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The Transformative Role of Nanoenzymes in the Diagnosis, Targeted Treatment, and Prognosis of Ovarian Cancer. A comprehensive Review

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ABSTRACT

Background: Ovarian cancer is one of the most aggressive and lethal gynaecological malignancies, primarily due to its silent progression and the limited accuracy of conventional diagnostic tools. Early-stage detection remains difficult, contributing significantly to poor survival outcomes. Nanoenzymes—nanotechnology-based artificial enzymes—have emerged as promising tools to enhance both diagnostic and therapeutic approaches.

Objective: To summarize the role of nanoenzymes in improving the diagnostic accuracy and therapeutic efficiency in ovarian cancer through advancements in biosensing, targeted drug delivery, and theranostic applications.

Methods: Recent evidence on nanoenzyme-enhanced optical and electrochemical biosensors, nanoformulated drug-delivery systems, and metallic nanoparticle-based theranostics was reviewed. Key biomarkers such as CA-125, HE4, and mesothelin, as well as nanoengineered drug carriers including liposomes, polymeric micelles, and nanocapsules, were evaluated for their performance and clinical relevance.

Results: Nanoenzymes significantly improve sensitivity and specificity in biosensing platforms by enabling real-time, high-precision detection of ovarian cancer biomarkers. Optical biosensors—especially fluorescence and surface plasmon resonance (SPR) systems—demonstrate excellent accuracy for early diagnosis, while electrochemical biosensors offer portable, cost-effective, and ultra-low-detection-limit alternatives. In therapeutics, nanoenzyme-integrated delivery systems enhance targeted drug transport, reduce systemic toxicity, and overcome chemotherapy resistance. PEGylated liposomal doxorubicin (Doxil) shows superior efficacy in platinum-resistant ovarian cancer with fewer adverse effects. Metallic nanoparticles such as gold and iron oxide further support combined therapeutic and imaging (theranostic) applications. However, clinical translation remains limited due to concerns regarding biocompatibility, toxicity, and large-scale manufacturing.

Conclusion: Nanoenzyme-based diagnostic and therapeutic platforms hold significant potential to transform ovarian cancer care by enabling early, accurate biomarker detection and improving targeted drug delivery. Despite encouraging progress, further research addressing safety, scalability, and regulatory challenges is essential for effective clinical integration.

Keyword: Nanoenzymes, Ovarian Cancer, Biosensing, Targeted drug Delivery, Theranostics

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INTRODUCTION

Cancer is characterized by unchecked proliferation of cells, often accompanied by aggressive dissemination and spread, resulting in the disruption of normal biological processes. Ovarian cancer, one of the most aggressive malignancies, arises from the cells in or on the surface of the ovaries. It is globally recognized as the most lethal gynaecological

cancer and a leading cause of death among women, with mortality expected to rise to 13 million annually by 2030[1]. Frequently referred to as the "silent killer," ovarian cancer is often asymptomatic during its early stages, leading to delayed diagnosis and poor survival outcomes. The disease can originate in the ovaries, fallopian tubes, or other reproductive tissues, with epithelial ovarian carcinoma constituting approximately 90% of cases. This subtype is particularly aggressive, characterized by diffuse intraperitoneal metastasis, malignant ascites, and involvement of adjacent organs, making it challenging to detect and treat [2].

Ovarian cancer has been strongly linked to hormone-related factors, including menstrual and reproductive variables, which play a role in its etiology and progression. In the United States alone, approximately 21,880 new cases and 13,850 fatalities were recorded in 2010, reflecting its significant burden on healthcare systems. Survival rates for ovarian cancer remain dismal, with Stage III patients exhibiting a five-year survival rate below 40% [3]. The CA-125 blood protein is the most widely used biomarker for ovarian cancer detection; however, elevated CA-125 levels can be observed in non-malignant conditions, reducing its specificity as a diagnostic tool. Moreover, while CA-125 is elevated in over 80% of women with ovarian cancer, its clinical utility in early-stage disease remains limited, necessitating the exploration of alternative diagnostic biomarkers and technologies [4].

The challenges of diagnosing ovarian cancer early are compounded by the limitations of current imaging techniques, such as ultrasound and physical examinations, which are often unable to detect subtle malignancies at their initial stages. Although lysophosphatidic acid has been proposed as a more efficient diagnostic biomarker, especially in early-stage ovarian cancer, its wide clinical adoption remains limited[5]. For this reason, technological advances are essential to improving diagnostic accuracy, improving therapeutic delivery, and addressing constraints in existing clinical approaches. In this respect, nano-based diagnostic tools, drug delivery systems, and biosensors promise solutions in terms of precise and efficient detection of ovarian cancer biomarkers and targeted treatment delivery using nanotechnology[6].

A specialized subset of nanotechnology referred to as nanoenzymes mimics the catalytic activity of natural enzymes and has become a transformative innovation for the diagnosis and treatment of ovarian cancer. Nanoenzymes overcome the limitations of conventional biomarkers and chemotherapeutic delivery systems through a multifaceted approach to improve patients' outcomes[7]. Optical and electrochemical biosensors have been demonstrated to be highly sensitive to the detection of key ovarian cancer biomarkers, including CA-125, using nanoenzymes[8]. In real-time, these biosensors offer quantitative detection with high specificity and their shortcomings can be overcome by traditional assays. Furthermore, nanoezyme-based drug delivery systems such as liposomes, polymeric micelles, and nanocapsules are employed to deliver therapeutic agents to tumor tissues while minimizing systemic toxicity. Not only are these advancements better at improving therapeutic efficacy, but they also help to diminish the inherent side effects of conventional chemotherapy[9].

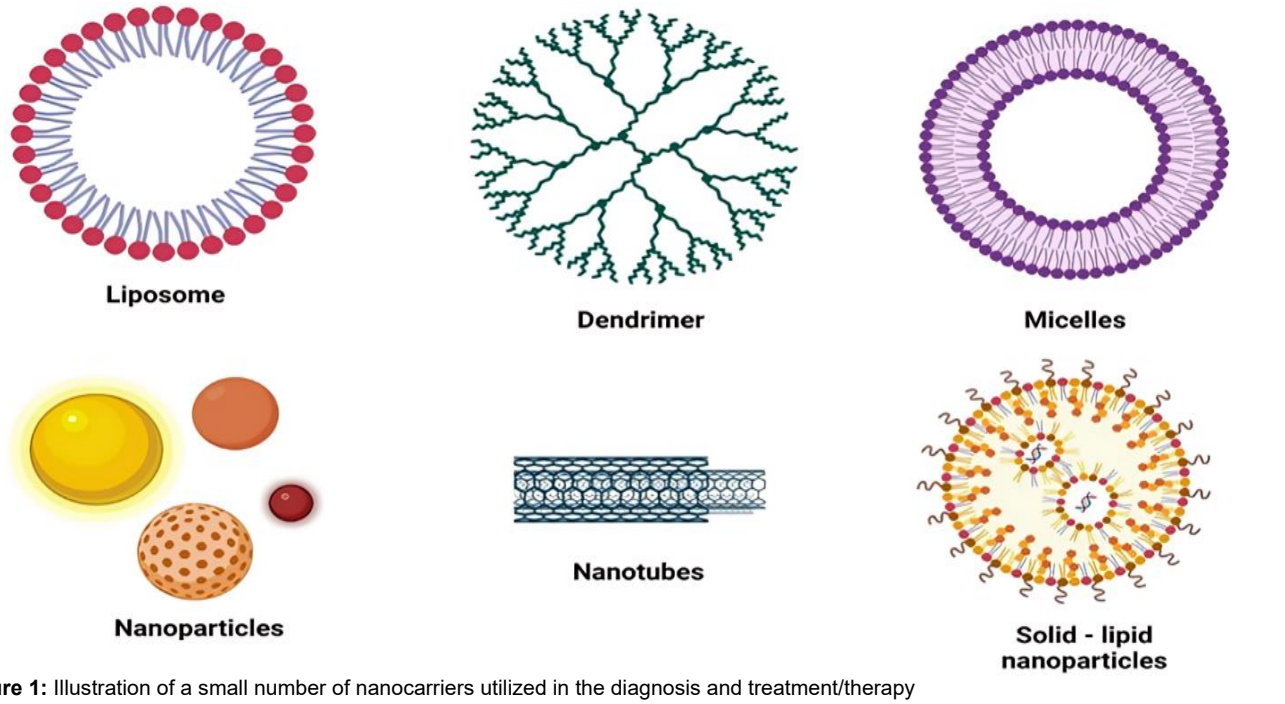

Figure 1: Illustration of a small number of nanocarriers utilized in the diagnosis and treatment/therapy

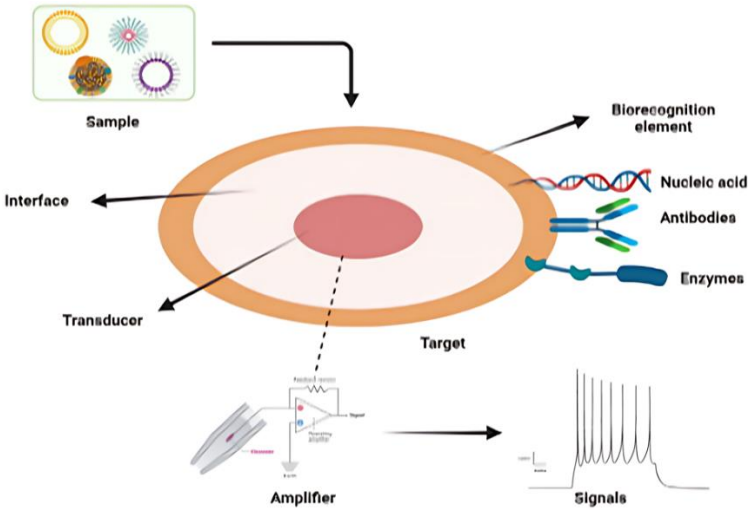

Figure 2: Biosensor schematics with optical applications for biosensing

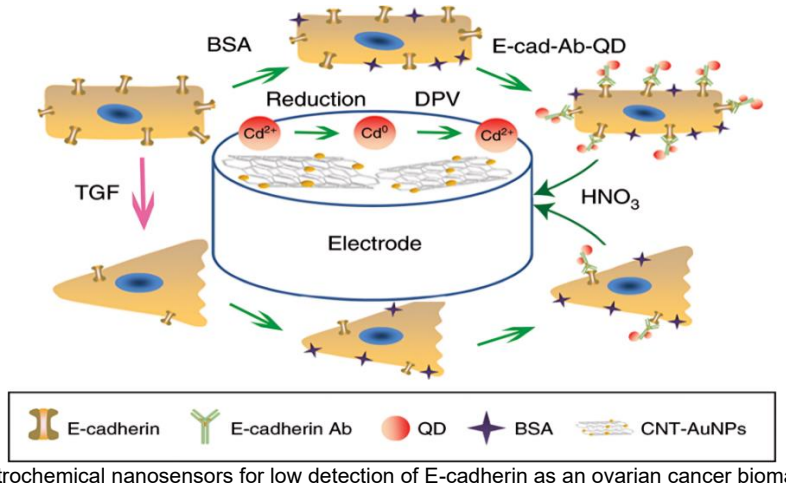

Figure 3: Design of the electrochemical nanosensors for low detection of E-cadherin as an ovarian cancer biomarker.

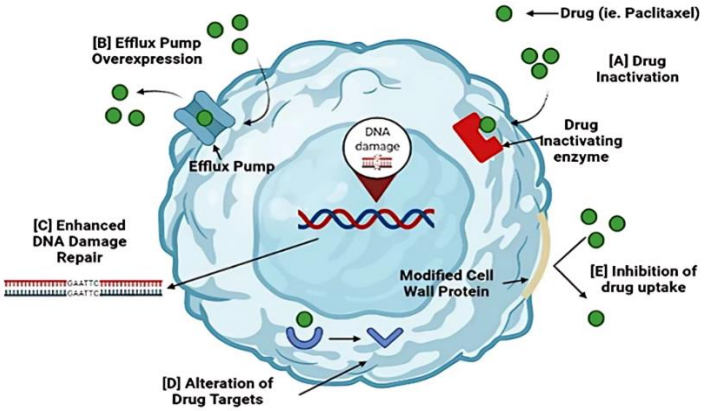

Fig-4: Mechanisms of drug resistance in ovarian cancer

Table 1: Staging of ovarian cancer, extent of disease, and corresponding 5-year survival rates.

Stage	Extent of Disease	5-Year Survival Rate (%)
Stage I	Tumor confined to ovaries	90–95
Stage II	Spread to pelvic organs	65–70
Stage III	Peritoneal metastases, lymph nodes	35–40
Stage IV	Distant metastasis	15–25

Table 2: Overview of the unique nanotherapeutic instruments created for the treatment of ovarian cancer.

Nano Systems	Polymer–Drug Conjugates	Polymer Micelles	Liposomes
Size	≤10 nm	10–100 nm	100–200 nm
Structural characteristics	Macromolecular structure	Spherical core-shell structure	Spherical bilayer vesicle structure
Carrier composition	Water-soluble polymer	Amphiphilic block copolymers	Phospholipid, cholesterol membrane lipids
Drug incorporation strategy	Covalent conjugation requires functional groups on drug and polymer	Noncovalent encapsulation/compatible with hydrophobic drugs	Noncovalent encapsulation/compatible with hydrophilic drugs

Table 3: Overview of nanosystems for ovarian cancer therapy, highlighting size, structural characteristics, advantages, and examples.

Nano System	Size	Structural Characteristics	Advantages	Examples
Liposomes	100–200 nm	Bilayer vesicle	Prolonged circulation, low toxicity	Doxil (PEGylated liposomal doxorubicin)
Polymeric Micelles	10–100 nm	Core-shell structure	Enhanced solubility, tumor targeting	Paclitaxel-loaded micelles
Nanocapsules	≤200 nm	Polymer-coated vesicular core	Controlled release, drug protection	Cisplatin-loaded nanocapsules
Metal Nanoparticles	10–100 nm	Spherical or irregular shape	Imaging, photothermal therapy	Gold nanoparticles

Table 4: Applications of various nanoparticles in ovarian cancer diagnosis and treatment.

Nanoparticles	Application	References
Polyamidoamine/gold nanoparticles	Electrochemical immunosensor for ultrasensitive detection of CA125 in ovarian cancer	[48]
Paper-based immune device modified with cysteamine-caped Au nanoparticles	Paper-based immunosensor for efficient diagnosis of ovarian cancer	[49]
Folate capped liposomes	Targeting macrophages associated with ovarian carcinoma	[46]
Hematite α-Fe2O3	Treatment of human metastatic ovarian cancer	[45]
PLGA nanoparticles	Treatment of ovarian cancer	[26]
Poly(amidoamine) dendrimers	Cytotoxicity study against ovarian cancer cell lines	[49]
Three-layered linear-dendritic telo dendrimer micelles	Synergistic combination monotherapy for ovarian cancer treatment	[50]

However, there are biological barriers, systemic toxicity, and scalability of nano formulations for nanoenzymes. However, biological clearance mechanisms tend to limit the accumulation of nanocarriers in target sites following intravenous administration. In addition, a correlation between nanoparticle accumulation in organs, including the lungs, and oxidative stress and cytotoxicity is of concern for long-term safety. The reliance on current studies on preclinical cell and animal models is another major limitation since they may not accurately mimic the complexity of human ovarian cancer metastasis[10, 11]. These challenges necessitate an interdisciplinary approach by combining nanotechnology with personalized medicine, clinical validation, and innovative regulatory approaches to facilitate the translation of nanoenzymes into clinical practice[12].Overall, ovarian cancer is a major clinical problem because of its asymptomatic progression, delayed diagnosis, and limited therapeutic options. Currently, CA-125 and imaging techniques are not sufficient for early-stage detection and thus novel technologies are needed to improve accuracy and specificity. However, nanoenzymes provide a promising solution to fill the critical gaps in current ovarian cancer management by combining high-sensitivity biosensing with targeted drug delivery systems[13]. However, to realize the full potential of nanoenzymes in clinical oncology, challenges in overcoming the biological barriers, toxicity, and scalability must be overcome. The role of nanoenzymes in ovarian cancer diagnosis and therapy is summarized, and the advantages, current advancement, and future direction of this field to further enhance these nanoenzymes in improving patient outcomes and precision medicine are reviewed[14]. The fig-1 illustrates six types of nanocarrier systems: Drug delivery and cancer treatment using Liposomes, Dendrimers, Micelles, Nanoparticles, Nanotubes, Solid Lipid Nanoparticles, etc., with distinct molecules in each. These systems improve therapeutic efficacy by providing targeted drug delivery, reduced toxicity, and improved bioavailability[15].

Types of Ovarian Carcinomas: Ovarian carcinomas are a heterogeneous group of cancers and are the most lethal of gynecological cancers. Type I and Type II carcinomas are categorized according to their molecular, histopathological, and clinical behaviors. These subtypes help us to understand disease progression, treatment, and prognosis[16].

Type I Carcinomas: Type I carcinomas arise gradually from precursor lesions such as borderline ovarian tumors or endometriosis. These tumors are low-grade malignant and have genetic stability and an indolent behaviour. The major

subtypes of Type I tumors are clear cell carcinoma, endometrioid carcinoma, and mucinous carcinoma[17].

Endometrioid Carcinomas and Clear Cell Carcinomas: Endometriosis, a chronic inflammatory condition that increases a woman's risk of developing malignant transformation, is strongly associated with clear cell and endometrioid carcinomas. These tumors are oncogenic and are due to persistent oxidative stress, chronic inflammation, and hormonal imbalances[18].

About 5–10% of ovarian cancers are clear cell carcinoma and typically show hobnail cells and clear cytoplasmic features. These tumors are usually seen in early stages, but are resistant to platinum chemotherapy, making treatment difficult. Endometrioid carcinoma, which resembles normal endometrial glands, accounts for about 10–20% of ovarian cancers and is responsive to chemotherapy[19].

Mucinous Carcinoma: Ovarian carcinomas of mucinous histology are rare, representing 3–4% of all ovarian carcinomas. Such tumors are large unilateral cystic masses filled with mucinous material and are frequently misdiagnosed as metastatic gastrointestinal tumors. CK7 (positive) and CK20 (negative) immunohistochemical markers assist in differentiating primary mucinous ovarian carcinoma from metastatic lesions. However, surgical resection remains the main treatment, however, many are chemoresistant in advanced stages[20].

Type II Carcinomas: Type II carcinomas are high-grade, aggressive tumors that progress rapidly and are often diagnosed at advanced stages. These tumors include high-grade serous carcinoma (HGSC), which is the most common and deadliest subtype, accounting for 70–75% of ovarian cancers.

High-Grade Serous Carcinoma (HGSC): HGSC originates predominantly from the fimbrial epithelium of the fallopian tube, highlighting the importance of salpingectomy as a preventive measure in high-risk populations. The molecular hallmark of HGSC is the near-universal presence of TP53 mutations, alongside frequent BRCA1/BRCA2 alterations and widespread genomic instability.

HGSC is characterized by rapid dissemination throughout the peritoneal cavity, often presenting with malignant ascites and omental involvement. While platinum-based chemotherapy remains the standard of care, recurrence occurs in over 80% of patients, with resistance emerging as a major clinical challenge. Advances in targeted therapies, such as PARP inhibitors for BRCA-mutated cases, have significantly improved outcomes in subsets of patients[20].

Prognosis and Staging of Ovarian Cancer: The prognosis of ovarian cancer depends primarily on the stage at diagnosis, as determined by the FIGO classification. Early-stage ovarian cancer (Stages I and II) has significantly better survival rates compared to advanced-stage disease (Stages III and IV) as shown in Table[21].

Unfortunately, over 70% of ovarian cancer cases are diagnosed at Stage III or IV due to the lack of specific early symptoms. Symptoms like abdominal bloating, pelvic discomfort, and urinary urgency are often misattributed to benign conditions, delaying diagnosis and reducing survival outcomes[22].

Biosensors for Early Detection of Ovarian Cancer: The early detection of ovarian cancer is critical for improving patient outcomes and reducing the associated high mortality rate. Ovarian cancer is often diagnosed at advanced stages due to its asymptomatic nature in the early phases and the limitations of conventional diagnostic tools. However, the sensitivity and specificity of traditional approaches like serum CA-125 measurement and transvaginal ultrasound are insufficient for early diagnosis and poor prognosis[20]. Although CA-125 is the most commonly used biomarker, it is elevated in ovarian cancer and can also be elevated in benign conditions, such as endometriosis and pelvic inflammatory disease, resulting in false positive results. Additionally, transvaginal ultrasound is not highly reliable as a stand-alone diagnostic test, as it is limited in its ability to differentiate between malignant ovarian masses and benign lesions[23].These challenges have been overcome with the development of cutting-edge diagnostic tools, and biosensors, that provide enhanced sensitivity, specificity, portability, and real-time monitoring of biomarkers. Ovarian cancer biomarkers are detected with unprecedented precision using biosensors that integrate biological recognition elements, such as antibodies, enzymes, nucleic acids, and aptamers, with physicochemical transducers including optical, electrochemical, and nanofluidic systems[21]. Biomarkers included CA-125, human epididymis protein 4 (HE4), mesothelin, circulating tumor DNA (ctDNA), and tumor-derived exosomes. Early diagnosis is critical, and biosensors allow this because ovarian cancer diagnosed at Stage I has a 5-year survival rate of over 90% and less than 30% in advanced stages[24].

Optical Biosensors: Because optical biosensors are highly sensitive, accurate, and able to provide real-time results, they have attracted a lot of attention for the detection of ovarian cancer. Biosensors based on light-based mechanisms, including surface plasmon resonance (SPR), fluorescence, and chemiluminescence, comprise these biosensors to detect interactions between biomarkers and recognition elements.

The use of SPR biosensors is particularly promising due to label-free, real-time monitoring of biomolecular interactions. SPR biosensors can detect changes in the refractive index on a sensor surface, thereby achieving detection limits in the nanomolar range by measuring the number of biomarkers bound to a sensor surface. As an example, the SPR-based sensor has demonstrated the detection of CA-125 in concentrations as low as 0.5 ng/mL, much higher than the sensitivity of conventional ELISA assays[25]. Also, SPR sensors were miniaturized for clinical

and point-of-care applications, with increased portability and ease of use at the expense of no loss of accuracy.

Based on fluorophore-labelled probes, fluorescent biosensors offer exquisite sensitivity for even trace concentrations of ovarian cancer biomarkers. The biosensors can detect CA-125, HE4, and ctDNA in blood, urine, and other biofluids, and are therefore versatile for use in a wide range of clinical applications. Multiplexed

fluorescent bio-sensors have recently become capable of detecting multiple biomarkers with improved diagnostic accuracy and decreased false positive rates. The advantage of this multi-marker approach is that combining CA-125 with HE4, or other biomarkers, improves diagnostic performance and compensates for weaknesses of single marker assays[26].

Additionally, there has been tremendous potential for ovarian cancer detection using quantum dot-based optical biosensors. Quantum dots (QDs), semiconductor nanocrystals, have special optical properties, such as tunable emission wavelengths, excellent quantum yields, and superior photostability[27]. QD-based biosensors have demonstrated the ability to detect mesothelin, CA-125, and HE4 with very low detection limits and high specificity. QD-based systems allow for simultaneous detection of multiple biomarkers which allows for comprehensive diagnostic profiling and early and accurate detection of ovarian cancer. The biosensor system shown in Fig 2 consists of biorecognition elements (nucleic acids, antibodies, enzymes), targets, and a transducer that converts the target interaction into a measurable signal. Specific biomarkers for cancer diagnosis are detected in the amplified signals[28]

Electrochemical Biosensors: Due to their cost effectiveness, portability, and detection of biomarkers at ultra-low concentrations, electrochemical biosensors are emerging as robust diagnostic tools for ovarian cancer detection. These biosensors are based on the quantification of biomarker concentrations with high precision using electrical signals produced from biomolecular interactions including changes in current, voltage, or impedance[29].We have developed nanoscale electrochemical biosensors for the detection of E-cadherin, a marker of ovarian tumor progression, with detection limits as low as 0.92 ng/μL. The biosensors are rapid, accurate, and reproducible, making them ideal for clinical applications. Electrochemical sensors added with nanomaterials, such as gold nanoparticles, graphene, and carbon nanotubes, increase sensitivity and specificity by increasing conductivity, surface area, and biomarker binding ability. As an example, the sensitivity of gold nanoparticle functionalized electrochemical sensors for CA-125 and HE4 biomarkers can be improved significantly compared to conventional devices to detect them at trace biomarker levels, even before a clinical diagnosis[30].Multiplex detection is also possible with electrochemical biosensors, i.e., the simultaneous quantification of multiple biomarkers in a single assay. This is an essential capability for comprehensive ovarian cancer screening and monitoring of treatment response, as no single biomarker is perfect in and of itself for diagnosis[31]. Furthermore, electrochemical biosensors have exceptional adaptability for point-of-care devices for real-time monitoring of disease progression and treatment efficacy. The fig-3 shows a mechanism of an electrochemical biosensor for the detection of disease biomarker, E-cadherin. The involved process includes the reaction of E-cadherin antibodies (E-cad-Ab) with QDs and CNT-AuNPs on electrodes, reduction, DPV (Differential Pulse Voltammetry) detection, and signal amplification[10].

Nanofluidic Lab-on-Chip Devices: Biosensor technology has taken a breakthrough with nanofluidic lab-on-chip devices integrating multiple biosensing capabilities into miniaturized platforms for highly precise and rapid analysis. Microfluidic and nanofluidic systems are used in these devices to analyze small fluid samples (e.g. blood, serum, and urine) with exquisite accuracy and turnaround times, making them perfect for point-of-care diagnostics[32].Due to their utility in detecting tumor-derived exosomes as well as circulating tumor biomarkers both of which are critical to ovarian cancer progression and metastasis, lab-on-chip devices are particularly suited for this application. Nano-sized exosomes released by tumor cells contain proteins, nucleic acids, and lipids that reflect the parent tumor molecular profile. The integrated exosome biosensor with nanofluidic platform isolates and quantifies exosomes from body fluids to detect ovarian cancer biomarkers with excellent sensitivity. On the other hand, this noninvasive approach can report real-time information about tumor dynamics and molecular changes, which makes it significantly different from traditional biopsy-based methods[33].Lab-on-chip devices are very sensitive to minute biomarker changes and this is why they are highly suitable for early-stage diagnosis. Additionally, the miniaturization of these platforms reduces sample and reagent requirements, decreasing diagnostic costs and keeping precision. Ovarian cancer can also be detected with advanced nanofluidic systems that enable multi-marker detection, thus increasing the level of accuracy in the diagnostics[4].

Nano Biosensors and Nanofluidics: The tiny fluidic laboratory-on-chip nanosensors are a multifunctional miniaturized device that combines the properties of numerous sensors with ease and at a lower reading rate. It provides a productive and rapid method of biomolecule recognition and creates affordable gadgets by using as few materials and chemicals as possible. Exosomes in our bodies guarantee different cells' signaling, and macromolecules also exhibit these tiny particles. Early diagnosis is one of the most crucial aspects that affects survival[34].Screening Increases the likelihood of recovery when ovarian cancer is discovered early in the illness. These days, the non-invasive technique of ultrasonography is employed to screen the human body. Every ovarian cancer

discovered would result in more than thirty false-positive results for every ovarian cancer screening performed annually with CA 125 or ultrasonography in women over 50 without a family history of the disease. Tests that turn out to be falsely positive frequently necessitate invasive procedures, such as laparotomies. There isn't any concrete proof, yet that screening would lower the death rate from ovarian cancer[35].

Ultrasonography Transvaginal By measuring the ovarian size, this imaging technique also evaluates the volume, septum thickness, papillary development, and internal ovarian structure. A fundamental component of all significant ovarian cancer screening trials is transvaginal ultrasonography or TVS.

Imaging Using Doppler Three-dimensional Strength Doppler ultrasonography could help in ovarian cancer early detection[36].

Current Ovarian Cancer Drug Delivery Strategies Using Nanotechnology: The subject of therapeutic nanotechnology is expanding quickly. To combat drug resistance, several nanoparticle systems have been thoroughly developed. Numerous nano-drug delivery systems, including liposomes, branching dendrimers, nanoconjugates, nanostructured lipid formulations, and polymer nano micelles, have been developed. These systems offer several benefits, such as enhancing therapeutic drug delivery and meeting various biopharmaceutical requirements. These include a significant improvement in therapeutic impact over free drugs, good biodegradability, and biocompatibility, non-toxic and non-inflammatory properties, and the potential for future manufacturing scaling-up as shown in table-2 [37].

The Role of Nanotechnology and Nano-materials in Ovarian Cancer Therapy: Nanotechnology has revolutionized ovarian cancer therapy through targeted drug delivery, improved treatment efficacy, and minimized systemic toxicity. The integration of nanomaterials such as liposomes, polymeric micelles, Nanocapsules, and metal nanoparticles has shown promising outcomes in overcoming drug resistance, reducing adverse effects, and enhancing therapeutic outcomes. Advances in nanoconjugates and nano-based systems have further optimized drug delivery mechanisms, making them indispensable tools in ovarian cancer treatment and diagnosis[37].

Liposomes: Enhancing Drug Delivery and Reducing Resistance: Liposomes are spherical, nanoscale vesicles composed of phospholipid bilayers that can encapsulate both hydrophobic and hydrophilic drugs. Vesicles of various sizes between 400 nm and 2.5 mm are widely used because they are biocompatible, can carry biomolecules such as proteins and RNAs, and can deliver drugs while preserving their intrinsic properties. Drug delivery by liposomes greatly increases therapeutic efficiency while reducing systemic toxicity[38]. PEGylated liposomal doxorubicin (Doxil) is one of the most notable advancements in liposomal therapy, which is approved for treating platinum-resistant ovarian cancer. The use of polyethylene glycol (PEG) to avoid immune system clearance, prolong circulation time, and improve tumor accumulation through the Enhanced Permeability and Retention (EPR) effect. Doxil has been shown in clinical studies to reduce cardiotoxicity and improve progression-free survival in patients with advanced ovarian cancer[39].Furthermore, innovative liposomal systems functionalized with transferrin receptors have been developed to bypass cisplatin resistance. Studies revealed that transferrin-targeted liposomes improve cellular uptake, where free cisplatin absorption was significantly lower in resistant cancer cells. Liposomes activate apoptosis pathways, particularly through increased production of caspase 3/9 and ERK signaling, enhancing their efficacy against ovarian cancer[40].

Polymeric Micelles: Improving Solubility and Targeting: Polymeric micelles are nanoscale self-assembling carriers composed of amphiphilic block copolymers. They feature a core-shell structure, with a hydrophobic core encapsulating poorly soluble drugs and a hydrophilic shell providing stability and biocompatibility. Micelles are typically 10–100 nm in size and are highly efficient in delivering chemotherapeutic agents like paclitaxel, a first-line drug for ovarian cancer[7].

These micelles improve solubility, reduce systemic toxicity, and achieve enhanced tumor accumulation via the EPR effect. By functionalizing micelles with ligands like folic acid or peptides, such as peptides, their tumor selectivity is improved and they demonstrate better cellular uptake and drug efficacy. Micellar formulations have been shown to decrease nonspecific targeting of normal cells and increase drug endocytosis in ovarian cancer cells, and are therefore promising tools for targeted therapy[41].

Nanocapsules: Effective Therapy by Controlled Release: Vesicular systems of a core enclosed by a polymeric shell are referred to as nanocapsules. This design provides an encapsulation of therapeutic agents and controlled and sustained drug release for improved pharmacokinetic properties. The nanocapsules have high stability that protects drugs from premature degradation and also helps to improve drug accumulation at the tumor site[42].

We showed that 20 days of treatment with cisplatin-loaded PEGylated nanocapsules induced a 90% tumor growth reduction in mice bearing ovarian carcinoma. These Nanocapsules have been functionalized with multiple drugs like paclitaxel-lapatinib and have exhibited remarkable growth-inhibiting potential against multidrug resistance. Advantages of the nanocapsules include prolonged retention of the drug, rapid protection from oxidation, and targeted delivery to ovarian cells[26].

Metal Nanoparticles: Therapeutic and Diagnostic uses: The unique physicochemical properties gained attention for metal nanoparticles (MNPs), including gold nanoparticles (AuNPs) and iron oxide nanoparticles.

To facilitate targeted drug delivery and photothermal therapy, gold nanoparticles are functionalized with antibodies, peptides, or small molecules. This approach involves localized heating by laser irradiation of tumor cells with minimal damage to healthy tissues.

Iron oxide nanoparticles, owing to their superparamagnetic properties, are widely used for Magnetic Resonance Imaging (MRI)-guided drug delivery. These nanoparticles enable real-time monitoring of drug distribution and therapeutic responses. Preclinical studies involving ferrous nanoparticles revealed increased apoptosis, reactive oxygen species production, and mitochondrial destabilization, demonstrating their strong anticancer potential as shown in table-3[43, 44].

Applications of Various Nanoparticles in Ovarian Cancer: Several nanocarriers have been studied for their diverse applications in ovarian cancer treatment and diagnosis. Polyamidoamine/gold nanoparticles serve as electrochemical immunosensors, enabling ultrasensitive detection of CA125, a key biomarker for ovarian cancer. Paper-based immune devices modified with cysteamine-capped gold nanoparticles have also been developed for efficient and cost-effective cancer diagnosis[45].Folate-capped liposomes have been utilized to target macrophages associated with ovarian carcinoma, improving drug selectivity and tumor penetration. Hematite α-Fe_2O_3 nanoparticles have demonstrated efficacy in treating human metastatic ovarian cancer, inducing apoptosis, and reducing tumor growth[46].PLGA nanoparticles, known for their biocompatibility and controlled release properties, have been explored for ovarian cancer therapy. Additionally, poly(amidoamine) dendrimers have exhibited strong cytotoxic effects against ovarian cancer cell lines, proving their potential as effective drug delivery systems. Three-layered linear-dendritic telo dendrimer micelles have also shown promise in delivering combination therapies, resulting in synergistic treatment outcomes for ovarian cancer as shown in Table-4 [47].

Some Side Effects of Common Treatments for Ovarian Cancer: Despite advancements in nanotechnology, chemotherapy treatments for ovarian cancer often cause significant side effects, including nausea, vomiting, neurotoxicity, and bone marrow toxicity. Neurotoxicity can affect both central and peripheral systems, leading to cognitive impairments or encephalopathy[51].

Drug resistance remains a major challenge in ovarian cancer therapy. Tumor cells develop resistance through mechanisms such as drug inactivation, efflux pump overexpression, and enhanced DNA repair pathways. Altered drug targets and changes in cell membrane proteins further inhibit drug absorption, reducing chemotherapy efficacy as shown in Fig-4 [52]

Ovarian cancer therapy has seen a significant improvement in drug delivery, tumor targeting, and treatment efficacy by integrating nanotechnology and nanomaterials. Innovative solutions for chemotherapeutic resistance overcoming, diagnostic enhancements, and side effect reduction are provided by liposomes, polymeric micelles, nanocapsules, and metal nanoparticles. Ongoing advances in nanocarrier systems portend a bright future for ovarian cancer therapy that will deliver precision medicine and improved patient outcomes[53].

DISCUSSION

By developing nanoenzymes, we bring a transformative improvement to the detection, treatment, and management of ovarian cancer, overcoming significant barriers to current diagnostic tools and drug delivery systems. Ovarian cancer is one of the most difficult cancers to diagnose because it is often asymptomatic during early stages and is often diagnosed at an advanced stage with poor survival outcomes[54]. In optical and electrochemical nanoenzyme-based biosensors, ovarian cancer biomarkers such as CA-125, HE4, and mesothelin have been demonstrated with exceptional sensitivity and specificity. Biosensors for these cancer-specific biomarkers are compared to conventional assays that frequently suffer from imprecision and high false positive rates, and allow real-time, quantitative monitoring of these biomarkers. This allows for a timely diagnosis and intervention, which is very important because it can lead to higher survival rates in cases where the disease is diagnosed at an early stage[55].

Principles such as fluorescence and surface plasmon resonance (SPR) are used to achieve highly accurate and sensitive detection by optical biosensors. Biomarker concentrations in blood samples can be identified with fluorescent biosensors, enhancing diagnostic precision[56].

The intrinsic superior photostability and tunable emission spectra of quantum dot-based biosensors allow for the detection of multiple biomarkers simultaneously. Like SPR, biosensors based on SPR allow label-free detection of biomolecular interactions in real time with detection limits in the nanomolar range[12]. However, rapid and low-cost detection of ovarian cancer is made possible by electrochemical biosensors. These systems, which measure changes in electrical signals caused by biomolecular interactions, can detect biomarkers at ultra-low concentrations, with thresholds as low as 0.92 ng/μL for markers like E-cadherin. The integration of nanomaterials, such as gold nanoparticles and graphene-based platforms, further enhances the sensitivity and multiplexing capability of electrochemical sensors[57, 58].In addition to diagnostics, nanoenzyme-based drug delivery systems offer substantial improvements over conventional chemotherapy, which is often limited by systemic toxicity, poor tumor selectivity, and multi-drug resistance[59]. Liposomes, nanocapsules, and polymeric micelles have emerged as highly effective nanocarriers for targeted drug delivery. Liposomes, which are lipid-based vesicular systems, encapsulate both hydrophilic and hydrophobic chemotherapeutic agents, improving their bioavailability, stability, and circulation time. PEGylated liposomal

doxorubicin (Doxil), for instance, has demonstrated significant efficacy in platinum-resistant ovarian cancer while minimizing cardiotoxicity. Modification of liposomes with tumor-specific ligands, like transferrin or folic acid, enables selective tumor drug accumulation, overcoming resistance mechanisms and improving the therapeutic outcome[24].The polymeric shell core structure of nanocapsules allows for controlled and sustained drug release, decreases systemic toxicity, and increases kinetics. In preclinical studies with mouse ovarian cancer models, we have demonstrated that PEGylated nano-capsules loaded with cisplatin result in 90% tumor growth reduction. The drug is protected in a polymeric shell from premature degradation which would prevent it from getting to tumor sites[60]. The challenge of nonspecific drug distribution is addressed by nanocapsules functionalized with targeting moieties, such as peptides or antibodies, further improving tumor selectivity[61]. Amphiphilic block copolymer polymeric micelles also provide additional benefits for the delivery of poorly soluble chemotherapeutic agents, such as paclitaxel. Self-assembling nanosystems based on these ways improve drug solubility, stability, and tumor selectivity by the enhanced permeability and retention (EPR) effect. It has been shown that micellar formulations improve drug accumulation in tumor tissues without high off-target toxicity[60].Another promising platform for ovarian cancer therapy is metal nanoparticles (gold and iron oxide nanoparticles). Targeted drug delivery and photothermal therapy using gold nanoparticles functionalized with antibodies or peptides is made possible via localized heating induced by laser irradiation, which selectively destroys tumor cells. The superparamagnetic nature of iron oxide nanoparticles offers both therapeutic and imaging advantages as magnetic resonance imaging (MRI)-guided drug delivery and real-time treatment monitoring. Nevertheless, owing to their therapeutic potential, they are of concern for their long-term toxicity and biodistribution and therefore require rigorous clinical evaluation[62].These advancements represent significant progress, but the clinical application of nanoenzymes and nanocarriers is hindered by many challenges. The biological clearance of nanoparticles by the reticuloendothelial system (RES) has been one of the main barriers to tumor accumulation and therapeutic efficacy[63]. Important factors influencing biodistribution and clearance of nanoparticles are particle size, shape, surface area, and solubility. Suboptimal outcomes result from the fact that nanoformulations used intravenously are frequently extracted from target tissues without reaching therapeutic levels. It is also of concern that nanoparticles can accumulate in nontarget organs, such as the lungs, liver, and spleen, triggering oxidative stress, inflammation, and cytotoxicity, and thus their long-term safety is also of concern[64].

Another major barrier to effective therapy is the development of multi-drug resistance (MDR), wherein tumor cells develop mechanisms to avoid chemotherapy. Resistance mechanisms include the over-expression of efflux pumps including P glycoprotein which actively transports chemotherapeutic agents out of the cancer cells, as well as enhanced DNA repair pathways that reverse drug-induced damage[65]. However, these resistance mechanisms severely limit the effectiveness of traditional chemotherapies. One focus of research is innovative approaches, including combining nanocarriers with gene silencing technologies such as RNA interference (RNAi) or CRISPR/Cas9, to attack these pathways at the molecular level[66].In addition, cell and animal models used in preclinical studies also suffer from the limitation of failure to recapitulate the complexity of the human physiological response. While metastasis, a critical feature of advanced ovarian cancer, is poorly understood, reliable models mimicking human disease progression are, to date, not available. Further research will be necessary to develop more sophisticated three-dimensional models of tumors and organs on a chip platform for the evaluation of the efficacy and safety of nanoenzymes and nanocarriers[67, 68].

Since nanoenzymes have the potential to maximize clinical potential, personalized medicine presents significant promise for tailoring therapies to individual patient profiles. Personalized approaches are achieved by integrating genetic, environmental, and familial factors in optimizing drug selection, dosing, and delivery[69, 70]. A new frontier in ovarian cancer therapy is represented by nanocarriers functionalized with tumor-specific ligands and loaded with patient-specific drug combinations. In combination with biosensors, liquid biopsy technologies, that analyse circulating tumor DNA, exosomes, and other biomarkers, could be used to monitor real-time treatment responses and disease progression[71].

Future studies should focus on the development of biocompatible and biodegradable nanoenzymes with low toxicity and still maintain high therapeutic efficacy. However, rigorous clinical trials are required to evaluate the safety, pharmacokinetics, and therapeutic outcomes of nanoenzyme-based systems. Interdisciplinary collaboration between researchers, clinicians, and regulatory bodies is needed to bridge the gap between preclinical research and clinical practice. Addressing these challenges may allow nanoenzymes to revolutionize ovarian cancer diagnosis and therapy, and improve patient outcomes while decreasing treatment-associated toxicity. To realize their potential, these transformative technologies must continue to be innovated and clinically validated so that they find widespread adoption in oncology practice[72, 73].

CONCLUSION

Diagnosis, treatment, and the prognosis of ovarian cancer have been revolutionized by nanoenzymes and nanotechnology which addressed the critical limitations of conventional approaches. Optical and electrochemical nanoenzyme-based biosensors are exceptionally sensitive and specific for ovarian cancer biomarkers, such as CA-125

and HE4, for early and accurate diagnosis. In addition, nanocarriers with advanced levels of sophistication such as liposomes, polymeric micelles, Nanocapsules, and metal nanoparticles have greatly improved drug delivery, and have been used to enhance tumor targeting, minimize systemic toxicity, as well as overcome drug resistance.

However, these advances are hindered by biological barriers, systemic toxicity, scalability, and long-term safety challenges to clinical translation. Overcoming these hurdles requires interdisciplinary research, clinical validation, and the development of regulatory frameworks. Personalized nanomedicine approaches integrating advanced biosensing technologies with targeted therapies are areas that should be targeted for future efforts. Harnessing the full potential of nanoenzymes and nanomaterials has great potential to deliver precision medicine, increase patient survival rates, and reduce the burden of ovarian cancer. The involvement of researchers, clinicians, and policymakers in continued innovation will facilitate the adoption of these technology transformations in clinical oncology.

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