

Review Article

Insights into the Role of Oxidative Stress in Ovarian Cancer

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Oxidative stress (OS) arises when the body is subjected to harmful endogenous or exogenous factors that overwhelm the antioxidant system. There is increasing evidence that OS is involved in a number of diseases, including ovarian cancer (OC). OC is the most lethal gynecological malignancy, and risk factors include genetic factors, age, infertility, nulliparity, microbial infections, obesity, smoking, etc. OS can promote the proliferation, metastasis, and therapy resistance of OC, while high levels of OS have cytotoxic effects and induce apoptosis in OC cells. This review focuses on the relationship between OS and the development of OC from four aspects: genetic alterations, signaling pathways, transcription factors, and the tumor microenvironment. Furthermore, strategies to target aberrant OS in OC are summarized and discussed, with a view to providing new ideas for clinical treatment.

1. Introduction

Ovarian cancer (OC) is the third most common cancer among women, with 290,000 women diagnosed and 180,000 dying every year globally, and OC is the most lethal gynecological cancer with a five-year survival below 45% [1, 2]. Currently, OC is divided into type I and type II tumors according to the clinical, genetic, and histopathological factors in the revised ovarian carcinogenesis model [3]. Type I tumors develop from benign extraovarian precursor lesions that are present in the ovary, and these tumors are mostly confined to the ovary and have a good prognosis, accounting for only 10% of OC-related deaths. Type II tumors are generally thought to develop from serous tubal intraepithelial carcinoma based on both shared TP53 mutations and integrated molecular analyses [4]. They are more aggressive, resulting in 90% of the deaths from OC, of which high-grade serous carcinoma (HGSC) is by far the most common form of diagnosis, resulting in 70–80% of deaths from OC [5, 6]. Understanding the etiology of OC is of great significance for its prevention and treatment. The current treat-

ment for OC includes surgical resection, chemotherapy, neoadjuvant chemotherapy, radiotherapy, and immunotherapy [7, 8]. However, more than 50% of OC patients eventually relapse and suffer from late metastasis, and secondary adverse reactions and drug resistance pose major challenges to treating OC [9].

Oxidative stress (OS) arises when there is an imbalance between the production of free radicals and reactive metabolites (so-called prooxidants, including reactive oxygen and nitrogen species) and intrinsic antioxidant defenses. This imbalance leads to damage of biological molecules and tissues and has the potential to impact on the whole organism [10, 11]. Reactive oxygen species (ROS) are represented by free radicals and nonfree radical oxygen-containing molecules, including superoxide anions ($O_2^{\cdot-}$), hydrogen peroxides (H_2O_2), singlet oxygens (1O_2), and hydroxyl radicals ($OH\cdot$) [12, 13]. Reactive nitrogen species (RNS) include nitric oxide ($NO\cdot$) and peroxynitrite anions ($ONOO^-$) [14] (Figure 1). The generation of ROS and RNS is dependent on both enzymatic and nonenzymatic reactions. Enzymatic reactions mainly involve nicotinamide adenine dinucleotide

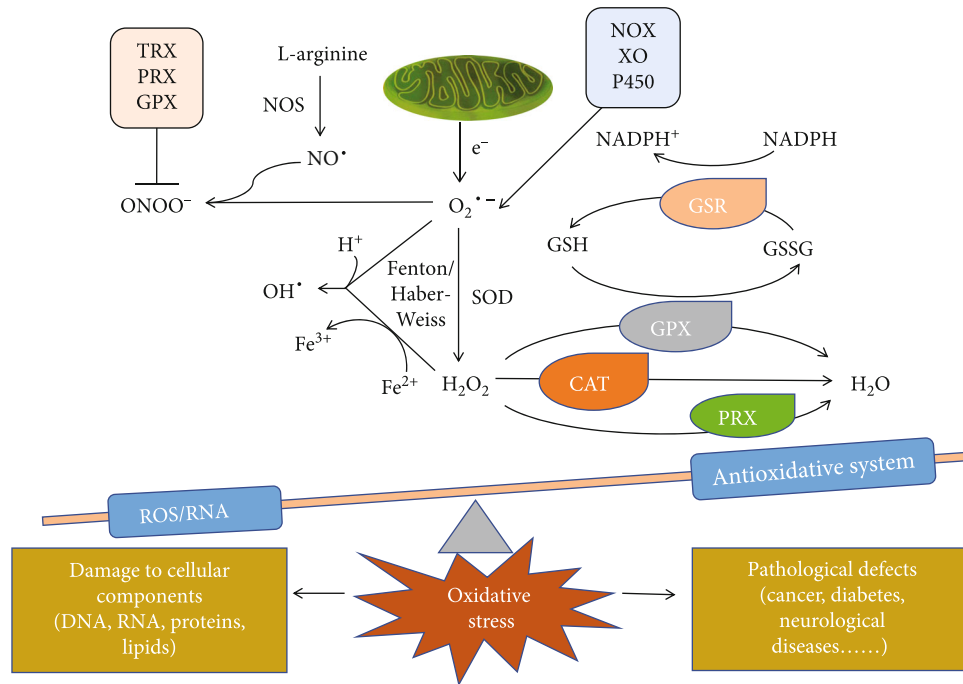


FIGURE 1: The major oxidative and antioxidant systems. Both electron leakage from the mitochondria and enzymatic activity of the oxidase system, as represented by NOX, XO, and cytochrome P450, produce $O_2^{\cdot-}$. SOD converts $O_2^{\cdot-}$ into H_2O_2 [233], and in the presence of reducing transition metals, such as ferrous ions, H_2O_2 is converted into highly active OH^\cdot by the Fenton or Haber-Weiss reaction [26]. H_2O_2 is converted into H_2O by CAT, PRX, and GPX. In the GPX reaction, GSH is oxidized to GSSG (glutathione disulfide), which can be converted back to GSH by GSR during $NADPH$ consumption [15]. L-Arginine is converted to NO^\cdot under the catalysis of nitric oxide synthase (NOS), which reacts with $O_2^{\cdot-}$ to form $ONOO^-$ [234]. TRX, PRX, and GPX can inhibit $ONOO^-$ generation [24]. Each ROS has different physical and chemical properties and half-lives. Among these, OH^\cdot has the strongest oxidizing property, followed by $O_2^{\cdot-}$, while H_2O_2 is relatively weak. H_2O_2 and NO^\cdot also play essential roles as signaling molecules [31].

($NADPH$) oxidase (NOX), xanthine oxidase (XO), peroxidase, and the cytochrome P450 system [15–17], while nonenzymatic reactions, i.e., electron leakage from the mitochondrial respiratory chain, are the main source of ROS [18]. To avoid OS, cells possess a series of nonenzymatic and enzymatic antioxidant defense systems. The nonenzymatic defense system includes flavonoids, vitamins (A, C, and E), and glutathione (GSH) [19, 20], while the enzymatic antioxidant system consists of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX), glutathione reductase (GSR), glutathione S-transferases (GST), peroxiredoxin (PRX), and thioredoxin (TRX) [21–25] (Figure 1). In healthy organisms, ROS and RNS are normal by-products of cellular metabolism and participate in the transduction of different signaling pathways, and the antioxidant defense system will quickly remove them before they cause damage to cellular structure and function [22, 26]. However, many endogenous factors (mental stress, inflammation, various enzymatic systems, etc.) and exogenous factors (ultraviolet radiation, ionizing radiation, air pollution, etc.) can induce excessive production of ROS and RNS in cells [27–29]. This heightened production of oxidants can overwhelm the body's antioxidant defense system leading to a state of OS, which in turn leads to irreversible oxidative damage to proteins, lipids, and nucleic acids [30]. Such damage interferes with key cellular functions, and this is closely related to the occurrence and development of cancer, diabetes, and cardio-

vascular and nervous system diseases, to name just a few [31, 32] (Figure 1).

OS has been widely confirmed to play a dual role in the pathogenesis of cancer [11, 33]. On the one hand, ROS/RNS can promote molecular genetic changes that lead to tumor initiation, growth, and development as well as to therapeutic resistance [34, 35]. On the other hand, long-term elevated ROS/RNS levels have cytotoxic effects and can induce the activation of apoptotic pathways [35, 36]. It is well known that cancer cells contain higher levels of reactive molecules that maintain the cellular phenotype and high proliferation rate, and tumor cells must find ways to optimize ROS-driven proliferation while avoiding ROS thresholds that trigger senescence, apoptosis, or ferroptosis [37, 38]. Several studies on OC have confirmed this and have shown upregulated responses to OS in OC cells. For example, NOX, inducible nitric oxide synthase (iNOS) [39–41], and SOD [42, 43] are overexpressed in OC compared with normal tissues, and GSTs have been reported to be overexpressed in human malignancies and to be associated with tumor progression and drug resistance [44]. OS triggers cancer cells to produce lactic acid by glycolysis rather than oxidative phosphorylation, even under aerobic conditions, which is referred to as aerobic glycolysis or the Warburg effect [45]. The Warburg effect has been used to detect and monitor tumor progression in the clinic using positron emission tomography to detect highly glycolytic regions in the body by measuring

2- ^{18}F fluoro-2-deoxy-D-glucose (a glucose analogue concentrated in highly proliferative tumorigenic tissues) [46]. Iron and its metabolites promote the generation of ROS via the Fenton reaction, and these ROS induce DNA damage thus leading to carcinogenesis. For example, when chocolate cysts form, the ovary contains old blood with excessive iron, which may increase the risk of malignant transformation of endometriosis into ovarian clear cell carcinomas [47]. At the same time, when cells are moderately exposed to non-toxic doses of H_2O_2 , glucose-6-phosphate dehydrogenase (G6PD) is activated, which leads to a switch in glucose metabolism from glycolysis to the pentose phosphate pathway (PPP) and nucleotide synthesis. This approach avoids exposing tumor cells to OS due to the production of ROS and provides a survival advantage for the development of cancer [48, 49]. In addition, NADPH produced by the PPP is used for reductive biosynthetic reactions in cells, which enhances the GSH and TRX-based antioxidant systems and maintains ROS levels in a state of dynamic equilibrium [50–53]. Cells adapt to OS through metabolic reprogramming in the short term while genetic reprogramming provides long-term adaptation [54–56]. OS can regulate the redox state of tumor cells by regulating gene expression or activating different transcription factors, such as activating protein 1, HIF-1 α , heat shock factor 1, NF- κ B, Nrf2, and the tumor inhibitor p53 [11, 57]. Additionally, ROS also interact with signaling molecules such as mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3K), phosphatase and tensin homolog (PTEN), and protein tyrosine phosphatase (PTP) by targeting reactive cysteine residues in proteins to activate a variety of cellular processes, thus regulating cell proliferation, differentiation, migration, and apoptosis [58–61].

Many factors are involved in OC, including genetic factors, age, infertility, nulliparity, microbial infections, obesity, and smoking [7, 8]. A number of studies have been conducted on the role of OS in the development of OC [16, 62–66], and the strong association between OS and OC is gradually becoming a hot topic of interest. This review updates the relevant literature and focuses on teasing out the effects of OS on OC from different perspectives. In addition, we comprehensively analyze the interaction between OS and genetic alterations, different signaling pathways and transcription factors, and different components of the tumor microenvironment (TME) to further explore the role of OS in the pathogenesis and treatment of OC.

2. OS-Related Pathogenesis in OC

OS leads to the development of OC through four aspects: genetic alterations, signaling pathways, transcription factors, and the TME (Figure 2).

2.1. OS-Mediated Genetic Alterations in OC. OC can be triggered through OS-mediated genetic alterations such as oxidative damage of nuclear DNA and mitochondrial DNA (mtDNA), DNA hypomethylation, and abnormal expression of microRNA. The specific mechanisms are as follows.

DNA damage and genetic instability caused by OS play a crucial role in the occurrence and development of OC [67, 68]. H_2O_2 and the hydroxyl radicals generated by the Fenton reaction have been shown to promote the transferrin- (Tf-) TfR1 axis, which induces DNA double-strand breaks in epithelial cells of the fallopian tube, which promotes the progression of OC [69]. The most common product of DNA oxidative damage is 8-hydroxy-2'-deoxyguanosine (8-OHdG), which is formed by guanine oxidation [70], and it is usually used as a biomarker of DNA damage as well as for assessing the risk associated with cancer progression [71–73]. In addition, 8-OHdG can induce C:G to A:T transformations, which are the most important somatic mutations in OC, breast cancer, lung cancer, and gastric cancer [74]. Also, about half of all patients with OC have abnormal homologous recombination repair (HRR) [8]. A recent study showed that inhibition or depletion of RAD51, a key protein involved in HRR, can lead to OS and increased DNA oxidative damage in OC, and this reflects the involvement of HRR in redox state regulation in OC [75].

mtDNA is more susceptible to oxidative damage than nuclear DNA because mitochondria house the electron transport chain that produces large amounts of ROS [76], and mitochondria lack effective DNA repair mechanisms [77]. mtDNA mutations have been reported in various cancers, including OC [78–81], and studies have shown that many chemical carcinogens preferentially bind to mtDNA rather than nuclear DNA [82]. In addition, damage to nuclear DNA can trigger mitochondrial reactions, while the increase in ROS in mitochondria can aggravate nuclear DNA damage [83, 84]; therefore, there may be a “vicious circle” between OS, DNA damage, and cancer development [85]. A correlation between mtDNA mutations and response to therapy in OC has also been reported. HGSC patients with heteroplasmic pathogenic mtDNA somatic mutations were found to have a higher incidence of platinum resistance and disease relapse compared to patients without pathogenic mtDNA somatic mutations (80% vs. 16.7%, $p = 0.035$), and the phenomenon of accumulation of oxidative damage-derived G>T and A>C somatic mutations in the tumor samples indicated that the tumor cells were exposed to OS [86]. Another study suggested that disruptive mtDNA mutations may be used as adjuvant prognostic molecular markers [87].

DNA methylation is one of the primary epigenetic mechanisms for regulating gene expression, and DNA hypomethylation has been reported to be associated with the initiation and progression of various cancers [88]. DNA methylation involves the covalent bonding of a methyl group to the 5th carbon position of the cytosine of the genomic CpG dinucleotide by DNA methyltransferase [89], and this process is inhibited by ROS, thus leading to DNA hypomethylation [90–92]. The change in DNA methylation is an early event in OC [93], and DNA hypomethylation has been shown to contribute to the high expression of SLC4A11 (a solute-linked cotransporter), which is related to the poor prognosis of OC caused by OS [94].

MicroRNAs (miRNAs) also play roles in the pathogenesis of OC [65, 95]. miRNAs are small noncoding RNAs that

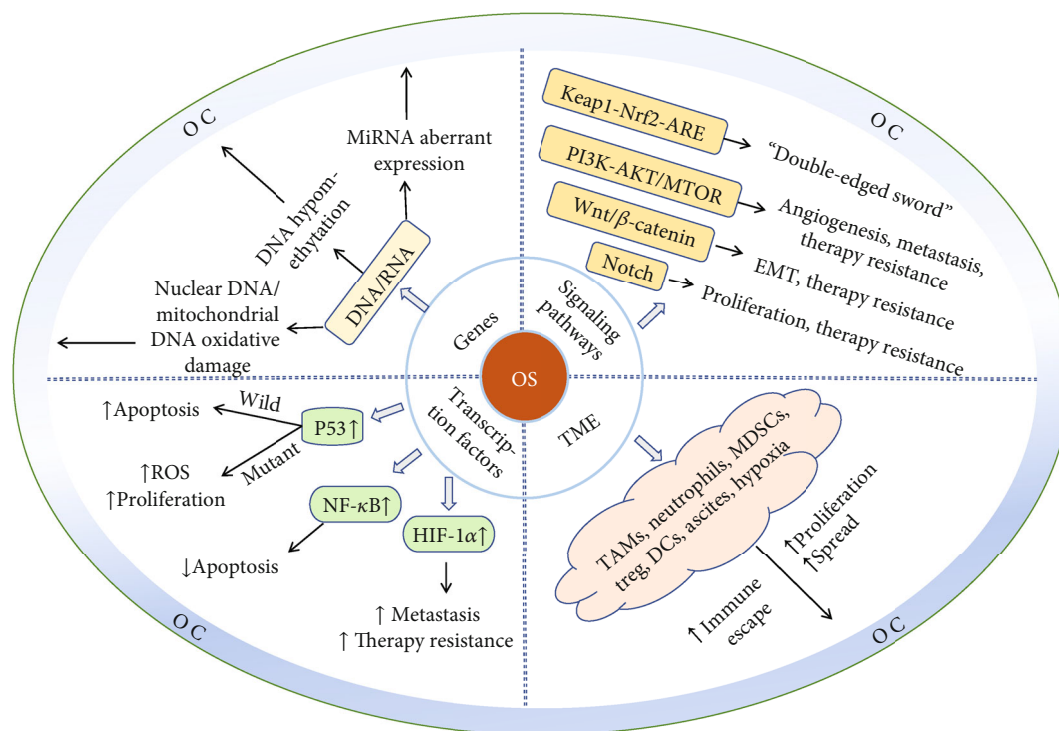


FIGURE 2: OS-related pathogenesis in OC.

participate in the regulation of posttranscriptional gene expression by inducing mRNA degradation or inhibiting translation [96]. In addition, miRNAs are considered to be important mediators of the immune system, to be involved in inflammatory reactions, and to be closely related to the progress and treatment of diseases [97]. Several studies have demonstrated that OS can increase the sensitivity of OC cells to paclitaxel and promote the mesenchymal-epithelial transition by stimulating the overexpression of miR-141 and miR-200s [98, 99].

2.2. OS-Mediated Alterations of Signaling Pathways in OC. Many studies have confirmed the important role of redox modification of signaling pathways in the pathogenesis of OC, including the Keap1-Nrf2-ARE, PI3K/AKT/mTOR, Wnt/ β -catenin, and Notch pathways [100–103].

2.2.1. Keap1-Nrf2-ARE Signaling Pathway. The Keap1-Nrf2-ARE signaling pathway is one of the most important pathways through which cells respond to OS, and it has attracted attention due to its ability to regulate a broad range of antioxidant and detoxification genes [31, 104]. Nuclear factor E2-related factor 2 (Nrf2), which is at the center of this pathway, regulates the transcription of genes that encode various detoxifying enzymes and antioxidant proteins [105]. Under homeostatic conditions, Nrf2 is usually localized in the cytoplasm, where it binds to the inhibitor Kelch-like ECH-associated protein 1 (Keap1). Keap1 is an adaptor protein for the Cullin3-dependent E3 ubiquitin ligase, which mediates the ubiquitination and subsequent degradation Nrf2 in order to maintain basal levels of the protein [106, 107] (Figure 3). When cells are exposed to OS, the cysteine

residues of Keap1 are oxidized, which causes Nrf2 to dissociate from the Keap1 complex and translocate into the nucleus. There it forms a heterodimer with the Maf (musculoaponeurotic fibrosarcoma) protein, which then binds to ARE, the first antioxidant response element to be identified. Thus, Nrf2-regulated antioxidant gene transcription can be activated to exert an antioxidant effect [108, 109] (Figure 3). The activation of the Nrf2 pathway is considered to be a double-edged sword in OC [104, 110, 111] (Figure 3). On the one hand, the Nrf2 pathway can maintain the stability of the normal ovarian cell environment and genome to prevent carcinogenesis induced by OS [112]. On the other hand, the Nrf2 pathway protects OC cells from oxidative damage [113, 114] and helps them cope with various cytotoxic drugs, thus enhancing the invasive ability and chemotherapy resistance of OC [110, 115].

The chemotherapy resistance of OC cells is related to mutations within highly conserved domains of the *Keap1* gene [116] and to the activation of downstream genes of the Nrf2 pathway [117]. The downstream antioxidant proteins of the Nrf2 pathway mediate detoxification through glutathione coupling and participate in ATP-dependent drug efflux, which may be one of the mechanisms of drug resistance in OC cells [107]. In addition, inhibiting the production of proteasomes promotes the translocation of Nrf2 into the nucleus via the Keap1/Nrf2 pathway, resulting in drug resistance in OC cells. Nrf2 and peroxisome proliferator-activated receptor- γ coactivator 1 α (PGC1 α) can synergistically regulate antioxidant functions and mitochondrial functions, thus regulating the maintenance of proteasome activity and affecting the sensitivity of OC cells to chemotherapy agents [101].

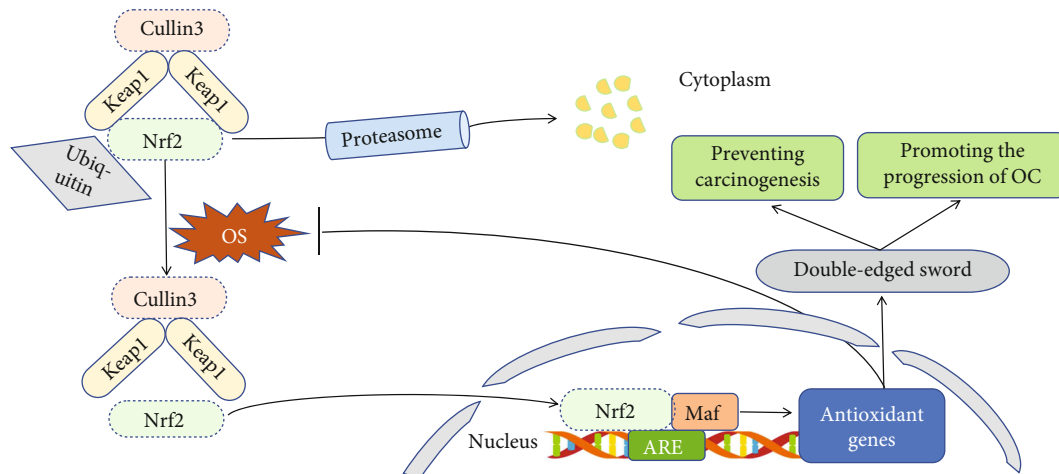


FIGURE 3: Transduction mechanism of the OS-mediated Keap1-Nrf2-ARE signaling pathway in OC. Under physiological conditions, Nrf2 is retained in the cytoplasm by Keap1. Keap1 binds Nrf2 to the Cullin3-dependent E3 ubiquitin ligase complex, which promotes the ubiquitination and subsequent proteasome degradation of Nrf2 [106, 107]. Under conditions of OS, the cysteine residues exposed on the surface of Keap1 are oxidized, which causes Nrf2 to dissociate from Keap1, translocate to the nucleus, form a heterodimer with Maf, and then bind with ARE, thereby transcriptionally activating Nrf2-regulated antioxidant gene expression and inhibiting OS [108, 109]. The activation of the Nrf2 pathway is a double-edged sword in OC, and it maintains the stability of the normal ovarian cell environment and genome in order to prevent OS-induced carcinogenesis [112], while it also protects tumor cells from OS thus enhancing the invasion and chemoresistance of OC [110, 115].

Recently, the Keap1-Nrf2-ARE pathway has been shown to play an important role in the prognosis of OC. Cho et al. detected the expression of Nrf2 and Keap1 in 100 cases of epithelial ovarian cancer (EOC) tissues by immunohistochemistry and followed up all patients for a mean of 55.3 months. They found that Nrf2 was overexpressed in the cytoplasm of OC cells. Further survival analysis showed that high Keap1 expression predicted better overall survival and was an independent prognostic factor. Specifically, high levels of Keap1 in the cytoplasm can inhibit the nuclear translocation and enhance the negative feedback control of Nrf2, thereby inhibiting the survival of OC cells [118].

2.2.2. PI3K/AKT/mTOR Signaling Pathway. The PI3K/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) signaling pathway plays a central role in the proliferation, migration, and chemoresistance of OC [119–122], and the specific transduction mechanism is shown in Figure 4. ROS can inhibit the activity of PTP and PTEN by oxidizing cysteine residues, thus activating the PI3K/AKT/mTOR pathway [123–125] (Figure 4). Moreover, the expression of PTEN was reported to be decreased in 104 of 151 analyzed EOC samples [126]. OS facilitates the growth and metastasis of OC by activating the PI3K/AKT/mTOR pathway in order to increase the expression of vascular endothelial growth factor (VEGF) [127] and to promote de novo fatty acid and cholesterol biosynthesis [100]. In addition, NO can protect OC cells from apoptosis and can enhance drug resistance by activating the PI3K/AKT/mTOR pathway [128]. Interestingly, another study on OC showed a contrasting phenomenon in which ROS mediated apoptosis by inhibiting the PI3K/AKT/mTOR signaling pathway [129], which was related to the concentration of ROS and confirmed the dual role of OS in cancer.

2.2.3. Wnt/ β -Catenin Signaling Pathway. Another important signaling pathway in OC is Wnt/ β -catenin, which plays a role in metastasis and therapy resistance [130–133]. Recent studies have also shown that it contributes to immune evasion of OC [134, 135]. NOX1-derived ROS have been reported to stimulate the Wnt/ β -catenin pathway by oxidizing and inactivating nucleoredoxin (a redox-sensitive regulatory protein that negatively regulates the Wnt pathway by interacting with the Dishevelled protein), thus promoting tumor cell proliferation [136] (Figure 5). As shown in Figure 5, in the absence of canonical Wnt ligands, the level of intracellular β -catenin is regulated by the polyprotein “destruction complex” [137]. CK1 and unphosphorylated GSK3 β phosphorylate β -catenin and target it for degradation [133]. The PI3K/AKT pathway is activated by ROS and phosphorylates GSK3 β , thus inhibiting its ability to phosphorylate and degrade β -catenin [138, 139] (Figure 5). Moreover, phosphorylated GSK3 β is often found in OC [133]. A study showed that tankyrase (an oncogenic regulator of OC cell proliferation) promotes aerobic glycolysis of OC cells by stimulating the Wnt/ β -catenin/Snail pathway [102]. Taken together, these results indicate that there is a bidirectional regulation between the Wnt/ β -catenin pathway and the redox state of OC cells, and the interactions of these regulatory mechanisms are involved in the pathogenesis of OC.

Many reports on the invasive properties of OC have shown that the activation of epithelial-mesenchymal transition (EMT) is critical for the acquisition of a malignant phenotype in OC, especially in HGSC [140, 141]. OC cells undergoing EMT have stem cell-like properties that enable them to spread and metastasize [133]. The Wnt/ β -catenin pathway is considered to be one of the main signaling pathways involved in EMT, and it plays a key role in the

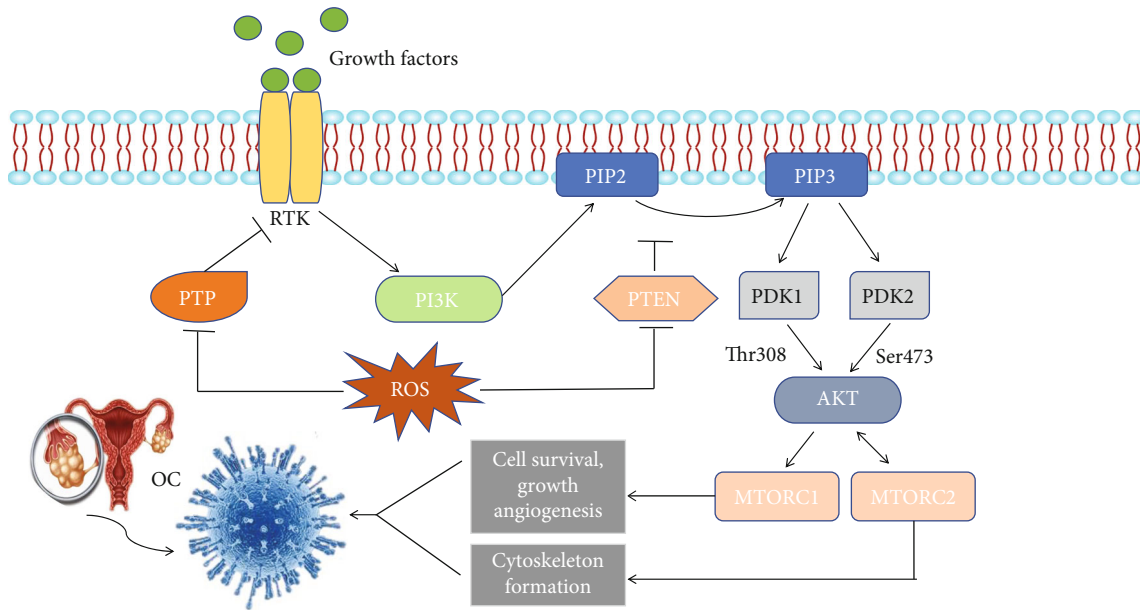


FIGURE 4: Transduction mechanism of the OS-mediated PI3K/AKT/mTOR signaling pathway in OC. Growth factors interact with receptor tyrosine kinase (RTK) leading to PI3K activation, which can be inhibited by PTP [136, 235]. Fully activated PI3K phosphorylates phosphatidylinositol bisphosphate (PIP2) to phosphatidylinositol trisphosphate (PIP3). This conversion results in the activation of AKT by phosphorylation of its kinase domain (Thr308) by PDK1 and phosphorylation of its C-terminal domain (Ser473) by PDK2. AKT can further activate mTOR, which includes mTOR complex 1 (mTORC1) and mTORC2. Activation of mTORC1 leads to cell survival, growth, and angiogenesis, while mTORC2 has been implicated in cytoskeleton formation and cell survival [235, 236]. PTEN reverses the effects of PI3K by dephosphorylating PIP3 [236]. ROS can inhibit the activity of PTP and PTEN by oxidizing cysteine residues, thus activating the PI3K/AKT/mTOR pathway [123–125] leading to the proliferation, migration, and chemotherapy resistance in OC.

regulation and maintenance of OC stemness [142–144]. In addition, the Wnt/ β -catenin signaling pathway is involved in the remodeling of the extracellular matrix in OC, which may be mediated by the activity of matrix metalloproteinase [132, 145].

A negative correlation has been demonstrated between Wnt activity and T cell signature [134, 146]. For example, Wnt inhibitors have been shown to significantly inhibit tumor progression and to increase the infiltration of CD8⁺ T cells in the TME in the OC model [146].

The Wnt pathway has been shown to be involved in drug resistance in OC, and inhibition of the Wnt pathway can increase the sensitivity of OC cells to chemotherapeutic agents [147]. In recent years, the Wnt pathway has also been shown to contribute to ameliorating adverse reactions caused by chemotherapy in OC. For example, in a mouse model of OC, the Wnt agonist BIO showed a significant therapeutic effect on cisplatin-induced acute kidney injury without affecting cisplatin's antitumor activity. One of the mechanisms was the activation of Wnt and its downstream pathway, which inhibits the production of excessive ROS in cells and thus reduces apoptosis in renal tubular cells [148].

2.2.4. Notch Signaling Pathway. Notch and its intracellular domain (NICD) have been shown to be overexpressed in OC, and this is closely related to poorer prognosis in patients with OC [149–152]. OC cells in which Notch is activated show resistance to carboplatin, and it has been reported that methylseleninic acid can synergistically enhance the killing

effect of carboplatin on OVCA429/NICD3 OC cells (which have a constitutively active form of Notch3) and that this can be promoted by ROS [153]. A correlation between Notch and NO/soluble guanylate cyclase (SGC) signaling has also been found. Low concentrations of NO can promote the progression of cancer, while many physiological functions of NO are mediated by SGC [103], and it has been confirmed that activation of the Notch pathway can enhance NO/SGC signaling in OC cells thereby promoting the proliferation and survival of OC cells [103]. In addition, a crosstalk has been shown between the Wnt/ β -catenin and Notch pathways in OC. On the one hand, the β -catenin and Notch pathways synergistically promote proliferation and migration of OC cells, while on the other hand, inhibition of β -catenin increases the activity of the Notch system, thus showing the compensatory activities between the two pathways [154]. A method for detecting the activity of Notch has been developed that calculates the pathway activity score based upon the expression level of the conserved Notch target genes, and this has had a positive effect on clinical research and drug development for various diseases, including OC [155].

2.3. OS-Mediated Alterations of Transcription Factors in OC. In addition to signaling pathways, the development and progression of OC caused by OS is also closely related to several transcription factors. The following will focus on the regulation of OC by P53, NF- κ B, and HIF-1 α under conditions of OS.

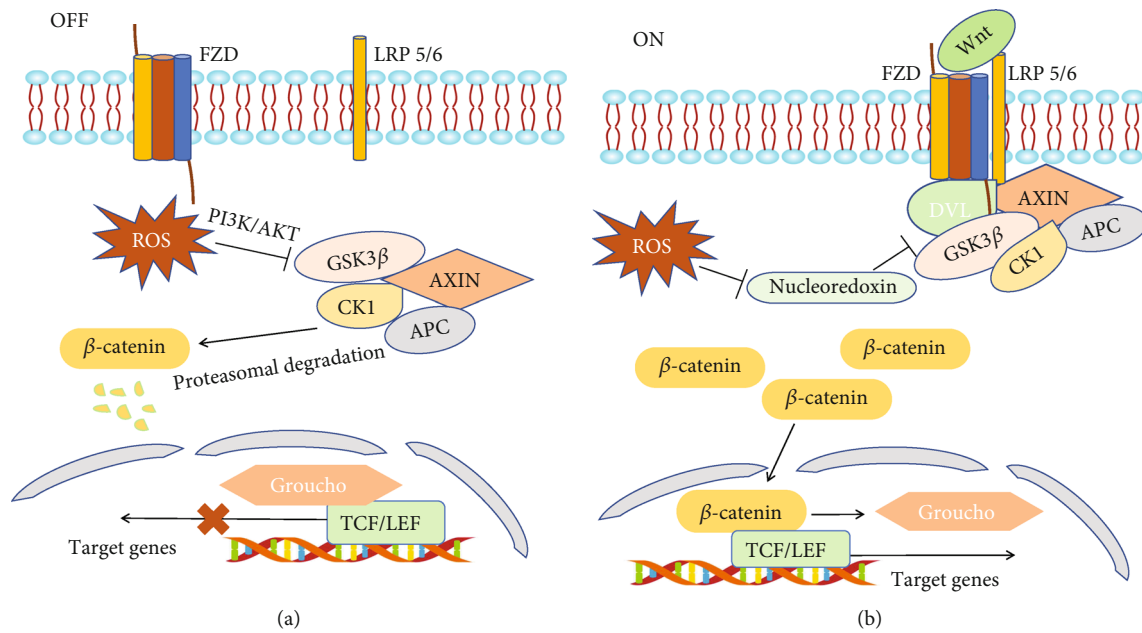


FIGURE 5: The transduction mechanism of the OS-mediated Wnt/ β -catenin signaling pathway in OC. (a) In the absence of the Wnt ligand, the level of intracellular β -catenin is controlled by a “destruction complex” formed by glycogen synthase kinase 3 β (GSK3 β), casein kinase 1 (CK1), adenomatous polyposis coli (APC), and AXIN (a cytoplasmic protein regulating G-protein signaling) [138]. The destruction complex ubiquitinates and degrades β -catenin, thus preventing it from entering the nucleus to bind to the TCF/LEF complex and activate its target genes [132, 137]. ROS phosphorylate and inactivate GSK3 β by activating the PI3K/AKT pathway and thus inhibiting GSK3 β 's ability to degrade β -catenin [138, 139]. (b) In the presence of the Wnt ligand, the ligand binds to the cell surface receptor encompassing frizzled (FZD) and low-density lipoprotein receptor-related protein 5/6 (LRP5/6), leading to their conformational changes [137]. Disheveled (DVL) is then recruited and phosphorylated by FZD. Phosphorylated DVL in turn recruits AXIN, which inactivates the destruction complex and promotes the accumulation of β -catenin in the cytosol [138]. Subsequently, β -catenin is translocated into the nucleus where it displaces Groucho and binds to TCF/LEF members. Together with coactivators, the transcription of downstream target genes is initiated [132]. ROS can upregulate the Wnt pathway by oxidizing and inactivating nucleoredoxin, which inhibits DVL [136].

As a well-known tumor suppressor gene, p53 plays a major role in regulating cell proliferation, apoptosis, DNA repair, and genomic stability [156, 157], and about 96% of HGSC cases carry p53 mutations [158]. In contrast to wild-type p53, mutant p53 has been shown to stimulate the production of ROS by regulating redox-related signaling pathways and enzymes [159–161]. In addition, mutant p53 has been shown to activate glycolysis in tumor cells in order to maintain the Warburg effect, thus promoting cancer progression and tumor growth [159]. OS plays a role in the changes in p53 activity. OS has been shown to upregulate p53 in OC cells, thus inducing apoptosis and autophagy [162, 163]. In addition, high levels of OS can enhance the stability of mutant p53 [160, 164]. Interestingly, Padmanabhan et al. showed that apoptosis in OC cells was induced by OS and protein toxicity triggered by zinc oxide nanoparticles independently of the p53 mutation state [165].

NF- κ B is another important transcription factor involved in inflammation, immunity, apoptosis, and drug resistance [166, 167]. NF- κ B has been shown to contribute to the initiation of tumorigenesis and to play a crucial role in tumor cell proliferation and survival [168]. The p65 and p50 NF- κ B subunits have been shown to be highly expressed in OC patients and to be associated with poor prognosis [169]. NF- κ B can protect OC cells from OS by regulating the expression of antioxidant genes [170], and MnSOD

(SOD2) seems to be the main target of NF- κ B [171]. Additionally, NF- κ B regulates the production of NO through iNOS, thus inducing angiogenesis and increasing resistance to apoptosis [172]. However, it has been shown that NF- κ B may also function as a potential tumor suppressor in some specific cases [168]. In contrast, ROS can promote the nuclear translocation of NF- κ B [173], and the inhibition of OS in OC cells has been shown to inactivate NF- κ B, thus inhibiting tumor progression [174]. Interestingly, Cys62, a key cysteine residue in the P50 domain, needs to be reduced in order to obtain effective NF- κ B DNA binding [173]. In addition, there is crosstalk between NF- κ B and Nrf2 under pathological conditions, and the two proteins inhibit each other [175].

Hypoxia-inducible factor 1 alpha (HIF-1 α) is a key regulator of cellular response to hypoxia, which can be detected in many carcinomas, including OC. HIF-1 α is closely related to tumor growth and angiogenesis [176, 177]. Under normal oxygen levels, HIF-1 α is hydroxylated by prolyl hydroxylase (PHD), after which it binds to von Hippel-Lindau tumor suppressor protein and is subsequently ubiquitinated and degraded by proteasomes. However, under hypoxic conditions, the activity of PHD decreases, resulting in HIF-1 α escaping from proteasome degradation [177, 178]. In addition to hydroxylation, SUMOylation and S-nitrosation are also related to the stability of HIF-1 α [179]. Under hypoxic

conditions, the levels of ROS in OC cells are increased paradoxically and this activates HIF-1 α [178, 180]. HIF-1 α has been shown to inhibit E-cadherin by upregulating the expression of its target genes, such as SNAIL [180], LOX [181], and AEG-1 [182], thus leading to EMT and promoting the invasion and metastasis of OC. Meanwhile, the reduced expression of HIF-1 α suppresses the growth of OC cells [183, 184]. HIF-1 α is also involved in the regulation of chemotherapy resistance, and it has been reported that HIF-1 α can promote chemotherapy resistance by blocking the cell cycle in the G0/G1 phase [185]. Additionally, the tumor pharmacokinetic DCE-MRI perfusion parameters in patients with OC are negatively correlated with the expression level of HIF-1 α , which can be used to screen the tumor characteristics of OC and help clinicians choose the best treatment options [186].

2.4. OS-Mediated Alterations of the TME in OC. The TME refers to the niche in which tumor cells interact with the host stroma, including different immune cells, fibroblasts, endothelial cells, and metabolites [187]. OC has a unique TME, and coevolution of cancer cells with their surroundings is an indispensable prerequisite for OC progression [188]. OS is involved in regulating OC progression by affecting components such as tumor-associated macrophages (TAMs), neutrophils, myeloid-derived suppressor cells (MDSCs), Treg cells, ascites, and lysophosphatidic acid (LPA) in the TME.

TAMs are a major inflammatory component of the tumor microenvironment and are associated with tumor growth and metastasis [189]. In TAMs, H₂O₂ triggers the expression of tumor necrosis factor- α (TNF- α) by activating the p38 and JNK pathways [190]. In turn, TNF induces ROS/RNS generation by controlling TNF signaling downstream of TNF receptors [191]. OS has been reported to drive TAMs to release different cytokines like TNF- α , interleukin1- α (IL1- α), IL-6, IL-10, and transforming growth factor β (TGF β) which results in the progression of OC [188, 192]. A study showed that OC cells can induce the production of itaconic acid (a metabolite resulting from tumor cell interactions with TAMs) in resident peritoneal macrophages, which contributed to the increase in oxidative phosphorylation and ROS and resulted in tumor growth [193].

Neutrophils, as the first line of defense against infection, are implicated in cancer-related inflammation [187]. Compared with the neutrophils of healthy women, the neutrophils isolated from OC patients show enhanced functional activity and higher ROS levels, which contribute to tumor progression and metastasis [194]. A study on dormancy models of OC and lung cancer showed that in response to stress hormones, the proinflammatory protein S100A8/A9 is released by neutrophils, and this leads to the accumulation of oxidized lipids in polymorphonuclear neutrophils by inducing the activation of myeloperoxidase. Moreover, oxidized lipids directly activate the proliferation of dormant tumor cells by upregulating the fibroblast growth factor receptor pathway [195].

MDSCs can inhibit immune responses in cancer patients and can lead to immune evasion [188] through the production and release of ROS and RNS [196] and are an important

source of immunosuppression in OC [197]. The number of MDSCs is significantly increased in OC patients, especially monocytic MDSCs [198], and MDSCs can enhance the stemness of EOC cells by inducing the CSF2/p-STAT3 signaling pathway [199]. MDSCs can induce an increase in ROS [200], while ROS inhibitors can reverse MDSC-mediated T lymphocyte inhibition [201]. Another study showed that MDSCs generate NO through iNOS and that NO induces T cell apoptosis by inhibiting the Jak3/STAT5 signaling pathway [202]. In addition, tumor-infiltrating MDSCs have been shown to produce ONOO⁻, which nitrates tyrosine residues in the T cell receptor-CD8 complex, thus disrupting the binding of specific peptide-major histocompatibility complex dimers to CD8⁺ T cells [203].

Other cells in the TME are also involved in regulating tumor progression under conditions of OS. For example, Treg cells are implicated in tumor-associated immunosuppression and are vulnerable to OS, which has been shown to induce apoptosis in Treg cells. Interestingly, apoptotic Treg cells have been shown to enhance immunosuppression and to mediate the immune escape of tumor cells [204]. In addition, tumor-derived microvesicles contribute to restoring and improving the antigen processing capacity of clinical grade dendritic cells, which is related to the increase in ROS [205, 206].

Ascites is a key factor in the TME of OC and serves as a carrier to promote the spread of tumor cells to other pelvic and peritoneal organs [188], and OS plays an important role in this process [207]. Pakula et al. reported that malignant ascites generated by serous ovarian tumors triggers OS in human peritoneal mesothelial cells (HPMCs) by inducing cytochrome C oxidase and NADH dehydrogenase, which results in the senescence of HPMC and thus promotes the adhesion, proliferation, and migration of OC cells [73]. In addition, malignant ascites can also increase the antioxidant capacity of OC cells [208]. GPx3 has been shown to be necessary for the survival of high-grade serous adenocarcinomas in ascites because it mediates the clearance of extracellular OS [209].

LPA, the second major group of lipids found in ascites [188], has been reported to be significantly increased in the ascites of OC patients and to promote the survival and proliferation of OC cells [210]. LPA stimulates the production of NOX-mediated ROS in OC cells, which is essential for the signal transduction of AKT, ERK, and NF- κ B, leading to the proliferation of OC cells [210, 211]. Blocking the LPA-dependent survival signaling pathway in OC cells has been shown to increase the production of ROS and to promote Taxol-induced apoptosis [212].

Hypoxia is a typical feature of the TME of malignant tumors and is attributed to the uncontrolled and rapid proliferation and irregular vascularization of the tumor [213]. Under hypoxic conditions, VEGF in malignant tumor cells is upregulated, which increases the metastatic ability of cancer cells [208].

3. Potential OS-Related Therapeutic Targets in OC

Based on the role of OS in OC, resolving the imbalance between oxidants and antioxidants is of great clinical

importance in treating OC, and agents that modulate OS are regarded as an important choice for the prevention and treatment of OC. In recent years, many agents, including chemotherapeutic drugs, natural extracts and Chinese medicines, and nanoparticles, have received broad attention from the public. These agents play different roles in dealing with aberrant OS in OC. Most of these agents, such as berberine and methotrexate, work by promoting OS to induce oxidative damage to DNA and subsequent apoptosis in OC cells. Some of these agents such as *Ganoderma lucidum* and bisdemethoxycurcumin can activate antioxidant enzymes and reduce superoxide generation to decrease OS and inhibit the adhesion, invasion, and migration of OC cells. Table 1 presents the three categories of therapeutic agents currently used for treating OC.

3.1. Chemotherapeutic Drugs. Chemotherapeutics can exhibit toxicity by inducing OS, inflammation, apoptosis, and abnormalities in neurotransmitter metabolism. ROS and RNS generated by anthracyclines and novel oxazolinanthracyclines have drawn attention as novel signal mediators that are involved in the growth, differentiation, progression, and death of cancer cells [214]. Platinum coordination complexes, alkylating agents, camptothecins, and arsenic agents can induce high levels of ROS, while taxanes, vinca alkaloids, nucleotide analogues, and antimetabolites, including antifolates and nucleosides, generate lower levels of ROS [215]. Diosmetin has been shown to upregulate the levels of BAX while downregulating the expression of Bcl2, inhibiting Nrf2, and inducing the production of ROS [216]. Methotrexate has been shown to induce apoptosis in SKOV-3 cells via the ROS-mediated BAX/Bcl-2-Cyt-c release cascade [217]. PARP inhibitors have been shown to upregulate NADPH oxidases 1 and 4 and to have an antitumor effect by elevating OS in OC cells [218]. Cisplatin has been shown to downregulate HIF-1 α in cisplatin-sensitive OC cells, and cisplatin plus-downregulated HIF-1 α has been shown to induce apoptosis in cisplatin-resistant OC cells by inducing the overproduction of ROS [219]. In addition, the methylseleninic acid mentioned earlier, a promising future chemotherapeutic agent, has been shown to contribute to inhibiting OC progression by enhancing T cell-mediated tumor cell killing.

3.2. Natural Compounds and Chinese Medicines. Many extracts of natural compounds and Chinese medicines have been used in treating OC. Juglone (5-hydroxy-1, 4-naphthoquinone) is isolated from various plants [220] and can increase ROS, resulting in ROS-dependent apoptosis by inducing cytochrome C and caspase-3, which are proapoptotic proteins involved in OS [221]. Moreover, juglone can upregulate BAX (a gene that promotes apoptosis) and downregulate BCL2 (an apoptosis suppressor gene). Ailanthone, a natural compound extracted from the tree *Ailanthus altissima*, has been shown to decrease the proliferation and migration of cancer cells through a mechanism involving the posttranslational reduction of Nrf2 proteins, which in turn entails an increase in OS [222]. Olive leaf extract reduces OVCAR-3 cell viability by inducing cell cycle arrest,

and it also induces apoptosis and increases the level of intracellular and mitochondrial ROS and decreases the activity of ROS scavenging enzymes [223]. Procyanidin, an extract from natural cocoa powder, increases ROS and activates caspase-3, thus leading to apoptosis [224]. Resveratrol (3,5,4'-trihydroxystilbene), from the roots of white hellebore and *Polygonum cuspidatum*, effectively induces OC stem cell death in a concentration-dependent manner, the mechanism of which might be through caspase-dependent apoptosis [225], the activation of caspase-9 and caspase-3 expression, and the downregulation of Notch expression [226]. The resveratrol derivative 3,3',4,4'-tetrahydroxy-trans-stilbene also induces apoptosis and reduces proliferation via ROS-induced DNA damage [227]. Gedunin inhibits proliferation by upregulating cytochrome C and caspase-9/3, thus causing ROS-dependent apoptosis [228]. *Ganoderma lucidum* was demonstrated to induce the antioxidants SOD, CAT, NADPH, and GSTP1 via the Nrf2-mediated signaling pathway to provide chemoprotection against carcinogenicity [229]. *Antrodia salmonea* acts as a potent inducer of apoptosis in OC by upregulating the proapoptotic proteins caspase-9/3 and BAX, downregulating the antiapoptotic protein Bcl-2, and inactivating PI3K/AKT, all of which are mediated by ROS generation [129].

3.3. Nanoparticles. As emerging novel anticancer therapeutics, nanoparticles with good histocompatibility and targeting ability are becoming a hot research topic in the diagnosis and treatment of OC because of their small diameter and uniform distribution [230]. ZnO nanoparticles can induce severe oxidative and proteotoxic stress in OC cells through a dramatic decrease in intracellular glutathione levels [165], and ZnO nanoparticles with an average size of 20 nm were able to induce significant cytotoxicity in HOC cells by inducing increased levels of intracellular ROS [162]. SeChry and folate-targeted polyurea dendrimer generation four (SeChry@PURE_{G4}-FA) nanoparticles can increase OS leading to GSH depletion and can inhibit the H₂S-synthesizing enzyme cystathionine β -synthase, while upregulating the expression of the cystine/glutamate antiporter system Xc [231]. Celastrol is derived from the Chinese herb *Tripterygium wilfordii*, and nanoparticles loaded with celastrol have been designed to specifically target OC cells thus leading to increased intracellular ROS levels and apoptosis of tumor cells and thus achieving a therapeutic effect against OC [232]. These studies suggest that nanomaterials, especially nanomaterials combined with therapeutic agents, will play a crucial role in treating OC, and future research should focus on exploring the mechanisms through which these particles exert their effects on OC.

4. Concluding Remarks and Future Prospects

Accumulating evidence has shown the critical role of OS in the pathogenesis of OC via genetic changes and alterations to signaling pathways, transcription factors, and the TME. OS-mediated genetic alterations, such as oxidative damage to nuclear DNA and mtDNA, DNA hypomethylation, and abnormal expression of microRNA, can trigger

TABLE 1: Agents targeting OS in OC.

Category	Materials	Cell lines	Targets	Mechanism	Effects	Refs.
Chemotherapeutic drugs	Diosmetin	A2780 and SKOV3 cells	BAX \uparrow , Bcl-2 \downarrow , Nrf2 \downarrow	ROS-mediated apoptosis	Inhibiting proliferation, migration, and invasion	[216]
	Methotrexate	SKOV3 cells	BAX \uparrow , Bcl-2 \downarrow , cytochrome C \uparrow	ROS-induced DNA damage	Inducing apoptosis	[217]
	PARP inhibitors	A2780 and HO8910 cells	NOX 1 \uparrow , NOX 4 \uparrow	ROS-dependent apoptosis	Inducing apoptosis	[218]
	Juglone	SKOV3 cells	Cytochrome C \uparrow , caspase-3 \uparrow	ROS-dependent apoptosis	Inhibiting proliferation	[221]
Natural compounds and Chinese medicines	Ailanthone	A2780 and A2780/CP70 cells	Nrf2 \downarrow	OS \uparrow	Reducing proliferation and migration	[222]
	Olive leaf extract	OVCAR-3 and OVCAR-8 cells	Caspase 9 \uparrow , SOD \downarrow , CAT \downarrow	ROS-dependent apoptosis	Suppressing proliferation, cell cycle progression, and aggregation	[223]
	Procyanidin	OAW42 and OVCAR3 cells	MMP \downarrow , caspase-3 \uparrow	ROS/caspase-3-mediated apoptosis	Inducing cell death and inhibiting invasion	[224]
	Gossypol	SKOV3 cells	GSH \downarrow , FAD \downarrow	ROS apoptosis	Increasing apoptosis	[237]
	Resveratrol	A2780 and SKOV-3 cells	Caspase-9 and caspase-3 \uparrow , Notch \downarrow	ROS-dependent apoptosis	Inducing cell death	[226]
	Resveratrol derivative	A2780, SKOV-3, and OVCAR-3 cells	SOD \downarrow , CAT \downarrow , 8-OHdG \uparrow	ROS-induced DNA damage	Inducing apoptosis, reducing proliferation, and activating senescence	[227]
	Gedunin	PA-1 and OVCAR-3 cells	Cytochrome C \uparrow , caspase-9 and caspase-3 \uparrow	ROS-dependent apoptosis	Inhibiting proliferation	[228]
	<i>Ganoderma lucidum</i>	OVCAR-3 cells	SOD \uparrow , CAT \uparrow , GSTP1 \uparrow , H ₂ O ₂ \downarrow , Nrf2-Keap1 signaling \uparrow	OS \downarrow	Inhibiting proliferation	[229]
	Berberine	A2780, HEY, SKOV-3, HO8910, HO8910PM, and OVCAR3 cells	8-OHdG \uparrow	ROS-induced DNA damage	Increasing apoptosis and reducing cell growth	[238]
	Cucurbitacin I	SKOV-3 cells	Caspase-3 \uparrow , BAX \uparrow , Bcl-2 \downarrow , Nrf2-Keap1 signaling \downarrow	ROS-mediated apoptosis	Inducing cell death	[239]
	Bisdemethoxycurcumin	SKOV-3 cells	Superoxide \downarrow	OS \downarrow	Inhibiting adhesion, invasion, and migration	[174]
	<i>Antrodia salmonea</i>	SKOV-3 and A2780 cells	Caspase-9, caspase-3 \uparrow , BAX \uparrow , Bcl-2 \downarrow	ROS-dependent apoptosis	Inducing cell death	[129]
<i>Vernonia calvoana</i>	OVCAR-3	GSH \downarrow , CAT \downarrow	ROS-induced DNA damage	Suppressing cell proliferation	[240]	

TABLE 1: Continued.

Category	Materials	Cell lines	Targets	Mechanism	Effects	Refs.
Nanoparticles	ZnO nanoparticles	SKOV-3, 3T3-L1 cells, TYKNu, ALST, OVCAR3, and OVCA420	Caspase-3↑, GSH↓	ROS-mediated apoptosis	Inducing cell death	[165]
	SeChry@PUREG4-FA	OVCAR3 HTB-161, OVCAR8 CVCL-1629, and ES2 CRL-1978™	GSH↓, CBS↓	ROS-mediated apoptosis	Increasing cell death; reducing toxicity of nonmalignant cells	[231]
	Celastrrol-loaded nanoparticles	SKOV-3 cells	GSH↓	ROS-dependent apoptosis	Inhibiting cell migration and invasion	[232]
	Flavonoids	A2780, OVCAR-3, and SKOV-3	Caspase-3↑	ROS/caspase-3-mediated apoptosis	Inducing apoptosis and reducing invasion	[241]
	CYT-Rx20	MDAH 2774, PA-1, and SKOV3 cells	Caspase-9, caspase-3↑	ROS-dependent apoptosis	Reducing cell viability and inducing cell death	[242]
	Sideroxylin	ES2 and OV90 cells	MAPK and PI3-K pathway transduction↓	ROS-mediated apoptosis	Suppressing cell proliferation and increasing apoptosis	[243]
Morusin	A2780, SKOV-3, and HO-8910	Mitochondrial Ca ₂ ⁺ ↑	ROS-dependent apoptosis	Inhibiting cell proliferation and survival	[244]	

8-OHdG: 8-hydroxy-2'-deoxyguanosin; CAT: catalase; CBS: cystathionine β-synthase; FAD: flavin adenine dinucleotide; GSH: glutathione; GSTP1: glutathione S-transferase P1; H₂O₂: hydrogen peroxide; Keap1: Kelch-like ECH-associated protein 1; MAPK: mitogen-activated protein kinase; MMP: matrix metalloproteinase; NOX: nicotinamide adenine dinucleotide oxidase; Nrf2: nuclear factor E2-related factor 2; OS: oxidative stress; PI3K: phosphatidylinositol 3-kinase; ROS: reactive oxygen species; SOD: superoxide dismutase.

OC. OS-mediated signaling pathways, such as Keap1-Nrf2-ARE, PI3K/AKT/mTOR, Wnt/ β -catenin, and Notch, play important roles in regulating the progression of OC. Among these, activation of the Nrf2 pathway is considered to be a double-edged sword in OC because it maintains the stability of the normal ovarian cell environment and genome in order to prevent OS-induced carcinogenesis, while at the same time, it protects tumor cells from OS thereby enhancing the invasion and chemoresistance of OC. The PI3K/AKT/mTOR and Wnt/ β -catenin pathways contribute to the proliferation, migration, and chemoresistance of OC, and they can be activated by OS. The OS-mediated Notch pathway is closely related to poor prognosis in patients with OC; however, the specific mechanism of action remains to be further studied. The transcription factors p53, NF- κ B, and HIF-1 α are also ROS sensitive, and redox modification of these molecules can be instrumental in the initiation and progression of OC. Finally, OS is involved in regulating OC progression by affecting components such as TAMs, neutrophils, MDSCs, Treg cells, ascites, and LPA in the TME of OC.

We have also outlined three treatment strategies to target aberrant OS in OC, including chemotherapeutic drugs, natural compound extracts or Chinese medicine, and nanoparticles. Their mechanisms of action may be through affecting oxidative damage to DNA, by regulating signaling pathways such as Notch and Keap1-Nrf2-ARE and transcription factors such as HIF-1 α and by affecting components of the TME. These agents play different roles in dealing with aberrant OS in OC. Most of them can promote OS to induce DNA oxidative damage and ROS-dependent apoptosis of OC cells, while some agents can activate antioxidant enzymes and reduce superoxide generation to decrease OS. All of them contribute to inhibiting the adhesion, invasion, and migration of OC cells. There is a multitarget effect between OC and OS, and future experiments in clinic are needed to validate the relationship between OS and OC.

Abbreviations

8-OHdG:	8-Hydroxy-2'-deoxyguanosin	GST:	Glutathione S-transferases
AKT:	Protein kinase B	H ₂ O ₂ :	Hydrogen peroxide
APC:	Adenomatous polyposis coli	HIF-1 α :	Hypoxia-inducible factor 1 alpha
ATF:	Artificial transcription factor	HGSC:	High-grade serous carcinoma
CAT:	Catalase	HPMCs:	Human peritoneal mesothelial cells
CBS:	Cystathionine β -synthase	HRR:	Homologous recombination repair
CK1:	Casein kinase 1	IL:	Interleukin
Cyt C:	Cytochrome C	iNOS:	Inducible nitric oxide synthase
DVL:	Disheveled	Keap1:	Kelch-like ECH-associated protein 1
EGF:	Epidermal growth factor	LPA:	Lysophosphatidic acid
EMT:	Epithelial-mesenchymal transition	Maf:	Musculoaponeurotic fibrosarcoma
EOC:	Epithelial ovarian cancer	MAPK:	Mitogen-activated protein kinase
FAD:	Flavin adenine dinucleotide	MDSCs:	Myeloid-derived suppressor cells
FZD:	Frizzled	MIEF2:	Mitochondrial elongation factor 2
G6PD:	Glucose-6-phosphate dehydrogenase	miRNA:	MicroRNA
GPX:	Glutathione peroxidase	mtDNA:	Mitochondrial DNA
GSH:	Glutathione	mTOR:	Mammalian target of rapamycin
GSK3 β :	Glycogen synthase kinase 3 β	mTORC1:	MTOR complex 1
GSR:	Glutathione reductase	NADPH:	Nicotinamide adenine dinucleotide
		NICD:	The intracellular domain of Notch
		NO:	Nitric oxide
		NOX:	Nicotinamide adenine dinucleotide oxidase
		Nrf2:	Nuclear factor E2-related factor 2
		OC:	Ovarian cancer
		¹ O ₂ :	Singlet oxygen
		O ₂ ⁻ :	Superoxide anion
		OH:	Hydroxyl radical
		ONOO ⁻ :	Peroxynitrite anion
		OS:	Oxidative stress
		PGC1 α :	Peroxisome proliferator-activated receptor- γ coactivator 1 α
		PHD:	Prolyl hydroxylase
		PI3K:	Phosphatidylinositol 3-kinase
		PIP3:	Phosphatidylinositol trisphosphate
		PIP2:	Phosphorylates phosphatidylinositol bisphosphate
		PPP:	Pentose phosphate pathway
		PRX:	Peroxiredoxin
		PTEN:	Phosphatase and tensin homolog
		PTP:	Protein tyrosine phosphatase
		ROS:	Reactive oxygen
		RNS:	Reactive nitrogen species
		RTK:	Receptor tyrosine kinase
		SeChry@PUREG4-FA:	SeChry and folate-targeted polyurea dendrimer generation four
		SGC:	Soluble guanylate cyclase
		SOD:	Superoxide dismutase
		SOD2:	MnSOD
		TAMs:	Tumor-associated macrophages
		Tf:	Transferrin
		TGF β :	Transforming growth factor β
		TME:	Tumor microenvironment
		TNF:	Tumor necrosis factor
		TRX:	Thioredoxin
		VEGF:	Vascular endothelial growth factor
		VHL:	von Hippel-Lindau tumor suppressor protein
		XO:	Xanthine oxidase.

Conflicts of Interest

The authors declare no conflict of interest.

Authors' Contributions

Dan-Ni Ding conceptualized the study. Dan-Ni Ding prepared the original draft. Fang-Yuan Liu, Liang-Zhen Xie, and Feng-Juan Han reviewed and edited the manuscript. Ying Shen and Jia Li were involved in finding references. Ying Guo and Yang Fu prepared the figures. Fang-Yuan Liu and Feng-Juan Han supervised the study. Feng-Juan Han was responsible for the funding acquisition. Fang-Yuan Liu and Feng-Juan Han are corresponding authors. All authors have read and agreed to the published version of the manuscript.

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