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Ovarian cancer and the heart: pathophysiology, chemotherapy-induced cardiotoxicity, and new therapeutic strategies

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Abstract

Ovarian Cancer (OC) is recognized as the most lethal gynecologic malignancy, characterized by numerous genetic mutations that trigger uncontrolled cellular growth and replication. Emerging evidence suggests that non-coding RNAs including miRNAs and lncRNAs significantly influence OC through their multiple roles including tumor initiation, progression, metastasis, immune evasion, and chemoresistance, making them promising diagnostic markers and therapeutic targets. The primary approach to treating OC typically involves cytoreductive surgery followed by chemotherapy. However, the chemotherapeutic agents, particularly the anthracyclines such as doxorubicin (DOX), are known for their cardiotoxic effects, which can range from acute to chronic, potentially leading to heart failure and death. To enhance the overall treatment response and to minimize cardiotoxicity, alternative strategies have been explored. These include the use of liposomal doxorubicin (DOXIL) as a substitute for DOX, various radiotherapies, immunotherapies, and the co-administration of angiotensin-converting enzyme inhibitors and/or beta-blockers. Phosphodiesterase-5 inhibitors (PDE5i) have also demonstrated efficacy in reducing cardiotoxicity linked to cancer treatments and in promoting apoptosis in cancer cells across multiple cancer types. Although there is no current clinical trial directly examining the impact of PDE5i on reducing cardiotoxicity in OC, however emerging therapies such as Withaferin A, PARP inhibitors, and nanoparticle combination therapy show promise. Additional research is essential to develop treatments that are both effective against OC and less harmful to the heart.

Keywords Ovarian cancer, PDE5 inhibitors, Cardiotoxicity, Chemotherapy, Doxorubicin

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Introduction

Globally, Ovarian Cancer (OC) is the seventh most common cancer in women and the eighth leading cause of cancer death with a five-year survival rate below 45% [1]. It is the most lethal among the gynecologic cancers, and the number of cases is increasing with life expectancy [1]. More than 22,000 new cases are diagnosed annually in the United States alone, with about 14,000 deaths [2]. The prevalence is higher in low and middle-income countries, while rates are stable or declining in most high-income countries [1].

The exact cause of OC remains unclear, but several lifestyle factors such as cigarette smoking, obesity, and an unhealthy diet, as well as exposure to environmental agents like talc, herbicides, and pesticides, may increase the risk of OC [3]. However, these factors are not significant contributors to the development of the disease. Instead, a family history of ovarian or breast cancer, loss of the p53 tumor suppressor gene, and mutations in the BRCA genes are more common and effective factors leading to OC [3]. It is noted that approximately 55% of women with OC lack the p53 gene [3].

Mechanisms of ovarian cancer

OC develops through complex mechanisms involving genetic, epigenetic, and cellular alterations. OC is characterized by the uncontrolled division of cells in the ovary, a female reproductive organ that produces eggs. Importantly, OC often does not originate in the ovaries themselves. In fact, many cases of OC start in the fallopian tubes [2]. Moreover, when analyzing the molecular profiles of these cancers, cells from the fallopian tubes, ovaries, and peritoneum are indistinguishable, indicating they are manifestations of the same disease [2]. The most serious OCs originate from malignant cells in the tubal epithelium, while endometrioid and clear cell OCs typically develop from endometriosis [4].

The disease encompasses a diverse range of neoplasms and subtypes, each with unique causes, structures, molecular characteristics, and prognoses [5]. Despite this diversity, they are often treated as a single disease. OCs are primarily classified into three groups: epithelial (the most common), germ cell, and sex-cord-stromal tumors, with the latter two categories representing only about 5% of cases [2]. Epithelial OC is further divided into four subtypes: serous, endometrioid, mucinous, and clear cell. High-grade serous ovarian carcinomas (HGSOC) are the most prevalent, accounting for 70–80% of all epithelial OC subtypes, whereas low-grade serous ovarian carcinomas (LGSOC) constitute less than 5% [2]. Additionally, endometrioid, mucinous, and clear cell subtypes each account for about 10%, 3%, and 10% of cases, respectively [2].

Comparing HGSOCs with LGSOCs, it is important to recognize that each type of serous carcinoma exhibits different molecular profiles, clinical presentations, and prognoses [2]. Typically, women diagnosed with LGSOCs are younger and have a more favorable prognosis, along with a significantly longer expected survival time, compared to those diagnosed with HGSOCs [2]. Moreover, LGSOCs usually originate in the ovaries, whereas HGSOCs often start in the fallopian tubes and may spread to the ovaries or peritoneum [6].

Endometrioid Carcinomas (ECs), associated with endometriosis are typically manifest at an earlier stage than OC. ECs have better prognoses than other OC due to their chemosensitivity to histology and thus facilitates more effective treatment outcomes [7]. Similarly, women with clear cell carcinomas (ccCC) are often diagnosed at earlier stage with better prognoses [8]. However, diagnosis of ccCC at late stage can lead to poorer outcomes due to insensitivity to platinum-based chemotherapy. ccCC are often associated with complications like blood clots and paraneoplastic hypercalcemia [9]. Mucinous carcinomas are often diagnosed at Stage I and are frequently associated with metastases from the gastrointestinal tract [10].

Germ cell and sex cord-stromal tumors are rare types of OC, typically present in younger women and usually between the ages of 10 and 30. They are often non-malignant and detected early sex cord-stromal tumors [2, 11]. Ovarian germ cell tumors are distinguished by the presence of specific tumor markers, which aid in the planning of appropriate treatment strategies. However, they are generally present with nonspecific symptoms such as abdominal swelling and irregular vaginal bleeding [12].

Epithelial ovarian malignancies often originate from one of three locations: the ovaries, the fallopian tubes, or other epithelial sites in the pelvis and can be classified into Type I or Type II tumors [2]. Type I tumors are generally less aggressive compared to Type II tumors and include low-grade serous, low-grade endometrioid, clear cell, and mucinous carcinomas [13]. These tumors are believed to arise from continuous ovulation cycles, inflammation, and endometriosis [2]. They are characterized by mutations in several genes including BRCA1 and BRCA2, p53, KRAS, BRAF, PTEN, PIK3CA, CTNNB1, ARID1A, and PPP2R1A [13]. Mutations in these genes regulate signaling pathways involved in cell growth, differentiation, and programmed cell death. Mutations in KRAS and BRAF are well-known gain-of-function mutations within the MAPK pathway and are frequently observed in several cancers. These mutations are reported in melanoma (15–60%), colorectal cancer (CRC, 5–34%), and OC (27–50%) [14]. BRCA1 and BRCA2 are tumor suppressor genes essential for repairing DNA double-strand breaks through homologous recombination (HR). Germline or

somatic mutations in these genes result in defective DNA repair, accumulation of mutations, and genomic instability, which drive tumorigenesis. BRCA1 and BRCA2 are tumor suppressor genes essential for repairing DNA double-strand breaks through homologous recombination (HR). Hypermethylation of the BRCA1 promoter leads to its silencing, mimicking the effects of genetic mutations and contributing to HR deficiency in OC [15]. Alterations in histone acetylation and methylation can lead to chromatin remodeling, affecting gene expression patterns that promote oncogenesis. Furthermore, epigenetic alterations, such as BRCA1 promoter methylation, can serve as biomarkers for predicting response to therapies like PARP inhibitors [15]. PI3K/AKT/mTOR is critical in regulating cell survival, proliferation, and angiogenesis. This pathway is activated through mutations or amplifications in PI3K or AKT, enabling mTORC1 activation both directly and indirectly [16]. Direct activation occurs via phosphorylation of mTOR at Ser2448 by AKT, while indirect activation involves AKT phosphorylating tuberous sclerosis complex 2 (TSC2), which inhibits the TSC1/TSC2 complex. The inactivation of this complex prevents the suppression of mTORC1, resulting in unchecked cell proliferation and resistance to apoptosis [16]. Alterations in the PI3K/AKT/mTOR pathway are prevalent in OC, driving tumor development and contributing to chemotherapy resistance. Consequently, this pathway has been investigated as a potential target for therapeutic intervention [15].

Type I OCs are usually confined to the ovary and tend to be resistant to chemotherapy [13]. In contrast, Type II tumors typically feature mutations in the TP53 gene [13], which play a crucial role in producing the tumor suppressor protein p53. The p53 protein is a critical regulator of the cell cycle, DNA repair, and apoptosis. Mutations in the TP53 gene lead to loss of p53 function, allowing damaged cells to survive and proliferate unchecked. TP53 mutations are found in approximately 96% of high-grade serous ovarian carcinoma (HGSOC), the most aggressive subtype [17]. Loss of p53 function promotes genomic instability and resistance to apoptosis. Mutant p53 may also gain oncogenic properties ("gain of function") that enhance invasion and metastasis [18].

On the other hand, Type II tumors, commonly manifest in clinical settings, include high-grade serous (accounting for 70% of cases), high-grade endometrioid, carcinosarcoma, and undifferentiated carcinomas, often originating from the fallopian tube [2, 13]. Due to the typically vague symptoms associated with Type II tumors, early detection of OC is uncommon. Often patients are diagnosed at an advanced stage, with a metastatic pattern that includes the upper abdomen, outside the peritoneal cavity, or within the liver's parenchyma [13].

Role of non-coding RNAs in ovarian cancer

Non-coding RNAs (ncRNAs) play critical roles in various human malignancies, including OC. They serve as oncogenes or suppressors by regulating cancer initiation, invasion, progression, chemosensitivity and resistance to therapies [19]. Four major types of ncRNAs- microRNA (miRNA), long ncRNA (lncRNA), circular RNA (circRNA) and PIWI interacting RNA (piRNA) with distinct functions have been increasingly shown to be involved in OC.

MicroRNAs (miRs) are endogenously expressed short sequence of non-coding molecules consisting of 18–24 nucleotides. MiRs mostly regulate target gene expression at the posttranscriptional level. Specific miRs play key roles in the pathophysiology of multiple cancers, including the development and progression of OC, through the regulation of different cancer-associated signaling pathways. LncRNAs are more than 200 nucleotides in length, whose expression are often dysregulated in various cancers. LncRNAs compete with endogenous RNA and often act as sponge of miRNAs to suppress their target mRNAs [20]. Circular RNAs (circRNAs) are more stable than linear RNAs and can sponge target oncogenic miRNAs and regulate their expression at transcriptional levels [21]. piRNAs consisting of 23–31 nucleotides bind with proteins belonging to Piwi subfamily to form piRNA complexes to regulate gene silencing pathways and regulate the stability of translation of mRNA [22]. piRNAs also play crucial role in cancer progression by regulating cancer cells proliferation, migration and apoptosis.

The aberrant miRNA expression plays a pivotal role in regulating OC development and prognosis [23–25]. Numerous miRs exhibit differential expression in OC tissues compared to normal tissue [25], highlighting their potential as prognostic or diagnostic markers for OC. Increased expression of miR-325, miR-429, miR-141, miR-492, miR-182, miR-30a, let-7 family and miR-200 family were identified in OC tissue. These miRs are considered as a clinical parameter for detecting OC invasion and metastasis, angiogenesis and promoting tumor progression or drug resistance [25–27] as outlined in Fig. 1. Higher expression of miR-146a and miR-150 in omental lesions increased drug resistance [28]. A tumor suppressor miRNA, miR-100, that inhibits mTOR (mammalian target of rapamycin) and proto-oncogene PLK1 (Polo-like kinase-1), is down-regulated in OC, which leads to shorter overall survival of the patients with advanced-stage OC [29–31]. In vivo mouse study with tumors derived from miR-100 mimic-transfected cells showed miR-100 resensitized epithelial OC to cisplatin by inhibiting cell proliferation, inducing apoptosis with targeted downregulation of mTOR and PLK1 expression [32].

On the other hand, higher expression of miR-214 in OC tissue is correlated with cancer cell survival,

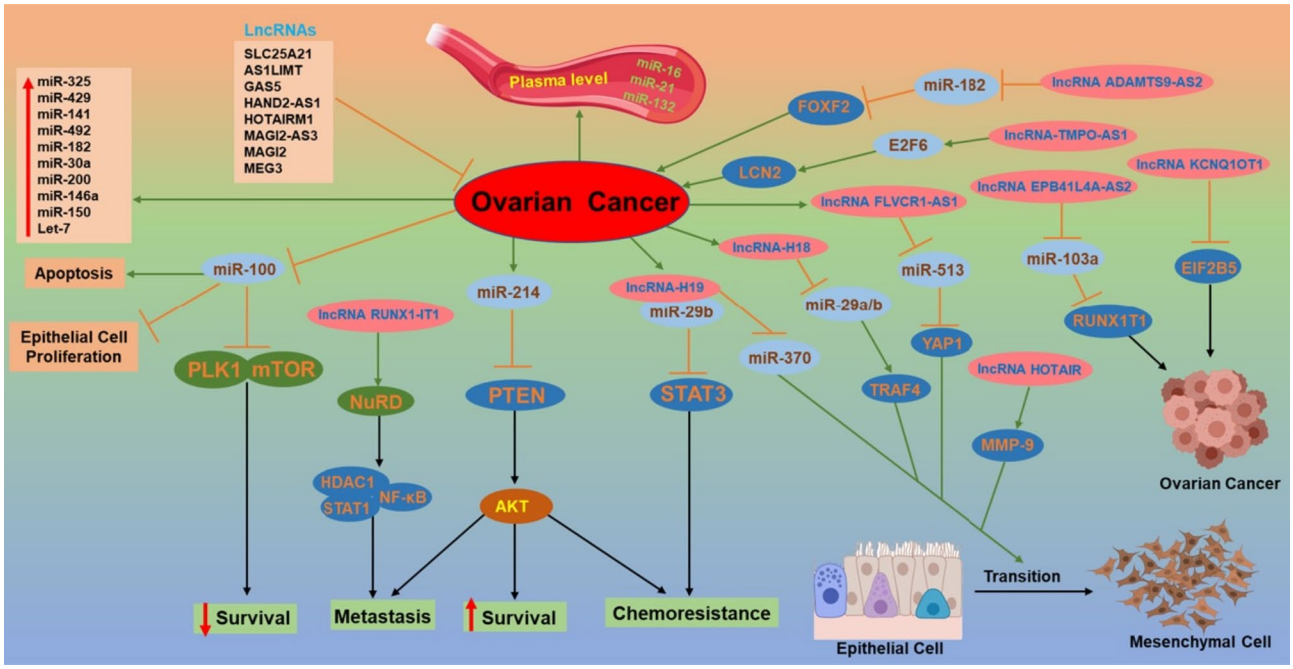

Fig. 1 The role of long non-coding RNAs (lncRNAs) and micro RNAs (miRNAs) in OC development, progression, and metastasis. The figure illustrates key lncRNAs and microRNAs (miRs) involved in various processes, including tumor growth, epithelial-to-mesenchymal transition (EMT), angiogenesis, immune evasion, and chemoresistance. Oncogenic lncRNAs (e.g., HOTAIR, MALAT1) promote these processes, while tumor-suppressive lncRNAs (e.g., MEG3, ADAMTS9-AS2) inhibit them. Mechanisms such as miRNA sponging, chromatin remodeling, transcriptional regulation, and post-transcriptional modulation are highlighted

chemoresistance and metastasis through targeting the PTEN/AKT pathway [33].

Multiple clinical trials have been conducted to profile the expression of miRNAs or lncRNAs in ovarian malignancies, which could be used as potential biomarkers (NCT03738319, NCT05146505, NCT02758652, NCT01391351, NCT03742856). Although plasma and blood miRNAs are the preferred source for non-invasive assay for early clinical diagnosis of multiple cancers, however, miRNA expression patterns are mostly differentially regulated in the patient's cancerous tissue and plasma samples. Nano-string technology has been utilized to establish a correlation profile in ovarian tissue and plasma [34]. This analysis identified miR-16, miR-21, and miR-132 as the most consistently highly expressed miRNAs in plasma, while miR-21 was consistently most highly expressed miRNA in ovarian tissue. miRNA-based interventions offer a promising therapeutic approach for addressing OC pathogenesis. These strategies involve inhibiting upregulated oncogenic miRNAs using antisense miRNAs (miRNA inhibition therapy) or restoring downregulated tumor suppressor miRNAs using miRNA mimics (miRNA replacement therapy) [35].

Numerous studies have demonstrated that various lncRNAs regulate OC pathophysiological processes by modulating the expression of target genes at epigenetic, transcriptional, and post-transcriptional levels. These findings highlight the potential therapeutic applications of lncRNAs in the diagnosis and prognosis of cancers [36]. The abnormal expression of lncRNAs, particularly oncogenic lncRNAs, influences various molecular mechanisms and is associated with tumor metastasis, drug resistance, and tumor immunity. These effects are mediated through processes such as miRNA sponging, and interactions with proteins or DNA. lncRNA-H19 interacts with miR-29b-3p and inhibits its downstream target gene STAT3, leading to carboplatin resistance in OC [37]. Increasing evidences suggested the oncogenic role of lncRNA H19 in various cancers, including OC by sponging miR-29b-3p or miR-370-30 [38] as shown in Fig. 1 [39]. lncRNA-H19 suppressed miR-29b-3p, leading to STAT3-induced chemoresistance in carboplatin-tolerated epithelial OC (EOC) [37]. Similarly, abnormal expression of lncRNA HCG18 (HLA complex group 18) in EOC induced TRAF4/TRAF5- facilitated proliferation, migration and EMT (epithelial-mesenchymal transition) by targeting miR-29a/b [67]. lncRNA TMPO antisense RNA 1 (TMPO-AS1) promotes lipocalin-2 (LCN2) transcriptional activity by binding to E2F6, a transcriptional repressor, which stimulates the progression of OC [40].

Abundance of lncRNA FLVCR1-AS1 expression in OC cell induces cell progression, migration, invasion and epithelial to EMT process by suppressing miR-513 with stimulation of YAP1 signaling [41]. Another lncRNAs,

HOTAIR (HOX transcript antisense RNA) and lncRNA CCAT1 were significantly elevated in epithelial OC tissues, which have been suggested as prognostic markers and potential therapeutic target in patients with OC [42]. LncRNA RUNX1-IT1 also plays a crucial role in the progression of OC by scaffolding STAT1 and NuRD complex to promote ROS-mediated NF-κB activation [43]. A recent study demonstrated that elevated levels of lncRNA KCNQ1OT1 exacerbate OC metastasis by repressing EIF2B5 expression through the recruitment of DNA methyltransferases to the EIF2B5 promoter [44]. Similarly, higher expression of lncRNA LINC01215 in OC tissue is associated with significant acceleration of tumor growth and metastasis by methylation of RUNX3 (Runt-related transcription factor 3, a tumor suppressor gene) promoter with reduction of its expression [45].

In contrast, several lncRNAs have been identified as suppressor lncRNA, which impede the expression and functional activity of oncogenic miRNA and increase the mRNA of the target cancer suppressor genes and proteins [46]. For example, lncRNA ADAMTS9-AS2 inhibits OC progression by regulating miR-182-5p/FOXF2 axis [47]. LncRNA, EPB41L4A-AS2 promotes the expression of RUNX1T1 via binding to miR-103a to repress OC progression [48]. Multiple lncRNAs, SLC25A21-AS1, LIMT (lncRNA inhibiting metastasis), GAS5 (growth arrest-specific transcript 5), HAND2-AS1(heart and neural crest derivatives expressed transcript 2 antisense RNA 1), HOX antisense intergenic RNA myeloid 1 (HOTAIRM1), MAGI2-AS3 (membrane-associated guanylate kinase, WW and PDZ domain-containing 2 (MAGI2) antisense RNA 3), MEG3 (maternally expressed 3) have been identified as critical suppressors of tumor progression in OC through diverse mechanisms and signaling pathways [38, 49–55]. Based on the key regulatory roles of lncRNAs o the pathogenesis and metastasis of OC, several ongoing studies aim to identify lncRNAs as potential diagnostic and prognostic markers for screening patients with OC as well as effective therapeutic targets.

Treatment strategies

First-line treatments for OC typically include surgery followed by chemotherapy, with platinum-based drugs like carboplatin and paclitaxel combination being standard [56]. Despite initial high response rates [56], about 70% of patients will experience a relapse, and the recurrent cancer often becomes resistant to standard treatments [56]. The resistance mechanisms are varied, including cisplatin resistance, multidrug resistance and issues related to DNA repair, among others [56]. In addition, cisplatin, a commonly used drug, can cause significant side effects like nephrotoxicity, ototoxicity, and hepatotoxicity, while carboplatin can cause hematologic toxicity, particularly thrombocytopenia [57].

For recurrent cases, doxorubicin (DOX) (Fig. 2) and its derivatives are often used as second-line options, acknowledging the progressive development of resistance to initial chemotherapeutic regimens [15]. In clinical

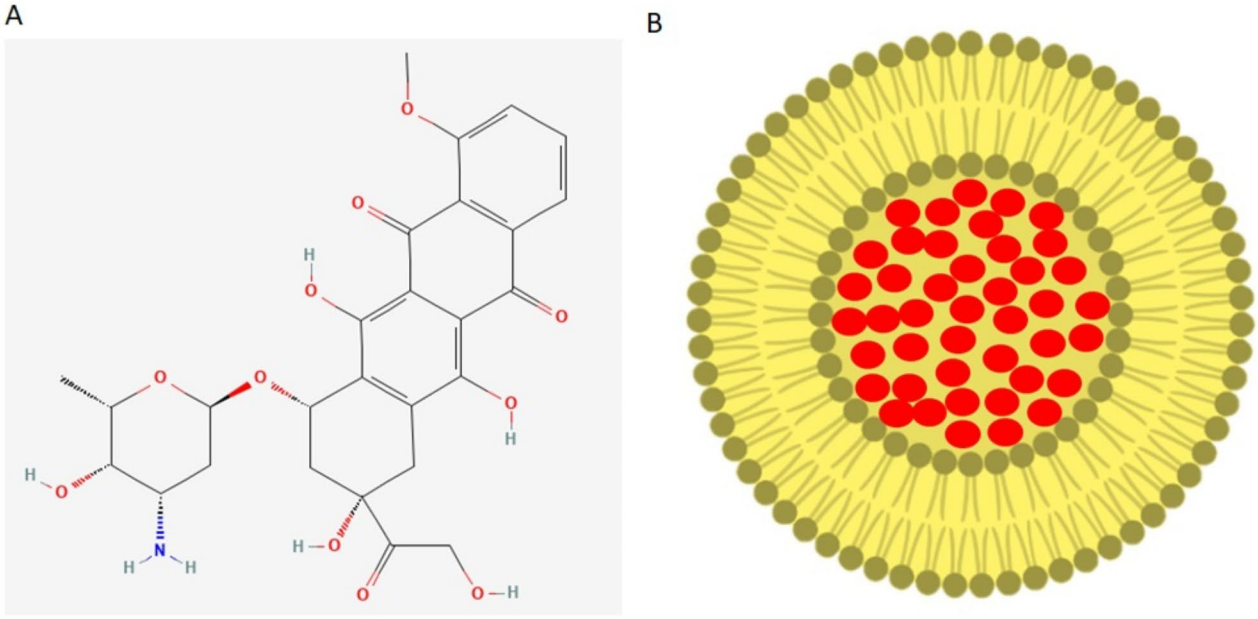

Fig. 2 Chemical Structure of doxorubicin. (**A**) Doxorubicin molecule consists of an anthraquinone chromophore core (red-colored tetracyclic structure) attached to a daunosamine sugar moiety. This structure facilitates DNA intercalation and topoisomerase II inhibition, critical for its anti-cancer activity. (**B**) Schematic illustration showing doxorubicin encapsulated within a phospholipid bilayer vesicle (liposome), surrounded by polyethylene glycol (PEG). The PEG coating enhances circulation time, reduces immunogenicity, and improves drug delivery to tumors via enhanced permeability and retention (EPR). As a result, this formulation minimizes systemic toxicity

settings, studies on the response of OC patients to DOX treatment after recurrence show typical response rates ranging from 10 to 20%, with an overall survival of approximately 12 months.

A key mechanism of antitumor effects of DOX involves its ability to integrate into the DNA helix and covalently bind to proteins essential for DNA transcription and translation [58]. DOX penetrates the cancer cell through simple diffusion and binds with high affinity to the proteasome in the cytoplasm [58]. It then attaches to the 20 S proteasomal subunit, forming a complex [58] that migrates into the nucleus via nuclear pores. Once inside the nucleus, DOX leaves the proteasome due to its stronger affinity for DNA [58], leading to the intercalation into DNA and disruption of the topoisomerase-II-mediated DNA repair process [59] as shown in Fig. 3.

Additionally, DOX impacts cellular mitochondria by binding to cardiolipin, which blocks the attachment of mitochondrial creatine kinase to mitochondrial membranes [58]. This interaction, along with the activation of complex I of the mitochondrial respiratory chain, enhances DOX's redox cycling, increasing the production of reactive oxygen species (ROS) [58]. As a result, DOX is oxidized to semiquinone, an unstable intermediate that reverts back to DOX, releasing ROS in the process [59] as illustrated in Fig. 3.

In clinical settings, studies on the response of OC patients to DOX treatment after recurrence show typical response rates ranging from 10 to 20%, with an overall survival of approximately 12 months. The concerns surrounding DOX are primarily due to its potential to cause irreversible cardiomyopathy, a condition that impairs the cardiac muscle's ability to contract, and potentially leading to heart failure [60]. This risk escalates with cumulative doses exceeding 500 mg/m², affecting over 30% of patients at such dosage levels [60]. The cardiotoxic effects are attributed to the disintegration of myofibrillar arrays, mitochondrial damage, and apoptosis of cardiomyocytes, which collectively contribute to the loss of myofibrils [60]. Symptoms of acute DOX cardiotoxicity include

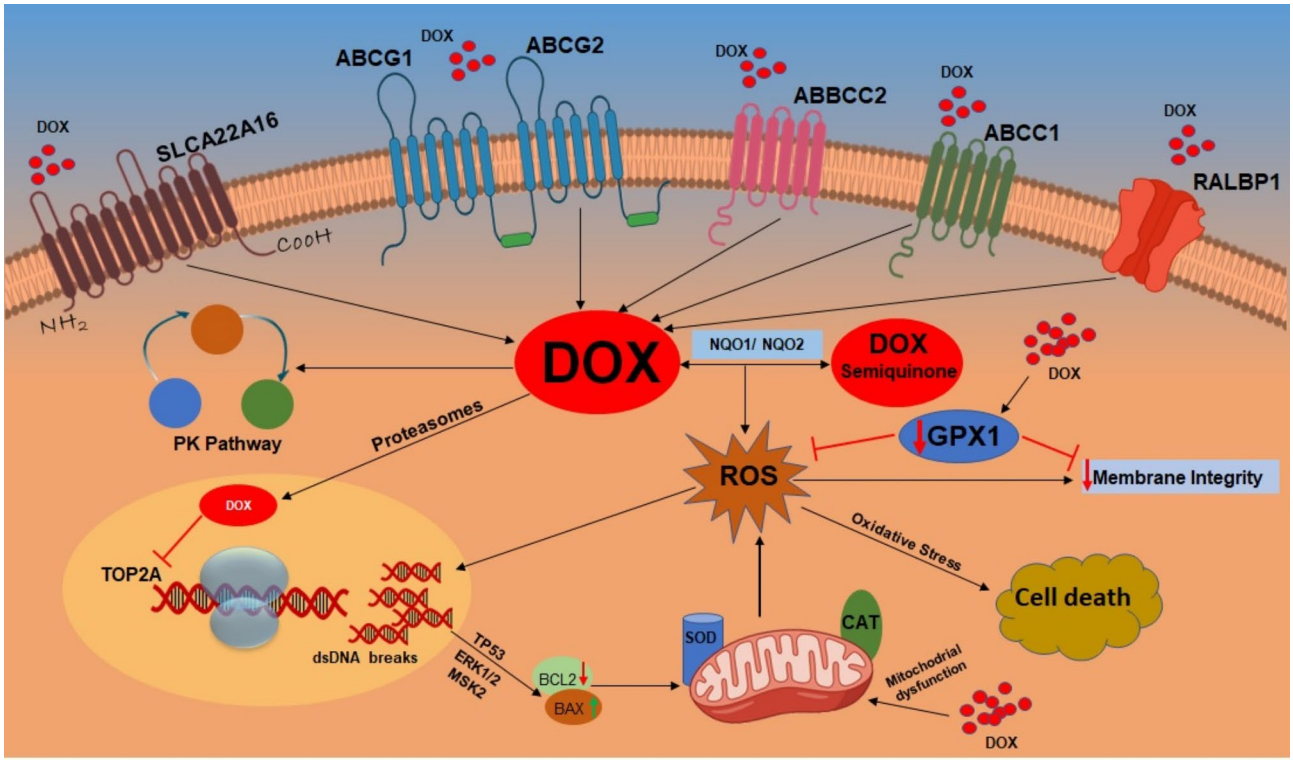

Fig. 3 Anti-cancer mechanisms of doxorubicin (DOX): DOX primarily exerts its cytotoxic effects by intercalating into DNA and inhibiting the activity of topoisomerase IIα (TOP2A), resulting in DNA double-strand (dsDNA) breaks and activation of apoptotic signaling pathways (e.g., TP53, ERK1/2, and MSK2). Additionally, DOX generates reactive oxygen species (ROS) through redox cycling, mediated by NAD(P)H: quinone oxidoreductases (NQO1 and NQO2), and through interactions with mitochondrial complexes. Excessive ROS production leads to oxidative stress, membrane damage, and mitochondrial dysfunction, culminating in cell death. Protective mechanisms within the cell, such as the activity of glutathione peroxidase 1 (GPX1) and catalase (CAT), counteract oxidative damage caused by ROS in the heart. However, the overwhelming ROS generation by DOX often surpasses these antioxidant defenses, leading to apoptosis. DOX also engages the protein kinase (PK) pathway and proteasomal degradation to further disrupt cellular homeostasis Efflux of DOX from the cell is regulated by ATP-binding cassette (ABC) transporters such as ABCG1, ABCG2, ABCC1, and ABCC2, as well as the multidrug resistance-associated protein RALBP1. These transporters contribute to chemoresistance by reducing intracellular DOX accumulation. Conversely, the solute carrier SLC22A16 facilitates DOX uptake, enhancing its intracellular effects

arrhythmia, tachycardia, and arterial hypotension, while chronic toxicity can lead to ventricular dilation and cardiac dysfunction, culminating in heart failure [60]. The myocardium's particular vulnerability to damage arises from DOX's higher affinity for heart tissue compared to other body tissues, further exacerbating cardiotoxicity [61].

DOX also depletes endogenous antioxidants like glutathione and catalase, causing redox imbalances and increasing oxidative stress, which contribute to myocardial toxicity [62]. The reduced levels of antioxidant enzymes in the heart, such as glutathione peroxidase-1 (GPX1), catalase (CAT), and superoxide dismutase (SOD), intensify this vulnerability [62].

Dexrazoxane is the only FDA-approved cardioprotective agent specifically for anthracycline-induced cardiotoxicity and works by chelating iron, reducing the formation of toxic anthracycline-iron complexes and subsequent ROS production [63, 64]. This mechanism helps mitigate the cardiomyopathy associated with anthracycline treatment and does not cause harmful DNA strand breaks [63]. It also enhances cell viability and cardiac function by attenuating apoptosis and necroptosis (inflammation-induced cell death) in cardiomyocytes, particularly through modulating the p38MAPK/NF-κB pathways [63]. However, the use of Dexrazoxane is limited by FDA to specific conditions due to the potential risk of secondary malignancies [64]. It is approved only for women with metastatic breast cancer who have received cumulative doses of 300 mg/m^2 or higher [64].

Additionally, studies have indicated that melatonin, a potent antioxidant, can mitigate DOX's cardiotoxic effects by reducing ROS production and lipid peroxidation [65]. Melatonin also helps preserve mitochondrial function by stabilizing mitochondrial membrane potential, restoring ATP production, and promoting mitochondrial biogenesis [65]. These protective effects suggest improvements in mitochondrial health which potentially enhance the overall efficacy of DOX treatment. While further clinical research is necessary, preliminary findings suggest melatonin could positively affect treatment outcomes, including improvements in ECG results, left ventricular function, and overall cardiac stability during DOX therapy [65].

Nanocarriers, including liposomes, polymeric nanoparticles, and micelles, have been developed to encapsulate DOX, enabling controlled release and targeted delivery to specific organs and cells [66]. Among these, liposomal formulations, such as Liposomal Doxorubicin (DOXIL)—also known as pegylated liposomal doxorubicin or doxorubicin hydrochloride (Fig. 2)—are widely used for treating recurrent OC. Additional liposomal nanoformulations, such as Lipodox® and Myocet®, have also been developed for cancer therapy [67]. These formulations leverage the enhanced permeability and retention effect, facilitating higher drug accumulation in tumor tissues while reducing exposure to healthy cells, as illustrated in Fig. 4.

Notably, the pegylated liposomal delivery system modifies the pharmacokinetics of DOX, leading to reduced drug accumulation in the heart, thereby minimizing cardiotoxicity [68]. Specifically, the liposomal carrier is unable to penetrate the tight capillary junctions of heart muscle but can exit the bloodstream in areas where cells are less tightly joined, such as tumor sites. The liposome encapsulating DOX is equipped with multiple ligands on its surface that are designed to bind to specific receptors on the tumor cell membrane. Once these ligands successfully attach to the receptors, the tumor cell internalizes the liposome through a process called clathrin-assisted endocytosis [69]. After entering the tumor cell, the clathrins detach from the liposome's ligands, facilitating the release of DOX directly into the tumor cell. Thus, the anthracycline is concentrated where it is needed in the tumor tissue, while exposure to the heart, a site of common anthracycline toxicity is minimized [68].

It should be acknowledged that while the stability of pegylated liposomes can lead to a slow release of the liposomal content around the tumor. This may reduce cytotoxicity to such an extent that there might not be a clear advantage over non-encapsulated drugs [70]. Additionally, the large size of the pegylated molecule could potentially hinder the liposome's ability to penetrate tumor tissue as the pegylated coating might reduce interactions between the liposomes and cellular targets [66]. The toxicity profile of DOXIL includes dose-limiting mucosal and cutaneous toxicities, mild myelosuppression, significantly reduced cardiotoxicity compared to free DOX, and minimal alopecia [71]. The reduced cardiotoxicity of DOXIL allows for administering higher cumulative doses than would be acceptable with free DOX [71].

Regarding cotreatments that could mitigate cardiotoxic effects and enhance response rates, combining DOXIL with dexrazoxane may decrease cardiotoxicity, though it does not eliminate it entirely [72]. Studies have shown promising results when DOXIL is combined with carboplatin. A 2007 study reported an overall response rate (ORR) of 51% with associated toxicities including neutropenia, RBC transfusions, and thrombocytopenia, compared to a 58% ORR for a treatment regimen of paclitaxel and carboplatin which led to alopecia and neutropenia [73]. Another study reported that combination of DOXIL and carboplatin showed a 52% ORR with toxicities such as neutropenia, thrombocytopenia, and anemia, whereas carboplatin monotherapy had a 29% ORR with only allergic reactions noted [24]. Another study further supported these findings that DOXIL/carboplatin treatment had a notably higher ORR of 251%, with associated

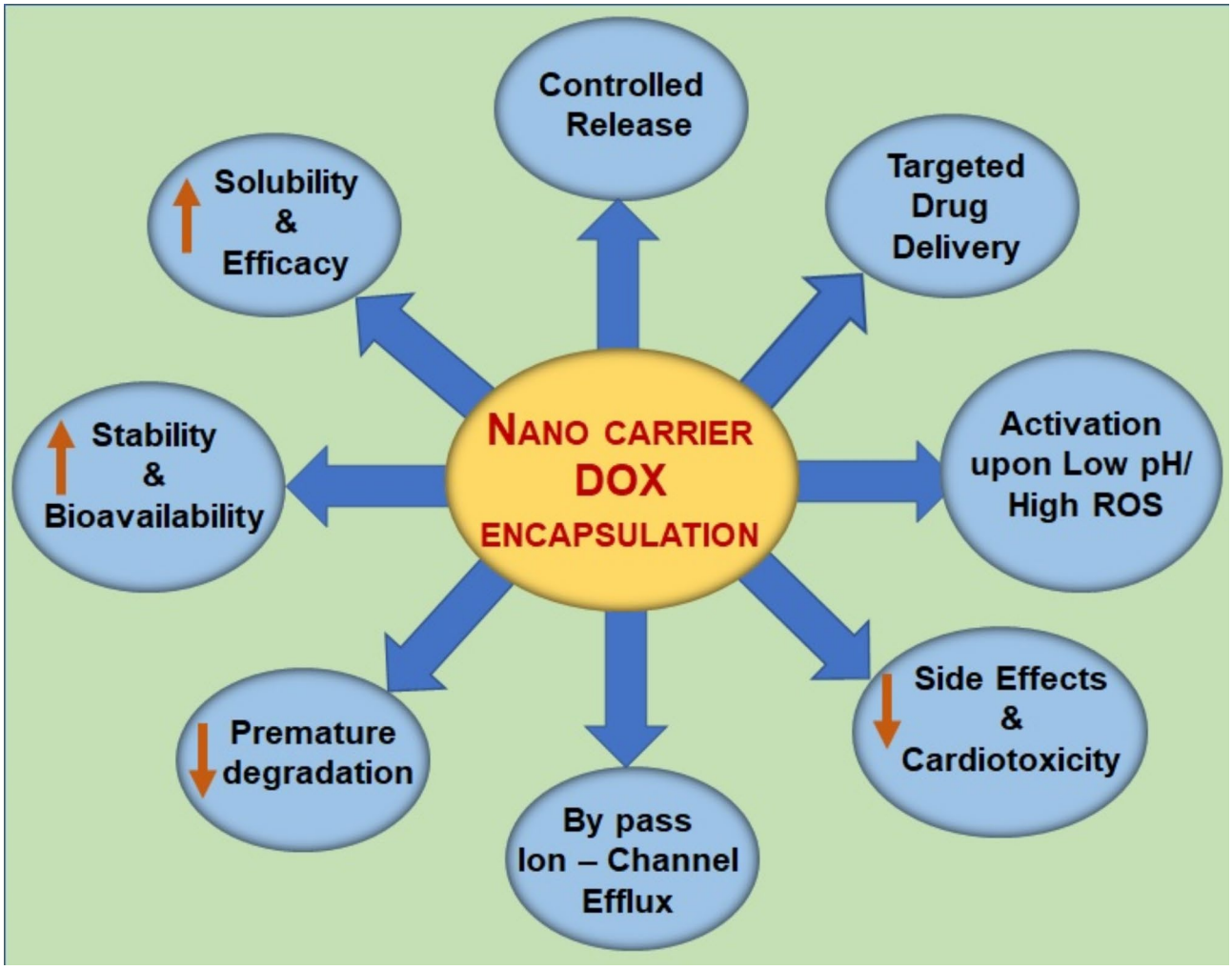

Fig. 4 Advantages of DOX encapsulation with Nano carrier lipid particle: The encapsulation strategy demonstrates the potential to optimize the therapeutic index of DOX while mitigating its adverse effects

toxicities including neutropenia, thrombocytopenia, hand-foot syndrome, and mucositis [24].

A Phase II trial has shown that pegylated-liposomal DOX not only has a reduced cardiotoxic potential compared to non-liposomal DOX but also stands as the only non-platinum monotherapy demonstrating a significant survival advantage as a second-line treatment for OC [24]. However, the potential for cumulative-dose cardiotoxicity when treating advanced and recurrent cancers, including OC, remains a clinical concern. High-risk factors for adverse effects of pegylated-liposomal DOX treatment include previous chest wall/mediastinal radiotherapy, older age, a history of congestive heart failure, and existing signs of cardiotoxicity [61]. Although pegylated-liposomal DOX is effective in its anti-tumor capacity, careful consideration of these risk factors is crucial in dosage administration. Continued clinical research is necessary to better manage the cardiotoxicity associated with these chemotherapeutic agents.

Treatment strategies for cardiotoxicity

During cancer treatment, patients may encounter various forms of cardiotoxicity, including acute coronary syndrome, myocarditis, arrhythmias, or heart failure [74]. Given the prevalence of both cancer and cardiovascular diseases, the field of cardio-oncology is gaining momentum. The primary goals of cardio-oncology include preventive strategies for cancer patients with or without cardiovascular risk factors, optimization of cardiovascular disease management, early identification and treatment of cardiotoxicities, and long-term cardiovascular monitoring for cancer survivors [74].

Given the cardiac risks associated with chemotherapeutic agents, there is a clear need for further research to preserve their anti-tumor effects while minimizing their cardiotoxic effects. One proposed method to directly assess these effects is through cardiac imaging techniques such as echocardiography, nuclear imaging, and magnetic resonance (MR) imaging [75]. This approach allows

for the early detection of chemotherapy-related cardiotoxicity, potentially improving patient prognosis.

The use of radiotherapy in treating OC has become limited in the modern era, primarily due to its ineffectiveness at controlling metastasis outside the pelvis and the high risk of gastrointestinal toxicity, especially when used with chemotherapeutic agents like cisplatin [15]. However, advancements in lower-toxicity radiotherapies such as intensity-modulated radiotherapy (IMRT), image-guided radiotherapy, and stereotactic body radiotherapy (SBRT) have renewed interest in this modality for managing metastatic cancers [15]. A clinical study evaluating radiotherapy for oligometastatic OC reported a disease control rate of 55.31% and an objective response rate of 34.08%, with no severe side effects reported [76].

Merging radiotherapy with immunotherapy shows potential for better controlling OC metastasis [77]. Cancer immunotherapy enhances the immune system's ability to fight cancer by activating native and adaptive immunity and countering the tumor microenvironment's suppressive effects [78]. Recent studies suggest that combination of radiotherapy with immunotherapy offered improved benefits compared to single treatment [79]. Techniques such as adoptive cell transfer involve collecting T-cells from a patient, expanding them ex vivo, and reintroducing them with supportive treatments like interleukin 2. Cancer vaccines and immune checkpoint inhibitors are also promising, although their success rates for OC are currently low, and adverse effects may include fatigue, gastrointestinal, endocrine, and dermatological events [80].

Overall, it is evident that integrating these advanced treatment options and protective strategies could significantly enhance patient care, necessitating continued research and clinical trials to optimize outcomes for those undergoing chemotherapy.

PDE5 inhibitors as dual-function drugs in cancer chemotherapy

Phosphodiesterase-5 inhibitors (PDE5i), well-known for treating erectile dysfunction (ED), work by blocking the breakdown of cGMP—a signaling molecule enhanced by nitric oxide (NO) that facilitates smooth muscle relaxation, particularly in the vascular smooth muscle of the penis [81, 82]. Common examples of these drugs include sildenafil, tadalafil, vardenafil, and avanafil. Beyond their role in treating ED, PDE5i have also been employed to promote apoptosis in various carcinomas [83, 84]. These drugs target cells that often exhibit high levels of PDE5, such as those in colon adenocarcinoma, bladder squamous carcinoma, and metastatic cancers of the breast, prostate, pancreas, and lung [84]. Research suggests that PDE5 activity may correlate with tumor aggressiveness, as higher grades and stages of tumors tend to have increased PDE5 expression [85]. Consequently, treatment with PDE5i leads to elevated cGMP levels, which are crucial for inducing apoptosis and arresting cell division in carcinoma cells overexpressing PDE5 [81].

In OC specifically, the p53 gene, a critical regulator of cell fate, is influenced by changes in cGMP and soluble guanylate cyclase (sGC) concentrations within the cancer cells [82, 86]. This modulation can suppress or induce apoptosis, with the effects varying based on the cell type or tissue. This variability is partly due to the dual role of nitric oxide (NO) acting as either cytotoxic or apoptotic at high concentrations. Furthermore, NO pathways can vary across various tissues and tumor components [82]. Additionally, drug combinations have demonstrated potential in enhancing the antitumor efficacy of PDE5i. For instance, the use of celecoxib, sildenafil, and sorafenib [87], as well as pemetrexed, sildenafil, and sodium valproate [87], have demonstrated improved in-vivo antitumor effects in OC models. Similarly, studies have found that sildenafil alone can boost the antitumor activity of DOX in treating OC and sarcoma cells [84]. Sildenafil has been effective in enhancing the immunogenicity of OC cells, facilitating increased apoptosis and potentially improving the efficacy of anti-tumor immunotherapies through mechanisms such as autophagy-dependent downregulation of histone deacetylases [88]. Interestingly, the PDE5 inhibitor Zaprinast has been noted to reduce DOX-resistance in prostate cancer cells [89], suggesting that these inhibitors could play a role in managing cancer-related hypoxia. These results highlight the potential of PDE5i as a versatile adjunct in cancer therapy, capable of enhancing the effectiveness of existing treatments.

PDE5i have also demonstrated cardioprotective properties when used as a co-treatment during chemotherapy. These effects arise from increased expression of NO synthases, activation of protein kinase G (PKG), PKG-dependent hydrogen sulfide production, and phosphorylation of glycogen synthase kinase-3β, some of the key elements in protecting against cardiac damage [84]. For example, studies have shown that sildenafil co-administered with DOX inhibited cardiomyocyte apoptosis, preserved mitochondrial function, and prevented left ventricular dysfunction and ST segment prolongation [90]. Similarly, tadalafil has been effective in preventing DOX-induced cardiomyopathy by enhancing cGMP and PKG activity and increasing levels of manganese superoxide dismutase without compromising the chemotherapeutic efficacy of DOX [91]. In fact, the unique pharmacokinetics of tadalafil, which includes prolonged PDE5 inhibition, slower metabolism, and independence from food effects [83], make it a particularly appealing option. It has shown potential in attenuating cardiac oxidative stress and boosting antioxidant capacity, which does not interfere with DOX's antitumor activity [60].

Despite these promising findings, additional research is needed to fully understand to promote the use of PDE5i as both a cardioprotective and anticancer co-treatment, especially in the complex treatment landscapes of cancers like OC. This ongoing exploration within cardio-oncology aims to balance efficacy in cancer control with the management of cardiovascular side effects induced by chemotherapeutic regimens.

Other combination therapies

Cardioprotective cotreatments to chemotherapy, such as renin-angiotensin system blockers and beta-blockers, have also been explored [92]. Angiotensin-converting enzyme (ACE) inhibitors help regulate blood pressure and have shown potential in reducing DOX-induced cardiac dysfunction by preserving mitochondrial function and reducing ROS generation [64]. Beta-blockers, particularly those with antioxidant properties, are effective in preserving left ventricular function post-chemotherapy, unlike those without such properties [64].

Other potential combination therapies with DOX for OC are under investigation. One such therapy involves the natural compound Withaferin A, known for its effects on inflammation and cachexia. Mouse studies have shown that Withaferin A reduces NF-κB-related proinflammatory cytokines in OC-induced cachexia, as well as phospho-p65 levels, a key NF-κB transcription factor in xenografted tumors [93]. Furthermore, studies indicate that Withaferin A can alleviate cardiac cachexia, preserving normal heart function, specifically the systolic and diastolic dysfunction [94]. It has also been noted to prevent reductions in cardiomyocyte cross-sectional area and fibrotic deposits in the hearts of tumor-bearing animals. The suppression of proinflammatory markers via the AT1R signaling pathway and mitigation of cachexia symptoms by Withaferin A suggest that its combination with DOX could potentially improve mortality rates in OC patients by reducing the severe impacts of cachexia [94].

Another intriguing approach is combining DOX with PDZ-binding kinase (PBK) knockdown followed by Poly (ADP-ribose) polymerase inhibitor (PARPi) treatment, particularly Olaparib. This strategy addresses resistance to PARPi — a significant challenge in OC treatment [43]. It has been shown that PBK increases chemoresistance in cancers by activating the TRIM37-mediated NFκB pathway, and knockdown of PBK has been shown to resensitize PARPi-resistant cells [93]. This combination could enhance the effectiveness of PARPi treatments, though it is important to be aware of potential cardiovascular toxicities such as left ventricular dysfunction and heart failure [94]. In such cases, advanced imaging techniques like three-dimensional echocardiography may be employed to manage any emergent cardiac issues [94].

These diverse approaches highlight the ongoing innovation in combination therapies for OC, each with the potential to enhance DOX's effectiveness and patient outcomes while mitigating associated risks.

Summary & conclusions

We have provided a comprehensive overview of the pathophysiology of OC, with particular emphasis on the complex nature and its origin, various treatment strategies, and the significant concern of chemotherapy-induced cardiotoxicity, particularly with drugs like DOX. The review also discussed emerging new mechanisms including the role of lncRNAs in the pathogenesis and metastasis of OC including their potential as diagnostic markers, prognostic indicators, and therapeutic targets for OC. We have also described some of the treatment modalities, including Withaferin A, PARP inhibitors, and nanoparticle combination therapy, which offer potential avenues for enhancing the effectiveness of chemotherapy while minimizing cardiotoxicity. These innovative approaches aim to address resistance mechanisms, improve drug delivery, and reduce adverse effects. PDE5i, traditionally used for erectile dysfunction, have demonstrated efficacy in promoting apoptosis in cancer cells and protecting against chemotherapy-induced cardiotoxicity. As the field of cardio-oncology continues to grow, ongoing research is expected to deepen our understanding of how cardiotoxicity interacts with OC treatments, potentially leading to improved therapeutic strategies. These advancements could help decrease the mortality rate among patients experiencing cardiotoxic effects from cancer therapies. Therefore, continued research into these promising treatments is essential for developing more effective and safer oncological therapies.

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Author contributions

M.N - Conceptualized and wrote the manuscript. A.S- Wrote the manuscript and prepared Figs. 1, 2 and 3. A.D- Wrote the manuscript. S.K- Edited and reviewed the manuscript. R.C.K- Conceptualized and wrote the manuscript. All authors reviewed the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Code availability

Not applicable

Declarations

Ethics approval
Not applicable.

Consent to participate
Not applicable.

Consent for publication
The authors have approved the publication.

Competing interests
Sham Kakar is Editor-in-Chief and Rakesh C Kukreja is Associate Editor of Journal of Ovarian Research. All decisions on this manuscript were made by another senior editor. The authors declare that they have no other competing interests.

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