"Nanoparticle based targeted drug delivery in ovarian cancer therapy using chemotherapeutic drugs."

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.).

School of Pharmacy
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Declaration

It is hereby declared that

1. The thesis submitted is our own original work while completing degree at BRAC University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. We have acknowledged all main sources of help.

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Ethics Statement

No animals or human were harmed during this study.

Abstract

Ovarian cancer is one of the most fatal gynecologic malignancies owing to delayed diagnosis, systemic toxicity as well as drug resistance associated with conventional chemotherapy. This study investigates the potential of nanoparticle based targeted drug delivery systems to enhance the therapeutic efficacy of chemotherapeutic agents namely cisplatin, doxorubicin and paclitaxel. A literature predicted review was conducted using PubMed, Science Direct and Google Scholar to explore the recent advances in nanoparticle formulations and applications in ovarian carcinoma treatment. Findings reveal that nanoparticles improve drug solubility, stability as well as bioavailability while lowering toxicity and reducing multidrug resistance through targeted drug delivery. Liposomes, polymeric particles and metallic nanoparticles show enhanced drug accumulation at tumor sites via improved permeability and retention effects. In general nanoparticle mediated drug delivery systems exhibit significant promise in increasing treatment effectiveness as well as patient compliance while minimizing adverse drug effects in ovarian cancer therapy.

Keywords: Nanoparticles, Ovarian Cancer, Chemotherapy, Targeted Drug Delivery, Drug Resistance.

Dedication

I want to dedicate this to my parents, who inspires me to do something for myself and always appreciates me.

- M. Abdullah Al Mahmud (21346016)

I dedicate this thesis to my beloved parents and my grandparents whose endless love, support and encouragement have been my greatest strength throughout this journey.

- Kh. Anika Tahia Suchi (22146026)

I dedicate this thesis to my parents, whose unconditional love, encouragement and support have been my greatest motivation.Their constant guidance, sacrifices, and belief in my abilities have shaped both my journey and my success.This accomplishment stands as a tribute to their endless dedication and the values they have instilled in me.

- Samiah Akhter (22146036)

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List of Acronyms

NP	Nanoparticle
MDR	Multi-drug Resistance
TDD	Target Drug Delivery

Chapter 1

Introduction

1.1 Ovarian Cancer

Cancer is a large group of diseases that can start in almost any organ or tissue of the body where abnormal cells grow out of control and form tumors. Ovarian cancer is one of the cancerous tumors that is the eighth most common gynecologic malignancies in women with high morbidity rates (Sung et al. 2023). It begins in ovaries, which are a pair of the female reproductive glands that make eggs and female hormones. The cells in the ovaries start to grow abnormally and uncontrollably, forming a tumor that spreads to nearby tissues or other parts of the body. There are different kinds of ovarian cancer depending on the type of cells it affects. The most common type is epithelial ovarian cancer (90% of cases) that starts on the outer surface of the ovarian cells. The two related types of epithelial cancer are fallopian tube cancer and primary peritoneal cancer. In fallopian tube cancer, the tumor forms in the tissue lining of the fallopian tube which are a pair of long, slender tubes on each side of the uterus and in primary peritoneal cancer, the tumor forms in tissue lining of the peritoneum that covers the organs in the abdomen (belly). These two epithelial ovarian cancers have the same treatment. Some other rarer types of ovarian cancer are malignant germ cell tumors (around 4% of cases) that arise in the oocyte and stromal tumors that arise from supporting tissues within the ovary (Sung et al. 2023). The gynecologic malignancies have the most significant death rate. According to the American Cancer Society survey report, 15,000 women lose their lives to ovarian cancer with a lifetime risk of 1.4% for ovarian cancer, which is significantly higher than the risk of endometrial or cervical cancer. It is estimated that 1,805 people were diagnosed with ovarian cancer and serous carcinomas of the fallopian tube in 2024 (Smolarz et al. 2025). The symptoms of ovarian cancer are often ambiguous. Most commonly it is

mistaken for common digestive or urinary problems. The expected symptoms are pelvic pain, abdominal pain, loss of appetite, constipation, frequent urination, menstrual changes or fatigue If the symptoms happen frequently more than 12 times a month or if persistent for several weeks then one must visit the hospital urgently. Then the healthcare provider will carry out several tests or scans such as a physical examination to check lumps in abdomen, blood test to check common tumor marker (CA125), pelvic ultrasound to create ovaries and uterus image, CT scan to check for cancer spread, PET scan that highlights abnormal tissues in body etc and many more.

The treatment for ovarian cancer uses a common staging system known as FIGO (International Federation of Gynaecology and Obstetrics) system which records the extent by whether it remains in the ovary, has spread to other pelvic structures or has spread into the lining of the abdomen with or without fluid (ascites). Ovarian cancer usually spreads by invading nearby pelvic organs, releasing malignant cells into the abdominal cavity and spreading through lymphatic vessels. A distinctive feature is the implantation of tumor cells on fatty tissues and surfaces within the abdomen, often causing fluid buildup. In advanced stages, the disease may spread through the bloodstream to distant organs such as the lungs, liver and bones, making early detection and treatment difficult. The types of treatment are: surgery, chemotherapy, radiation therapy or palliative care. Surgery is used to determine the extent of disease and to remove tumor as much as possible. Chemotherapy uses anti-cancer drugs to destroy cancer cells. Most women will have chemotherapy after surgery (adjuvant chemotherapy) to destroy any remaining cancer cells. Some women will have chemotherapy before surgery (neoadjuvant chemotherapy) with the aim to shrink tumours and make them easier to remove and radiation therapy can be used to treat the pelvis or other sites of cancer that have spread. It may be used on its own or after chemotherapy. The prognosis (expected outcome) depends on the type and stage of cancer as well as their age and general health at

the time of diagnosis. The survival rates will vary between individuals and may depend on their response to treatment (Sung et al. 2023; Smolarz et al. 2025).

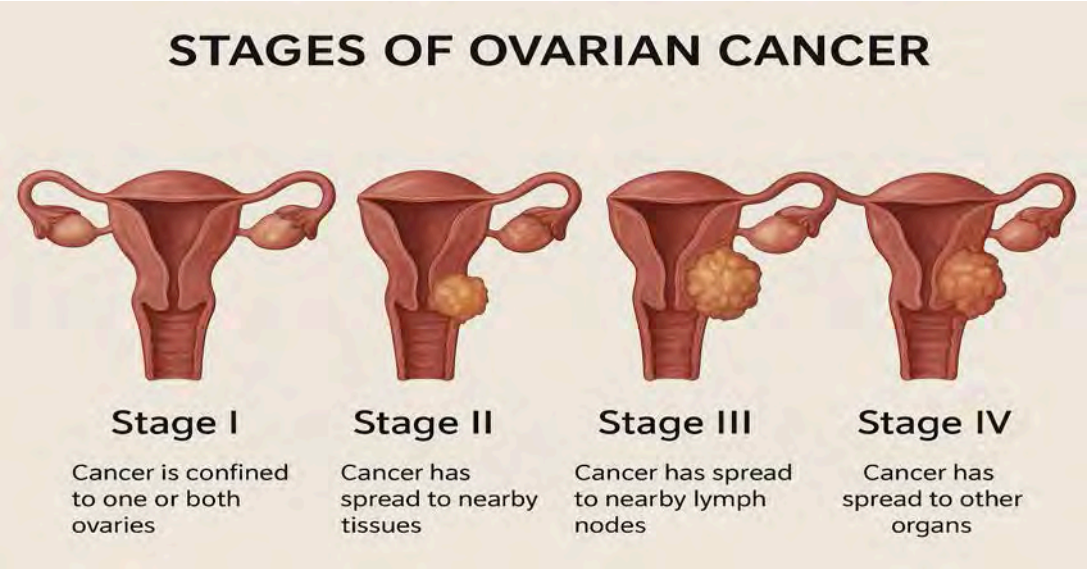

Figure 1:Stages of ovarian Cancer (Adapted from Smith et al., 2020)

1.2 Aim of the study

The primary aim of this study is to investigate and highlight the potential of nanoparticle-based targeted drug delivery systems in the treatment of ovarian cancer using conventional chemotherapeutic agents. The study seeks to explore how nanoparticles can specifically target cancer cells thereby maximising therapeutic efficacy. The study will also tell us how nanoparticles can enhance anticancer drugs stability, bioavailability, pharmacokinetics, solubility, sustained release and patience compliance. It will also investigate how targeted drug delivery such as cisplatin, paclitaxel and doxorubicin will minimize the adverse effects of chemotherapy such as hair loss, less drug exposure to non-cancerous cells, kidney damage etc. The ultimate aim is to analyze whether nanoparticle-mediated delivery can prevent the drug resistance in ovarian cancer such as efflux pumps and cellular detoxification pathway.

1.3 Rational of the study

The rationale of this study comes from the significant challenges that are associated with conventional chemotherapy treatment for ovarian cancer which includes poor solubility, poor pharmacokinetics and higher risk of drug resistance. The nanoparticle technology strategy uses precise biomarkers for selective targeted drug delivery which is a promising solution to enhance the therapeutic effects of the chemotherapeutic agents. It directly attacks tumor cells without damaging the healthy tissues. The mechanism of permeability and retention effect minimizes adverse effects and increases stability of the chemotherapeutic drugs. This technology also prevents premature degradation of drugs before reaching the tumor cell and reducing the doing frequency for patients. In addition, it can also be used to co- deliver multiple therapeutic agents that increase the treatment success rate. In this review, we will discuss the above points in details and how nanoparticle based targeted drug delivery enhanced the ovarian.

Chapter 2

Methodology

2.1 Type of Study

This review is literature-based, aiming to summarize and discuss the primary studies regarding Nanoparticle-Based Targeted Drug Delivery in Ovarian Cancer Therapy. This study provides systematic overview of the nanoparticle drug delivery systems (DDS) for the treatment of ovarian cancer, and focuses attention on delivering chemotherapeutics including Doxorubicin, Paclitaxel as well as Cisplatin (Oyowvi et al., 2025). The aim of the current investigation is to review and evaluate benefits, limitations and potentiality of these NP-based technologies upon ovarian cancer treatment performance toward overcoming problems like its poor bioavailability, systemic toxicity factors and multidrug resistance (MDR) (Li et al., 2024).

2.2 Databases Searched

To guarantee the coverage of the research topic, the search was conducted in a few important academic databases. These databases are sources of access to peer-reviewed journals, clinical trials reports, and preclinical studies of nanoparticle-based drug delivery systems used for ovarian cancer therapy (Li et al., 2024). The following databases were utilized:

PubMed: Due to being one of the most important sources of biomedical literature, search in PubMed was carried out to retrieve studies of clinical trials, drug-delivery systems and cancer-therapies.

ScienceDirect: This resource provides digital content of physician journals dedicated to pharmaceutical sciences, nanomedicine and therapeutic treatments for cancer.

Google Scholar: Google Scholar was used to search a wider spectrum of academic articles, theses, conference papers and patents related to nanoparticle-based therapy in ovarian cancer.

These DBs were selected based on their credibility and the extensive information they provide in the area of oncology, nanomedicine and drug delivery systems.

2.3 Inclusion and Exclusion Criteria

The review was centered on publications covering the period from 2013 to 2023 and highlighting recent progressions made in nanoparticle-mediated drug delivery for ovarian cancer. The studies consisted of preclinical (in vitro and in vivo), clinical trials, and systematic reviews that explored the nanoparticle formulations for ovarian cancer treatment (McFadden et al., 2021). Liposomes, polymeric nanoparticles, micelles, dendrimers and other nanocarriers to be used for chemotherapeutic drugs such as Doxorubicin, Paclitaxel and Cisplatin were evaluated (Satpathy et al., 2019). Moreover, experiments on tumor targeting, bioavailability, toxicity, effectiveness, drug resistance and therapeutic effect were incorporated (Zhai et al., 2018). Non-English studies, cancer types other than ovarian cancer and studies with no data on drug encapsulation, bioavailability or therapeutic efficacy were used as exclusion criteria.

2.4 Data Extraction and Synthesis

Relevant data from the review studies was extracted and trends regarding nanoparticles for ovarian cancer drug delivery systems were analyzed. The study was separated into a structure of nanoparticle analysis (liposomes, polymeric micelles, dendrimers and nanogels), drug loading strategies and encapsulation techniques. Comparison of passive and active drug loading and encapsulation efficiency for Doxorubicin, Paclitaxel, Cisplatin. It has also been reviewed, targeting strategies (in particular, using ligands like folate, antibodies and peptides to enhance tumor selectivity). Clinical and preclinical results such as therapeutic

effectiveness, tumor shrinkage, reversal of drug resistance sensitivity or toxicity reduction in patients were evaluated (Ammar et al., 2025). Statistical methods, namely ANOVA and t-test employed in the studies were also screened to determine whether the NP delivery system is efficient (Bhardwaj et al., 2022). Results were summarized by themes according to the type of nanoparticle, method for drug delivery and targeting strategy (Gralewska et al., 2024).

2.5 Risk of Bias and Quality Analysis

The risk of bias in the included studies was assessed by utilising the CASP (Critical Appraisal Skills Programmed) checklist for biases such as selection, performance, detection and reporting. The methodological quality, patient/sample selection criteria, replication of procedures and measurement of outcomes were carefully examined in the studies. The objective was to have only high-quality, credible data.

2.6 Synthesis of Findings

The results of the review concentrated on three central aspects, such as the efficacy of nanoparticle formulations. Nanoparticle types (e.g., liposomes, micelles) affected drug bioavailability, tumor targeting and therapeutic efficacy were compared. The focusing points of the review included targeting strategies, which deliver a selective drug from folate and antibody conjugation to ovarian cancer cells. Clinically, we evaluated patient survival and tumor shrinkage; both drug resistance therapeutic reversal and side effect reduction were achieved by nanoparticle formulations. Preclinical evidence (animal models) and clinical trials were compared (R. Li et al., 2014). The results were then tabulated and visually formalized in Tables and Figures to facilitate comparisons between different classes of NP-based delivery systems used for therapeutic intervention in OC.

2.7 Review Methodology Limitations

The method of the review is subjected to a number of limitations. The restriction of articles to the English language might have missed relevant studies in other languages. The results may also be influenced by publication bias (ie, positive results more likely to have been published). Finally, the review is based solely on publications indexed in those databases and the possibility that relevant research published elsewhere has been overlooked cannot be ruled out. Furthermore, the analysis has only chosen to examine a 10-year period (2013–2023) and therefore may not represent all historical developments.

Chapter 3

Nanoparticles in Ovarian Cancer Treatment

3.1 Overview of Nanoparticles

Nanoparticles are designed to deliver drugs into the cancer cells with precision without exposing harmful radiation to healthy tissues (Kalimuthu et al., 2023). Antibodies or ligands can be used with nanoparticles to recognize specific receptors responsible for overexpression on ovarian tumor cells while minimizing adverse effects. This technique enhances selective binding to cancer cells. In recent years, advances in nanoparticle-based target drug delivery have shown promising approaches in overcoming ovarian cancer. There is a mechanism that is widely used by chemotherapeutic drugs like Doxil(liposomal doxorubicin) known as permeability and retention effect. When the tumor grows in rapid speed, it needs blood vessels to supply nutrients and oxygen. However, the blood vessels formed are very abnormal, leaky and have wide gaps in between cells which allows nanoparticles to take the advantage of the gap to pass through blood vessels and enter tumor cells more easily (permeability). It also develops poor lymphatic drainage which traps the anticancer drugs inside the tumor for a long time (retention). Thus, this duo mechanism helps anticancer drugs directly enter the cancer cells, thereby minimising systemic toxicity, improving therapeutic effectiveness, stability and reducing damage to healthy cells in the body (Rahman & Ali, 2024). There are many chemotherapeutic drugs like paclitaxel, doxorubicin that are almost insoluble in water. However, nanoparticles can encapsulate these hydrophobic drugs, making them easier to dissolve and circulate in the bloodstream. It also acts like a protective shield against degradation enzymes, ensuring more drugs reach the cancer cells. Moreover, it can maintain a steady plasma drug concentration at the tumor site by releasing the drugs slowly over time or in response to tumor specific triggers. Thus, reducing the need for frequent

dosing, increasing adherence to the therapy and lowering side effects. Another widely used approach is co-delivery of multiple agents where more than one drug is induced at the same time that doubles the effectiveness. This approach can be used during the late stages of cancer (e.g., chemo + gene therapy or chemo + immunotherapy). Not only that, but nanoparticles can overcome drug resistance which is the most common problem faced during ovarian cancer treatment. It has a protective carrier that prevents drug from being recognised and pumped out so they have the ability to bypass multi drug resistance where tumor cells pump drugs out using efflux pumps (Singh et al., 2025). In conclusion we can say that nanoparticles enhance drug solubility, protect drugs from premature degradation,improve API bio distribution and pharmacokinetics as well as enable sustained release, reducing the frequency of dosing and improving patient compliance. This targeted drug delivery system improves survival rates and quality of life

3.2 Types of Nanoparticles Used with chemotherapeutic agents

In ovarian cancer research, several types of nanoparticles have been investigated for targeted delivery of doxorubicin. Depending on their composition, the nanocarriers are classified into two groups- organic and inorganic nanocarriers. The majority are organic nanocarriers such as micelles, liposomes and polymeric nanoparticles that are biodegradable whereas mesoporous silica nanoparticles and metals like gold, iron oxide, magnetic iron etc are inorganic nanocarriers. The different types of nanoparticles used with chemotherapeutic agents like dosorubicin, paclitaxel cisplatin are further discussed below (Mahajan et al., 2020).

3.3 Liposomes (LPs) - Organic nanocarriers

Liposomes are vesicles that have a varying size of 30 to 500nm. Since liposomes are composed of lipid and phospholipid molecules they have both hydrophilic head portion and a hydrophobic tail portion which makes them suitable to transport both hydrophobic and hydrophilic drugs. Liposomes for ovarian cancer are used in many ways for maximum efficacy such as liposomes resembles the structure of cell membrane which makes it highly biocompatible and biodegradable so chemotherapeutic drugs can be physically encapsulated inside the liposomes that maximize the dosage for medication delivery.This strategy can also be used to insert ligands or other functional groups to the phospholipid bilayer's surface either chemically or physically which increases tissue specificity,increases stability and lowers toxicity like cardiotoxicity. Polyethylene glycol (PEG) is a biocompatible and inert polymer that is added to the liposomes surface to prevent the normal reticuloendothelial system (RES) macrophages from eliminating drugs and pathogens from the body (Mahajan et al., 2020). As a result, chemotherapeutic drugs can stay in the blood circulation for a longer period of time to exert their therapeutic effect. For doxorubicin, LPs (Doxil®/ Caelyx®) were the first nanocarriers approved by FDA for systemic delivery as chemotherapeutic DOX nanodrugs (Singh et al., 2025).

3.4 Polymeric Nanoparticles- organic nanocarriers

Polymeric nanoparticles are colloidal systems that have the shape of either hollow spheres with void space in the middle (nano-capsules) or as solid spheres (nanospheres). It is composed of synthetic polymers like polyvinyl alcohol (PVA), poly (lactic-co-glycolic acid) (PLGA) and natural polymers including chitosan and cellulose. The polymeric shell surrounding the core makes it convenient to encapsulate hydrophobic medications, increasing half-life and providing controlled release (Kalimuthu et al., 2023). Since the manipulation of

physicochemical characteristics of polymers, such as their molecular weight, flexibility, surface charge etc. is easier, it has the ability to produce effective biodegradability, superior drug loading at targeted tumor locations with lower cytotoxicity and increased efficacy (Rahman & Ali, 2024). The polymeric nanoparticles can also be used to covalently conjugate doxorubicin where drugs are attached to polymer backbone via labile bonds to provide good stability and easy conjugation. Thus, polymeric nanoparticles can be used for the treatment of early as well as late phases of ovarian cancer.

3.5 Metallic nanoparticles- inorganic nanocarriers

Metallic nanoparticles are the most prevalent and the most studied type of doxorubicin delivery systems because of their easy surface functionalization compared to other types of nanoparticles. The typical metals used for the synthesis of nanoparticles include gold, silver and iron. Among all of the metallic nanoparticles, covalent conjugation of doxorubicin to gold nanoparticles gained major attention. The gold nanoparticles were attached with PEG to increase its solubility then it was stabilized using thiolate methoxy polyethylene glycol (MPEG-SH) and methyl thioglycolate (MTG) to form hydrazone bond. The successful covalent conjugation of DOX to gold nanoparticles resulted in controlled drug release, particularly in the acidic tumor microenvironment (Rahman & Ali, 2024). Another frequently used metallic nanoparticle is magnetic iron oxide nanoparticles (MIONs) that is popular because of its superparamagnetic properties. The MIONs is formed in a single step synthesis process by using thioether end-functionalized polymer ligand dodecanethiol–polymethacrylic acid (DDT–PMAA). Then it was reacted with iron precursor to form ultra-small magnetic iron oxide nanoparticles which was again covalently conjugated with DOX via the formation of amide bond between carboxyl groups and amino acids (Kalimuthu et al., 2023). It is widely used to monitor real-time drug delivery using magnetic resonance imaging (MRI). It

is often coated with biomolecules to prevent rapid agglomeration and loss of magnetism. Despite all the benefits of using this nanoparticle it has few drawbacks as well such as the process is costly, toxicity response to inorganic components and longevity of elimination from the body

In conclusion, these widely studied nanoparticle carriers are used for the treatment of ovarian cancer. These nanoparticles are tiny in size which facilitates efficient cellular uptake and tumor accumulation by enhancing permeability and retention (EPR) effect. Thus, the targeted drug delivery is enhanced, reducing off target effects and maximizing therapeutic effectiveness

Nanocarrier	Loading Efficiency	Advantages	Disadvantages
Liposomes	Moderate to high loading	High biocompatibility	Rapid reticuloendothelial system (RES) clearance
Micelles	High for hydrophobic drugs	Small size for deep tissue penetration	Potential premature drug release
Nanogels	Moderate loading	Excellent for stimuli-triggered release	Lower loading for very hydrophobic drugs
Dendrimers	Very high loading	High functionalization versatility	Complex synthesis and high cost
Nanographene Oxide (NGO)	Extremely high loading	Ease of surface modification for targeting	Potential toxicity and poor aqueous dispersibility
Carbon Nanotubes (CNTs)	High loading	Exceptional mechanical and thermal stability	Potential toxicity and poor water solubility
Mesoporous Silica Nanoparticles (MSNs)	Very high loading	High surface area and tunability	Possibility of long-term accumulation in organs
Cell Membrane-Coated Nanoparticles	Depending on the core nanoparticle	Enhanced targeting and reduced immunogenicity	More complex and costly to fabricate

Table 1 :Comparison of various nanocarrier systems (Xia & King, 2025).

Chapter 4

Limitations of conventional chemotherapy highlight the need for targeted Drug Delivery in ovarian cancer

Ovarian cancer is one of the most fatal gynecologic malignancies worldwide with an approximate 313,959 new instance and above 207,000 demise reported in 2020 (World Cancer Research Fund, 2023). The worldwide lifetime standardized prevalence rate is around 6.6 per 100,000 women and impermanence remains inflated with a rate of around 4.2 per 100,000. Regardless of having advancement in therapeutic as well as diagnosis systems, approximately 80% of cases are detected in advanced stages (stage III-IV) resulting in less survival outcome. In Bangladesh ovarian carcinoma reports for almost 5% of all female carcinomas resulting in around 2,231deaths in 2020 with an age adjusted death rate 3.34 per 100,000 women (World Life Expectancy, 2024). In general, the worldwide incidence of ovarian cancer has increased by more than 100% between 1990 and 2019 mainly owing to population aging as well as lifestyle factors although death rates remain relatively stable.

The conventional treatment of ovarian cancer commonly involves surgery followed by chemotherapy. The goal is to remove the targeted cancer cell as much as possible then chemotherapy is given to remove the remaining cells. At first, the treatment starts with the surgery of removal of tumors from the fallopian tubes, ovaries, uterus as well as any visible tumor present in the abdomen is also removed. This type of surgery is termed as debulking surgery. Once the surgery is done most patients are given chemotherapy of platinum-based drugs such as carboplatin or cisplatin combined with paclitaxel, beside this doxorubicin is also used (Mahajan et al., 2020). Doxorubicin is an anthracycline agent which can be used as both in combination or as a single agent in the treatment of ovarian cancer to achieve maximal cell killing. Chemotherapy treatment uses powerful drugs to eliminate vigorous

dividing cells. It works by interfering with the cell cycle either by damaging the DNA of cancer cells or preventing them from replicating rapidly (Kalimuthu et al., 2023). However, if conventional chemotherapeutic drugs (paclitaxel, cisplatin, doxorubicin) are used alone without nanoparticle-based targeted delivery for ovarian cancer, the treatment can still kill cancer cells but less effectively. Several complications arise in this treatment strategy. The anticancer drug can kill both cancerous and healthy cells in hair follicles, bone marrow or GIT due to lack of specificity. It cannot distinguish between tumor cells and normal cells thus, maximising systemic toxicity that lead to severe side effects like immune suppression, anemia, kidney damage, hair loss, nerve damage etc. Moreover, chemotherapeutic drugs used alone tend to have poor pharmacokinetic properties because some of them are either degraded by enzymes or rapidly excreted by kidneys before reaching the target tumor cells (Rahman & Ali, 2024). As a result, large doses of drugs are required to achieve the desired therapeutic level, thus increasing dosing frequency and reducing patient compliance. With conventional therapy,cancer cells are more likely to develop drug resistance. The resistant cell populations can survive and expand, eventually leading to treatment failure so it has a higher risk of recurrence in patients within the first two years of a repeat diagnosis and the survival rate is only roughly three years. This is why nanoparticle targeted drug delivery systems are used to enhance both the efficacy and safety of ovarian cancer therapy (Kalimuthu et al., 2023).

Pathogenesis and Development of Ovarian Cancer

Ovarian cancer is a type of heterogeneous disease with several pathogenic expressions. The preponderance of ovarian cancer is epithelial ovarian carcinomas which are divided into multiple histologic sub types among these high-grade serous carcinomas is most familiar and hostile. Previously it was believed that ovarian cancer arises from ovarian surface epithelium but recent molecular as well as histologic studies suggest that high grade serous carcinoma arises from the secretory epithelial cell of the distal fallopian tube specifically from the

fimbrial end. Different types of factors and theories are associated with ovarian cancer. Earlier ovarian carcinoma was considered to be developed from the epithelium cell surface of the ovary. At the time of every ovulation cycle these cells go through minor physical traumas which get repaired rapidly. In the course of women's reproductive cycle these cells continuously undergo damage and cell repair which ultimately leads to DNA damage of the epithelial cells. These damaged cells are more easily influenced by structural changes as well as may pleat inward into the inner tissue of the ovary known as cortical stroma. These pleated cells become confined and devise cyst like structures referred as cortical inclusion cyst. Within the ovary these cells are subjected to ovarian hormones which assist cell multiplication and replication. Rapid stimulation of abnormal cell division within the cyst leads to evolution of cancerous cells which ultimately turns into ovarian carcinoma.

4.1 Genetic Factors

The genetic mutation of BRCA1 and BRCA2 genes are vigorously related with ovarian cancer. These genes play a vital role in cell growth as they repair damaged DNA. Deletion or insertion in these genes disrupts the coding sequence resulting in formation of incomplete genes as a result of the cell growth is hampered. This causes irregular cell growth leading to formation of ovarian cancer.

4.2 Fallopian Tube Theory

Fallopian tubes serve as a site of origin for several high-grade ovarian cancers. Previously it was believed that ovarian cancer could only develop in ovaries but later with recent studies it was found that fallopian tubes epithelium serves as a site of origin of high grade serous ovarian carcinoma. The fimbrial end of these tubes act as a key site where preliminary cancer alteration takes place. These alterations form lesions which are termed as serous tubal intraepithelial carcinoma (STIC); these lesions further turn into progressive cancer over time.

4.3 Two pathways theory

The two pathways model of ovarian cancer introduces two different molecular and pathological sub types of ovarian cancer (Budiana et al., 2019).

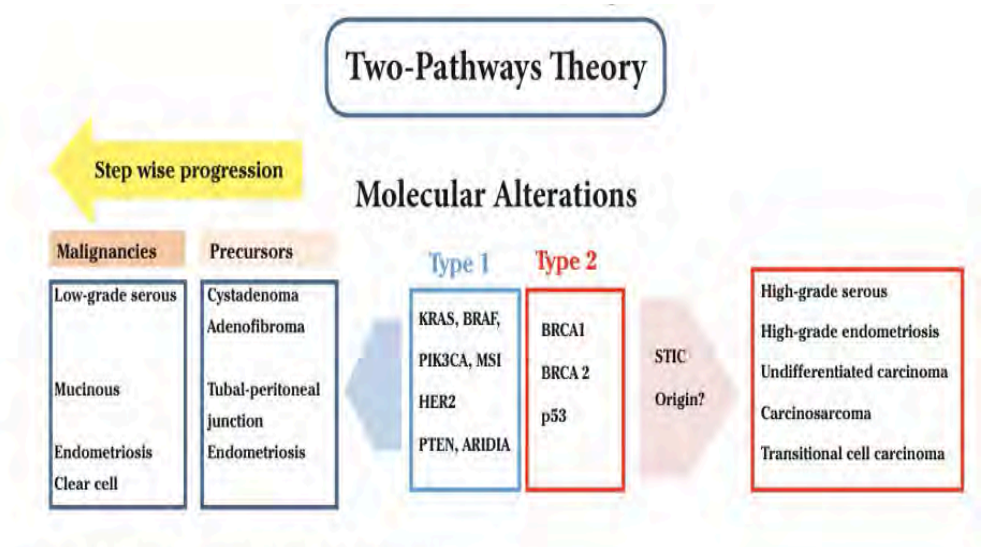

Figure 2: *The two-pathways theory of ovarian cancer.* (Budiana et al., 2019, p. 49)

Type I ovarian cancer

The type I ovarian cancer generates from the ovarian surface epithelium or from the inclusion cyst. In general, the tumors are low grade serous, low grade endometrioid, clear cell as well as mucinous carcinomas. This type of cancer is associated with specific genetic mutations in KRAS and BRAF genes which come up with gradual development. This type of cancer is stable at an early stage and shows more favorable prognosis. Their gradual development provides a way for early detection and intervention of the disease.

Type II ovarian cancer

Type II ovarian cancers are genetically unstable, rapidly multiplying and are aggressive in nature. They are high graded carcinoma originated from the lesions in the fallopian tube

which are called serous tubal intraepithelial carcinoma (STIC). The type II cancers are often associated with the genetic mutations in TP53 and also involve defects in BRCA1 or BRCA2 genes, resulting in compromised DNA repair through the homologous recombination pathway. These molecular alterations of the gene result in fast disease progression as well as genomic disability. The type II cancer is present at an advanced stage

Chapter 5

Drugs in the treatment of ovarian cancer

Cisplatin

Cisplatin is a potent and effective platinum based anticancer agent that is used in the treatment of ovarian cancer. This chemotherapeutic agent is a complex molecule with a planar structure. It contains two chlorine atoms as well as two ammonia atoms which are connected by cis arrangement with the platinum atom.

5.1 Mechanism of drug action Cisplatin

Cisplatin, a platinum-based compound exerts its mechanism of action by expressing its cytotoxic effects into the genomic DNA. After cellular intake the cisplatin goes through aquation in this process the chloride atoms get replaced with water molecules and the reactive platinum species gets bound to the guanine of the purine bases. This result in formation of intrastand DNA crosslinks that damage the DNA replication and transcription resulting in cellular apoptosis and ultimately the cancer cell dies (Jain et al. 2017).

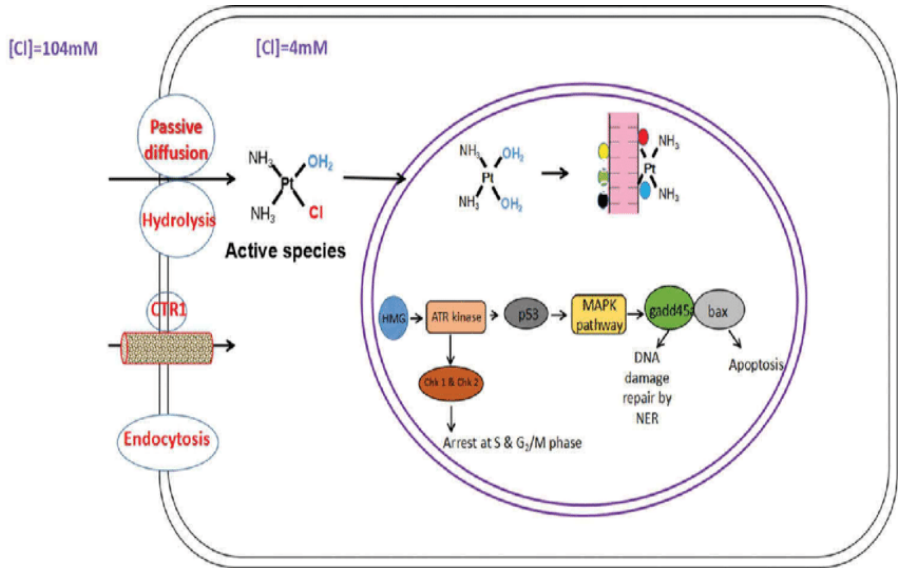

Figure 3: Mechanism action of cisplatin in ovarian cancer (Jain,A., et al.,2017).

5.2 Dosage of administration of Cisplatin

Cisplatin is administered intravenously through a saline solution. In every 3 weeks it is given at 60-75 mg/m² in combination regimens. Intraperitoneal cisplatin is given at 100 mg/m² on day 2 of a 3-week cycle, which is frequently combined with intravenous paclitaxel (Jain et al., 2017). On the basis of renal function, hematologic parameters, and toxicity profiles the dosage of the drug is adjusted.

5.3 Limitation of Cisplatin

Even with having a large range of anticancer activity of cisplatin which makes it appropriate for the treatment of ovarian cancer it has several disadvantages this include nephrotoxicity, neurotoxicity, ototoxicity, gastro toxicity, cardio toxicity and hepatotoxicity. These side effects lower the grade of patient life span forcing to lower the dosage of drug or further discontinuation of the drug reduce the effects of the therapy. Beside these the apoptosis of cancer cells fail to take place due to the resistance to cytotoxic drugs. This resistance can be natural or can be obtained after drug exposure. In ovarian carcinoma cisplatin resistance comes light through complicated complex mechanisms. Another limitation of cisplatin is changes in cellular transport. In this process two mechanisms are involved. One way by which ovarian cancer cells resist cisplatin is by altering the movement of drugs in and out of the cell. Generally cisplatin enters the cell by passive diffusion and two transporter proteins are involved in this process namely CTR1 and CTR2 this also controls the copper balance (Jain et al., 2017). In resistant cells the CTR1 level rises and CTR2 level decreases this leads to reduction in cellular uptake of cisplatin. The higher CTR1 levels are related with better survival at the same time lesser CTR2 levels enhance cisplatin retort forming their ratio a potential biomarker. Another mechanism that is involved is rising in drug export. The two proteins ATP7A, ATP7B respectively remove copper from the cell and also remove the

cisplatin. The resistant cell generally shows larger levels of these protein transporters leading to reduction in drug accumulation as well as lowering treatment effectiveness.

5.4 Strategies to Improve the Effectiveness of Cisplatin in Ovarian Cancer

Due to the side effects and resistance of cisplatin several analogues have been evolved. Carboplatin, a 2nd generation drug similarly works like cisplatin but has less toxicity thus has less effectiveness. Oxaliplatin a 3rd generation drug also exerts its effect by DNA binding but has less toxicity but mainly used in colon and gastric cancer but shows promising results in ovarian cancer. Another effective way is the use of combination therapy. The most commonly used drugs are Cisplatin or Carboplatin with Paclitaxel, a taxane that maintains the microtubules, blocks the cell division and thus resulting in cell apoptosis. This regimen significantly improves the surviving rate. Another taxane docetaxel can also be used which performs in the same manner like paclitaxel but it is slightly stronger when combined with cisplatin it also performs effectively increasing the survival rate. To further evaluate the therapeutic potential and clinical efficacy of chemotherapeutic agents. We have conducted a clinical trial of liposomal doxorubicin in the management of ovarian cancer, involving patients with progressive disease following prior platinum and taxane-based chemotherapy. This study aimed to assess treatment response, survival outcomes and toxicity profiles associated with liposomal doxorubicin in this patient population. The following section summarizes the key patient characteristics, treatment regimen, clinical responses, and safety data observed during the study.

Doxorubicin

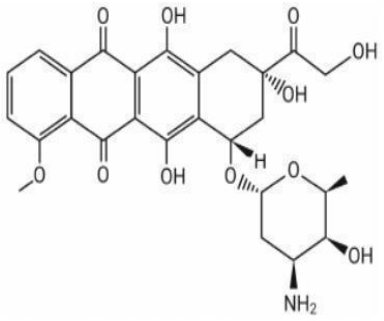

Figure 4: Molecular Structure of Doxorubicin (Smith et al., 2019).

5.5 Physicochemical Properties

Doxorubicin hydrochloride is a red-orange crystalline powder that is amphiphilic, meaning it has both hydrophilic and hydrophobic regions which enables it to interact with various cellular components (Cancer Research UK, 2023). It is freely soluble in water but relatively insoluble in nonpolar solvents. The molecule is chemically unstable in alkaline conditions and highly sensitive to light and oxidation. Its molecular weight is 543.52 g/mol and it possesses a pKa of approximately 8.2, reflecting its weakly basic nature. However, one of the major drawbacks of doxorubicin is its dose-dependent cardiotoxicity, primarily caused by the generation of free radicals in cardiac tissue, which lacks sufficient antioxidant enzymes like catalase (Wang et al., 2020). Other toxicities include myelosuppression, alopecia, mucositis, and hepatotoxicity.

5.6 Pharmacokinetics

Doxorubicin follows a triphasic plasma concentration-time profile, consisting of rapid distribution, intermediate elimination and a slow terminal phase. In absorption, the oral

absorption is negligible thus, parenteral administration is preferred (Cancer Research UK, 2023). In distribution, the drug exhibits a large volume of distribution (20–30 L/kg), indicating extensive tissue uptake. It binds strongly (approximately 75%) to plasma proteins and lipoproteins (Kapoor et al., 2020). Then in the liver it gets metabolized primarily by carbonyl reductases into doxorubicinol, a major and active metabolite that retains cytotoxic activity but contributes to cumulative cardiotoxicity. Finally, the drug and its metabolites are excreted mainly via the biliary system into feces (about 40–50%), while approximately 5–12% is excreted in urine. The terminal half-life ranges from 20 to 48 hours (NCI, 2022).

5.7 Pharmacodynamics

Pharmacodynamically, doxorubicin's cytotoxic effects are both concentration- and time-dependent (Cancer Center, 2023). Its therapeutic efficacy correlates with the area under the plasma concentration-time curve (AUC) and tissue exposure. The drug interferes with DNA replication, transcription, and cell division, ultimately triggering apoptosis in rapidly dividing tumor cells. Moreover, doxorubicin induces immunogenic cell death (ICD), leading to the release of tumor antigens and promoting an anti-tumor immune response — an emerging aspect of its pharmacological profile (Nature, 2020). In ovarian cancer therapy, the combination of doxorubicin's multifaceted mechanisms, along with advances in nanoparticle-based delivery systems, has enhanced its therapeutic index by improving tumor targeting, prolonging circulation time, and minimizing systemic toxicity (MDPI, 2023).

5.8 Doxorubicin Mechanism of Action

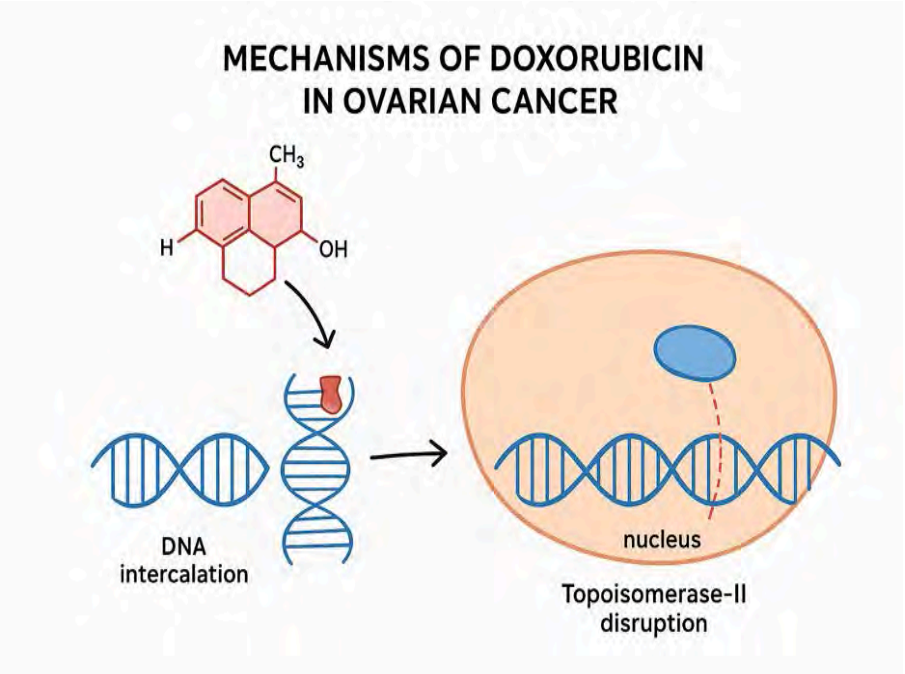

Figure 5: Mechanism of Doxorubicin (adapted from Carvalho et al., 2024).

Doxorubicin or Adriamycin is an antibiotic and a powerful chemotherapy drug that has been continuously used to treat a wide range of cancer since the 1960s. (BreastCancer.org, 2023). It belongs to the anthracycline class of drugs and is named as red devil because of the way it works. It can kill cancer cells at any point in their life cycle as it is a cell cycle non-specific drug. There are several mechanisms of doxorubicin to induce its cytotoxic effects. Firstly, it intercalates between DNA or RNA base pairs which blocks the progression of DNA and RNA polymerases. Thus, it inhibits DNA and RNA synthesis, creating nonfunctional DNA. Secondly, doxorubicin has the ability to bind and inhibit Topoisomerase-ll enzymes after double strand DNA has been cut. This prevents re-ligation of DNA, causing irreversible double stranded DNA breakage and induces apoptosis (NCI, 2022). Doxorubicin interchalation introduces torsional stress into the polynucleotide structure that destabilises nucleosome structure, leading to nucleosomes being eliminated and replaced. It can also generate free radicals. Doxorubicin can generate reactive oxygen species (ROS) such as

superoxide radicals. This causes lipid peroxidation of membranes and oxidation of purines and pyrimidines to make nonfunctional DNA. Thus, cumulative oxidative damage induces apoptosis. The most well-known method for DOX administration is intravenous injection. It has a distribution half-life of only three to five minutes and is quickly absorbed by cells after injection. Plasma proteins act as carriers by binding with DOX and doxorubicinol to distribute them throughout the body tissues (Kapoor et al., 2020). Once inside the cell, DOX is found predominantly in the nucleus rather than the cytoplasm.

5.9 Strategies used in ovarian cancer

There are two main types of strategies used in ovarian cancer which are loading and targeting methods.

5.9.1 Loading methods

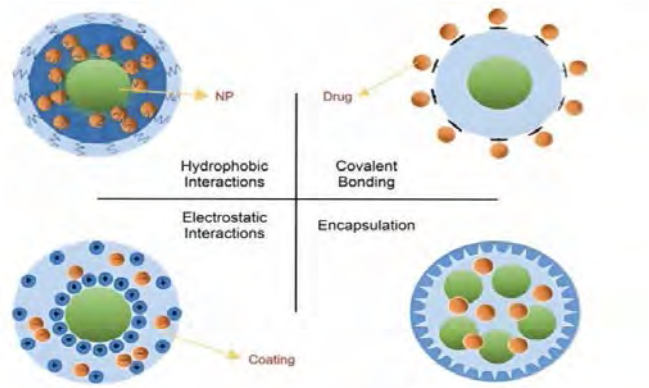

Figure 6: Methods of loading/bonding drugs into nanoparticles (Xia & King, 2025)

Nanoparticles (NPs) are extremely small particles, typically ranging from 1 to 100 nanometers in size. In cancer treatment, drugs can attach to the outer surface or corona of NPs either through covalent bonds or physical adsorption, such as electrostatic interactions (Figure 1). These bonds, however, are often unstable and sensitive to pH changes. Non-covalent attachment is more convenient and flexible, as it requires minimal modification

of the drug's structure or activity (Zhang et al., 2020). It also allows the drug to respond quickly to environmental changes. The controlled release of drugs depends on the type of linkers used. When drugs are covalently linked to nanocarriers, their solubility and effective concentration at the target site significantly increase. Moreover, hydrogen bonds, electrostatic forces, or hydrophobic interactions can trap the drugs within the NP core, protecting them from enzymatic degradation or hydrolysis (Ahmed & Lee, 2021). This not only delays immune clearance but also slows down drug release, effectively extending the drug's half-life inside the body (Kim et al., 2022).

5.9.2 Targeting

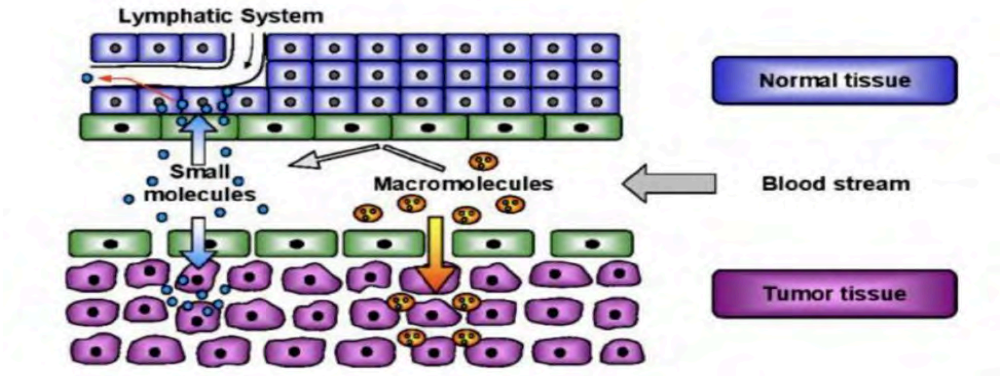

Figure 7: Nanoparticles passive targeting using enhanced penetration retention (Xia & King, 2025).

When nanocarriers are designed at an optimal size, they can take advantage of the enhanced permeability and retention (EPR) effect in tumor tissues to passively deliver drugs (Figure 2). The distinctive features of tumor tissues such as irregular gaps between endothelial cells and poor lymphatic drainage, leads to drug trapping, accumulation and selective uptake through the leaky blood vessels in cancerous regions (Fang et al., 2011). However, relying solely on passive targeting has major limitations. Nanoparticles may accumulate in organs like the liver and spleen due to their porous vasculature and they often fail to penetrate deeply into the

dense and heterogeneous tumor structure (Danhier et al., 2010). For this reason, it became crucial to design systems that combine both passive and active targeting approaches. Active targeting depends on molecular recognition that directs the drug precisely to its intended site. Since tumor cells commonly overexpress receptors linked to growth and survival, nanocarriers can be attached to natural ligands such as monoclonal antibodies, folate, or peptides that specifically bind to these receptors, resulting in targeted accumulation within cancerous tissues (Peer et al., 2007). The nature of the ligand receptor interaction influences how efficiently the drug enters cells. Incorporating targeting molecules often enhances drug uptake through receptor-mediated endocytosis. Many researchers are currently focusing on improving the targeting precision of nanoparticles and advancing targeted therapies based on these mechanisms (Mitchell et al., 2021).

5.10 Clinical Use of Doxorubicin in Ovarian Cancer

Doxorubicin is most commonly used for ovarian cancer especially when they have become metastatic, which means they have spread to other parts of the body (Thigpen et al., 2005). It can be used as first and second line therapy. Patients with epithelial cancer are recommended standard first line therapy that uses a platinum agent (cisplatin or carboplatin) as initial treatment combined with a texane (paclitaxel or docetaxel). However, research has shown that only 40%–60% of patients will achieve complete remission and less than 40% of women with ovarian cancer are ever cured (Hanker et al., 2012). This is when second-line chemotherapy is used for the recurrent ovarian cancer after platinum-based therapy. Here, doxorubicin is used as a pegylated liposomal doxorubicin form in which the drug is encapsulated in liposomes that improves targeting specificity, increases the circulation time from approximately 3 hours to 55 hours and alters its toxicity profile (Gabizon et al., 2003).

PLD is reported to have significantly less cardiac toxicity and myelosuppression than conventional doxorubicin. Research has shown that conventional doxorubicin leads to dose-dependent cardio toxicity by generating free radicals that induces apoptosis and inhibits mitochondrial biogenesis in cardiomyocytes. As a result, ventricular muscles are lost and degraded so ventricles will dilate and cardiac muscles become thin and weak, leading to impaired contraction and inability to pump blood properly. Thus, pegylated liposomal doxorubicin are used to prevent the most serious adverse reaction in cardiomyocytes. These combinations of drugs have been utilized for therapy for many years, ensuring survival benefits and disease control when other agents fail. In addition, cancer cells require topoisomerase-II enzymes for division and growth. If this enzyme is inhibited then cancer cells can no longer replicate and spread into nearby cells or to other parts of the body. Thus, altering its DNA base pairs can break the DNA strands and inhibit both DNA and RNA synthesis (Tacar et al., 2013).

Paclitaxel

5.11 Mechanism of Action

As a taxane-based chemotherapeutic drug, paclitaxel is widely used for the treatment of breast cancer, ovarian cancer and other solid tumors. The action of this drug is that it stabilizes microtubules, a vital part of the cytoskeleton in eukaryotic cells. Microtubules are dynamic structures that affect several cellular processes including mitosis, the intracellular transport or maintenance of cell shape.

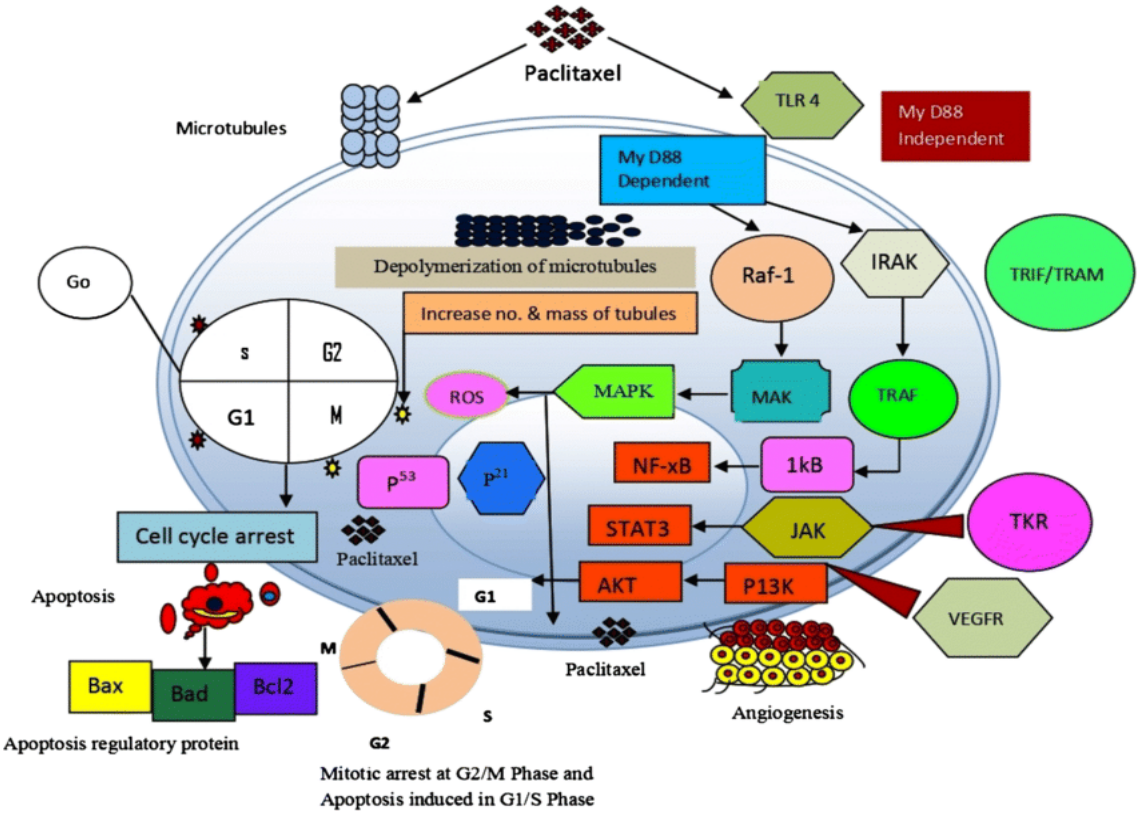

Figure 8: Mechanism of action Paclitaxel in ovarian cancer (Kampan et al., 2015)

The spindle apparatus is composed of microtubules that are generated during mitosis and for which there exists a dynamic instability in normal cells, i.e., they continue to grow followed by shrinking. The Spindle ensures that chromosomes are properly lined up and separated. By

interacting with β-tubulin, a protein that stabilizes microtubule formation, paclitaxel interferes with this dynamic process by preventing depolymerization in the usual end slippage fashion and stabilizing the molecule in its polymerized estado. The consequence of this stabilization is the arrest of mitosis in the M-phase, which prevents proper spindle assembly during mitosis.

Cells that become mired in mitosis do not divide and will eventually die of a process called apoptosis, or programmed cell death. This is particularly effective at cancer cells, which divide rapidly. Paclitaxel is useful against tumors with extensive cell division (including ovarian cancer) because it binds to the proteins that normally help cells divide.Paclitaxel is a very effective anticancer drug, but like most drugs it has some limitations, particularly when administered in its free (drug) form as we will discuss in the subsequent sections (Kampan et al., 2015).

5.12 Limitations of free paclitaxel

Although paclitaxel is an effective chemotherapeutic medication, its clinical use is restricted due to a number of significant challenges, including its inability to dissolve in water, its systemic toxicity, and its resistance to other drugs (Kumar et al., 2010).

5.13 Solubility Issues

Free Paclitaxel's poor water solubility is one of the primary obstacles to its intravenous administration, as it significantly reduces its bioavailability. Dissolution in aqueous media is impeded by the highly hydrophobic nature of paclitaxel. In order to resolve this issue, paclitaxel is typically combined with Cremophor EL, a polyethoxylated castor oil that functions as a solubilizant. However, the use of Cremophor EL comes with many disadvantages. The hypersensitivity reactions, including anaphylaxis, nausea, vomiting and cardiovascular effects that Cremophor EL is known to cause represent inconvenient aspects

related to the treatment schedules. These side effects can result in dose reduction or discontinuation of treatment in some patients (Saman et al., 2023).

5.14 Systemic Toxicity

Free Paclitaxel is well known to be associated with systemic toxicity which can often be attributed to a non-specific distribution of the drug within the body. As Paclitaxel does not seek any special binding site than cancerous cell, it also acts on other healthy tissues giving rise to highly diverse side effects:

Bone marrow suppression: Paclitaxel commonly causes a decrease in the number of neutrophils (a type of white blood cell), causing increased risk for infections, and thrombocytopenia resulting in increased risk of bleeding and anemia.Peripheral Neuropathy–Paclitaxel can cause damage to nerves especially in the hands and feet causing tingling, numbness, pain. This can have a great effect on the patients' QoL.

GI: Patients may experience nausea, vomiting, diarrhea and mouth sores from paclitaxel therapy that could affect their ability to eat and hydrate.

Alopecia: Hair cells are one of the rapidly dividing cells in the body and a drug like Paclitaxel targets these cancer cells but can destroy non-cancerous hair as well, hence leading to hair loss. This is a sad side effect.

These systemic toxicities are due to the non-selective distribution of paclitaxel and have the potential for toxicity against both normal and tumor cell elements, which results in nonspecific side effects (Dunton, 2002).

5.15 Drug Resistance

The onset of drug resistance is a further major challenge to the efficacy of Paclitaxel in ovarian cancer therapeutic intervention. The upregulation of the membrane transporter protein P-glycoprotein (P-gp), responsible for the active transport out of the cells of chemotherapy agents, is a frequent mechanism to develop MDR in ovarian cancer. The

intracellular concentration of paclitaxel is reduced by this efflux pump, thus rendering it ineffective in therapy (McFadden et al., 2021b).

Other resistance mechanisms include mutations in β-tubulin that lessen the effect of binding Paclitaxel and modifications of the microtubule dynamics. In addition, the induction of pro-survival signaling in cancer cells can allow them to evade apoptosis after Paclitaxel treatment. These mechanisms mediate Paclitaxel resistance in recurrent ovarian cancer and highlight the importance of improved drug delivery systems.

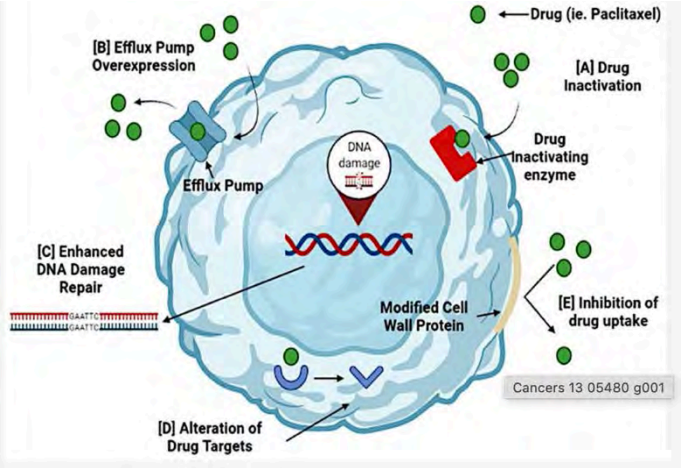

Figure 9: Mechanisms of drug resistance in ovarian cancer (McFadden et al., 2021b).

5.16 Nanoparticle-Based Delivery of Paclitaxel

Various nanoparticle-based delivery platforms were developed to circumvent the limitations of free Paclitaxel. These vehicles not only minimize systemic toxicity, but also increase the bioavailability, solubility and site-specific delivery of Paclitaxel. Solubility of Paclitaxel can also be improved by nanoparticle formulation designed to encapsulate and target delivery of the drug directly to the tumor. This way the drug will be at a higher concentration at the specific area but with lower side effects (Levit et al., 2020).

5.17 Polymeric Micelles (Genexol-PM)

Polymeric micelles are self-assembly nanoparticles comprising amphiphilic block copolymers. These micelles consist of a hydrophobic core for holding the hydrophobic drug (e.g., Paclitaxel) and a hydrophilic shell, which prevents their immediate disspation in aqueous solution. One of these formulations is Genexol-PM which contains poly (lactic acid)(PLA)-polyethylene glycol (PEG) copolymer.polyvinyl alcohol film for the preparation of nanoparticles was developed.

Paclitaxel is protected by PLA core via encapsulation, which increases the drug's solubility, as well as stability of the system and limiting clearance by the early immune system from PEG external surface. The bioavailability, tumor targeting and therapeutic efficacy of paclitaxel have been much improved by the micelle formulation (Genexol-PM) in preclinical studies as well as clinical trials. Furthermore, it has been shown to reduce the hypersensitivity reactions caused by Cremophor EL and so an improved formulation in terms of safety over free Paclitaxel (Gong et al., 2012).

5.18 Targeting Strategies

Nanoparticle delivery systems may be conjugated with targeting ligands ensuring drug is only delivered to ovarian cancer cells enhancing therapeutic efficacy and reducing off-target effects. These targeting strategies depend on the unique ovarian cancer cell biomarkers and facilitate specific delivery, leading to improvements in therapeutic effect (Bazak et al., 2014).

5.19 Folate Receptor Targeting

The overexpression of the folate receptor α (FR-α) on many ovarian cancer cells makes it an ideal target of folate-conjugated nanoparticles. Folate-coated nanoparticles would target only

ovarian cancer cells that have this receptor expression. In addition to tumor targeting improvement, the bioavailability of Paclitaxel that is localized at the site of a tumor increases with this method and which, for that reason, said drug will have stronger efficacy and less adverse effect on normal tissues (Zhu et al., 2015).

5.20 Antibody-Targeted Delivery

Monoclonal antibodies (mAbs) against tumor associated antigens such as HER2, EGFR and VEGF can be used to surface functionalized nanoparticles. By targeting overexpressed receptors on the ovarian cancer cell-surface, they ensure that the drug is taken directly to the tumor site. This method enhances treatment selectivity, reduces off-target effects, and increases tumor drug accumulation.

5.21 Peptide Based Target

Peptides that selectively bind to certain receptors or proteins on ovarian cancer cells are conjugated with nanoparticles. This peptide targeting strategy delivers Paclitaxel into the tumor with accuracy and efficiency, reducing collateral damage to normal tissues.

5.22 Benefits of the Nanoparticle-Mediated Paclitaxel Delivery

Drug delivery for Paclitaxel by nanoparticles offers various advantages over naked drug, such as improving its solubility, bioavailability and tumor targeting effects and reducing systemic toxicities (Desai, 2013; Bhardwaj & Burgess, 2013).

Increased Solubility and Bioavailability: Polymeric micelles and liposomes are examples of nanoparticles that significantly improve the solubilization of paclitaxel in an aqueous environment. This, in turn, increases the drug's bioavailability, even in cases of drug-resistant ovarian cancer (Chen, Larson, & Torchilin, 2012; Bhardwaj & Burgess, 2013).

Minimization of Systemic Toxicity: Encapsulating Paclitaxel into nanoparticles might reduce the risks of systemic toxicity and improve patient tolerance. This would be achieved by sparing the Cremophor EL, the main agent responsible for the toxicity of the drug, which includes hypersensitivity and anaphylactic responses. In addition, as cancer cells are selectively targeted this ensures that the Paclitaxel side effects induced to healthy tissues do not occur (Desai, 2013).

5.23 In Vivo Enhanced targeting of the tumor

Nanoparticles can be modified to specifically attach to ovarian cancer cells by attaching targeting ligands such as antibodies or folate. Such targeting ensures that the more Paclitaxel is included in the tumor, exerting therapeutic effects with lower toxic responses.

Overcoming Drug Resistance: Nanoparticles can help in overcoming resistance in ovarian cancer cells by enhancing the intracellular drug levels and circumventing the resistance pathways, such as P-gp-mediated efflux.

❖ Pre-clinical Studies/Clinical Cases

❖ Preclinical Studies

Nanoparticle mediated delivery of Paclitaxel has provided proven efficacy in preclinical models of ovarian cancer. For example, the polymeric micelle-encapsulated paclitaxel (Genexol-PM) has shown a lower systemic toxicity and tumor inhibition in xenograft models of ovarian cancer (Kim et al., 2004; Lee et al., 2007). These targeted micelles increased the therapeutic effects of Paclitaxel by selectively acting on ovarian cancer cells and improving bioavailability.

Similarly, liposomal Paclitaxel has also exhibited enhanced drug delivery and reduced toxicity in preclinical models of ovarian cancer including neurotoxicity and cardiotoxicity that are common with free Paclitaxel.

5.24 Clinical Examples

In phase I/II clinical dose-escalation studies, probable antitumor efficacies and less hypersensitivity reactions were observed when compared with free Paclitaxel. Doxil, a formulation containing paclitaxel-based liposome, has been approved by the FDA against a range of malignant diseases including ovarian cancer. In the clinic, doxil is often utilised in ovarian cancer as it lowers toxicity significantly, especially neurotoxicity.

Chapter 6

Clinical trial

To further evaluate the therapeutic potential and clinical efficacy of chemotherapeutic agents. We have conducted a clinical trial of liposomal doxorubicin in the management of ovarian cancer, involving patients with progressive disease following prior platinum and taxane-based chemotherapy. This study aimed to assess treatment response, survival outcomes and toxicity profiles associated with liposomal doxorubicin in this patient population. The following section summarizes the key patient characteristics, treatment regimen, clinical responses, and safety data observed during the study.

6.1 Patient Characteristics

Characteristics	**Details**
Total patients	35
Institutions	2 (22 in one, 13 in the other)
Disease status	Progressive disease after platinum (cisplatin/carboplatin) and paclitaxel or at least one regimen with each

Table 2: Patients Characteristics (Muggia et al., 1997).

6.2 Treatment Regimen

Parameter	Description
Drug	Liposomal doxorubicin
Dose	50mg/m² IV every 3 weeks
Dose modification	Reduced to 40 mg/m² for grade 3/4 toxicities
Interval modification	Extended to 4–5 weeks if grade 1/2 toxicities persisted

Table 3: Treatment Regimen (Muggia et al., 1997).

6.3 Clinical responses

Response Type	Number of Patients
Complete Response (CR)	1
Partial Response (PR)	8
Total Response Rate	9/35 (25.7%)
Confirmed by CT	7

Table 4: Clinical Response (Muggia et al., 1997).

6.4 Survival outcomes

Outcome	Result
Median Progression-Free Survival (PFS)	5.7 months
Overall Survival (OS)	1.5–24+ months (median 11 months)

Table 5: Survival outcome (Muggia et al., 1997).

6.5 Toxicity Profile

Toxicity	Observation
Grade 3/4 Nonhematologic Toxicities	13 patients (hand-foot syndrome, stomatitis)
Management	Dose modification or interval adjustment
Not observed	Nausea (drug-related), alopecia, extravasation necrosis, ejection fraction decrease

Table 6: Toxic Profile (Muggia et al., 1997).

Chapter 7

Future Direction of Nanoparticles in Treatment of Ovarian Cancer

Currently nano particle-based target therapies in the treatment of ovarian cancer are greatly emerging. The future direction of this platform is anticipated that it will transcend the preclinical studies and will move towards the realistically convertible as well as application in patient centered care. First and foremostly there is a powerful prominence on the arrangement of biocompatible and degradable nano carriers as well as with well-defined pharmacokinetics, clearance and toxicity to ensure clinical safety. Moreover, nanoparticles are expected to be more progressively desegregated with biomarkers and proceed towards genomic profiling as well as authorizing the evolution of personalized nanomedicine and uniform individualized treatment concord. Lastly there is an increasing focus on the evolution of low-cost nano sensors as well as microfluidic and paper-based procedures for untimely cancer identification and real time observing. These promote and hold up by obvious regulatory frameworks along with environmental safety standards for nanoparticles manufacturing and implementation.

Chapter 8

Conclusion:

Nanoparticle therapy is an approach to ovarian cancer treatment. Even though conventional chemotherapy has been proven to be effective, it tends to harm healthy cells leading to severe side effects such as healthy cell death, hair loss, suppressed immune systems and renal damage. The development of new, more effective drugs is urgently needed. Conventional therapeutics are less effective than nanoparticles. Studies have demonstrated that to a large extent they can home in and target cancer cells without damaging normal tissues **(**McFadden, Singh, Oprea-Ilies, & Singh, 2021**)**. Encapsulation of pharmaceuticals such as Cisplatin, Paclitaxel and Doxorubicin in nanoparticles Improves their solubility stability and bioavailability; therefore, improving therapeutic efficiency. allow controlled and sustained drug release, thereby reducing administration frequency and promoting patient compliance Hu, Gong, Xu, Huang, Wu, & He, 2022**).** Furthermore, nanoparticles also improve the pharmacokinetics of chemotherapeutic agents and overcome drug resistance, which is a big challenge for ovarian cancer. efflux pumps that pump medication out of the cells are bypassed and detoxification processes within the cell are also avoided, thereby allowing a greater amount of medication to enter into the tumor(s). This strategy could lead to better results in chemotherapy and can prevent initiation of cancer. Various nanoparticles including liposomes, polymeric nanoparticles and metallic nanoparticles have been investigated for the treatment of ovarian cancer (Rahiman, 2025; You & Zhang, 2025). Liposomes can deliver both hydrophilic and hydrophobic drugs, similar to cell membranes, enhancing drug distribution (Rahiman, 2025). Polymeric nanoparticles offer sustained drug release, while metallic ones such as gold and magnetic iron oxide allow for surface functionalization and monitoring of drug delivery by imaging (Naghinezhad et al., 2025). Targeted delivery is only

possible when ligands, antibodies or peptides are able to bind an ovarian cancer cell biomarker (McFadden et al., 2021; Park et al., 2025). This increases the absorption of medication in the tumor and reduces side effects for healthy tissues. Studies revealed that liposomal Doxorubicin (Doxil®) and polymeric micelles could lower the release of drugs from DDSs and augment their therapeutic efficacy, reducing side effects analogous with a drug such as Paclitaxel (McFadden et al., 2021; Hu et al., 2022). Clinical and preclinical observations demonstrate that nanoparticle drugs such as Doxil® and Genexol-PM, are efficacious in treating ovarian cancer by reducing toxicity while increasing tumor response. However, several major barriers such as high production costs and complexity of nanoparticle synthesis need to be overcome. Further clinical trials have to be conducted that show the long-term safety and treatment effects of these drugs. Overall, nanoparticle-mediated drug delivery is a promising approach for the treatment of ovarian cancer. These systems have the potential to overcome deficiencies of standard chemotherapy (low water solubility, high toxicity and drug resistance) that improve treatment outcome. New cancer drugs could be safer and more effective due to technology know-how gained from advances in nanoparticles and personalized medicine (Hu et al., 2022; McFadden et al., 2021).

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