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# The recent advancements of ferroptosis of gynecological cancer

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**Abstract**
Ovarian, endometrial, and cervical cancer are the most common types of gynecologic tumor in women. Surgery, combined with radiotherapy and chemotherapy, is commonly used to treat these tumors. Unfortunately, difficulties in early diagnosis and acquired drug resistance have resulted in poor outcomes for most patients. Ferroptosis is a form of regulated cell death that depends on iron and is characterized by iron accumulation, reactive oxygen species production, and lipid peroxidation. The strong association between ferroptosis and many diseases, especially tumor diseases, has been confirmed by numerous studies. Many studies have demonstrated that ferroptosis is involved in initiating, progressing and metastasizing gynecologic tumors. This review summarizes the pathogenesis of ferroptosis and its association with the development, treatment, and prognosis of gynecologic tumors, and further explore the potential utility of ferroptosis in treating gynecologic tumors.

**Keywords** Ferroptosis, Gynecological tumors, Ovarian cancer, Endometrial cancer, Cervical cancer, Treatment

## Introduction

Ovarian cancer (OC) represents a significant threat to women's health and lives worldwide, constituting a malignancy of the female reproductive system [1–3]. The World Health Organization (WHO) classifies OC into the following categories: epithelial carcinoma, malignant ovarian germ cell tumors, interstitial carcinoma of the sex cord, and metastatic ovarian cancer [4]. As the early symptoms of OC are atypical, approximately 70% of cases are diagnosed at a late stage, resulting in a low 5-year survival rate of 30% [5]. Currently, cytoreductive surgery and platinum-taxane combination chemotherapy represent the primary treatment approach. However, a significant challenge remains, as the majority of OC patients often develop chemoresistance. Consequently, there is a pressing need to identify potential biomarkers and therapeutic targets for OC to enhance short- and long-term survival outcomes.

Endometrial cancer (EC) is a prevalent gynecologic cancer with an increasing incidence worldwide [6–9]. Type I EC represents the most prevalent form, accounting for over 70% of cases. In contrast, type II EC represents only 10% of EC cases but is responsible for 40% of associated mortalities [10, 11]. Type I EC is associated with the absence of antagonistic endometrial exposure to estrogen and obesity [12]. While type II EC was not found to be associated with hyperestrogenemia or endometrial hyperplasia. The standard treatment for EC is a total hysterectomy, which includes the removal of both fallopian tubes and ovaries [6]. The decision to administer postoperative chemotherapy and radiotherapy is contingent upon the risk of recurrence [13–18].

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Cervical cancer (CC) is histologically classified into two main categories: squamous cell carcinoma (SCC) and adenocarcinoma (ADC). These two types account for 70% and 25% of all CC cases, respectively [19, 20]. The development of CC is most commonly associated with oncogenic human papillomavirus (HPV) [21]. The implementation of the HPV vaccine, cytology screening, and high-risk HPV DNA testing has resulted in a notable decline in the incidence of CC. However, the prevalence of CC remains a significant concern in developing countries. The prognosis for CC remains suboptimal due to the emergence of drug resistance and recurrence.

Ferroptosis is a form of regulated cell death that is dependent on iron and distinct from apoptosis. It is characterized by the accumulation of iron, the production of reactive oxygen species (ROS), and lipid peroxidation [22]. In comparison with the other types of cell death, ferroptotic cells typically exhibit mitochondrial abnormalities at the ultrastructural level. These include condensation or swelling, increased membrane density, reduction or loss of mitochondrial cristae, and rupture of the outer mitochondrial membrane [23–25]. The robust correlation between ferroptosis and a multitude of pathological conditions, particularly neoplastic disorders, has been substantiated by a plethora of investigations [26–33]. Ferroptosis has been identified as a form of immunogenic cell death (ICD). It has been demonstrated to enhance anti-tumor immunity [34, 35]. Recent studies have demonstrated a close correlation between ferroptosis and the pathogenesis and drug resistance mechanisms of gynecological cancers and numerous researchers have attempted to predict the prognosis of gynecological cancers through the analysis of ferroptosis-related genes (FRGs). This article summarizes the relationship between ferroptosis and gynecologic cancers, with a view to proposing new diagnostic and therapeutic approaches for gynecologic cancers.

## Regulatory mechanisms of ferroptosis

### Lipid metabolism

Polyunsaturated fatty acids (PUFAs) are a significant component of cell membranes, contributing to the maintenance of cell membrane fluidity. PUFAs can be classified into omega-3 (n-3) and omega-6 (n-6) FAs [36]. The principal n-6 FA is arachidonic acid (AA) and adrenal acid (AdA; 22:4) (hereinafter referred to as AA/AdA), which serve as the primary substrates for lipid peroxidation in ferroptosis [37]. It has been demonstrated that the peroxidation of PUFAs in the cytoplasmic membrane is a significant factor contributing to ferroptosis [38]. It has been demonstrated that acyl-coa synthetase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3) are pivotal enzymes in the synthesis of AA/AdA derivatives [2, 37, 39, 40]. Consequently, the inhibition of either ACSL4 or LPCAT3 results in the suppression of ferroptosis. Furthermore, monounsaturated fatty acids (MUFAs) exert a competitive effect on the activity of polyunsaturated fatty acids (PUFAs) in ferroptosis. This implies that the exogenous administration of MUFAs, such as oleic acid (C18:1), leads to the inhibition of ferroptosis [41–43].

Two distinct forms of lipid peroxidation are observed during ferroptosis: non-enzymatic and enzymatic lipid peroxidation. Non-enzymatic lipid peroxidation (also referred to as lipid autoxidation) is a free radical-mediated chain reaction in which the hydroxyl radical, produced by the Fenton reaction, oxidizes polyunsaturated fatty acids to lipid hydroperoxides [44]. Enzymatic lipid peroxidation refers to the process by which free polyunsaturated PUFAs are directly oxidized to various types of lipid hydroperoxides under the catalysis of lipoxygenase (LOX) [45, 46]. The arachidonate lipoxygenase (ALOX) family of enzymes represents the most prominent group involved in the process of lipid peroxidation. This family includes ALOXE3, ALOX5, ALOX12, ALOX12B, ALOX15, and ALOX15B. The inhibition of ferroptotic cancer cell death by microsomal glutathione S-transferase 1 (MGST1) is mediated by its binding to ALOX5, leading to a reduction in lipid peroxidation [49]. ALOX12 was identified as a crucial factor in p53-mediated ferroptosis under conditions of ROS stress [47]. The spermine/spermine N1-acetyltransferase 1 (SAT1) gene is a transcriptional target of p53. It has been demonstrated that the induction of SAT1 is correlated with the expression level of ALOX15. Furthermore, it has been shown that SAT1-induced ferroptosis is significantly attenuated in the presence of PD146176, a specific inhibitor of ALOX15 [48]. In addition to relying on ALOX, cytochrome P450 oxidoreductase (POR) can directly provide electrons from nicotinamide adenine dinucleotide phosphate (NADPH) to P450 enzymes, thereby promoting the peroxidation of PUFA [50].

### Iron metabolism

$Fe^{3+}$ binds to transferrin and enters the cell's endosomes with the help of the transferrin receptor 1 (TFR1). Within the endosome, STEAP3 reduces $Fe^{3+}$ to $Fe^{2+}$, which is then released into the cytoplasmic labile iron pool (LIP) via divalent metal transporter 1 (DMT1, also known as SLC11A2), which catalyzes the Fenton reaction that generates large amounts of ROS [51, 52]. Membrane phospholipids (formed by the conversion of free PUAs by the enzymes ACSL4 and LPCAT3) can be oxidized by ALOXs to PE-PUFAs-OOH, causing lipid peroxidation, membrane damage, and ferroptosis [53, 54]. Therefore, regulators involved in iron metabolism may influence the development of ferroptosis.

### Oxidation system

The production of free radicals and the inactivation of cellular antioxidant systems are the primary causes of ferroptosis [55]. Free radicals, such as ROS and RNS, are regulators of ferroptosis [52].

Unlike RNS, ROS have undergone extensive investigation for their ferroptosis-promoting functions. ROS are primarily mediated by mitochondria and NADPH oxidase (NOX) [52]. The oxidative phosphorylation of the electron transport chain in the inner mitochondrial membrane is the primary source of mitochondrial ROS [52, 55]. Mitochondrial ROS can induce not only apoptosis but also iron ferroptosis. Voltage-dependent anion channel (VDAC) family and BCL2 family regulate ferroptosis by modulating mitochondrial ROS [52]. Furthermore, ATP has two roles during ferroptosis [56]. On the one hand, in the absence of ATP, PUFA-PL synthesis is inhibited, thereby suppressing ferroptosis. On the other hand, when ATP is sufficient, PUFA-PL synthesis is increased, thereby promoting ferroptosis [56, 57]. The NOX family includes NOX1, Cytochrome B-245Beta (CYBB/NOX2), NOX3, NOX4, NOX5, DUOX1, and DUOX2. NOX 1, CYBB / NOX2, and NOX4 was found to promote lipid peroxidation in ferroptosis by producing other downstream ROS [52, 58–61].

### Antioxidant system

A disequilibrium between the production of free radicals and an organism's capacity to neutralise or eliminate their deleterious effects through the action of antioxidants gives rise to oxidative damage. Antioxidant defences have been identified as playing a pivotal role in the process of ferroptosis [62]. The systemic $Xc^-$-GSH-GPX4 pathway represents a fundamental antioxidant system, which plays a pivotal role in the protection of cells from ferroptosis. Further research has identified additional antioxidant systems that regulate ferroptosis. These systems comprise the FSP1-CoQ10 pathway, the GCH1-BH4 pathway, and the DHODH-CoQH2 pathway.

#### *The systemic Xc−-GSH-GPX4 pathway*

The systemic $Xc^-$-GSH-GPX4 pathway plays a pivotal role in the antioxidant defence mechanism against ferroptosis. System $Xc^-$ is a cystine-glutamate antiporter, consisting of solute carrier family 7 member 11 (SLC7A11/xCT) and solute carrier family 3 member 2 (SLC3A2/CD98) [63]. The system $Xc^-$ transports cystine into the cell where it is oxidized to cysteine, which is then used to synthesize GSH [64]. Because GSH acts as a reduction cofactor, GPX4 is able to reduce reactive PLOOH to a non-toxic phospholipid alcohol (PLOH), thus protecting cells from ferroptosis [62, 65, 66] (Fig. 1).

#### *The FSP1-CoQ10 pathway*

The two forms of CoQ10 are ubiquitinone and ubiquitinol. CoQ10 is a lipophilic compound that is essential for the production of energy in the mitochondrial electron transport chain and lysosomal membranes [55, 67, 68]. Additionally, it can be employed as a lipophilic free radical trapping agent. CoQ10 exerts potent antioxidant effects, capable of inhibiting ferroptosis. It has been shown that the administration of farnesyl pyrophosphate (an upstream product involved in the synthesis of CoQ10) or idebenone (a hydrophilic analogue of CoQ10) can effectively prevent ferroptosis induced by FIN56. Conversely, the process of ferroptosis may be accelerated when the production of CoQ10 is inhibited. The apoptosis-inducing factor mitochondria-associated 2 (AIFM2/FSP1/AMID), which was previously considered to be a mitochondrial apoptosis inducer, has been demonstrated in recent studies to be an antioxidant regulator of ferroptosis [69, 70]. FSP1 is primarily associated with the outer mitochondrial membrane and is translocated from the mitochondria to the plasma membrane via N-myristoylation, thereby mediating CoQ10 production and inhibiting ferroptosis in a manner that is independent of GSH [69, 70] (Fig. 1).

#### *The GCH1-BH4 pathway*

Tetrahydrobiopterin (BH4) is involved in the synthesis of nitric oxide (NO) synthase, dopamine and melatonin [71]. Studies have shown that exogenous dopamine or melatonin can inhibit ferroptosis [72]. Homma et al. found that NO protect against ferroptosis by aborting the lipid peroxidation chain reaction [73]. Conversely, inhibitors for NO and/or iNOS may prove effective in suppressing ferroptosis in multiple myeloma (MM) cells induced by palmitoyl-lysine (PAL). These studies indicate that NO can either induce or inhibit ferroptosis depending on the context [74, 75]. GTP cyclohydrolase-1 (GCH1) is the key enzyme in BH4 biosynthesis, inhibiting lipid peroxidation to protect against ferroptosis [76]. The emergence of the GCH1-BH4 axis offers possible potential chemotherapeutic strategies for gynecological cancer treatment (Fig. 1).

#### *The DHODH-CoQH2 pathway*

DHODH is the rate-limiting enzyme for de novo pyrimidine nucleotide biosynthesis [77]. DHODH inhibitors can inhibit tumor growth not only by inhibiting the biosynthesis of pyrimidine, but also to enhance ferroptosis. DHODH can oxidize dihydrolactic acid (DHO) into whyotic acid (OA) and then reduce CoQ10 to CoQ10H2. CoQ10H2 reduces inner mitochondrial lipid ROS [78] (Fig. 1).

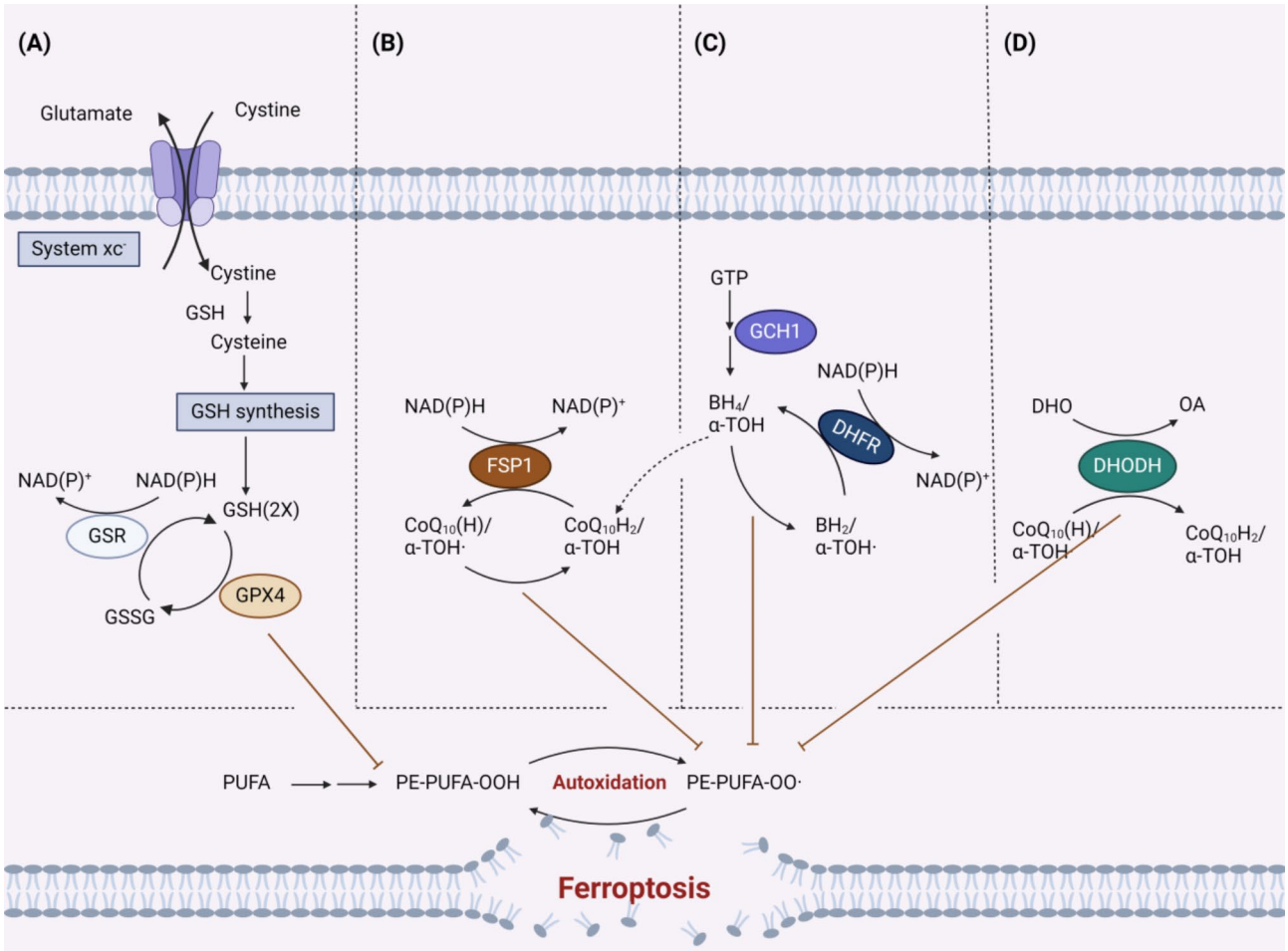


**Fig. 1** Ferroptosis-suppressing pathways. (**A**) The systemic $Xc^-$-GSH-GPX4 pathway. System $Xc^-$ contains two key components, SLC7A11 and SLC3A2. Cystine enters the cell via the system $xc^-$ and is then converted to cysteine for the synthesis of GSH. Because GSH acts as a reduction cofactor, GPX4 is able to reduce reactive PLOOH to a non-toxic phospholipid alcohol (PLOH), thus protecting cells from ferroptosis. (**B**) The FSP1-CoQ10 pathway. FSP1 prevents lipid peroxidation and associated ferroptosis by reducing CoQ10 /α-tocopherol at the level of lipid radicals. (**C**) The GCH1-BH4 pathway. GCH1 is the key enzyme in BH4 biosynthesis. GCH1 mediates the production of BH4 and prevents ferroptosis by inhibiting lipid peroxidation. (**D**) The DHODH-CoQH2 pathway. DHODH can oxidize DHO into OA by transferring the electrons to the ubiquinone, and then reduce CoQ10 to CoQ10H2. CoQ10H2 subsequently reduces lipid ROS in the mitochondrial inner membrane

## Ovarian cancer and ferroptosis

### Ferroptosis and initiation of ovarian cancer

It was shown that high-grade plasma cytotic OC tissues had elevated iron levels compared to normal ovarian tissues, suggesting that OC is associated with increased intracellular iron levels [79, 80]. In addition, researchers found that sodium molybdate can induce elevated LIP in OC cells [81]. Ferrous ammonium citrate (FAC) was found to promote the level of intracellular iron expression in OC cells, thereby inhibiting OC cell proliferation [82]. In OC cells, downregulation of GPX4 inhibited the occurrence of ferroptosis as well as FAC. These findings suggest that interfering with iron metabolism in early-stage OC cells may inhibit cancer development. Mitochondrial ROS can activate the mitochondrial permeability transition pore pathway, leading to DNA damage and cell death [62, 83–85]. Tesfay et al. [42] found that OC cells express high levels of steroyl coa desaturase (SCD1). Inhibiting SCD1 may alter lipid metabolism and increase the sensitivity of OC cells to ferroptosis inducing agents (Fig. 2).

### Ferroptosis and treatment of ovarian cancer

Studies have shown that OC is associated with the abnormal expression of FRGs. This provides new ideas for treating OC. Wang et al. [86]. demonstrated that eriodictyol exerts its anti-tumour effects by regulating cell viability, ferroptosis and mitochondrial function through the Nrf2/HO-1/NQO1 axis in OC cells [87]. Lidocaine and ropivacaine have been reported can accelerate OC cells ferroptosis [88, 89]. Curcumin has been shown to have anti-tumor proliferation properties,

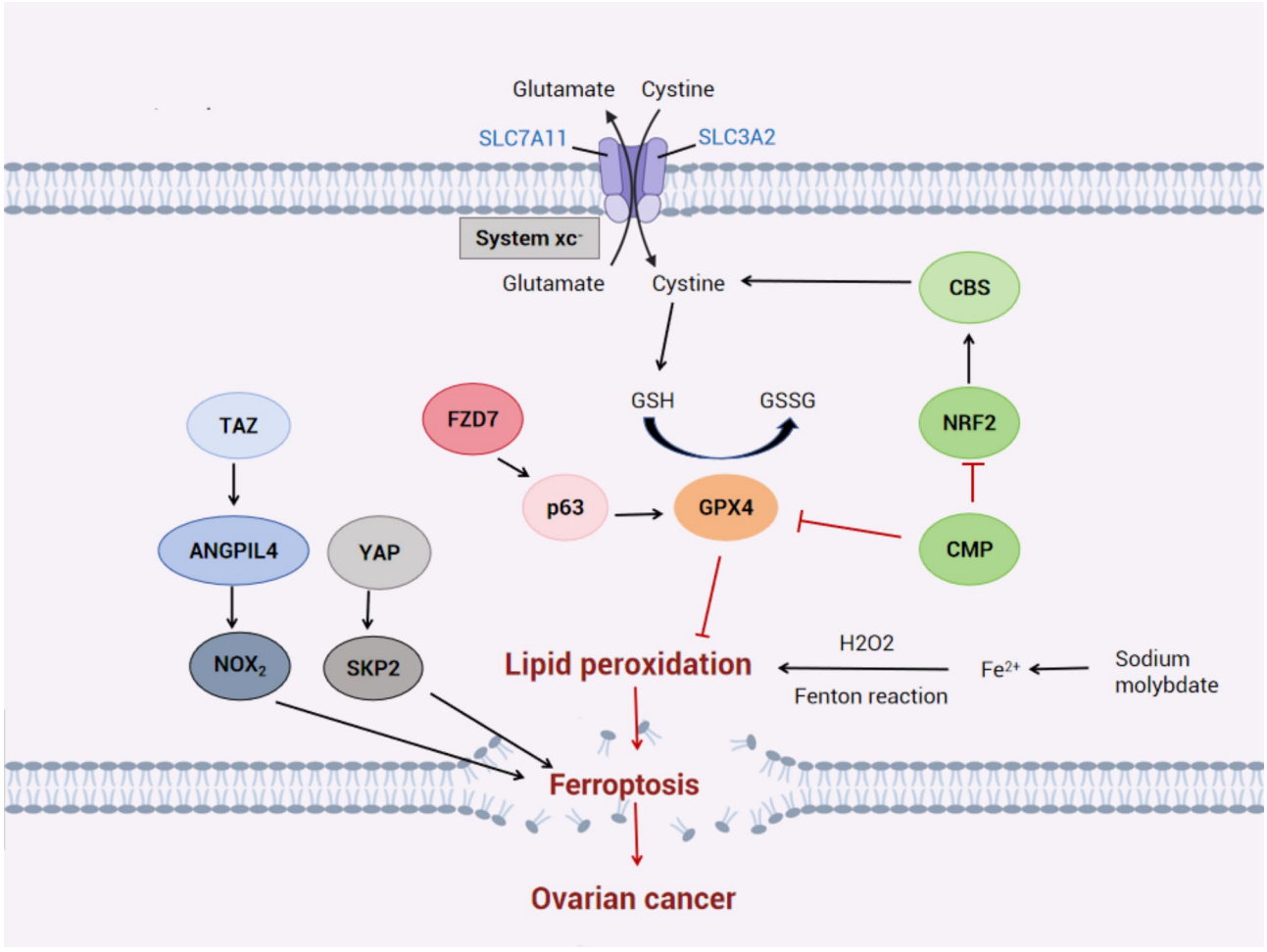


**Fig. 2** Mechanisms of ferroptosis in ovarian cancer. The systemic $Xc^-$-GSH-GPX4 pathway protects cells from ferroptosis. Nrf2 upregulates CBS expression to promote the systemic $Xc^-$-GSH-GPX4 pathway. Overexpressing FZD7 can activate the oncogenic factor P63 to upregulate GPX4 and prevent ferroptosis. TAZ regulates the level of ANGPTL4 to control NOX2 activity, ultimately leading to ferroptosis. YAP regulates SKP2 to promote ferroptosis. Sodium molybdate induced the increase of LIP

and the curcumin derivative NL01 has been shown to induce ferroptosis via the HCAR1/MCT1 pathway and has better anti-tumor growth properties [90]. Moreover, MEX3A-mediated degradation of p53 drives ovarian cancer growth by bypassing the tumor-suppressor function of p53, suggesting that that targeting MEX3 A may be a potential treatment for WT p53-expressing OC [91]. Besides, researchers found that SPIO-Serum induced ferroptosis in OC cells, suggesting that nanomaterials have a potential to treat OC by induicng ferroptosis [92]. A study reported that MAP 30, a bioactive protein isolated from bitter melon seeds, can exhibit anti-ovarian cancer properties and anti-chemoresistant effect [93]. However, the above findings are not supported by clinical trials and require further study (Table 1).

### Ferroptosis and prognosis of ovarian cancer

Despite advances in the diagnosis of ovarian cancer over recent decades, there remains a significant shortfall in the accuracy of diagnosis and prognostic prediction for patients with the disease. In a study, a prognostic grading model for ovarian cancer was developed through a comprehensive biological analysis, which incorporated five ferroptosis-associated factors (ALOX12, ACACA, SLC7A11, FTH1, CD44) [94]. Furthermore, Li et al. [95] investigated the interplay between immune infiltration and ferroptosis, developing a novel E-FRG score model comprising 15 FRGs to predict the survival of patients with OC. Long non-coding RNAs (lncRNAs) are RNA molecules comprising more than 200 nucleotides that have been demonstrated to possess the capacity to regulate normal or cancerous cells [96]. A number of studies have indicated that lncRNAs may exert regulatory effects on cancer through the process of ferroptosis [97]. Recent studies have demonstrated that lncRNAs exert regulatory effects on ferroptosis and its associated signal transduction pathways, thereby playing a pivotal role in the regulation of cancer processes involving ferroptosis [98, 99].

**Table 1** Ferroptosis and ovarian cancer treatment

| Therapeutic target and drug | Ovarian cancer cell line | Animal models | Human tissue samples | Mechanism of action | Effect | References |
|---|---|---|---|---|---|---|
| Lidocaine | SKOV3 | / | / | miR–382–5p /SLC7A11 Axis | Promote ferroptosis in OC cell | [93] |
| Ropivacaine | SKOV3, OVCAR3 | / | / | PI3K/AKT signaling pathway | Promote ferroptosis in OC cell | [94] |
| Eriodictyol | A2780, CaoV3 | 10 BALB/c nude mice | / | Nrf2/HO–1/NQO1 signaling pathway | Promote ferroptosis in OC cell | [91] |
| MEX3A | TOV21G, OVCA–429, JHOC9, RMG2, OVISE, RMG–1 | / | 15 OCCC, 13 HGSOC | p53 degradation | Suppress ferroptosis in OC cell | [96] |
| SPIO-Serum | SKOV3, A2780 | / | / | Increased intracellular iron content, lipid peroxidation | Promote ferroptosis in OC cell | [97] |
| Momordica charantia | A2780, HEY, HEYA8, OVCA433, SKOV3, HOSE | / | Human omental tissues | Activate AMPK, suppresse mTOR and the AKT/ERK/FOXM1 signaling pathway | Promote ferroptosis in OC cell | [98] |

Zheng et al. [100] identified and validated a set of nine ferroptosis-related lncRNAs (FRLs) with prognostic value, which had not previously been reported in OC. The risk model, which was identified and validated based on nine FRLs, has been established as an independent prognostic factor. The model is anticipated to serve as a valuable tool for forecasting the outlook of OC patients.

## Endometrial cancer and ferroptosis

### Ferroptosis and initiation of endometrial cancer

It was determined that FRGs were in close correlation with EC. It is hypothesized that GPX4-inhibited ferroptosis may be associated with EC. The studies revealed that GPX4, FSP1, TFRC, and glutathione synthase (GSS) exhibited high expression levels in early EC [101]. The p62-Keap1-Nrf2 signaling pathway has been demonstrated to promote endometrial proliferation through the inhibition of ferroptosis [102]. First, Nrf2 exerts control over GPX4 expression, either directly or indirectly. GPX4 overexpression has been demonstrated to inhibit ferroptosis. Secondly, Nrf2 has been found to promote SLC7A11 expression and increase GSH levels, thereby inhibiting ferroptosis [103]. Additionally, p53 has been demonstrated to inhibit SLC7A11 expression, thereby inducing ferroptosis [104]. Moreover, p53 has been observed to induce ferroptosis by regulating the expression of several key enzymes, including spermidine/spermine N1-acetyltransferase 1 (SAT1), glutaminase 2 (GLS2), and dipeptidyl peptidase 4 (DPP4) [105]. Nevertheless, the precise mechanism by which ferroptosis contributes to the development of EC remains elusive and warrants further investigation to enhance our understanding of the underlying process (Fig. 3 ).

### Ferroptosis and treatment of endometrial cancer

FRGs are associated with the development of EC, making FRGs a new target for treating EC. Zhang et al. [102] reported that Guizhi Poria capsule (GFC) could trigger ferroptosis by inhibiting the p62-Keap1-Nrf2 pathway, thereby alleviating estrogen-induced endometrial hyperplasia in mice. It was found that amentoflavone (AF) inhibited the proliferation of EC cells by promoting ferroptosis by activating the ROS/AMPK/mTOR pathway [106]. Zhou et al. [107] demonstrated that simvastatin inhibited proliferation of EC Ishikawa cells through inhibition of the RAS/MAPK pathway. The study revealed that circRAPGEF5 was significantly upregulated in EC. Additionally, it was found that circRAPGEF5 decreased unstable iron in EC cells, resulting in resistance to ferroptosis [108]. Researchers found that NaBu indirectly downregulated the expression of SLC7A11 and inhibited EC progression [109]. In addition, the researchers found that quercetin, as well as dihydroisotanshinone I (DT) found in Danshen, induced ferroptosis in EC cells [110, 111]. A new study shows that LINC02936 binds to SIX1 to upregulate CP expression and inhibit ferroptosis, thereby promoting EC progression [112]. These studies suggest that investigating ferroptosis could have therapeutic implications for EC (Table 2).

### Ferroptosis and prognosis of endometrial cancer

A number of studies have demonstrated that FRGs may serve as predictors of EC prognosis. Liu et al. [113] developed a prognostic model for endometrial cancer based on the analysis of six genes associated with ferroptosis. In a subsequent study, the researchers also discovered that elevated serum ferritin levels are associated with an increased risk of endometrial cancer recurrence [114]. This finding suggests that ferritin levels may potentially be employed as a prognostic indicator for endometrial cancer. Zhang et al. [115] conducted a study that identified FRGs that are differentially expressed in type I and type II EC. These findings may be useful in identifying and treating type II EC. The researchers developed a model based on six differentially expressed genes (DEGs): TP53, AIFM2, ATG7, TLR4, PANX1, and MDM2, which

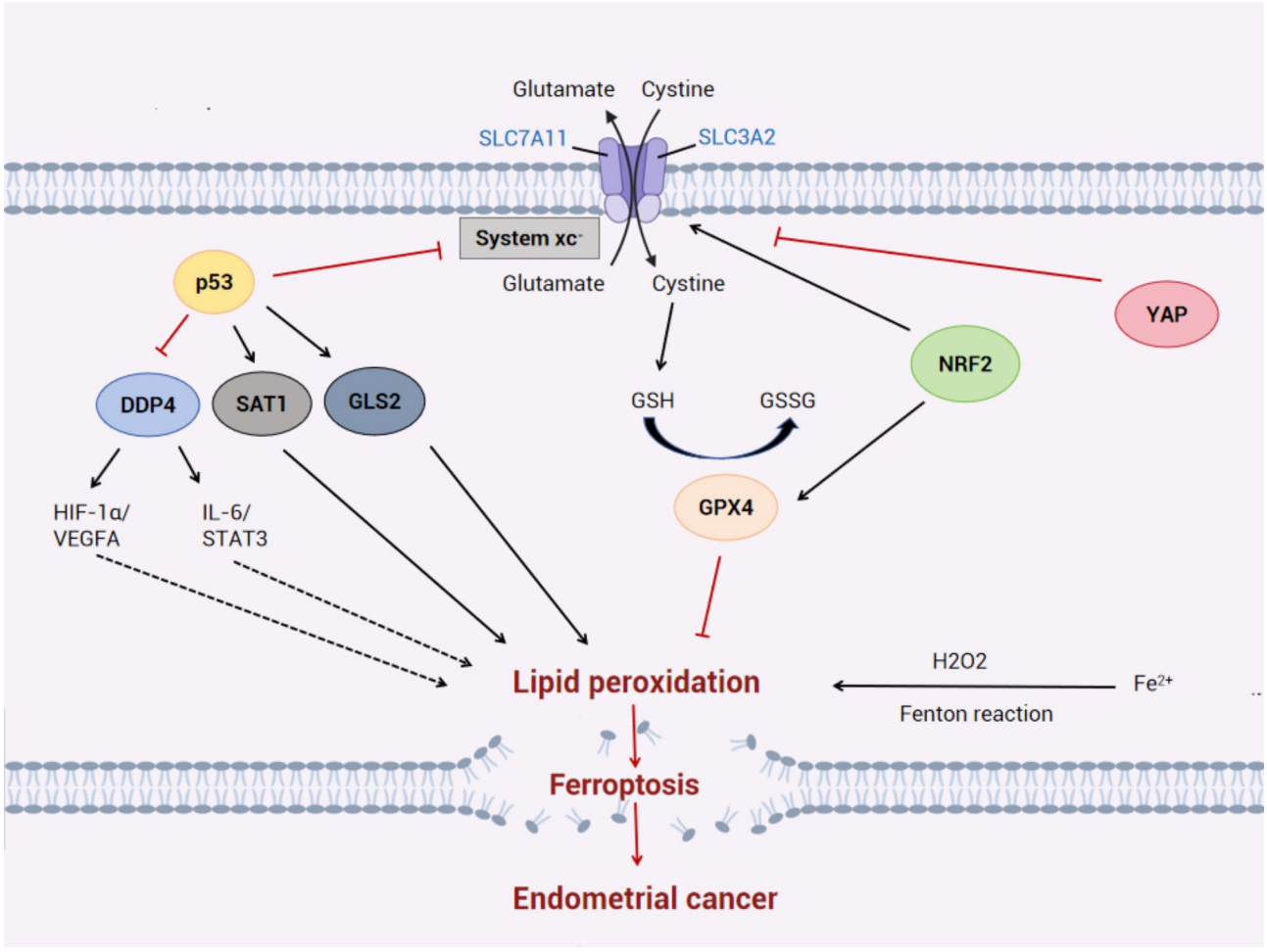


**Fig. 3** Mechanisms of ferroptosis in endometrial cancer. The systemic $Xc^-$-GSH-GPX4 pathway protects cells from ferroptosis. P53 could promote the function of lipid peroxidation and ferroptosis by inhibiting the systemic $Xc^-$. And p53 regulates ferroptosis and endometrial cancer initiation by regulating SAT1, GLS2, and DDP 4. Nrf2 inhibits lipid peroxidation and ferroptosis by enhancing the function of SLC7A11 and GPX4. YAP suppresses ferroptosis by promoting SLC7A11 expression

**Table 2** Ferroptosis and endometrial cancer treatment

| Therapeutic target and drug | Endometrial cancer cell line | Animal models | Human tissue samples | Mechanism of action | Effect | References |
|---|---|---|---|---|---|---|
| Guizhi Poria capsule (GFC) | / | / | C57BL/6 mice | Inhibit the p62-Keap1-Nrf2 signaling pathway | Promote ferroptosis, inhibit endometrial hyperplasia | [107] |
| Amentoflavone (AF) | ESC, KLE | / | / | the ROS/AMPK/mTOR signaling pathway | Promote ferroptosis in EC cells | [111] |
| Simvastatin | Ishikawa | / | / | The RAS/MAPK signaling pathway | Promote ROS and ferroptosis in EC cells | [112] |
| CircRAPGEF5 | KLE, Ishikawa, HEC−1-A, HEC−1-B, RL95−2 | / | 30 EC tissues | Modulate the splicing of TFRC pre-mRNA, promote exon-4 skipping of TFRC | Increased resistance to ferroptosis in EC cells | [113] |
| Sodium | Ishikawa, HEC−1B | / | / | The RBM3/SLC7A11 axis | Promote ferroptosis in EC cell | [114] |
| Quercetin | HEC−1-A | / | / | Promote ROS generation | Promote ferroptosis in EC cell | [115] |
| Dihydroisotanshinone I (DT) | ARK1, ARK2 | / | / | Inhibit the expression of GPX4 | Promote ferroptosis in EC cell | [116] |
| LINC02936 | Ishikawa, RL−952, HEC1A, HEC1B | / | / | The SIX1/CP axis | Suppresse ferroptosis and promote EC progression | [117] |

could predict the prognosis of EC patients [116]. However, there is a lack of large, multicenter clinical samples to validate their clinical significance.

## Cervical cancer and ferroptosis

### Ferroptosis and initiation of cervical cancer

While the precise role of ferroptosis in CC development remains uncertain, substantial evidence indicates that ferroptosis is significantly linked to CC progression [117–119]. ACSL4 can catalyze several PUFAs to promote ferroptosis. A study found that the circular RNA circLMO1 upregulates the expression of ACSL4, which promotes the ferroptosis in CC cells [120]. This provides a potential approach for the treatment of CC. Oleanolic acid (OA) was found to promote ACSL4 expression to activated ferroptosis and reduce the survival rate of Hela cells [121]. The systemic $Xc^-$-GSH-GPX4 axis plays a fundamental role in the antioxidant defense system during the process of ferroptosis. Wu et al. [122] discovered that inhibiting the circular RNA circEPSTI1 resulted in the inhibition of SLC7A11 and subsequently the systemic $Xc^-$, which led to ferroptosis in CC. Wang et al. [123] discovered the mitochondrial carrier 1 (MTCH1)-FoxO1-GPX4 signaling pathway and proposed that MTCH1 defects inhibit FoxO1 activation, which leads to downregulation of GPX4 transcription and accumulation of ROS, which ultimately triggers ferroptosis in CC cells. The researchers designed and reported a novel microtubule inhibitor called MP-HJ-1b that can enhance ferroptosis by downregulating SLC7A11 and GPX4 [124]. It was found that circACAP2 promoted the expression of GPX4 by sponging miR-193a-5p, thereby inhibiting ferroptosis in CC cells [125] (Fig. 4 ).

### Ferroptosis and treatment of cervical cancer

Cisplatin is widely regarded as one of the most effective agents for treating CC. However, patients who develop metastatic disease often receive concurrent cisplatin/radiotherapy as primary treatment, which may render them insensitive to single-agent platinum therapy. This

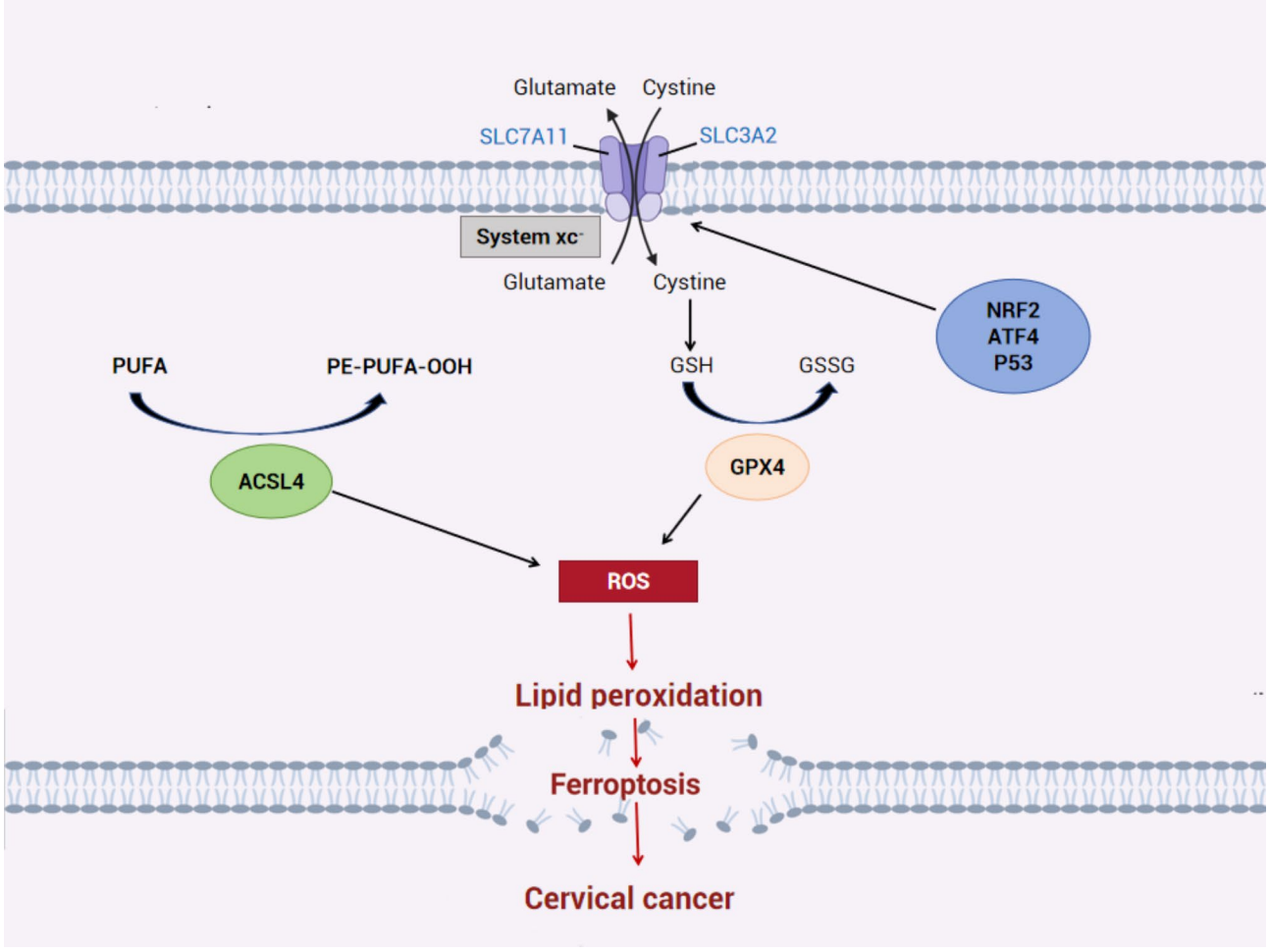


**Fig. 4** Mechanisms of ferroptosis in cervical cancer. The systemic $Xc^-$-GSH-GPX4 pathway protects cells from ferroptosis. ACSL4 Promote ferroptosis by promoting ROS, which leads to cervical cancer. Moreover, Nrf2, ATF 4, and p53 could promote ferroptosis by promoting the systemic $Xc^-$-GSH-GPX4 pathway

leaves very few treatment options available [126, 127]. A number of reports have demonstrated that targeting ferroptosis could be a promising therapeutic strategy to assist CC patients in overcoming resistance to cisplatin. The researchers discovered that the combination of propofol/PIE and paclitaxel increased intracellular ROS and induced ferroptosis. This suggests that propofol or PIE may enhance paclitaxel's ability to improve chemosensitivity in cervical cancer cells [128]. A study found that DHA inhibits the proliferation of CC cells through its association with ferroptosis [129]. Studies have shown that oxaliplatin resistance in CC cells can be reduced by the combination of desferrioxamine (DFO) and oxaliplatin [130]. Furthermore, a significant amount of evidence suggests that targeting ferroptosis may be a feasible strategy for treating CC and overcoming drug resistance [131–134] (Table 3).

### Ferroptosis and prognosis of cervical cancer

At the present time, CC is one of the most common malignant neoplasms affecting women. Improvement in the prognosis rate of patients with metastases or recurrence is of critical importance from a clinical standpoint. It is therefore important to investigate the potential of FRGs as prognostic biomarkers in CC patients. A considerable number of researchers have conducted extensive searches of various databases with the aim of identifying FRGs that can predict the prognosis of CC.They have subsequently developed predictive models and provided valuable ferroptosis-targeted therapeutic approaches for CC [135, 136]. Furthermore, Yu et al. have not only identified FRGs that are associated with prognosis, but have also examined FRGs methylation levels and constructed a risk model based on such FRGs methylation levels [137]. Additionally, the researchers have explored the potential link between ferroptosis and LncRNA [138, 139].

## Discussion

The most prevalent gynaecological malignancies encompass ovarian, endometrial, cervical, vaginal and vulvar cancers. Given the absence of studies examining the role of ferroptosis in vaginal and vulvar cancers, this paper will focus on the relationship between ferroptosis and ovarian, endometrial, and cervical cancers. In a previous study, Hushmandi et al. [140] demonstrated that non-coding RNAs (ncRNAs) influence the development of gynaecological tumours, as well as the progression of breast cancer. In this paper, we highlight the important role of ferroptosis in the development, treatment, drug resistance and prognosis prediction of gynaecological malignancies. To this end, we provide a comprehensive overview of the regulatory mechanisms of ferroptosis, including lipid metabolism, iron metabolism, oxidative systems and antioxidant systems.

Ferroptosis is a form of regulated cell death that is unique in its iron-dependence and non-apoptotic nature. Dysregulation of the lipid peroxidation pathway and iron metabolism are the primary causes of ferroptosis. The systemic $Xc^{-}$-GSH-GPX4 pathway, the FSP1-CoQ10 pathway, the GCH1-BH4 pathway, and the DHODH-CoQH2 pathway are among the regulatory mechanisms of ferroptosis.

Researchers are investigating the potential correlation between ferroptosis and gynecological cancers with the objective of facilitating the diagnosis and treatment of gynecological cancers. Studies have shown that inducing ferroptosis can improve the sensitivity of tumor cells to radiotherapy and targeted therapy, as well as synergistically activate immune cells. This brings new hope for the treatment of gynecological tumors. Additionally, many scholars have established a gene-related prediction model of ferroptosis through data analysis, with the aim of effectively predicting the prognosis of gynecologic tumor patients.

**Table 3** Ferroptosis and cervical cancer treatment

| Therapeutic target and drug | Cervical cancer cell line | Animal models | Human tissue samples | Mechanism of action | Effect | References |
|---|---|---|---|---|---|---|
| Propofol/PIE | C-33 A, HeLa | / | / | Inhibit the LC7A11/GPX4, ubiquinol/CoQ10/FSP1, and YAP/ACSL4/TFRC signaling pathway | Promote ferroptosis in CC cells | [133] |
| Dihydroartemisinin (DHA) | HeLa, SiHa | | | Inhibit the xCT/GPX4 axis | Promote ferroptosis in CC cells | [134] |
| Desferal | SiHa, S3 | / | / | Up-regulate hCtr1 and TfR1 | Restore the sensitivity of CC cells to platinum-based drugs | [135] |
| Matrine | SiHa | CB17 SCID mice | / | Activate Piezo1 | Promote ferroptosis in CC cell | [136] |
| Cdc25A | SiHa, CaSki | / | Human cervical cancer specimens | Up-regulate the Cdc25A/PKM2/ErbB2 axis | Inhibits autophagy-mediated ferroptosis in CC cells | [138] |
| HBP1 | HEK293T, HeLa, HepG2 | nude mice | / | Inhibit the UHRF1-CDO1 axis | Promote ferroptosis in CC cell | [139] |

It should be noted, however, that the present article is not without limitations. Firstly, the mechanism of ferroptosis remains inconclusive, and it is unclear whether there are additional, significant mechanisms at play. Secondly, although some studies have indicated a correlation between ferroptosis and gynaecological tumours, the precise mechanisms through which ferroptosis exerts its influence on these tumours remain uncertain. Thirdly, the majority of existing findings are limited to specific types of tumour cells, including EOC, SCC, ADC, and so forth. The role of ferroptosis in other types of gynaecological tumour cells remains to be elucidated through further investigation. Fourthly, the majority of studies investigating ferroptosis-induced cell death in gynaecological tumours are based on in vitro experiments, with a paucity of large-scale clinical trials. Further clinical studies are required to elucidate the means of safely and effectively inducing ferroptosis in tumour cells without damaging normal cells. Fifth, the majority of prognostic prediction models for gynaecological tumours have been established through bioinformatics analysis, and thus their clinical applicability and accuracy have yet to be established. Finally, there is currently no study which has described an association between ferroptosis and vaginal and vulvar cancers, and therefore this paper will only describe studies on ferroptosis and ovarian, endometrial, and cervical cancers.

## Conclusion

This review provides an overview of the mechanisms of ferroptosis and their relationship to the development, treatment and prognosis of gynaecological tumours. The current findings indicate that ferroptosis has significant potential for use in the diagnosis, treatment and prognosis prediction of gynaecological tumours, particularly in the context of anti-drug resistance. Nevertheless, further research is required. It is anticipated that ferroptosis will emerge as a promising treatment modality for patients with gynaecological tumours in the future.

**Abbreviations**

| | |
|---|---|
| OC | Ovarian cancer |
| EC | Endometrial cancer |
| CC | Cervical cancer |
| HPV | Human papillomavirus |
| ICD | Immunogenic cell death |
| PUFAs | Polyunsaturated fatty acids |
| AA | Arachidonic: acid |
| AdA | Adrenoic: acid |
| ACSL4 A | Synthase long chain family member 4 |
| LPCAT3 | Lysophosphatidylcholine acyltransferase 3 |
| MUFAs | Monounsaturated fatty acyl tails |
| LOX | Lipoxygenase |
| POR | Cytochrome P450 oxidoreductase |
| TFR1 | Transferrin receptor 1 |
| LIP | Labile iron pool |
| DMT1/SLC11A2 | Divalent metal transporter 1 |
| VDAC | Voltage-dependent anion channel |
| CYBB/NOX2 | Cytochrome B-245Beta |
| SLC7A11/xCT | Solute carrier family 7 member 11 () |
| SLC3A2/CD98 | Solute carrier family 3 member 2 () |
| AIFM2 | Apoptosis-inducing factor mitochondria-associated 2 |
| BH4 | Tetrahydrobiopterin |
| NO | Nitric oxide |
| GCH1 | GTP cyclohydrolase-1 |
| FAC | Ferrous ammonium citrate |
| SCD1 | Steroyl coa desaturase |
| FRGs | Ferroptosis-related genes |
| SAT1 | Spermidine/spermine N1-acetyltransferase 1 |
| DPP4 | Dipeptidyl peptidase 4 |
| OA | Oleanolic acid |
| MTCH1 | Mitochondrial carrier 1 |

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