ScienSage

Journal of Advanced Scientific Research

Available online through http://www.sciensage.info

ISSN
0976-9595
Review Article

NANOTECHNOLOGY BASED DETECTION AND THERAPY OF OVARIAN CANCER

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ABSTRACT

Ovarian carcinoma is the leading reason behind death from gynaecologic malignancies, which could be a direct outcome of missing its diagnosis at an early stage. Nanotechnology has great promise in addressing existing problems to boost the diagnosis and therapy of Ovarian Cancer. Nanocarriers are multifunctional as several varieties of molecules are often loaded onto them through physical adsorption or chemical conjugations including drugs, imaging agents, targeting moieties like ligands or Antibodies. Present research for earlier detection of Ovarian Cancer focuses on identifying Ovarian Cancer biomarkers through developing a profile of aberrantly expressed molecules and by enhancing imaging techniques. This early detection will ultimately lead to a stronger prognosis and an increased survival rate. Also, Nanotechnology can improve screening for ovarian Cancer by fabricating lab-on-a-chip microfluidic devices for immuno-screening. Overall, the incorporation of nanotechnology into existing detection methods of Ovarian cancer demonstrates great promise in detecting the disease at an earlier stage. With the arrival of nanotechnology, it'll be possible to detect the previously undetectable concentrations of Ovarian Cancer biomarkers and visualize Ovarian Cancer cells in real-time.

Keywords: Ovarian Cancer, Nanotechnology, Nanocarriers, Detection, Screening, Imaging, Theranostic

1. INTRODUCTION

Cancer is one amongst the foremost dreadful diseases, which occurs due to the adulterated food consumption, genetic hereditary mutation, virus infection, some environmental factors, and a few imbalances induced by hormonal changes. Cancer is largely underbred sudden growth of the cell whose self-control is lost to divide which can alter the biochemical pathway, also capable to invade the host immune defenses and it travels through different blood vessels and potentially develop into tumor or cancerous cell masses which eventually damages the healthy cells of various organs, demolish the organ systems and ultimately death. Cancer can occur at various organs or tissues, one amongst the foremost common areas is that the female reproductive system which incorporates cervical, ovarian, uterine, vaginal, and vulvar. After cervical cancer, ovarian cancer is the most prominent one which is the leading reason behind mortality from gynaecologic malignancies. Ovarian cancer is the eighth commonest cancer in women globally (18th commonest cancer overall), with 295,414 new cases diagnosed in 2018 [1]. In most of the population-based cancer registration in India, Ovarian cancer is the third leading site of cancer among women trailing behind cervix carcinoma [2]. With the rise old, the prospect of getting ovarian cancer is additionally increased. Epithelial ovarian cancer is predominantly a disease of perimenopausal and postmenopausal women, with 80% of ovarian cancers occurring after age 40 [3]. Women with ovarian cancer and age, younger than 50, have a 5-year survival rate of 70.5% compared with 40.6% in those 50 or older age [4]. The epidemiology of ovarian cancer is multifactorial, with genetic, environmental, and reproductive factors directly or indirectly associated with carcinogenesis. The first reason behind epithelial ovarian cancer is on account of incessant ovulation, after which the ovarian epithelial cells proliferate, which can propagate mutations or promote carcinogenesis [5]. Women who are been pregnant are at 30-60% reduced risk of getting ovarian cancer as compared to nulliparous women [6]. A history of pelvic disease and endometriosis (endometrioid and clear cell histology) has been related to ovarian cancer [7]. Approximately 75% of ovarian cancer patients are initially diagnosed with the disseminated intra-abdominal disease (stage IV) and since of this late diagnosis, but 20% of stage IV and fewer than 40% of (stage III) patients survive for five years [8]. The rationale for this can be the

missing early detection and mistaking symptoms like considering gastrointestinal pain, infelicitous management, lacking sensitivity of screening detection methods that might diagnose the diseases at a really early stage. Keeping that objective see able, Nanotechnology has great promise in addressing existing problems to enhance the diagnosis and therapy of Ovarian Cancer. Nanocarriers are multifunctional as several varieties of molecules may be loaded onto them through physical adsorption or chemical conjugations including drugs, imaging agents, targeting moieties like ligands or Antibodies. With the arrival of nanotechnology, it'll be possible to detect ovarian cancer in real-time to extend the survival rate of the patient.

2. NANOTECHNOLOGY PROSPECTS IN SERMONIZING OVARIAN CANCER DIAGNOSIS AND THERAPY

Nanotechnology is an objectively young field which defined on the practical application of nanostructure which leads to manufacture or process a product in the range of one dimension 1-100 nm. With the combination of biology, it emerges out with nanobiotechnology which is the new field in medicine which came up with the nanomedicine, drug delivery system, and various nano models. Nanobiotechnology deals to improve the diagnosis of ovarian cancer with higher potential and greater efficiency for the detection or it come up with the amalgamation of both therapy and diagnosis (Theranostics).

In this review, we will refer to the nanomaterials utilized in therapy, diagnostics, and theranostics as nanocarriers, as summarized in pictorial art Figure1.

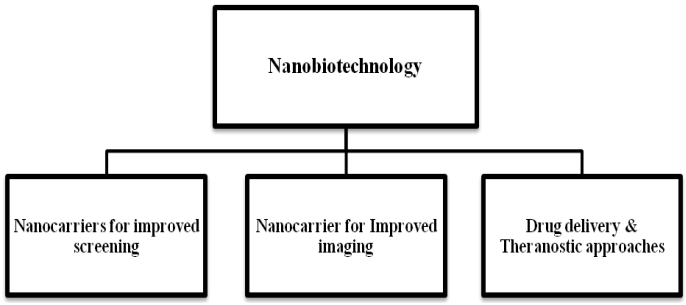

Fig. 1: This is pictorial art representation of Nanotechnology approaches to diagnosis of the ovarian cancer

Multifunctional nanocarrier are of different types which can be loaded onto them through physical adsorption or chemical conjugations including drugs, imaging agents, targeting moieties such as ligands or antibodies, and polyethylene glycol which increases the half-life of therapeutic agents and promotes passive and active tumor targeting [9] which is presented in the Figure 2.

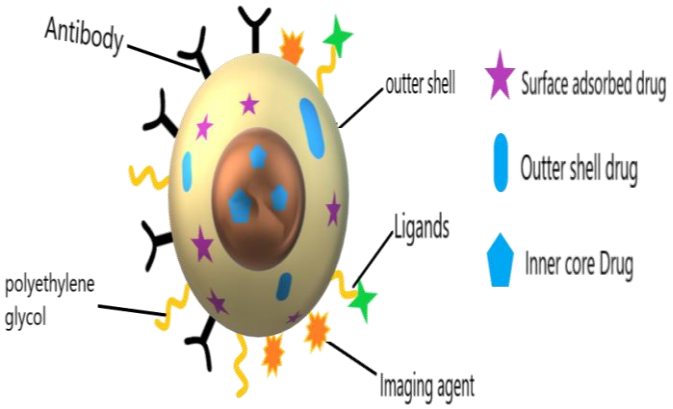

Fig. 2: Nanocarriers are multifunctional vehicles. This is the pictorial art schematic of a spherical nanocarrier. Various sorts of molecules may be utilized to functionalize nanocarriers either through chemical conjugations or physical adsorption. Imaging and therapeutic agents may be loaded onto the surface or be encapsulated within the nanocarrier.

Nanocarriers include liposomes, self-assembled polymers, micelles, hydrogels, dendrimers or dendriplexes, quantum dots, magnetic nanoparticles, carbon-based nanocarriers (Bucky balls and carbon nanotubes), solid nanoparticles and metal or oxide-based nanoparticles (colloidal gold, silica, and titanium dioxide). Using nanocarriers for various purpose such as mentioned below:

- Conjugating poorly soluble drugs as an interface or serving as a carrier in the blood stream.
- For reducing the systemic toxicity of the chemotherapeutic agent.
- Stabilizing and prolong circulation of the drug by encapsulating with the cargo in order to protect from inactivation by metabolic enzyme in addition to renal clearance [10].
- Enhancing biodistribution and pharmacokinetics of the therapeutic agent.
- Overcoming drug resistance through targeting cancer cells as the nanocarriers are taken up through cellular endocytic pathways and by delivering multiple chemotherapeutic agents to the tumor while bypassing the cellular drug efflux pump [11].

3. NANOCARRIERS FOR IMPROVED SCREENING

Screening is the application of a test to detect potential cancer when no signs or symptoms of the cancer are present [12, 13]. The value of a screening test is compromised if symptomatic individuals are included within the target population, since those with symptoms may have already got an advanced disease that warrants a diagnostic evaluation. Therefore, the goal of ovarian cancer screening is to reduce mortality by detecting cancer in earlier stages, when survival rates are improved. The Present research focuses on the components or expressed molecules which are found in the body fluids before its malignancies. When screening is performed for at risk women, it relies on routine pelvic examination, transvaginal sonography and examining levels of the blood serum biomarker CA125 and many more serum peptides such as Transthyretin (or prealbumin), Apolipoprotein A-1, Beta2-Microglobulin, Transferrin [14]. In pregnant women or women with cervical cancer recently manifested by identifying the biomarker which has a great potential to develop ovarian malignant masses [15-17]. The elevated level of CA125 is most extensively used for detection of ovarian cancer because it is a high-molecular weight mucin found in Mullerian-derived epithelium, which includes the fallopian tube, endometrium, and endocervix. Normal surface epithelium does not express CA-125, but it is elevated in 80% of patients with the epithelial ovarian cancer and in over 90% of patients with advanced-stage disease [18]. With the advent of nanotechnology, CA125 serum protein is efficiently detected by utilizing the chemiluminescence resonance energy transfer to graphene quantum dots which increase the sensitivity of ELISA in chip [19], here graphene quantum dots are used as the energy acceptor avoids the photo-bleaching problem, which usually is associated with organic dyes. In addition, the use of graphene quantum dots enables the nanometal surface energy transfer mechanism, which does not require the spectral overlap between the energy donor and the acceptor [20]. This provides more flexibility for selection of the energy donors. Moreover, graphene quantum dots are typical, hydrophilic, and rich in carboxylic acid moiety, which is convenient for bioconjugation. The capture antibody is linked to the graphene quantum dots on a transparent solid substrate, which has a potential for further development of high-throughput and automated sensor chips. For studying characteristics of ovarian cancer and immunoscreening now-a-days advanced fabricating lab-on-a-chip microfluidic devices are available, for example, a system showing great promise is lab-on-a-chip for high performance multiplexed protein detection using quantum dots made of cadmium selenide core with a zinc sulphide shell linked to antibodies to carcinoembryonic antigen, CA125 and Her-2/Neu [21]. With the use of mass-spectrometry certain protein or peptide are detected in the sera sample, NCI/FDA proteomics technology that uses matrix-assisted laser desorption ionization (MALDI) mass spectrometry analysis of undiluted native sera samples [22]. The harvested low molecular weight peptide from the biological fluids can be captured or enriched with the nanoparticle for improved screening [23]. Programmable bio-nano-chip, an integrated, microfluidic, and modular platform for CA125 within which ailed sera is sequestered and assessed with a fluorescence-based sandwich immunoassay, completed within the nano-nets of sensitized agarose microbeads localized in individually addressable wells (Chip), housed in a very microfluidic module, capable of integrating multiple samples, reagent and biowaste processing, and handling steps. Antibody pairs that bind to distinct epitopes on CA125 were screened [24]. Nanoparticles such as mesoporous silica particles, hydrogel nanoparticles, and carbon nanotubes compete with the carrier proteins through their Surface characteristics such as charge, functional groups and porosity or through their functionalization's with biomolecules (baits) that have high affinity to markers that are basic or acidic or have specific post-translational modifications [25,26]. Some of the limitations of screening method implicate nanotechnology to reduce the risk of false positive and false negative result without jeopardizing its specificity.

4. NANOCARRIER FOR IMPROVED IMAGING

The imaging technique is one of the prominent ones to monitor tumour masses, ovarian lesion or to detect the recovery of the ovarian masses but what if the detection imaging system becomes more sensitive and efficient to diagnose ovarian cancer? Yes, with the advent of nanotechnology improved imaging is possible due to nanoscale imaging agent that helps to detect cancer at an early stage. Briefly, ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) are established imaging modalities in the estimation of ovarian cancer, and positron emission tomography (PET) is a transpiring modality. Currently, the acceptable

imaging technique for early detection of ovarian cancer is transvaginal sonography. Recent advances of ultrasonography for early detection of ovarian cancer employed introducing intravenous contrast agents to quantify aberrant vascularity and blood flow [27]. Transvaginal sonography improved by using nanoimaging agent lipid microsphere, it makes it possible to visualize the small microvascular changes that occur during the tumor formation. Perflutren lipid microbubbles are very minute to flow through newly formed capillaries; this contrast agent can then be used to detect neovascular tissue, a hallmark of cancer, thus enabling clinicians to detect differences between malignant and benign ovarian masses [28, 29]. Many nanocarriers play a major role in targeting the new tumor cell due to their intrinsic characteristics (e.g.: fluorescent agents like quantum dots, or contrast agents in magnetic resonance imaging (MRI) such as super magnetic iron oxide nanoparticles (SPIONs) [30, 31] and colloidal gold or because they can be loaded with a contrast agent combined with a targeting moieties as represented in Figure 3.

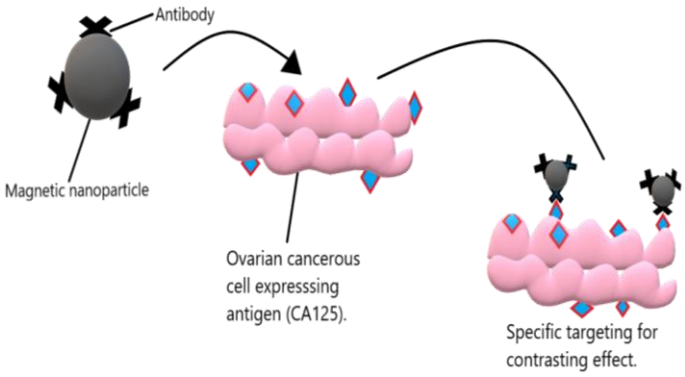

Fig. 3: This pictorial art represents the binding of magnetic nanoparticles which contain antibody against ovarian cancer antigen 125 for specific targeting of ovarian cancer masses of cell as a contrasting agent in MRI.

Jesse V. et al demonstrated ovarian cancer imaging, using gold nanorods contrasting agent with surface-enhanced Raman spectroscopy in vivo xenograft into the mice which revealed enhanced contrasting effect by differentiating benign and malignant tumor [32]. Shahbazi- Gahrouei et al. conducted a research using conjugated SPIONs- C595 for the detection of MUC1- expressing ovarian cancer. Their result revealed great tumor accumulation and detection of ovarian cancer by the nontoxic nanoprobe as a specific ovarian MRI contrast agent [33, 34]. Liu et al. synthesized and applied hydrophilic calcium fluoride based multifunctional nanoparticles modified using polyethylene glycol- poly acrylic acid copolymer doped with gadolinium for efficient tumor diagnosis [35]. All these are possible imaging modalities that could improve imaging but mostly not yet explored in ovarian cancer due to their non-biodegradability, intrinsic optical properties of some nanocarriers (such as gold, carbon nanotubes and magnetic nanoparticles) can be converted to a destructive energy to cells [36-38] therefore some of the diagnostics company are coming up with the conjugation of antioxidant with the nanocarrier for self-clearance after its work is done.

5. DRUG DELIVERY AND THERANOSTIC APPROACHES

Many chemotherapy drugs have improved the survival rate of a patient with ovarian cancer. Many anti-cancer drugs are available, including cisplatin, paclitaxel, doxorubicin, decitabine, gemcitabine, and their combinations for ovarian cancer treatment. There are several kinds of research is going on to develop such drug which shows more specificity to the ovarian cancerous cell rather than the non-cancerous cell or by improving the existing therapeutic modalities. A number of randomized trials treating advanced ovarian cancer using combination chemotherapy with hexamethyl melamine, cyclophosphamide, methotrexate and fluorouracil have achieved higher survival rates than using a single therapeutic agent [39]. To enhance chemotherapy, it may be combined with biological therapies (also referred to as molecular therapies or targeted therapies) using inhibitors of molecular pathways contributing to carcinogenesis; among them are epidermal growth factor receptor (EGFR), HER2, vascular endothelial growth factor (VEGF), and poly-(ADP-ribose)-polymerase [40,41]. Chemotherapeutic agents which are delivered orally or intravenously have poor pharmacokinetics with a narrow therapeutic window. These agents reach a maximum tolerated concentration immediately and then are terminated from the blood while drug with nanocarrier reach minimum concentration with prolong exposure to the targeted site as represented in Figure4.

An ideal drug composition with maximum benefits for patients should release at a minimum effective concentration over duration of time. Nanotechnology promises to play an essential role in satisfying these aspects as a drug delivery carrier/vector as shown in Figure 5.

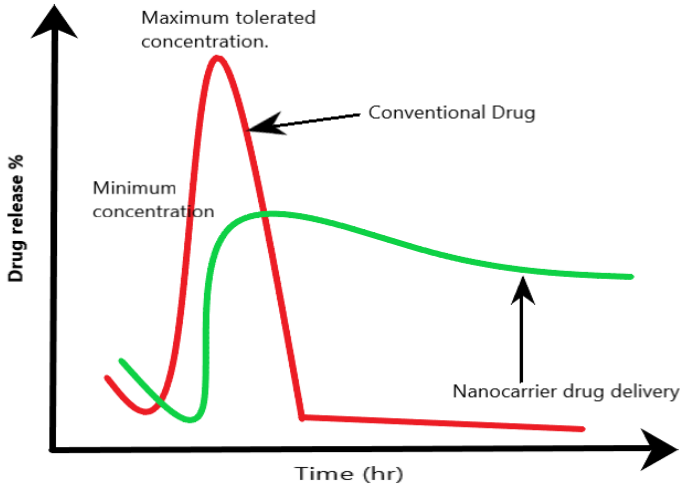

Fig. 4: This pictorial graph represents Improved and sustained therapeutic effect of chemotherapeutic agents using nanotechnology. Oral or intravenous route delivery of conventional formulations and nanocarriers.

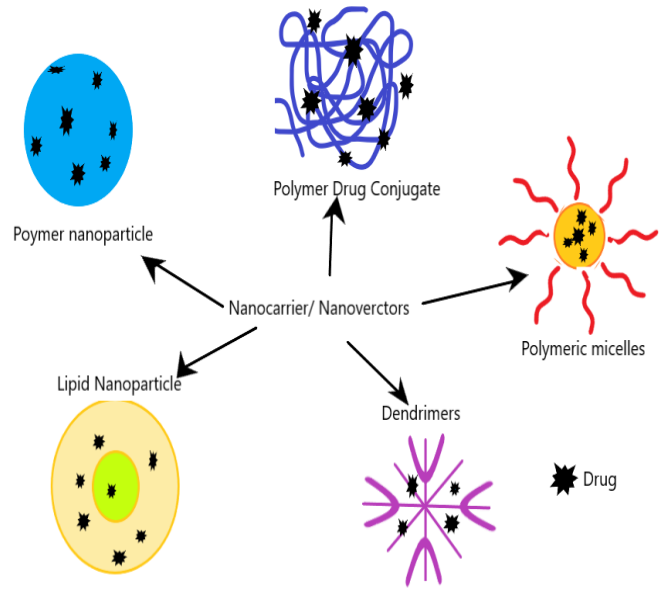

Fig. 5: This Pictorial represent structures of various drug delivery devices such as polymer-drug conjugates, dendrimer, polymer micelle, polymer nanoparticles, and lipid nanoparticles/capsules for efficient targeting of ovarian cancer cell.

The nanoscale drug carriers or nanocarriers are effective in carrying non-soluble chemotherapeutics and enable specific cancer cell targeting by reducing unwanted interaction, toxicity and clearance of drugs.

For nano base carrier sensitivity and effectiveness can be understood by its two approaches which show the targeting of the cancerous cell in which chemotherapeutic drug is conjugated or encapsulated with the nanocarrier which especially adhere to the cancerous cell rather than the normal cell without affecting healthy surrounding cell.

5.1. Active targeting

Active targeting utilizes the principle of ligand receptor recognition to deliver the drug carrier / cargo (chemotherapeutic agent) directly to the cells which exhibit a specific receptor and which may facilitate drug uptake through numerous phagocytosis and endocytosis mechanism as in Figure 6.

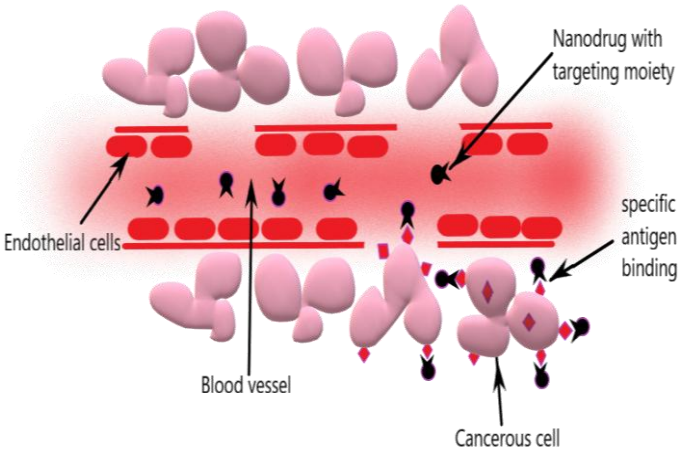

Fig. 6: This image represents the nanocarrier are entering through the leaky vasculature to the target cancerous cell through Receptor mediated with specific antigen interaction (Active targeting).

Cancer cells may express some specific receptors on the surface that are absent from normal cells, or some receptors on cancer cells may be overexpressed. To stimulate such receptors, a distinguishable cancer specific ligand must be anchored on to carrier surface. In ovarian cancer biology, mainly cell membrane protein is targeted to differentiate the normal and the cancerous cell on the basis of it nanocarrier are targeted to deliver to drug with greater efficiency and targeted specificity some of the proteins include folate receptor alpha (FRα), EGFR, HER2 receptor, CA125 receptor, and TAG-72 [42,43]. Examples of ovarian cancer-targeted nanocarriers through these receptors and others are listed in Table 1.

Table 1: Various nanocarriers evaluated for active targeted drug delivery to ovarian cancer

Targeted Antigen or receptor	Nano system	Structure	Tested	Ref.
Folate receptor α (FRα)	Gold nanoparticle	Gold nanoparticle conjugated to mercapto-PEG that in turn had through its functionalized termini interactions with cisplatin and folic acid.	*In vitro*	Patra, 2010 [44]
CA 125 antigen	liposomes	Bifunctional fusion protein composed of a variable chain of anti- CA125 fused to streptavidin which binds to biotinylated liposomes.	*In vitro*	Wang W, 2007 [45]
Heparin-binding glycoproteins: VPF and VEGF	Gold	Intrinsic property of gold nanoparticles to bind specifically to heparin-binding glycoproteins that induce angiogenesis such as vascular permeability factor/vascular endothelial growth factor (VPF/VEGF).	In vitro and in vivo	Mukherjee, 2005 [46]
TAG-72 glycoprotein	Polymeric micelle	Poly (lactic acid-co-glycolic acid) (PLGA) nanoparticles conjugated to anti-TAG-72 antibody. PLGA was loaded with curcumin (diferuloyl methane) as a sensitizer of chemo/radioresistant epithelial ovarian cancer cells.	*In vitro*	Yallapu, 2010 [47]

5.2. Passive Targeting

Passive targeting exploits the intrinsic cancer properties that lead to the accumulation of nanocarriers at cancer tissue; it causes accumulation of nano-sized carriers in the tumor tissues through its leaky vasculature and its lack of effective lymphatic drainage, to enhanced permeability and retention effect as mention in Figure 7. This leads to higher drug concentrations at tumor tissue sites and thus higher drug efficacy. These nanocarriers are capable of substituting the conventional available chemotherapeutic treatments, where in the intravenous injection of most of cytotoxic agents results in serious dose-limiting side effects to healthy tissues. With the advent of nanotechnology, nanocarriers are used the precedence of ERP (enhanced permeability and retention) effect to improve the targeting of ovarian cancer.

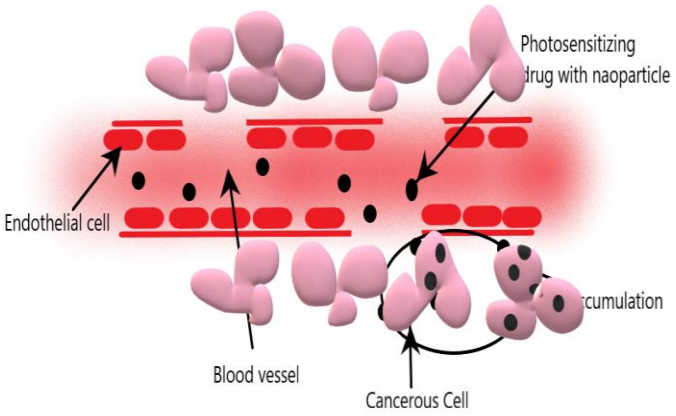

Fig. 7: This picture shows the blood vessel in which nanodrug are targeted specifically with greater efficiency and accumulation of the drug with photosensitizing nanoparticles which release the drug at the site of tumour (Passive targeting)

Table 2: Various nanocarriers that have potential to target Ovarian cancer passively

Nanocarrier	Structure	Tested	Ref.
Lipid-based nanocarriers	Solid lipid nanoparticle with trimyristin core and egg phosphatidylcholine and PEGylated phospholipid as stabilizers loaded with paclitaxel	*In vitro*	Lee MK, 2007 [48]
Nanocrystals	A nanocrystal of Paclitaxel with D-R-tocopheryl PEG1000 succinate	*In vivo and In vitro*	Liu H, 2010 [49]
Dendrimers	PEGylated polyamioamino (PAMAM) dendrimer conjugated to Cisaconityl-doxorubicin (acid labile) or succinic-doxorubicin (acid stable)	*In vitro and in vivo*	Zhu, 2010 [50]

Companies like Centocor Ortho Biotech developed nanodrug for ovarian cancer cell targeting which based on liposomes that are functionalized by polyethethylene glycol (PEG) and encapsulating doxorubicin referred to as pegylated liposomal doxorubicin; these include Caelyx® (Schering-Plough) and Doxil® [51]. Table 2 lists different nanocarriers, with potential in passive targeting, that were analysed with ovarian cancer either in vitro or in vivo or both for increased cytotoxicity of their loaded chemotherapeutic agents.

6. CONCLUSIONS

Nanotechnology emerges out with the efficient modalities which solve the problems of current technology and give the new ways to detect ovarian cancer or modify the current diagnosis with targeted specificity, it also offers the personalized medicines with low toxicity and side effects. The specialties of nanobiotechnology are that it works on the nanoscale with high surface to volume ratio with greater permeability and efficient targeting to differentiate between the ovarian cancerous cell and healthy cells which provide the sufficient amount of drug to reduce its side effects. In context to screening and imaging nanocarrier play a great role in early diagnosis of ovarian cancer with the current technology in real-time so that medical practitioner provides targeted therapy to increase the survival rate of the patient. In addition to the improvements in the detection of ovarian presented in this review, nanotechnology is currently applied to many cancers in isolating blood circulating tumour cells and rare cells [52]. There are subsidiary challenges to using nanocarriers in diagnosis and therapy of diseases it includes drug loading capacity, chemical and physical stability, controlling drug release, the problem of toxicity it causes due to accumulation [53] and many more but researchers which include engineers, physicists, and chemists, biologists, biochemists, pharmacists, advances the field further into a direction of research that accelerates specific disease needed solutions.

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