS-induced damage. For this reason, the study of natural or synthesized antioxidant may be of great beneficial in diabetes and related conditions treatment.

Curcuminoids (including curcumin, demethoxycurcumin and bisdemethoxycurcumin) are turmeric-extracted polyphenolic pigments that possess numerous health benefits such as its anti-oxidative function. Recently, study indicates that curcuminoids supplementation can significantly decrease serum malondialdehyde (MDA) and increase SOD activities in patients with T2DM [169]. The triglyceride-lowering effects of curcuminoids have been confirmed in several experimental studies. Curcuminoids reduce hepatic fat accumulation and prevent steatosis by downregulating lipogenic factors and activating AMPK in liver [170].

Gallic acid is a major bioactive polyphenol possesses antioxidant, anti-inflammatory effects [171]. Growing evident showed that gallic acid exhibited antihyperglycemic and insulin secretagogue properties in streptozotocin-induced insulin deficient diabetic rats [172]. Gallic acid supplementation can regenerates β-cells of the islets to restore the normal level of insulin and alleviate the oxidative stress [172]. Gallic acid can also stimulates glucose uptake through translocation and activation of GLUT4 in phosphatidylinositol-3 kinase (PI3K)/p-Akt pathway [173]. Gallic acid attenuates high-fat diet fed-streptozotocin-induced insulin resistance via partial agonist of PPARγ in experimental type 2 diabetic rats and enhances glucose uptake through translocation and activation of GLUT4 in PI3K/p-Akt signaling pathway [173].

Conclusion

Generation of ROS is an evolutionarily conserved process that serving an important role in the cell signaling mechanism as well as the cellular defense mechanism against microbial invasion. The active ROS are continuously produced during normal cellular metabolism. Physiological amount of the ROS is considered to function in signal delivering. However, oxidative stress will occurs when excessive amount of ROS generation induced by environmental factor or disease, which will triggers many physiological and pathophysiological processes such as autophagy, apoptosis, and necrosis. Numerous studies have demonstrated that the oxidative stresses are closely associated with IBD, diabetes and cancer.

The antioxidant systems, including enzymatic antioxidants such as SOD, GPxs, Trx as well as the exogenous antioxidants, can manipulate the ROS level by regulating the genes

expression and related signaling pathways to keep the redox balance and cellular component integrity. Therefore, the antioxidant therapeutic will offers a promising way to prevent and treat the diseases caused by the excessive exposure to ROS.

Abbreviations

AFMK (N1-acetyl-N2-formyl-5-methoxykynuramine); AhR (Aryl hydrocarbon receptor); AIF (apoptosis inducing factor); AIP (Aryl hydrocarbon receptor interacting protein); AMK (N-acetyl-5-methoxyknuramine); AMPK (AMP-activated protein kinase); AREs (antioxidant-responsive elements); ARNT (Aryl hydrocarbon receptor nuclear translocator); ASK1 (apoptosis signal-regulating kinase 1); CAR (Constitutive androstane receptor); CNS (central nervous system); CoQ (CoEnzyme Q); CYP (Cytochrome P450 enzymes); EGCG (epigallocatechin-3-gallate); ETC (Electron transporting chain); ER (endoplasmic reticulum); GLUD1 (Glutamate dehydrogenase 1); GLUL (Glutamate-ammonia ligase); GPxs (Glutathione peroxidases); GR (glutathione reductase); GSH (Glutathione); HO-1(heme-oxygenase-1); HSP90 (Heat-shock protein 90kDa); IBD (Inflammatory bowel disease); IGF (Insulin-like growth factor); IKKβ (IκB kinase β); IR (Insulin receptor); IRS-1 (Insulin receptor substrate-1); JNK (C-Jun-N-terminal kinase); KEAP1 (Kelch-like ECH-associated protein 1); MAPK (Mitogen activated protein kinase); MDA (malondialdehyde); mTOR (Mechanistic target of rapamycin); MLKL (Mixed lineage kinase domain-like); NF-κB (Nuclear factor kappa B); NLRP3 (NLR family, pyrin domain-containing3); NOX (NADPH oxidase); NRF2 (nuclear erythroid 2-related factor 2); PXR (Pregnant X receptor); RIP1 (Receptor-interacting serine/threonine protein kinase 1); PYGL (Glycogen phosphorylase); RIP3 (Receptor-interacting serine/threonine protein kinase 3); PI3K (Phosphatidylinositol-3 kinase); PTEN (phosphatase and tensin homologue); RNS (Reactive nitrogen species); ROS (Reactive oxygen species); SAT1 (spermine N 1-acetyltransferase 1); STAT3 (Signal transducer and activator of transcription 3); SOD (Superoxide dismutase); T2DM (Type II diabetes); TrxR (thioredoxin reductase); Trx (Thioredoxin); TNF (Tumor necrosis factor); TRAIL (TNF-related apoptosis-inducing ligand); TCA (Tricarboxylic acid cycle); VPS34 (vacuolar protein sorting 34).

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Disclosure Statement

The authors have no Disclosure Statement to declare.

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