Journal of Associated Medical Sciences 2024; 57 (1): 124-134

JAMS
Journal of Associated Medical Sciences

Scopus Indexed & Thai-Journal Citation Index Centre (TCI)

Journal of Associated Medical Sciences

Journal homepage: https://www.tci-thaijo.org/index.php/bulletinAMS/index

Emerging updates on tracking new landscapes in nanotechnology for the diagnosis and ovarian cancer therapy

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ARTICLE INFO

Article history:
Received 2 August 2023
Accepted as revised 21 November 2023
Available online 27 November 2023

Keywords:
Cytoreductive surgery, dendrimers, nanoparticles, nanotherapeutic approaches, nanotechnology, ovarian cancer, nanocapsules

ABSTRACT

The sixth most common recurrent malignancy worldwide is ovarian cancer in women, and it causes more women to die compared to any other issue impacting the female reproductive system. Ovarian cancer has several histological subgroups differing in clinical traits, risk factors, cell sources, molecular makeups, and treatment possibilities. There is no effective screening procedure, and it is typically discovered at a late stage. Newly found cancer is currently treated with platinum-based chemotherapy and cytoreductive surgery. Due to its recurrence and late diagnosis, ovarian cancer has the highest fatality rates in contrast to all gynecological cancers. The discipline of medical nanotechnology has made great strides in recent years in resolving issues and enhancing the detection and treatment of various illnesses, including cancer. However, most studies and recent reviews on nanotechnology are devoted to how it might be utilized to treat other tumors or disorders. This review's main objective was the precise diagnosis and treatment of ovarian cancer using nanoscale drug delivery systems. Various nanocarrier systems, such as dendrimers, nanoparticles, liposomes, nanocapsules, and nano micelles, have been discussed. Additionally, we explore how the potency of the combination of immunotherapy and nanotechnology may help to overcome the current therapeutic constraints connected with each application and reveal a novel paradigm in cancer therapy. The unique nanotherapeutic approaches that have demonstrated promising outcomes in preclinical in vivo research are highlighted, along with new nanoformulations actively advancing into clinical trials. Additionally, the possible use of nanomaterials in diagnostic imaging methods and the capacity to use nanotechnology for early ovarian cancer detection are also highlighted.

Introduction

Ovarian cancer, which only becomes apparent in an advanced stage, is the foremost reason for transience for women universally. During the initial stages of the malady, patients exhibit a few basic symptoms because there aren't any reliable ways to diagnose the condition. Contrary to stromal or germ cells, ovarian epithelium frequently contributes to significant occurrences of ovarian cancer.[1] There are numerous morphological and symptomatic changes present in these ovarian cancer subtypes.[2,3] Modern approaches for ovarian cancer diagnosis include CT, CA-125 (cancer antigen 125) levels in the serum, transvaginal ultrasonography, MRI, etc. Years of research have consistently shown how dynamic the disease is, and despite better treatment options, there are still serious side effects from aggressive chemotherapy.[4,5] Patients suffer when more severe therapy is required, especially

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doi: 10.12982/JAMS.2024.014
E-ISSN: 2539-6056

when aggressive tumors lie dormant and subsequently reappear.[6-8]

The prevalence of resistance mechanisms is one of the major obstacles to the creation of effective cancer treatments. Resistance mechanisms are engaged in concurrent signaling pathways and reroute to promote cancer progression after the key oncogenic pathways are shut down.[9] Due to the wide range of cancer cells, patient tumors, genetic abnormalities, and epigenetic patterns, drug resistance might develop and limit the efficacy of therapeutic measures.[10] Most anticancer medications also have low bioavailability due to their poor physicochemical stability, low water solubility, or overall electronegative surface charge, which inhibits the medications from penetrating the cells due to the negative charge of the cytomembrane. The natural negative charge of cell membranes repels these medications, resulting in poor cell adhesion and low bioavailability.[11] This incites doctors to prescribe more medication than is required to preserve diffusion-controlled phenomena. The existing methods of diagnosis and therapy are insufficiently sensitive and effective to detect and treat ovarian cancer (OC) at an early stage. Furthermore, a delayed diagnosis is brought on by the absence of a distinct detection point and significant costs.

Integrating immunotherapy and chemotherapy could enhance the remedial outcome because immunotherapy may prevent immunological harm and balance the acute immunosuppression induced by chemotherapy. In contrast, chemotherapy might activate antitumor immunity and create antigenic molecules. However, there are several issues with immunotherapeutic drugs that chemotherapy suffers from as well, including immune-related adverse effects, instability, and ineffective administration.[12] There are ways to get over the limitations mentioned above, involving the use of nanoparticulate drug delivery techniques to deliver two or more medicines. Controlling medication ratios and ensuring co-localization of the combination treatments at the tumor site is made possible by a delivery method that simultaneously combines several therapeutic agents.[13]

In order to produce aqueous dispersions that make it easier to administer hydrophobic therapeutic agents like paclitaxel (PTX), or to accommodate hydrophilic therapeutic agents like RNA that make it easier for them to enter cells, nanoparticulate drug delivery devices can encapsulate these agents.[14,15] To enhance the accumulation of delivered cargoes in the tumor by passive targeting or the enhanced permeability and retention (EPR) effect, nanoparticle-based therapies frequently use nanosized particles having a diameter in a spectrum of 10 to 200 nm. (Figure 1).[16,17] Targeted substances that can precisely bind to receptors overexpressed by tumor cells, such as antibodies, growth factors, peptides, or fragments of antibodies, can also be included in nanoparticles. By boosting their internalization by the targeted cells, active targeting improves the selectivity and therapeutic responsiveness of drug-loaded nanoparticles.[18]

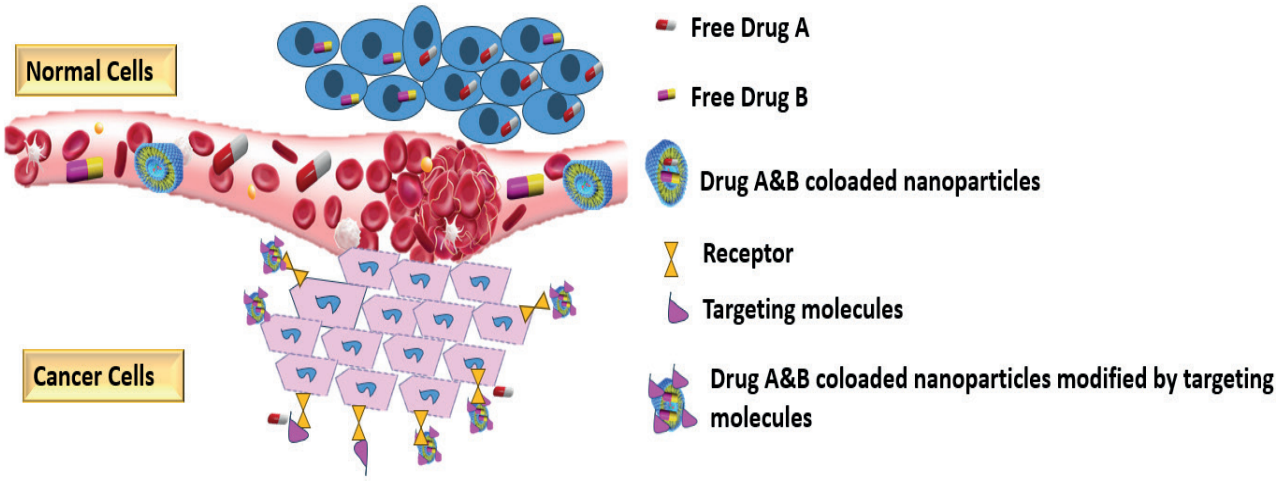

Figure 1. *Benefits of co-delivery of 2 treatments employing nanoparticles in contrast with free pharmaceuticals are illustrated schematically. These benefits include better water solubility, regulated ratios of the drug, and guarantee of the same drug disposition behavior at the tumor site. Other benefits include increased drug co-accumulation at tumors via the EPR effect and/or receptor-mediated endocytosis, commonly known as active or passive targeting.*

Additionally, by modifying the kind and features of the nanoparticle-forming materials, such as their molecular weight, compositions, and architectures, nanoparticles can be altered to enhance their cargo-loaded features, involving circulation time, In-vivo stability, retention of the drug, and renal clearance. Numerous reports have explored and depicted how well different types of nanoparticles can be used to encapsulate different medicinal ingredients, including liposomes, polymeric micelles, dendrimers, and nanoparticles related to lipids (Shown in Figure 2), for several cancer therapies, particularly ovarian cancer.[19-21] Additionally, we explore how the power of combining immunotherapy and nanotechnology may help overcome the current therapeutic limits connected to each application and reveal a novel paradigm in the treatment of this cancer. Nanotechnology-based therapies support the controlled delivery of chemotherapeutic drug(s) in a targeted manner that acts for an extended period directly on the cancer site with low or non-toxicity to normal organs. Designing nanotechnology formulations for the treatment of ovarian cancer will thus be the main emphasis of this review.

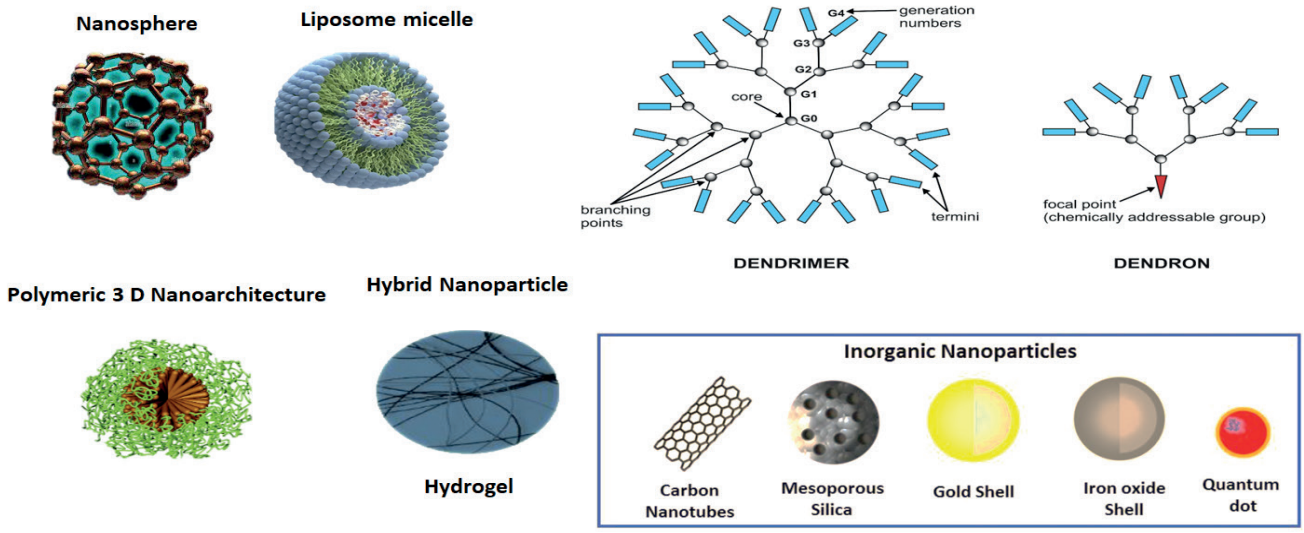

Figure 2. *Different kinds of nanoparticles are employed for drug delivery depending on the cancer treatment medication.*

Impediments to OC perception and intervention

Surgery to reduce the size of a tumor

To ascertain the stage and prognosis of the cancer, an ovarian cancer patient must have tumor debulking surgery.[22] The 5-year survival probability for Stages I, II, III, and IV is predicted to be between 90% and 10% [23,24] based on the surgical pathologic degrees used in the International Federation of Gynecology and Obstetrics (FIGO's) staging evaluation system. The tumor in the patient and the therapy measures can all be categorized as prognostic variables for ovarian cancer.[25] By the Gynecologic Oncology Group, a residual tumor less than 1 cm after surgery is considered to have undergone appropriate cytoreduction. In contrast, one more than that is considered to have undergone poor cytoreduction.[26-28] Complete cytoreduction is frequently not attainable for tumors in their advanced stages (stages III and IV). Three cycles of neoadjuvant chemotherapy are administered to patients who are too sick or have lesions that cannot be removed surgically. If the chemotherapy is effective, there will be six rounds given, followed by an interval debulking surgery.[29] The removal of all residual diseases, whether treated as a primary or secondary disease, is the ultimate goal of tumor debulking surgery. Despite an initial response, recurrence occurs in 75% of individuals. Finding a different strategy to treat ovarian cancer is the final goal.

Chemotherapeutic drugs

Chemotherapeutic medications are used to treat patients after surgery. Carboplatin and cisplatin are the two medications used the most frequently to treat OC.[30] Due to its resemblance to cisplatin in terms of response rate and survival statistics, carboplatin was launched at the beginning of the 1980s as an alternative. However, carboplatin is preferable over cisplatin due to the risk of ototoxicity, nephrotoxicity, and nausea or vomiting found with cisplatin. [31-33] Platinum is inserted into DNA by the alkylating chemical carboplatin, creating crosslinks. Apoptosis is brought on by a signaling cascade that is set off by the ensuing structural deformation of the DNA.[34-36]

Frontline treatment with PARPi for ovarian cancer

For several years, researchers have been exploring drug resistance and tailored treatment approaches for ovarian cancer patients. Many patients experience recurrence, even though there is frequently no sign of the disease after the initial surgery and chemotherapy.[37] The recurrence following the initial therapy and knowledge and analysis of the issue from a molecular perspective led to the creation of poly-ADP-ribose polymerase (PARP) inhibitors. Rucaparib Niraparib, or Olaparib, [38] medications in a recent study revealed less DNA repair in tumors with a BRCA gene mutation, which led to the

demise of cancer cells. Numerous clinical trials have been undertaken to encourage progression-free survival (PFS) because empirical data points to an anti-tumorigenic role (NCT04573933). According to the phase-2 trial of rucaparib,[39] patients with platinum-sensitive, high-grade ovarian cancer who also had a BRCA mutation (germline or somatic), a high level of chromosomal loss of heterozygosity, and several other variables had increased PFS. This medication has been given FDA approval to treat advanced OC. Olaparib monotherapy, which is given to OC patients who have had chemotherapy and may have a germline BRCA mutation, received another groundbreaking FDA approval. The European Medicines Agency (EMA) further endorsed olaparib for high-grade fallopian tubes, primary peritoneal cancer, serous epithelial ovarian, or with a somatic mutation or germline responsive to platinum treatment.

Nanotechnology-based drug carriers

As shown in Figure 3, when administered orally or intravenously, chemotherapeutic drugs in solution or pharmacokinetics of polymer solutions are unsatisfactory, with limited beneficial properties. These substances immediately influence the highest concentration that may be tolerated before being removed from circulation. For maximal patient advantages, a medication formulation should be released over time at the lowest possible effective concentration. As a medication delivery carrier, nanotechnology has the potential to significantly contribute to meeting these requirements. Drug delivery systems based on nanotechnologies, such as carbon nanotubes, polymer micelles, dendrimers, polymer nanoparticles, and lipid/solid nanoparticles, have many advantages over traditional approaches. Nanotechnology-based therapies have been shown to improve therapeutic efficacy, reduce toxicity in healthy tissue, and increase patient compliance. The therapy of cancer currently makes use of several of these nanoparticles.[40]

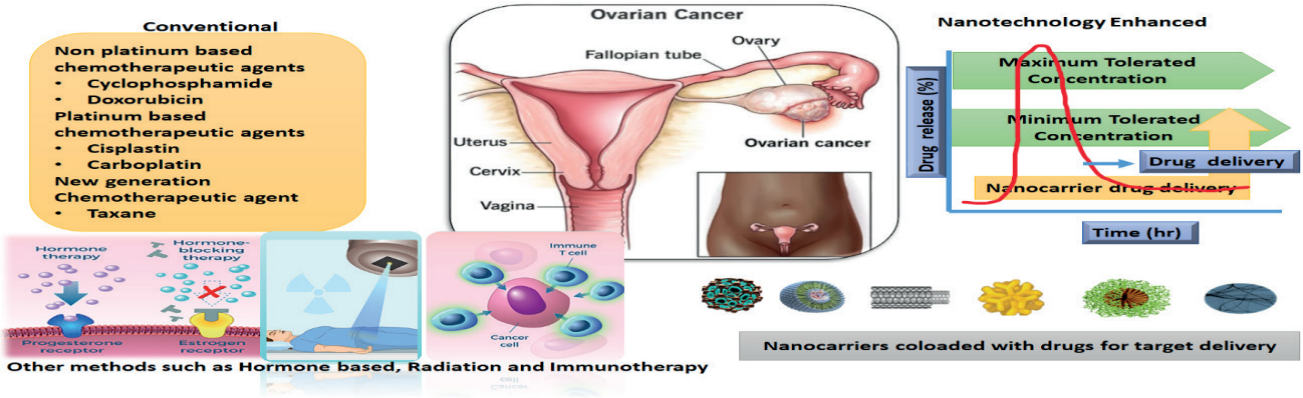

Figure 3. *Application of nanotechnology to increase efficacy via toxicity reduction in contrast to conventional techniques and provide effective treatment against ovarian cancer.*

Nano micelle-based ovarian cancer diagnosis

Due to the relative paucity of timely detection and exploratory capabilities in the early stages, ovarian cancer is frequently discovered in the late stages.[41,42] Both the administration and regulated release of medications for site-specific targeted treatment and imaging for early cancer identification are crucial.[43] Imaging can be used to monitor the progression of OC illness, assess the effectiveness of therapy and how medications are distributed throughout the tumor, or find potential molecular biomarkers.[44] Utilizing modern medical visualization techniques, such as anatomical probes (Computed Tomography scanning), basic radiography, magnetic resonance imaging (MRI), ultrasound, disease inspection, and therapy efficacy monitoring can be accomplished.[45] Currently, nanotherapeutic applications such as non-invasive cancer molecular imaging offer prospects in early prognosis for enhancing the accuracy efficiency of chemotherapeutics and enabling enhanced infection detection. When imaging malignancies with image modalities, contrast nanocarrier devices internalize increased tumor intensity. Nanoparticles can deliver drugs to specific molecular targets, encapsulate drugs, or improve pathological areal imaging. PEG-b-poly(Lysine) copolymers, among other polymeric nanoparticles, show enormous potential for analytical molecular imaging and the tracking of cancer progression or remission. Gold-plated and coated metallic quantum molecules are the most frequently utilized nanometer-sized particles. Still, other nanoparticles and biomarkers are also showing promise as efficient tools for prospective transmission development and therapeutic administration in the diagnosis of infected locations. By enhancing the targeting capabilities of existing medicines, increasing the effectiveness of locally administered medications, lowering systemic toxicity, enhancing imaging, and minimizing the requirement for radiation therapy, nanotechnology may hold the secret to the cure.[46,47]

Nanotechnology: A scientific viewpoint on diagnostic vs. therapeutic applications

According to reports from the World Health Organization (WHO) [48] and the European Federation of Pharmaceutical Industries and Associations,[49] cancer is one of the most common diseases, with an increase of more than 14 million new cases and 8.8 million fatalities worldwide each year. Thankfully, in many cases, the origins of cancer have been discovered (at least from a genomic perspective), and new therapeutic approaches have been created. No other illness is anticipated to advance as quickly as cancer despite these developments. By 2040, the incidence and mortality rates will be 70%.[50] This startling forecast is based on several coexisting elements, including population aging, environmental conditions, gender, lifestyle, food, gut microbiota, and molecular heterogeneity. Creating innovative technologies for the early detection of cancer-specific molecular aberrations before tumor formation is the only other way to stop the current trend. A promising replacement for conventional therapies and treatments is offered by recent applications of nano-biotechnology for the early diagnosis and treatment of cancer.[51] Nanotechnology may provide novel ways to target chemotherapies to cancer cells selectively, enabling speedier and more accurate tumor removal during surgery and improving the efficacy of radiation-based therapies.[52] Some of the world's most advanced nanoscience laboratories have been built over the past ten years thanks to significant government funding for this field of study, and most of them are currently working to develop cutting-edge cancer treatments.

Biosynthesis of natural products with nanoparticles for cancer therapy

Most of the chemical processes used to create nanoparticles (NPs) are excessively expensive and also involve the use of dangerous, poisonous chemicals that pose several biological concerns. This increases the rising demand to create environmentally friendly procedures using biological techniques and green synthesis. The "green synthesis" of NPs uses chemicals that are safe for the environment and are not harmful. Utilizing diverse plant resources to biosynthesize metallic NP'S is known as green nanotechnology. Numerous bioactive substances, including proteins, alkaloids, flavonoids, phenols, reducing sugars, steroids, carbohydrates, and tannins, were discovered in natural products. In addition to the most recent cutting-edge technologies, natural ingredients from many different sources are also studied for cancer treatment. Low toxicity and good tolerability are characteristics of natural compounds utilized in cancer therapy.[53-56] Through various modes of action, they demonstrate anti-cancer effects (Table 1).

Table 1. Biological processes by which natural chemicals fight OC cells.

Bioactive natural product	Type of cell	Mode of action
Thymoquinone	SKOV-3 cells	reduces the expression of Bcl-2 and increases the expression of Bax to cause apoptosis.[57]
Piperine	OVCAR-3 cells	suppresses the Akt / PI3K /GSK3 signaling alleyway, causes G_2/M stage in the arrest of the cell cycle, is caspase-activated, and prevents migration of cells.[58]
Quercetin	Epithelial OC cell line	reduced surviving, produced cell cycle arrest, inflicted apoptosis, and inhibited proliferation
Zeylenone	SKOV-3 cells	Signal transducer and activator of transcription (p-STAT) and the Janus family of tyrosine kinases (p-JAK) countenance levels were both lowered in separate ways. Zeylenone induced MMP, apoptosis-inducing factor (AIF), and cytochrome c depletion in a dose-dependent fashion. Additionally, it enhanced the production of caspase-3, Fas, Fasl, and Bax in both mRNA and protein forms while reducing the expression of Bcl-2.[60]
Curcumin	Cisplatin-resistant OC cells	promotes apoptosis and phosphorylation of p53, induces G_2/M cell-cycle arrest.[61]
Flavonoid	PA-1 Cells	lowers viability, causes apoptosis, upsurges caspase-3, 9, Bad, Bid, Bax, & cytochrome-c while dwindling Bcl-2 & Bcl-xL.[62]
Sideroxylin	ES2, OV-90	ERK1/2 signalling mechanism Increased expression of miR-27a and FBXW7 results in increased DNA and ROS damage and depolarizes the mitochondrial membrane.[63]

Ovarian cancer prevention via Cassia auriculata (Avartaki) plant-based nanoformulations

The impact of natural remedies on ovarian cancer has recently attracted the attention of numerous studies. The mechanisms through which bioactive substances prevent ovarian cancer have been clarified through several experimental experiments. The results showed that quercetin induced apoptosis via intrinsic and caspase-dependent mitochondrial pathways. In addition, quercetin produced ER stress in ovarian cancer cells, which led to mitochondria-mediated death. Among several natural products, we primarily focused on *Cassia auriculata* (*Avartaki*). An annual or biennial plant known as Tanner's Cassia (Ceasalpinaceae) or Avartaki in Ayurveda, *Cassia auriculata Linn.* is found in open woods all over India.

A protective function of autophagy in ovarian cancer cells was also induced by *Cassia auriculata*. Overall, this research showed that plant-based products activated the p-STAT3/Bcl-2 axis to cause ER stress, apoptosis, and autophagy (Figure 4). According to a different study, quercetin reduces viability and triggers apoptosis in cells harboring metastatic ovarian cancer. Several anti-apoptotic molecules, including Bcl-2 and Bcl-xL, are decreased by bioactive compounds, whereas pro-apoptotic molecules, such as caspase-3, caspase-9, Bid, Bax, Bad, and cytochrome c, are increased. Additionally, natural products induce mitochondrial-mediated apoptosis, which stops the spread of ovarian cancer cells that have metastasized. A recent study investigated the anti-cancer capabilities of quercetin's nano-formulation.[64] In vitro and in animals that had received ovarian cancer xenografts, this type of quercetin greatly slowed the growth of ovarian cancer cells. By upregulating caspase-3, caspase-9, and Bax while down-regulating MCL-1 and Bcl-2, quercetin in nanoformulations also induced apoptosis.[65]

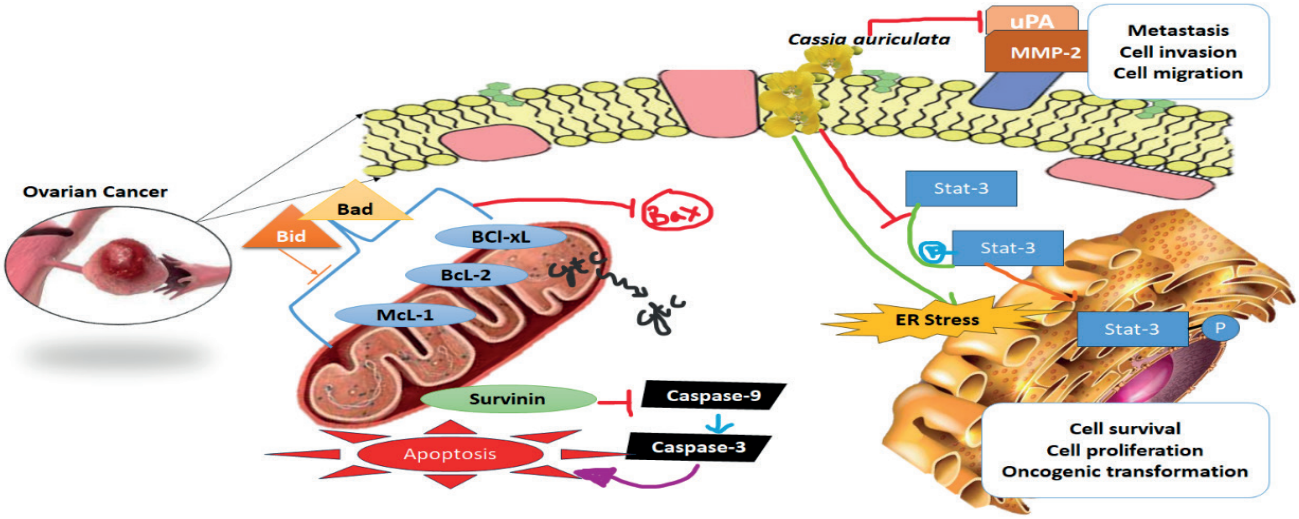

Figure 4. *Schematic representation of a potential therapeutic strategy for treating ovarian cancer that targets multiple signaling pathways with plant-based products.*

Nano medication delivery issues

The utilization of various nanomaterials with desired properties and significant obstacles to the management and treatment of cancer have been brought to light by recent developments in the drug delivery sector. It is anticipated that the usage of nanoparticles would radically revolutionize the healthcare industry, based on the tremendous breakthroughs made in the pharmaceutical delivery sector over the past few decades. Only a few nanoformulations have entered clinical trials, and it is still difficult to create effective cancer nanotherapeutics. Figure 5 shows a schematic illustration of the principal difficulties in delivering cancer nanotherapeutics.

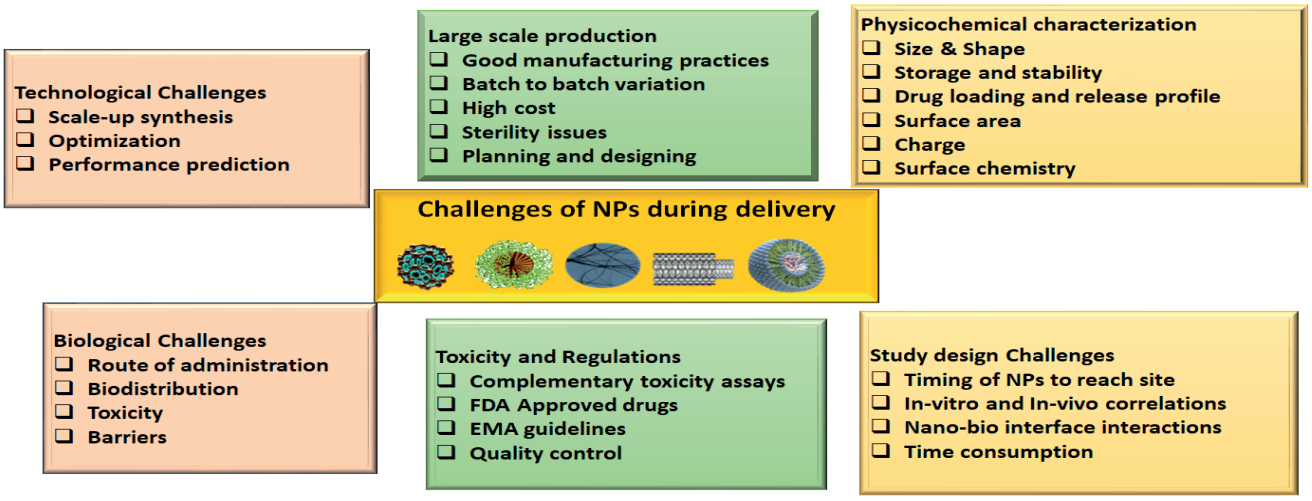

Figure 5. *Illustrates the grand challenges and perspectives for nanotechnology in healthcare systems.*

The advancement of nanotechnology has significantly expanded our understanding of and research into nanoparticles. Only a small portion of them, nevertheless, participate in the in-vivo and in-vitro clinical studies to reach their conclusion. Every nano-formulation has unique difficulties in the clinical setting. Even though most NPs deal with broad issues that fall into three categories-biological, technological and study-design-related, the majority of them are dealt with by these three categories. Lack of administration routes, biodistribution regulation, NPs' ability to overcome biological barriers, degradation, and toxicity are a few biological concerns.[66,67] Since NPs are frequently injected intravenously into the bloodstream, they are frequently removed from the body and find it challenging to interact with the target region. Some biological issues are lack of administration routes, regulating biodistribution, NPs' capacity to cross biological barriers, degradation, and toxicity.[68-70]

NPs have trouble interacting with the target area since they are typically injected intravenously into the circulation, where they are regularly eliminated from the body. The technical barriers for NPs are scale-up production, equal optimized performance, and efficacy projections. These are vital in assuring the beneficial accomplishment of nanoparticles. Many of the NPs used in in vivo and in vitro experiments are usually made in small batches, and scaling up for large volumes is occasionally impossible due to equipment and other factors. There is no systematic design or optimization process used to identify the lead therapeutic candidates that perform best in animal models. To circumvent this, we can practice certain procedures that can assess a range of nano-formulations after careful repetition and further choose one optimized formulation.[71-74] These hits, however, should be used later in human trials. It is challenging to predict the performance and effectiveness of nanoparticles, and it is impossible to reproduce in vivo outcomes in human investigations.

The fact that NPs are never used as first-line therapy is another serious issue. Nano-formulations have been successfully approved; however, they are normally saved for use in later treatment lines if disease progression is found. Most patients in the fictitious clinical trial have either gotten worse despite receiving multiple treatments or have developed drug resistance. The likelihood that NP treatment will help patients who are probably still curable is decreased in these circumstances, which frequently skew clinical trial outcomes.

Smart outlook on cancer nanomedicine

Smart thinking, logical reasoning, and realistic reasoning are all necessary to increase the therapeutic impact of cancer nanomedicines. In this vantage point, we outline four strategic objectives to enhance the performance, ease of application, and utilization of cancer nanomedicine.

- Probes and techniques for patient stratification are urgently required to improve cancer nanomedicine clinical trials, just as they are in other areas of oncology medication development.
- The likelihood that formulations created and tested in preclinical settings would eventually function well in patients will be increased through intelligent modular (pro)drug and nanocarrier design techniques, as well as library screening.
- The pharmacokinetic and/or pharmacodynamic advantages provided by entrapping pharmaceuticals in nanomedicine formulations will be amplified by rationally developed pharmacological and physical combination regimens.
- Last but not least, identifying the pathophysiological aspects that limit the effectiveness of current cancer immunotherapies and creating immuno-modulatory nanomedicines in response may assist in enhancing the results of immuno-oncological interventions and increase the number of long-term survivors.

The subject of cancer nanomedicine has rapidly grown in recent years. Only a handful of nano medicinal anticancer

medications, including antibody-drug conjugates, have made it to the market, in stark contrast to the numerous novel materials and publications being created. To remedy the situation, we must stop developing ever-more sophisticated nanomedicine materials and reevaluate our approach to translational cancer nanomedicine research. To ensure that nanomedicines are effective in as many people as possible, we must develop clever ways. This transition calls for consortia made up of academics, clinicians, pharmaceutical corporations, and regulatory agencies to think logically and realistically and to work together in concert. In addition to promoting the clinical impact and patient performance of nanomedicine-based anticancer medications, the strategic directions presented in this publication seek to streamline translational cancer nanomedicine research.

Conclusion

Numerous clinical settings for various disease types use cancer treatments based on the unique properties of NPs. NP-based DDS have been shown to have improved stability, tumor targeting, biocompatibility, and pharmacokinetics when compared to conventional medications. A hopeful new era in cancer treatment has begun with nanotechnology to deliver small molecules for cancer detection, diagnosis, and therapy. NPs also offer a superb platform for combination therapy that aids in conquering MDR. As a result of expanding research, many NP types, including metallic, hybrid, and polymeric NPs, have been shown to improve drug delivery effectiveness. The properties of the recommended nanoplatforms and those of medicinal drugs need to be closely studied by researchers.

In conclusion, we are quickly developing a far greater grasp of the difficulties and chances posed by cancer nanomedicine. For the more successful research and clinical translation of nanotherapeutics, this review has examined the significance of the convergence of nanotechnology and cancer biology. Additional effort must be made in “understand toxicity, cellular and physiological factors that regulate NP-based drug delivery, EPR, and PC mechanism” in the human body if one is to develop nanotechnology with any degree of rationality. We assume that the development of cancer therapies and, based on the results discussed above, nanotechnology will lead to a revolution in the clinical translation of NP-based cancer therapeutics. We anticipate that nanomedicines will change how cancer is treated and that in the not-too-distant future, the fundamental objective of cancer nanomedicine’s dramatic improvement in patient survival will become a reality.

Author contribution and acknowledgements

K.R. Padma and S.Mamatha Ramani solely drafted the paper under the guidance of Prof.P.Josthna. All the authors approved and are thankful to the Department of Biotechnology, Sri Padmavati Mahila Visvavidyalayam (Women’s University), Tirupati-Andhra Pradesh, India.

Conflict of interest

The authors do not have any conflict of interest (financial or other) other than those declared.

Consent for publication

NA.

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