Research Progress of Estrogen Receptor in Ovarian Cancer

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Abstract

Objective: This review aims to provide some theoretical guidance for the precise treatment of ovarian cancer and the development of estrogen-related drugs. Mechanism: Ovarian cancer is one of the leading causes of death in gynecological cancer patients, mainly affecting middle-aged and elderly women. It has the characteristics of hidden location, strong heterogeneity and lack of specific symptoms in the early stage. Numerous studies have shown that estrogen receptor (ER) plays an important role in different types of cancer, including ovarian cancer. Accordingly, the study of ER signaling pathways and related regulatory factors in ovarian cancer cells should help us understand the pathogenesis of ovarian cancer. Findings in Brief: The expression of estrogen receptor subtypes is related to ovarian cancer gene and leads to ovarian cancer. Estrogen receptor modulators appear to be an important factor in the prognosis of patients with ovarian cancer after hormone therapy. Conclusions: This review summarizes the regulatory mechanism of ER in the occurrence and development of ovarian cancer and outlines the specific role of estrogen receptor modulators (SERMs) in the treatment and prevention of ovarian cancer.

Keywords: ovarian cancer; estrogen; estrogen receptor; receptor modulators; precise treatment

1. Introduction

Ovarian cancer, one of the most common cancers in women, is evaluated as one of the leading causes of death in the world. A cancer survey report in Poland in 2019 showed that the incidence of ovarian cancer in women in the country ranked fifth, lower than breast cancer and cervical cancer, but higher than gastric cancer, colon cancer and pancreatic cancer [1]. Due to its late diagnosis, it is typically diagnosed at an advanced stage. In recent years, the overall survival rate has not significantly improved, while treatment efficacy remains unsatisfactory; it is therefore necessary to intensify the study of the occurrence and development of ovarian cancer [2,3]. New findings on estrogen have uncovered its association with ovarian cancer, highlighting the pivotal role of estrogen receptors (ER) as its primary target. These investigations propose that ER could serve as a crucial contributing factor in the development of ovarian cancer [4,5]. Drawing upon recent research advancements, this comprehensive review highlights the intricate relationship between ovarian cancer, estrogen and its receptors. It thoroughly examines the regulatory influence exerted by ERs and selective estrogen receptor modulators (SERMs) on the initiation and progression of ovarian cancer. Furthermore, this review anticipates the promising potential of SERMs in the treatment of ovarian cancer, paving the way for a broader spectrum of therapeutic avenues [6].

2. Overview of Estrogen and Ovarian Cancer

Estrogen (E), a class of steroid hormones that includes estradiol and estrone, is mainly secreted by the ovaries. It plays an important role in reproductive organs such as the ovaries, testes, uterus, and non-reproductive organs such as skeletal muscles and mammary glands [7]. ER is a protein receptor found in many tissues such as ovary that binds to estrogen. It can be divided into nuclear receptor and membrane receptor: Among them, ERα (ESR1) and ERβ (ESR2) in the nuclear receptor superfamily have complex action pathways and slow genomic response. Thus, nuclear receptors are often referred to as SLOW-ER [8]. In addition to the classical ERs, recent research has shed light on the significance of membrane receptors in estrogen-related processes. The discovery of GPER1 (GPR30), Gq-mER, and ER-X within the membrane receptor family has revealed their role in mediating rapid cellular responses upon ligand binding, without involving genomic reactions. The membrane receptors, often referred to as RAPID-ER, exhibit a shorter duration of action. As one of the earliest studied estrogen nuclear receptors, ERα plays the role of transcription factor, while ERβ, as a DNA-binding protein, has a significant multi-level inhibitory effect on ERα by affecting the expression of ERα regulatory genes, which is associated with cell signal transduction and periodic proliferation or death [9–11]. ERα and ERβ, as isoforms, are...
full-length proteins composed of six different domains, including the A/B region, and ligand-independent transcriptional activation region (AF-1). Region C (DNA binding region) has a double zinc finger structure, which assists this region in binding to specific DNA. Zone D (hinged zone) may serve as the connection between zone C and zone E as well as the E/F zone containing AF-2 (LBD) [12]. The seven-transmembrane membranous G-protein-coupled estrogen receptor 1 (GPER1/GPR30) belongs to the G-protein-coupled receptor (GPCR) family and is widely distributed in the ovary and various tissue cells such as granulosa cells, related to the occurrence of ovarian granulosa cell tumor (GCT) [13].

As a common cancer affecting women, ovarian cancer can be divided into different types. Based on the classification of the primary anatomical location, ovarian cancer is divided into two main types: primary ovarian cancer (POC), which originates within the ovary itself, and secondary metastatic ovarian cancer (SMOC), which is characterized by the spread of cancer cells from other tissues to the ovary. POC can be divided into epithelial, germ cell and specific sex cord interstitial sources, among which epithelial ovarian cancer accounts for the highest proportion [14]. Kajiyama et al. [15] found that there are roughly four primary sites of SMOC, ranked in descending order of occurrence: the gastrointestinal tract, appendix, breast and pancreas. The incidence of gastrointestinal ovarian cancer is the highest, far more than the sum of the other three, and the harm range is the most extensive [16].

ERs have different mechanisms and outcomes depending upon the types of ovarian cancer, and the same ER can have different outcomes in different types of ovarian cancer. At present, most of the clinical literature focuses on the study of ER on a few types of high-risk ovarian cancer, such as serous ovarian cancer, mucinous ovarian carcinoma. However, some types of ovarian cancer with a low incidence and a high degree of malignancy are rarely mentioned in the current literature. The reasons are as follows: such patients have a high degree of malignancy, low 5-year survival rate, low incidence, few research cases, and lack of funding and research. It is thus of great significance to study how this type of ovarian cancer plays a role in disease progression by affecting ER, and to increase the research on the lesser studied types of ovarian cancer to elucidate the pathogenesis of ovarian cancer and subsequent new drug development. In several rare cases of ovarian cancer, the literature only describes the clinical manifestations, while the relationship with ER has not been studied thoroughly or at all. Simultaneously, owing to the heterogeneity of ovarian cancer, the efficacy of drug therapy varies. Each drug exhibits distinct effects in the treatment of specific ovarian cancer subtypes. While certain drugs may play a role in one ovarian cancer subtype or in a variety of ovarian cancer subtypes, the role of currently known modulators is not fully elucidated. Exploring the detailed effects of various modulators on different types of ovarian cancer and achieving accurate treatment of drugs will be crucial for the treatment of ovarian cancer. Accordingly, we summarize the degree and source of benign and malignant ovarian cancer according to the type of ovarian cancer (Table 1, Ref. [17–32]), in an effort to supplement the content of this review.

3. The Mechanism of Estrogen Nuclear Receptor in Regulating the Occurrence and Development of Ovarian Cancer

Estrogen, as a fat-soluble steroid hormone, can enter the cell membrane and bind to nuclear receptors in a free diffusion state, that is, the two combine to form an E-ER polymer complex on the nuclear membrane [33]. After estrogen binds to nuclear receptors, the quaternary spatial structure of the complex will change under the induction of heat shock protein (Hsp90), and then binds to an ERE/β to form a homologous or heterologous ER dimer complex [33–35]. Estrogen-response element (ERE) is a DNA fragment containing a palindrome structure. It has confirmed that ER recruits and collects costimulatory factors such as P160. Under the synergistic effect of these costimulatory factors, the complex polymer binds to the estrogen response element, and then binds to form an E-ER-ERE complex. The complex regulates the expression of transcription products such as a long non-coding RNA (ElncRNA1) in the upstream of ovarian cancer target genes [36–39]. Studies have shown that this long non-coding RNA is induced by estrogen and promotes the occurrence of epithelial ovarian cancer (EOC) [39,40]. If the ERE element is absent, the AP-1 transcription factor can replace it, but ER cannot directly act on the AP-1 sequence, so other proteins (such as Jun/Fos coactivator) must be used as mediators [9,41]. It should be emphasized that the action pathways of ERα and ERβ are different here. The AF domain on the E-ERα complex binds to Jun/Fos, facilitating the transcription of target genes, an interaction that may contribute to the development and progression of ovarian cancer. The E-ERβ complex can inhibit the downstream transcription pathway initiated by AP-1 [42,43].

Cyclin D1 gene is a kind of proto-oncogene downstream of AP-1 sequence. Cyclin D1 promotes the proliferation of serous ovarian carcinoma (SOC) cells by regulating cyclin-dependent kinases (CDKs) to phosphorylate specific target proteins. The combination of cyclin D1 and CDKs is the rate-limiting step in regulating the cell cycle [44]. Studies have shown that ERα up-regulates the expression of cyclin D1 gene without affecting ovarian cancer cells such as PEO14 and BG1. ERβ down-regulates the expression of cyclin D1 in a ligand-independent manner and inhibits the development of ovarian cancer cells such as PEO14 and BG1 [12]. Nuclear PELP1 is a proto-oncogene in the vast majority of ovarian cancer cases, and its combined expression with cyclin D1 gene is closely related to the incidence of ovarian cancer [12,45,46]. There-
fore, immunohistochemical staining of cyclin D1 and nuclear PELP1 gene coding products can be used to predict the diagnosis of ERα overexpression and ERβ loss of expression. In addition, ecotropic viral integration site-1 (EVII) is also associated with the occurrence of ovarian cancer. The expression of this gene is related to the invasion of ovarian cancer cells into other cells. It has been reported that EVII expression of this gene is related to the invasion of ovarian cancer cells into other cells. The occurrence of high-grade serous ovarian cancer (HGSOC) through non-genomic pathways, can not only regulate the occurrence of high-grade serous cancer cells into other cells. Ithas been reported that EVI1 expression of this gene is related to the invasion of ovarian cancer cells into other cells. In addition, EVI1 is mediated by MAPK and AKT pathways. It competitively antagonizes estradiol, occupies receptors, and inhibits ERα to play a role in inhibiting the growth of ovarian cancer cells. Moreover, moderate to high doses of tamoxifen can significantly suppress the growth and proliferation of SKOV3 ovarian cancer cells by regulating vascular endothelial growth factor (VEGF) –[56–58]. In line with these findings, Velden et al. [59] reported that 40% of ovarian cancer patients had stable CA125 titer following tamoxifen treatment, and there was no clinical progress. In addition, the nuclear receptor can initiate the transcription of some special substances related to the expression of estrogen, such as LDL, progesterone receptor B, GATA1, and STAT5 after binding with the important factor Sp1 that plays a transcriptional intermediary role. Transcriptional regulators can also regulate these processes: Li et al. [64] found that transcriptional regulator PES1 regulates the expression of ERα or ERβ, while its ablation results in a significant down-regulation of ERα and promotes transcriptional activity in EOC. This process is limited by receptor modulators.

### 4. Mechanism of Regulating the Development of Ovarian Cancer beyond Nuclear Receptors

Several studies have shown that the combination of estrogen and GPER1 can activate MAP kinase pathway

<table>
<thead>
<tr>
<th>Type of ovarian cancer</th>
<th>Benign/Malignant</th>
<th>Primary/metastatic (source)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibroma</td>
<td>Benign</td>
<td>Primary (H specific sex cord stroma)</td>
<td>[17]</td>
</tr>
<tr>
<td>Mucinous tumors</td>
<td>Benign</td>
<td>Primary (ovarian germinal epithelium)</td>
<td>[18]</td>
</tr>
<tr>
<td>Serous cystadenoma</td>
<td>Benign</td>
<td>Primary (ovarian germinal epithelium)</td>
<td>[18,19]</td>
</tr>
<tr>
<td>Immature Teratoma</td>
<td>Benign</td>
<td>Primary (germ cell)</td>
<td>[20]</td>
</tr>
<tr>
<td>Asexual cell tumor</td>
<td>Malignant</td>
<td>Primary (germ cell)</td>
<td>[21]</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
<td>Malignant</td>
<td>Primary (germ cell)</td>
<td>[22]</td>
</tr>
<tr>
<td>Clear cell carcinoma</td>
<td>Malignant</td>
<td>Primary (ovarian germinal epithelium)</td>
<td>[23]</td>
</tr>
<tr>
<td>Embryonal carcinoma</td>
<td>Malignant</td>
<td>Primary (germ cell)</td>
<td>[24]</td>
</tr>
<tr>
<td>Endodermal sinus tumor</td>
<td>Malignant</td>
<td>Primary (germ cell)</td>
<td>[25]</td>
</tr>
<tr>
<td>Endometrioid tumor</td>
<td>Malignant</td>
<td>Primary (ovarian germinal epithelium)</td>
<td>[26]</td>
</tr>
<tr>
<td>Granulosa cell tumor</td>
<td>Malignant</td>
<td>Primary (H specific cord stroma)</td>
<td>[27]</td>
</tr>
<tr>
<td>Mixed germ cell tumor</td>
<td>Malignant</td>
<td>Primary (germ cell)</td>
<td>[28]</td>
</tr>
<tr>
<td>Metastatic carcinoma of digestive tract</td>
<td>Malignant</td>
<td>Metastatic (digestive tract)</td>
<td>[29]</td>
</tr>
<tr>
<td>Metastatic carcinoma of breast</td>
<td>Malignant</td>
<td>Metastatic (Mammary gland)</td>
<td>[30]</td>
</tr>
<tr>
<td>Metastatic carcinoma of genital tract</td>
<td>Malignant</td>
<td>Metastatic (genital tract)</td>
<td>[31]</td>
</tr>
<tr>
<td>Serous Ovarian Carcinoma</td>
<td>Malignant</td>
<td>Primary (ovarian germinal epithelium)</td>
<td>[18,19]</td>
</tr>
<tr>
<td>Sex cord stromal tumor</td>
<td>Malignant</td>
<td>Primary (H specific cord stroma)</td>
<td>[32]</td>
</tr>
<tr>
<td>Testicular blastoma of ovary</td>
<td>Malignant</td>
<td>Primary (H specific cord stroma)</td>
<td>[31]</td>
</tr>
</tbody>
</table>
by releasing heparin-binding epidermal growth factor (HB-EGF). Overexpression of mitogen-activated protein kinase kinase kinase 3 (MAP3K3) is recognized as an indicator of poor prognosis in ovarian cancer. High expression of phosphorylated p38 MAPK in EOC leads to an increased risk of death in ovarian cancer patients [65,66]. The increase of GPER1 expression is accompanied by the increase of matrix metalloproteinase-9 (MMP9) ($r = 1.000$, $p = 0.002$) [67]. The high expression of MMP9, MMP10, MMP12 and MMP25 is positively correlated with the overall survival rate of ovarian cancer [67,68]. Based on these findings, GPER1 may be involved in the invasion and metastasis of EOC, and is a potential indicator for early diagnosis and malignant degree prediction of EOC. Schüler-Toprak et al. [69] demonstrated that treatment with GPER1 agonist G-1 led to transcriptome responses related to growth inhibition and reduced the growth of OVCAR-3 and OAW-42 ovarian cancer cell lines.

Nuclear and membrane receptors both play an independent role and can synergistically interfere with ovarian cancer: hormones bind to a small number of nuclear receptors in the cytoplasm, which dimerize and migrate to the nucleus and bind to transcription factors phosphorylated by GPER1, and then bind to ERE and other sites through nuclear receptors to regulate transcription. ERα, ERβ and GPER1 can also initiate gene transcription by phosphorylation of transcription factors AP-1, STATs, Elk-1, CREB and nuclear factor kappa b (NF-κB) outside the nuclear membrane through protein-kinase cascade [9,70]. The classical NF-κB pathway involves the activation of the NF-κB transcription factor complex in the cytoplasm, followed by ERα binding to NF-κB, exhibiting a priming effect. The complex quickly enters the nucleus and binds to the promoter region of DNA, inducing the occurrence of ovarian cancer [71,72]. ERs have two signal pathways: nuclear initiated steroid signaling (NISS) and membrane initiated steroid signaling (MISS), both of which are signal transduction in the form of E-ER complex [45]. Studies have shown that some protein fragments of ERα and ERβ can bind to other cofactors or be phosphorylated by PKA and PKC signaling pathways to activate ER [73]. Some cytokines that do not require estrogen-mediated action alone also fall into this category: Salako et al. [74] found that the decrease of tumor necrosis factor-α (TNF-α) increased the sensitivity of ovarian cancer cells to oncolytic adenoviruses. The viral complex inhibited the expression of cellular inhibitor
of apoptosis-1 and -2 (cIAP1 and cIAP2) by producing cytokines such as TNF-α, which reduced the expression of X-linked inhibitor of apoptosis protein (XIAP). The knockdown of this protein gene enhanced the effect of carboplatin on ovarian cancer cells and decreased cell viability [74]. In addition, ligands on the surface of cancer cells can promote ovarian cancer metastasis after binding to the domain of the selectin in the adhesion molecule [75]. We map the mechanism by which estrogen nuclear receptors and non-nuclear receptors regulate the initiation and progression of ovarian cancer (Fig. 1) at the conclusion of this article.

5. Treatment and Prevention of Ovarian Cancer

We summarized the risk factors of ovarian cancer and the different effects of ER modulators on ovarian cancer. Our summary of the risk factors of ovarian cancer should enhance women’s awareness of prevention and help protect women from ovarian cancer. Our focus on SERMs should contribute to researchers’ further exploration of non-toxic and efficient anti-cancer drugs [76,77]. Risk factors of ovarian cancer include postmenopausal estrogen therapy, unmarried infertility, smoking, obesity, and age. [77]. The ovaries of unmarried infertile women will continue to ovulate, causing damage to the ovarian epithelium, which may lead to mutations in tumor suppressor genes such as TP53 and BRCA1/2. Bilateral salpingectomy and delayed salpingectomy (BS/DO) have been found to reduce the risk of ovarian cancer in BRCA1/2 mutation carriers. Meanwhile, a study investigated that loss of paired box 2 (PAX2) in murine oviductal epithelium (MOE) implies a precursor of high-grade serous ovarian cancer (HGSOC) with secretory cell proliferation (SCOUT), deletion of which generates a messenger RNA expression pattern [78,79]. It is closely related to the enrichment of estrogen signaling genes and the increase of estrogen receptor α expression [78]. Therefore, the removal of fallopian tubes may delay the development of cancer by affecting the expression of genes related to ER and estrogen transmission [78,79]. Tobacco can accelerate cell proliferation and invasion and inhibit cell apoptosis by promoting mesenchymal transformation at the cellular level. Obesity may promote the occurrence of ovarian cancer by producing IGF-1 and hyperinsulinemia [70,76]. Studies have shown that the incidence rate of women aged 65 years and older accounts for approximately half of the total age group, which may be due to the damage to ovarian epithelium caused by the longer ovarian ovulation time of elderly women [2]. Where possible, minimizing these conditions can serve as a more effective approach for ovarian cancer prevention.

Chan et al. [80] reported that MPP inhibits the growth of SKOV3 ovarian cancer cells by targeted regulation of ERα and blocking ERα-mediated phosphorylation of Ser473 (serine 473) in AKT. In addition, MPP can indirectly reduce the expression level of AKT by inhibiting ERα and increasing the expression of pro-apoptotic protein (caspase-3 and Bax) and tumor suppressor gene p53, thus breaking the balance of cell apoptosis. This pathway can promote the apoptosis of ovarian cancer cell A2780, inhibiting the cell cycle and proliferation of ovarian cancer cells [81]. Sun et al. [82] found that the AKT/mTOR/p70S6 pathway can promote the apoptosis of ovarian cancer. Curcumin, which has an inhibitory effect on this pathway, can increase the expression of pro-apoptotic protein (caspase-3 and Bax) and inhibit the expression of proliferation protein (PCNA). As an ERα inhibitor, curcumin can inhibit the malignant proliferation of ovarian cancer cells SKOV3 and A2780 [82,83]. Ki67 is a nuclear protein related to the proliferation of tumor cells such as ovarian cancer; its low expression indicates that the activity of cell proliferation is inhibited [84]. At the same time, two epigenetic regulators, DOT1L and menin, can also play a synergistic anti-proliferation role in OC cells by regulating the estrogen receptor signaling pathway, thereby improving the survival and treatment of OC patients [85]. By comparing the ovarian cancer in the combination group with the control group, it was found that the combination of cisplatin-curcumin can reduce the volume and weight of ovarian cancer in rats by more than 80%, while the expression of Ki67 protein in rats significantly decreased, which reduced the size of ovarian tumors in appearance and inhibited the resistance of ovarian cancer rats to cisplatin [86]. After treatment of SKOV3 cells with ERβ agonist DPN, the expression of phosphorylated AKT was reduced by 80%, which inhibited ovarian cancer cells [80]. At the same time, the tumor formation was also significantly reduced after the inhibitor AZD8835 inhibited AKT phosphorylation, both of which demonstrated the necessity of PI3K/AKT signaling pathway in the progression of EOC. FAK and PI3K/AKT signaling pathways can also be induced by ERβ agonist ERB-041, mediating cell cycle arrest and apoptosis, reducing the migration and invasion of ovarian cancer cells [87]. Experiments have shown that the affinity of ERβ agonist S-DPN to ER (Ki = 0.27 ± 0.05) is very close to that of cognate ligand E2 (Ki = 0.13 ± 0.02). Compared with its enantiomer R-DPN (Ki = 1.82 ± 0.21), S-DPN is an in vitro transcriptional activator and a bioactive form of DPN [88].

The combination of ER modulator and receptor can not only regulate ovarian cancer through PI3K/AKT signal pathway, but also through NF-κB channel for adjustment: Schüler-Toprak et al. [89] treated OVCAR-3 and OAW-42 cells with four ERβ agonists (ERB-041, WAY200070, 3β-Adiol, Liquiritigenin) and found that the expression of PTCH2, an ERβ agonist-regulated gene, was significantly down-regulated, indicating growth inhibition of ovarian cancer cell lines. Liquiritigenin and S-equol, two ERβ agonists, significantly reduce the activity of NF-κB in ovarian cancer cells such as SKOV3, which is beneficial to the apoptosis of ovarian cancer cells. Liu et al. [90] found that caffeic acid phenethyl ester (CAPE) can inhibit the
Table 2. Comparison of CAS numbers of different estrogen nuclear receptor modulators and the classification of regulatory effects.

<table>
<thead>
<tr>
<th>Regulator</th>
<th>CAS number</th>
<th>ERα agonist</th>
<th>ERα inhibitor</th>
<th>ERβ agonist</th>
<th>ERβ inhibitor</th>
<th>Mechanism of action</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen</td>
<td>10540-29-1</td>
<td>√</td>
<td></td>
<td>√</td>
<td></td>
<td>Tamoxifen blocks the mitosis of estrogen by competitively binding to ER and exerts its antiproliferative effect.</td>
<td>[57]</td>
</tr>
<tr>
<td>curcumin</td>
<td>458-37-7</td>
<td>√</td>
<td></td>
<td>√</td>
<td></td>
<td>Curcumin promotes the expression of apoptosis promoting protein and Circ-PLEKHM3, inhibit the expression of proliferation protein and AKT/mTOR/p70S6 pathway.</td>
<td>[82,83]</td>
</tr>
<tr>
<td>Bisphenol AF</td>
<td>1478-61-1</td>
<td>√</td>
<td></td>
<td>√</td>
<td></td>
<td>BPAF can exert a higher estrogenic effect than BPA through the GPER pathway.</td>
<td>[101]</td>
</tr>
<tr>
<td>Bisphenol C</td>
<td>79-97-0</td>
<td>√</td>
<td></td>
<td>√</td>
<td></td>
<td>Due to the enlarged halogen bond, BPC has a strong binding ability to the two ERs, and is very active for ERα, but antagonizes ERβ.</td>
<td>[102]</td>
</tr>
<tr>
<td>Bisphenol AP</td>
<td>1571-75-1</td>
<td>√</td>
<td></td>
<td>√</td>
<td></td>
<td>Halogen atom-based dispersion is the main driving force for the activity of ERα-agonists and ERβ-antagonists.</td>
<td>[103]</td>
</tr>
<tr>
<td>Bispheno B</td>
<td>77-40-7</td>
<td>√</td>
<td></td>
<td>√</td>
<td></td>
<td>Combination of BPB and GPER leads to activation of subsequent signaling pathways.</td>
<td>[101]</td>
</tr>
<tr>
<td>Bisphenol Z</td>
<td>843-55-0</td>
<td>√</td>
<td></td>
<td>√</td>
<td></td>
<td>Halogen atom-based dispersion is the main driving force for the activity of ERα-agonists and ERβ-antagonists.</td>
<td>[103]</td>
</tr>
<tr>
<td>Apigenin</td>
<td>520-36-5</td>
<td>√</td>
<td></td>
<td>√</td>
<td></td>
<td>Apigenin competitively binds to E2 and has weak selectivity for ERβ.</td>
<td>[104]</td>
</tr>
<tr>
<td>Liq</td>
<td>578-86-9</td>
<td>√</td>
<td></td>
<td>√</td>
<td></td>
<td>Liq significantly down-regulation of PTCH2 gene expression and decrease of NF-κB activity in SKOV3 and other ovarian cancer cells.</td>
<td>[89]</td>
</tr>
<tr>
<td>ERB-041</td>
<td>524684-52-4</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td>ERB-041 reduces migration and invasion of ovarian cancer cells by mediating FAK and PI3K / AKT signaling pathways to induce cell cycle arrest and apoptosis.</td>
<td>[87]</td>
</tr>
<tr>
<td>WAY200070</td>
<td>440122-66-7</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td>Downregulation of PTCH2 gene expression regulated by ERβ agonist inhibits growth of ovarian cancer cell lines.</td>
<td>[89]</td>
</tr>
<tr>
<td>3β-Adiol</td>
<td>unk</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td>3β-Adiol significantly down-regulated the expression of ERβ agonist-regulated gene PTCH2 and inhibited the growth of ovarian cancer cell lines.</td>
<td>[89]</td>
</tr>
<tr>
<td>OSU-ERb-12</td>
<td>unk</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td>Increased expression of tumor suppressors FOXO1 and FOXO3a inhibits epithelial-mesenchymal transition (EMT).</td>
<td>[92,93]</td>
</tr>
<tr>
<td>LY500307</td>
<td>533884-09-2</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td>LY500307 upregulates cell cycle arrest gene CDKN1A to promote ovarian cancer stem cell apoptosis.</td>
<td>[94]</td>
</tr>
<tr>
<td>Diaryl propionitrile</td>
<td>1428-67-7</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td>Diaryl propionitrile reduced phosphorylated AKT expression by 80%.</td>
<td>[80]</td>
</tr>
<tr>
<td>Cyclic Ketoximes</td>
<td>unk</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td>Cyclic Ketoximes recruits coactivators to form active complexes with ERβ with nanomolar affinity.</td>
<td>[105]</td>
</tr>
</tbody>
</table>

ER, estrogen receptor; √, the regulator has a promoting effect; unk, unknow.
progression of ovarian cancer cells by NF-κB pathway, inhibiting the survival, metastasis and immune escape of cancer stem cells. Morin can also inhibit the expression of NF-κB and IL6/8 induced by TNF-α and reduce the tumor volume of ovarian cancer in nude mice [91]. These studies show that inhibition of the NF-κB pathway has a positive effect on inhibiting ovarian cancer progression. In breast cancer cell lines, ERβ agonists (OSU-ERb-12 and LY500307) can promote the expression of tumor suppressor FOXO1 and FOXO3a [92]. OSU-ERb-12 also reduces the occurrence of ovarian cancer stem cells (OCSCs) by inhibiting epithelial-to-mesenchymal transition (EMT) [93]. At the genetic level, LY500307 (Erteberel) significantly reduced the invasiveness of OCSCs and up-regulated the cell cycle arrest gene CDKN1A to promote OCSCs apoptosis [94]. Studies have shown that decreased expression of apoptosis and cell cycle arrest gene CDKN1A in epithelioid SKOV3 and HEY ovarian cancer cells can lead to cell proliferation [95]. Overexpression of FOXO1 is associated with a low survival rate of EOC, and miRNA-96 negatively regulates FOXO3a in the miRNA-96/FOXO3a axis. A decrease in miRNA-96 levels reduces ovarian cancer cell invasion by targeting FOXO3a and increasing its levels [96,97]. Studies evaluated that the high incidence of tumor suppressor gene p53 mutation and high expression of ERβ2 and FOXM1 are markers of HGSOC, and ERβ2-mutant p53-FOXM1 axis promotes proliferation of HGSOC cell lines, inhibits apoptosis, and increases carboplatin resistance. This axis may thus be used as a new therapeutic target for HGSOC with a therapeutic potential for HGSOC [98]. In addition, curcumin can also promote the expression of a tumor suppressor (Circ-PLEKHM3), which increases the expression of suppressor of morphogenesis in genitalia 1 (SMG1) after down-regulating the expression of miR-320a, which is beneficial to the apoptosis of cancer cells and reduces the degree of aggregation [82,99,100]. Curcumin has a dual inhibitory effect on tumor growth and development [82,99,100] (Table 2, Ref. [57,80,82,83,87,89,92–94,101–105]).

6. Summary and Outlook

This review provides an overview of ovarian cancer, estrogen and its receptors, highlighting the mechanisms underlying ovarian cancer development, the involvement of estrogen receptors, and the significance of ER modulators. Current evidence suggests that ER signaling is associated with the development of ovarian cancer. However, the underlying mechanism of how ER and related signals regulate the growth of ovarian cancer needs to be further elucidated; further prospective research is warranted. Goals of such research should be to clarify the pathway of ER activity, find suitable and convenient therapeutic targets, and to choose efficient ERα inhibitors, ERβ agonists or alternative modes of ovarian cancer treatment.

Author Contributions

YG and KM contributed to the study conception and design. KM, MZ and HX performed the research. MZ, HX, ZL and WM wrote the manuscript. YG and KM revised the manuscript critically for important intellectual content. ZL, WM, HX, YZ, JX and WL contributed to the acquisition, analysis, or interpretation of data for the work. All authors contributed to editorial changes in the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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