Drug Resistance in Breast Cancer and Nanotherapeutical Advancements

Syeda Iqra Basharat^{1,*}, Cecilia Konima Conteh² and Mina Jamil³

¹Department of Chemistry, University of Agriculture, Faisalabad, Pakistan ²National Institute of Food Science and Technology, University of Agriculture, Faisalabad, Pakistan ³Department of Zoology, Wildlife and Fisheries, Faculty of Sciences, University of Agriculture, Faisalabad, Pakistan *Corresponding author: <u>syedaiqra970@gmail.com</u>

Abstract

Breast cancer can be caused by drug resistance, which leads to a reduction of therapeutic effectiveness and causes a high mortality level. It can be divided into intrinsic and acquired, which consist of the tumor microenvironment, cancer stem cells (CSCs), tumor heterogeneity and efflux pumps. There is a critical need for new therapeutic strategies to improve patient' outcomes, which has been proven by increased understanding of these processes. Nanotechnology can be a possible solution, offering methods for increasing treatment effectiveness and overcoming drug resistance. In this case, precision engineering of nanotherapeutics enables encapsulation and controlled release of chemotherapeutic agents, simplifies eradication of body toxins, and overcomes biological barriers. Liposomes, metallic nanoparticles, polymeric nanoparticles, lipid-based carriers and nanomicelles form some of the most notable innovations. These nanocarriers improve drug solubility, their availability in circulation, modulate gene expression, and combined therapies. The following chapter discusses the fundamental aspects of the molecular level of drug resistance in breast cancer. Such innovations will likely help change the face of management of drug-resistant breast cancer.

Keywords: Breast cancer, Drug resistance, Nanotechnology, Nanotherapeutics, Cancer treatment

Cite this Article as: Basharat SI, Conteh CK and Jamil M, 2025. Drug resistance in breast cancer and nanotherapeutical advancements. In: Zaman MA, Farooqi SH and Khan AMA (eds), Holistic Health and Antimicrobial Resistance: A Zoonotic Perspective. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 162-168. <u>https://doi.org/10.47278/book.HH/2025.48</u>



A Publication of Unique Scientific Publishers Chapter No: 25-311

Received: 09-Feb-2025 Revised: 12-March-2025 Accepted: 25-Apr-2025

Introduction

Breast cancer is the most common cancer incidence and a leading cause of cancer death in women across the globe. Based on updated statistics of 2023, breast cancer accounts for about 24.5% contribution toward the new cancer diagnoses globally, indicating its significant burden to the population. Early detection techniques including liquid biopsy and mammogram, alongside therapeutic measures, including precision medicine and immunotherapy, have seen many patient improve on their outcomes. However, drug resistance continues to re-emerge, defeating the traditional approaches to treatment and leading to relapse and poor prognosis despite such new findings (Mutair et al., 2024).

Breast cancer can therefore be attributable to an intrinsic, genetic cause, but also be due to mechanisms that may develop during treatment, and these include changes in efflux pumps and resourceful signaling pathways. Breast cancer itself is diverse due to the subtypes as hormone receptor-positive, HER2-positive, and triple-negative breast cancers (TNBC), each of which has different molecular features and resistance mechanisms, adding to the complexity of this multifaceted resistance (Lu et al., 2025).

Nanotechnology is the innovative solution for these challenges. It can be postulated that it is possible to increase therapeutic efficiency, overcome drug resistance, and decrease toxic effects using nanoscale carriers for the delivery of drugs. In particular, the breakthroughs in preclinical and clinical application of nanotherapeutics, including biomimetic systems and multifunctional nanoparticles, have shown potential, which will bring new hope to overcome drug resistance. This chapter discusses the molecular basis of drug resistance as well as the role of nanotherapeutics in overcoming these challenges (de la Fuente-Nunez et al., 2023; Gao et al., 2024).

1.1 Mechanism of Drug Resistance in Breast Cancer

The present therapeutic management of many breast carcinomas is partially compromised by drug resistance. They also added that treatment failure is due to intrinsic and acquired resistance mechanisms, which lead to relapse and poor prognosis for patients. Cancer stem cells can explain a tumor's capability to evade cytotoxicity induced by chemotherapy, targeted therapies, and hormone endocrine therapies via genetic, epigenetic, and stem cell niches (Bukhari, 2022).

1.2 Type of Drug Resistance

1.2.1. Intrinsic Resistance

The present therapeutic management of many breast carcinomas is partially compromised by drug resistance. They also added that treatment failure is due to intrinsic and acquired resistance mechanisms, which lead to relapse and poor prognosis for patients. Cancer stem

cells can explain tumor's capability to evade cytotoxicity induced by chemotherapy, targeted therapies and hormone endocrine therapies via genetic, epigenetic, and stem which cell niches (Qiu et al., 2025).

• Basic Mechanism:

• Genetic Mutations: Drug resistance may result from baseline genetic variations in vital oncogenes receptors such as HER2, or estrogen receptor, or tumor suppressor genes like BRCA1/2 or alterations that hinder drug binding to its target or alter the downstream signaling pathway (Lu et al., 2025).

• Modified Drug Transporters: The expulsion of these drugs out of cells before they are able to produce their effects is due to increased expression of efflux transporters such as P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP).

Chemotherapy or targeted therapy is recommended to cancer patient due to intrinsic resistance of tumor (Gillet & Gottesman, 2010).

1.2.2. Acquired Resistance

Obtained resistance is developed after prior satisfactory reaction to treatment when cancer cells adapt to pressure from therapy, for example, through mutations or signaling.

Basic Mechanism

• Genetic Alterations: Second level mutations to medication target genes such as HER2 or PIK3CA may change the affinity or effectiveness of targeted treatment (Braun et al., 2020).

Pathway Activation: High expression of MET or HER2 may induce activation of other survival signaling, for example PI3K/Akt or MAPK, thereby, canceling out targeted therapy lines Gao et al., 2024).

• Acquired resistance is still a question with considerable difficulty; thus, cure fails even if medicine appears efficient at the start and requires changes in the therapeutic strategy (Braun et al., 2020; Fessart & Robert, 2023).

1.3. Major Patterns of Drug Resistance in Breast Cancer

1.3.1 Efflux Pumps

Efflux pumps are probe transport proteins rooted in the cell membrane and decrease intracellular medication levels and effectiveness by expelling medications from the cell. The efflux transporters members of the ATP-binding cassette (ABC) family, such as P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP) play an important role in resistance.

• P-glycoprotein (P-gp): P-gp a protein product of the ABCB1 gene, is one of the primary cause of MDR in breast cancer cells. This pump releases many chemotherapeutic medicines, which are doxorubicin, paclitaxel, and vincristine to diminish medicines efficacy (de la Fuente-Nunez et al., 2023).

• BCRP: BCRP which is also known as MXR/ABCG2 is implicated in resistance including that to topotecan, mitoxantrone, and many other chemotherapeutic drugs. The associated gene product of Enhanced Green Fluorescence Protein (EGFP), BCRP, is overexpressed with innate and acquired resistance (Ibrahim, 2025).

Impact: These efflux pumps such as p-glycoprotein and breast cancer resistance protein reduce the concentration of drug in cancer cells significantly enough to have poor results of the cancer treatment (Ibrahim, 2025).

1.3.2. Modified Pharmacological Targets

Cancer can arise from mutations, amplification, or overexpression of the drug targets; therefore decreasing the effectiveness of drugs that modulate mention names of molecules epidermal growth factor receptors, human epidermal growth factor receptor 2, and tumor protein p53.

• HER2 Overexpression: Amplification and subsequent overexpression of the HER2 receptor tyrosine kinase is a hallmark of HER2-positive breast cancer (Braun et al., 2020)

• Mutations of the Estrogen Receptor (ER): Some biochemical alterations in the mechanism of estrogen receptor (ER) gene in the hormone receptor-positive breast tumors cause resistance to endocrine therapy like tamoxifen and aromatase inhibitors. They may bring conformational changes that prevent the binding of a drug or stimulate cell development pathways Qiu et al., 2025).

Impact: Target alterations involve changes to the therapeutic targets by mutation or overexpression leading to decreased response to drugs acting on these targets, necessitating new treatment strategies (Braun et al., 2020; Qiu et al., 2025).

1.3.3. Tumor Microenvironment

Once again, the presence of stroma and immune cells, together with newly formed blood vessels, constitutes a critical part of the tumor mass responsible for therapy refractoriness. Some of the interactions incorporated into the ticker could foster cell survival and limit drug penetration within the tumor microenvironment.

1.3.4. Hypoxia: Hypoxia inducible factors (HIFs) are stimulated by hypoxia in tumors, they promote survival pathways, thus increasing resistance towards chemotherapy/ irradiation. Some conditions exert selective pressure on the tumor, and hypoxic tumors are less sensitive to treatment regimens requiring oxygen for the cytotoxic effect. CAF and other stromal cells could secrete cytokines and growth factors which are involved in supporting the tumor cell survival and resistance against therapy. The stroma may enhance immune escape in cancer cells by allowing the tumor cells to secrete immunosuppressive substances or recruit factors that downregulate immune reactions to the treatment. The tumor microenvironment (TME) in the current chemotherapy and drug delivery systems forms a barrier by reducing oxygenation, providing stroma support for tumor survival, and sustained immune escape (Jain et al., 2020; Duan et al., 2023).

1.3.5. Neoplastic Stem Cells (NSCs)

Cancer stem cells (CSCs) are sub subpopulation of tumor cells capable of both self-renewal and giving rise to all cellular phenotypes

present in the cancer. These cells have broad immunological tolerance to traditional treatment modalities, including chemotherapy and radiation, by the ability to maintain a dormant state, repair DNA, and overexpression of drug pump proteins.

• Self-Renewal: CSCs can self-renew, thus reconstructing the tumor after conventional treatment following tumor relapse and metastasis.

• Drug Efflux: Cancer stem cells may have amplified levels of P-glycoprotein and breast cancer resistance protein that aid them to avoid the toxicity of Chemotherapy and molecular snapshots.

Impression: Cancer stem cells are considered one of the primary factors regulating resistance to treatment and tumor recurrence, thus making them a relevant target in identifying novel therapeutic strategies (Fessart & Robert, 2023).

1.3.6. Augmented DNA Repair

DNA repair is another factor for treatment failure in breast cancer since it is activated during the progression of the disease. DNA damaging treatments such as chemotherapy and radiotherapy induce DNA double strand breaks that have to be repaired if the cancer cells are to survive.

• Homologous Recombination (HR): Tumors with low or no BRCA1/2 cause DNA damage initially to respond to the treatments because, there is improper HR repair mechanism. However, compensational repair uptake, such as NHEJ or other forms of end joining, may restore DNA repair, thus, the resistance.

Impression: Enhanced DNA repair capacity allows cancer cells to tolerate the DNA damage caused by treatments and thereby promote resistance (Gillet & Gottesman, 2010).

1.4. Nanotherapeutics in the Fight Against Drug Resistance

Nanotechnology offers future directions to combat medication resistance in cancer, especially breast malignant tumor by modifying drug delivery systems, enhancing bioavailability, reducing toxicity and emphasizing combination therapy. Exploiting peculiarities of the nanoparticles allows for targeting the delivery of therapeutic drugs to tumor sites with lesser side effects and avoidance of many forms of drug resistance (Aravindan et al., 2024).

1.4.1. Benefits of Nanotechnology

1. Focused Pharmaceutical Administration

Mechanism: Ligands may attach to nanoparticles where they feature unique binding sites that exhibit affinity to receptors on cancer cells, such as antibodies, peptides, or small chemicals. It ensures that the anticancer drug reaches only the target cancer cells, enhancing its performance and at the same time reducing side impacts (Sabnis & Bivona, 2019).

Advantage: Targeted delivery increases the local concentration of therapeutic agents at the target tumor's site while reducing the off-target health-destructive drugs' exposures to surrounding tissues (Sabnis & Bivona, 2019).

2. Diminished Systemic Toxicity

Mechanism: Pharmaceuticals to be delivered are first loaded in nanocarriers and thus shielded from degrading or being metabolized until they get to the target tissue. This encapsulation minimizes drug release to non-desired organs, thus reducing systemic toxicity.

Advantage: It has benefits in the struggle against the instability and poor solubility of products in medicine, enabling the introduction of greater quantities of dosages without harming the health of the patient (Jain et al., 2020).

3. Overcoming Efflux Pumps

Mechanism: Nanoparticles may avoid efflux pumps, such as P-glycoprotein and BCRP that eject medicines from cancer cells thereby reducing drug concentrations. The potential of using nanocarriers can reach the intended site of action to deliver medications as the problem of multidrug resistance is solved.

Advantage: Because efflux processes are avoided, nanoparticles ensure that therapeutic agents remain within cancer cells for longer periods, thus increasing their efficacy (Ibrahim, 2025).

4. Combination Therapy

Mechanism: The delivery vehicle of nanoparticles may contain several therapeutic drugs, for instance, chemotherapeutic and resistance modulators. This helps combination therapy where the actions of multiple drugs are enhanced in the body, may even turn the clock on resistance to a specific drug and increase overall therapeutic effect.

Advantage: The combination of drugs may reduce the establishment of resistance since all the several processes are being dealt with at the same time, thus improving the efficacy of the treatment (Gote et al., 2021).

1.4.2. Types of Nanoparticles

1. Liposomes

Liposomes are circular structures assembled from phospholipid bilayers to become concentrators of hydrophobic and hydrophilic medications. They afford a certain level of protection to the pharmaceuticals from degradation and enable the drug to be accumulated at tumor sites by virtue of enhanced permeability and retention (EPR).

Doxil®, doxorubicin liposome, is a liposomal formulation approved by the FDA approved formulation for the treatment of breast cancer. The liposome ensures that the chemotherapeutic drug, doxorubicin, is delivered only to the tumor and thus reducing the cardiotoxic effect associated with free doxorubicin.

Advantage: Medications are locked within liposomes, hence enhancing stability, biopreparedness and selective targeting of neoplastic cell (Torres et al., 2024).

2. Polymeric Nanoparticles

Polymer nanoparticles are formed out of biodegradable polymers such as poly (lactic-co-glycolic acid), commonly known as PLGA. These nanoparticles afford controllable pharmacokinetic properties, thus ensuring long-term therapeutic efficacy. Polymeric nanoparticles may be functionalized with targeting moieties (e.g., HER2 antibodies) to control the specificity for cancer cells that have high HER2 levels. The functionalized PLGA nanoparticles benefit the pharmacokinetics and treatment impact of medicines like paclitaxel too.

Advantage: YNPNs therefore offer versatility, biodegradability, and controlled drug delivery, hence improving the efficacy of treatment and reducing side effects.

3. Metallic Nanoparticles

Gold and silver metallic nanoparticles have been the most considered for the potential application in photothermal therapy. These have photothermal properties that, when exposed to specific wavelengths, the nanoparticles convert the absorbed light into heat, killing cancer cells through local hyperthermia. Gold nanoparticles have been employed with chemotherapy to increase the therapeutic efficacy while reducing the required dose of the chemotherapy drug (Viale et al., 2023).

Advantage: Metallic nanoparticles have a dual-functioning role in therapy, photothermal, and enhanced drug delivery system (Viale et al., 2023).

4. Lipid-Derived Nanoparticles

Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) are examples of lipid based nanocarriers of hydrophobic active pharmaceutical ingredients (APIs). These carriers offer a sustained-delivery system of release of their medical drugs coupled with a comparatively less degree of toxicity compared to traditional dosage forms. For example, solid lipid nanoparticles (SLNs) have been employed to upscale the solubility and delivery of hydrophobic drugs like paclitaxel; thereby, increasing their therapeutic use ratio and reducing side reactions.

Advantage: Lipid-based nanoparticles offer a better opportunity than conventional compounds to dissolve drugs that are poorly soluble in water and also improve the prospects of a drug to accomplish its therapeutic effect.

5. Nanomicelles

Nanomicelles are amphiphilic molecules self-assemble in a spherical structure in water. These structures can dissolve hydrophobic drugs and make them more beneficial to the body. In this topic, it is established that paclitaxel-loaded nanomicelles have the ability to overcome surmounting paclitaxel resistance by increasing the solubility of the drug and decreasing the efflux pump-mediated resistance mechanisms. Advantage: Nanomicelles are highly efficient in solubilization of hydrophobic pharmaceutical compounds with low solubility in aqueous solutions, thus increasing their therapeutic value in oncology treatments (Tanaka et al., 2009; Torres et al., 2024).

1.5. Nanotechnology as a Solution to Drug Resistance

In the area of cancer treatment, nanotechnology has now emerged as a powerful tool against the drug resistance mechanism through targeting the principal mediators of resistance and enhancing the palette of drugs (Figure 1). Approaches to the problems posed by drug resistance are described through the features associated with nanoparticles, including drug encapsulation, tissue targeting, and suppression of cellular barriers (Gote et al., 2021).

1.5.1. Targeting Efflux Pumps

Chemotherapeutic agents are transported out of cancer cells by efflux pumps, especially those of the ABC transporters, P-gp and BCRP. This process lowers the agent's concentrations and effectiveness within the cell. Nanotechnology seems to be able to overcome this resistance mechanism (Beretta et al., 2017).

Nanotechnology Application: Antimicrobials can be designed to either inhibit the efflux pump system or to avoid it entirely, given that nanoparticles possess that advantage. For example, action of the drug may be stopped by the incorporation of P-gp inhibitors in the drug formulation, potentially prolonging the retention time of the chemotherapeutic agents within the cancer cells.

Impact: These result in an increased bioavailability of the drug within the target cells since the nanoparticles overcome the efflux barrier as an effective form of cancer therapy (Gupta et al., 2021; Kinnel et al., 2023).

1.5.2. Silencing of Genes

Other methods of gene silencing like the use of miRNA or siRNA, can be used to eliminate the genes that are involved in drug resistance. Based on current scientific literature, nanocarriers are the best way to transport these genetic materials to the tumor site.

Nanotechnology Application: Nanoparticles carrying siRNA or miRNA can block genes that are considered to be responsible for resistance. For example, it has been shown that using siRNA to down regulation of the breast cancer resistance protein (BCRP), makes cancer cells sensitive to chemotherapy medications again.

Impact: This method also does not only directly affects the resistance mechanisms but also strengthens the effects of the traditional drugs so as to enhance the clinical efficacy (Lu et al., 2025).

1.5.3. Reprogramming the Tumor Microenvironment

There is an incredible potential for repurposing the tumor microenvironment in favor of the immunotherapy treatment. Tumor microenvironment (TME) is among the important factors that enhance drug resistance through physical and biochemical barriers that hinder

the delivery of drugs and at the same time promote survival mechanisms of cancer cells. The TME is often described as hypoxic, with a disordered vasculature and stroma and all of these factors contribute to resistance.

Nanotechnology Application: It remains possible to deliver agents that can decrease the hypoxic environment or correct the tumor vasculature and therefore improve the delivery of chemotherapeutic agents, using nanoparticulate carriers. For instance, nanoparticles can deliver oxygen or oxygen-releasing substances or anti-angiogenic molecules to remodel the TME.

Impact: Nanoparticles improve oxygenation, depress the tumor's shielding abilities, and increase drug delivery by reorganizing the TME, making cancer cells more sensitive to therapy (Gupta et al., 2021).

1.5.4. Combination Therapy

It has been established that the use of several therapeutic agents at once, as proven in the use of the combination therapy, can be an effective way to fight drug resistance. Nanotechnology allows the design of the delivery systems for both resistance modulators and chemotherapy drugs at the same time.

Nanotechnology Application: Nanoparticles can be used for the dual targeting of chemotherapeutic agents together with resistance modulators like inhibitors of PI3K or any other pathway. For instance, the cumulative consequences of mixed treatment by doxorubicin and PI3K inhibitors in overcoming resistance have been illustrated.

Impact: A tablet formulation of nanoparticles builds synergism of drugs that treat different resistance profiles and reduces chances of acquiring other resistance profiles (Sabnis & Bivona, 2019).

1.5.5. Cancer Stem Cells

Cancer stem cells (CSCs) are a subset of cancer cells that are generally known to give rise to tumor recurrence and therapy failures. They self-renew property. and are extremely resistant to standard chemotherapeutic agents due to the post-mitotic quiescence, higher DNA repair activity, and expression of efflux transporters in them (Viale et al., 2023).

Nanotechnology Application: Due to the special characteristics of nanoparticles, the drugs targeted to CSCs or pathways actively involved in the maintenance of CSC-mediated characteristics can be delivered effectively. For example, salinomycin that is previously incorporated in nanoparticles or inhibitors of the Wnt/β -catenin pathway can destroy CSCs selectively.

Impact: Nanoparticle-based different therapies focused on CSCs can be more integrating for avoiding the over composure of drug resistance because CSC-based therapies get to the root of issue for tumor recurrence and metastasis (Tanaka et al., 2009; Kinnel et al., 2023).

1.5. Future Directions and Hindrances in Nanotherapeutics

Several nanotherapeutics offer a new way of addressing the problem of drug resistance in the treatment of cancer diseases and the prospects of nanomedicine for oncology are stable due to new staking components. However, there are number of challenges in adoption of these technologies in clinical practices. (Mao et al., 2022; Gao et al., 2024).

1.6. Complications

1.6.1. Manufacturing and Scalability Challenge: To date, one of the main challenges of development in this area is to obtain functional, uniform nanoparticles in large amounts. The process used to produce the nanoparticles has to ensure that nanoparticles retain the appropriate characteristics throughout production, which consist of size, surface charge, and drug-loading capacity and may vary from one batch to another (Cervantes et al., 2024).

Impact: Therapeutic effects may vary depending on the variability in production; therefore, the regulation and application of such immunomodulators may be challenging. A major challenge in using nanoparticles is the limited access to quality and easily synthesized large quantities of the nanoparticles.

Solution: To overcome these challenges and ease clinical transference, it insists on the ongoing examination of nanofabrication methods and the quantification of nanoparticle synthesis (Maimaitijiang et al., 2024).

1.6.2. Biodistribution and Stability Challenge: One of the major challenges is the ability to keep nanoparticles stable throughout storage and during their transport in the body. In addition, the biodistribution of the nanoparticles needs to be improved in order for these nanoparticles to 'favor' the malignant tissue and that they do not concentrate in normal healthy tissue.

Impact: Specificity and better targeting can be compromised, as well as the effectiveness of the nanoparticle-based therapy may be reduced because of instability. It has been observed that passive targeting efficiency, which is the ability of the nanoparticles to transfer throughout the body and lodge in the tumor site, is a function of size, shape, and the surface functionalization of the nanoparticles.

Solution: To improve clinical results, the strategy of nanoparticle formulation provides essential opportunities for the modulation of the release rate and targeting, as well as the enhancement of nanoparticle stability (Viale et al., 2023).

1. 1.6.3. Complications to Regulation Challenge

The regulatory approval of nanomedicines is highly complex, and requires extensive information about the safety, efficacy, and the process of preparing nanoparticles. To assess the acute and chronic impacts of nanoparticles, the US Food and Drug Administration requires unstipulated in vitro and in vivo experiments.

Impact: The success of nanotherapeutics in clinical practice can be reduced by safety concerns associated with bio-uncertainty and the slower approval of nanotherapeutics because of the lack of guidelines.

Solution: The approval process may be the following: regulation standards, which include specific nanomedicines criteria, may be set, as well as effective cooperation between researches, manufacturers, and regulatory agencies may be sought (Mao et al., 2022).

1.6.4. Potential Toxicology Challenge: There is still little information on the chronic in vivo cytotoxicity of nanoparticles for humans and on

the impact of nanoparticles on the environment. However, the concentration of nanoparticles to cancer cells might have dire consequences due to uptake by other body tissues, leading to immune reactions, inflammation amongst others.

Impact: The toxicity potential of nanoparticles requires rigorous characterization of their biocompatibility, and clearance related to nanoparticles used for drug delivery and their impact on human health. Nanoparticle-based remedies cannot be disseminated to patients without significant safety concerns without detailed toxicity investigations.

Solution: Therefore, long-term preclinical toxicity studies and prospective environmental evaluation need to be performed to effectively understand this and or minimize any perceived risks of danger from nanoparticles (Cervantes et al., 2024).

1.7. Prospective Courses of Action

1.7.1. Personalized Nanomedicine

Nanomedicine directed to personalized treatment is a potential approach for increasing treatment efficiency, because it is based on the genetic and proteomic characteristics of each patient. It becomes possible to increase the impacts of intercessions and decrease the harm with the help of patients' specific targeting of nanoparticles.

Advantage: Individualized medicine can help to deliver correct and ineffective drugs to correct and ill patients, and the offering of positive effects by personalizing the dosage and administration of drugs.

• The ability to significantly improve personalized cancer therapies based on the combination of nanoparticle design and genomic and proteomic information (Karim et al., 2023).

1.7.2. Multipurpose Nanocarriers

Obtaining multifunctional nanoparticles with diagnostic capabilities well as therapeutic purposes is a major boost to nanomedicine. These so-called 'smart' nanoparticles can help diagnose the course of the illness while delivering the medicines at the same time.

Advantage: The multifunctional nanocarriers can help clinicians control the effectiveness of the therapies and change dosage accordingly, while also aiding the clinician in tracking the progress of the treatment in real time. For example, functionalized nanoparticles to be used in drug delivery and magnetic resonance imaging (MRI) would allow the non-invasive tracking of drug release and effectiveness of the treatment (Aravindan et al., 2024).

1.7.3. Artificial Intelligence Integration

The potential for rationalizing nanoparticle design and the outcome of therapy is enormous. It predicted that AI-driven models could predict the behavior of nanoparticles in a number of biological settings, which can be utilized for better therapies.

Advantage: Artificial intelligence (AI) has the potential to expedite the design and testing of nanoparticle formulations, thereby reducing the time and expenses associated with the development of novel treatments. The efficacy and safety of nanoparticles could be improved by the optimization of their material selection through the use of machine learning algorithms. The integration of AI into the design of nanoparticles will simplify the process of developing more personalized, efficient treatments (Maimaitijiang et al., 2024).

4. 1.7.4. Innovative Materials

The potential of novel, bio-inspired materials for nanoparticle-based therapies is significant. The stability, biocompatibility, and targeting capabilities of hybrid nanomaterials can be improved by the combination of inorganic and organic components.

Advantage: The potential for novel materials to enhance therapeutic outcomes by overcoming the limitations of current nanoparticles, such as poor biocompatibility or limited drug-loading capacity.

• The development of nanoparticles that are more effective and safer could be achieved by investigating bio-inspired and hybrid nanomaterials, thereby furthering clinical cancer therapies (Gao et al., 2024).

Conclusion

Conventional therapies are considerably diminished by drug resistance, which continues to pose a significant obstacle in the treatment of breast cancer. Through innovative combination therapies, targeted delivery, and enhanced drug retention, nanotechnology provides a revolutionary platform to surmount these obstacles. The future of nanotherapeutics in breast cancer appears promising, despite the fact that challenges persist in terms of scalability, stability, and regulatory approval. It is imperative that researchers, clinicians, and regulatory bodies collaborate to implement these advancements in clinical practice, thereby facilitating the development of personalized treatment strategies and enhanced patient outcomes.

References

- Aravindan, A., Gupta, A., Moorkoth, S., & Dhas, N. (2024). Implications of nanotherapeutic advancements to leverage multi-drug resistant breast cancer: The state-of-the-art review. *Journal of Drug Delivery Science and Technology*, 100, 106007. https://doi.org/10.1016/j.jddst.2024.106007
- Beretta, G. L., Cassinelli, G., Pennati, M., Zuco, V., & Gatti, L. (2017). Overcoming ABC transporter-mediated multidrug resistance: The dual role of tyrosine kinase inhibitors as multitargeting agents. *European Journal of Medicinal Chemistry*, *142*, 271–289. https://doi.org/10.1016/j.ejmech.2017.07.025

Braun, T. P., Eide, C. A., & Druker, B. J. (2020). Response and resistance to BCR-ABL1-targeted therapies. *Cancer Cell*, 37(4), 530-542. https://doi.org/10.1016/j.ccell.2020.03.004

Bukhari, S. N. A. (2022). Emerging nanotherapeutic approaches to overcome drug resistance in cancers with update on clinical trials.

Pharmaceutics, 14(4), 866. https://doi.org/10.3390/pharmaceutics14040866

- Cervantes, B., André, T., & Cohen, R. (2024). Deficient mismatch repair/microsatellite unstable colorectal cancer: Therapeutic advances and questions. *Therapeutic Advances in Medical Oncology, 16*, 17588359231170473. https://doi.org/10.1177/17588359231170473
- de la Fuente-Nunez, C., Cesaro, A., & Hancock, R. E. (2023). Antibiotic failure: Beyond antimicrobial resistance. Drug Resistance Updates, 101012. https://doi.org/10.1016/j.drup.2023.101012
- Duan, C., Yu, M., Xu, J., Li, B. Y., Zhao, Y., & Kankala, R. K. (2023). Overcoming cancer multi-drug resistance (MDR): Reasons, mechanisms, nanotherapeutic solutions, and challenges. *Biomedicine & Pharmacotherapy*, 162, 114643. https://doi.org/10.1016/j.biopha.2023.114643
- Fessart, D., & Robert, J. (2023). Mechanisms of cancer drug resistance. Bulletin du Cancer. 111, 37-50. https://doi.org/10.1016/j.bulcan.2023.07.001
- Gao, L., Meng, F., Yang, Z., Lafuente-Merchan, M., Fernández, L. M., Cao, Y., & Cai, Y. (2024). Nano-drug delivery system for the treatment of multidrug-resistant breast cancer: Current status and future perspectives. *Biomedicine & Pharmacotherapy*, 179, 117327. https://doi.org/10.1016/j.biopha.2024.117327
- Gillet, J. P., & Gottesman, M. M. (2009). Mechanisms of multidrug resistance in cancer. In *Multi-drug resistance in cancer* (pp. 47-76). Totowa, NJ: Humana Press. https://doi.org/10.1007/978-90-481-8575-1_3
- Gote, V., Nookala, A. R., Bolla, P. K., & Pal, D. (2021). Drug resistance in metastatic breast cancer: Tumor-targeted nanomedicine to the rescue. International Journal of Molecular Sciences, 22(9), 4673. https://doi.org/10.3390/ijms22094673
- Gupta, P., Neupane, Y. R., Parvez, S., & Kohli, K. (2021). Recent advances in targeted nanotherapeutic approaches for breast cancer management. *Nanomedicine*, *16*(29), 2605–2631. https://doi.org/10.2217/nnm-2021-0186
- Ibrahim, Z. (2025). Targeting and combating drug resistance in triple-negative breast cancer using nano polymer: Efficacy of A6 peptide-PLGA-PEG nanoparticle loaded with doxorubicin and anti-miR-21 in in vitro and vivo model. *bioRxiv*, https://doi.org/10.1101/2025.01.04.631287
- Jain, V., Kumar, H., Anod, H. V., Chand, P., Gupta, N. V., Dey, S., & Kesharwani, S. S. (2020). A review of nanotechnology-based approaches for breast cancer and triple-negative breast cancer. *Journal of Controlled Release*, 326, 628–647. https://doi.org/10.1016/j.jconrel.2020.07.005
- Karim, A. M., Kwon, J. E., Ali, T., Jang, J., Ullah, I., Lee, Y. G., & Kang, S. C. (2023). Triple-negative breast cancer: Epidemiology, molecular mechanisms, and modern vaccine-based treatment strategies. *Biochemical Pharmacology*, 212, 115545. https://doi.org/10.1016/j.bcp.2023.115545
- Kinnel, B., Singh, S. K., Oprea-Ilies, G., & Singh, R. (2023). Targeted therapy and mechanisms of drug resistance in breast cancer. *Cancers*, 15(4), 1320. https://doi.org/10.3390/cancers15041320
- Lu, J., Ding, F., Sun, Y., Zhao, Y., Ma, W., Zhang, H., & Shi, B. (2025). Unveiling the role of MDH1 in breast cancer drug resistance through single-cell sequencing and schottenol intervention. *Cellular Signalling*, 127, 111608. https://doi.org/10.1016/j.cellsig.2025.111608
- Maimaitijiang, A., He, D., Li, D., Li, W., Su, Z., Fan, Z., & Li, J. (2024). Progress in research of nanotherapeutics for overcoming multidrug resistance in cancer. *International Journal of Molecular Sciences*, 25(18), 9973. https://doi.org/10.3390/ijms25189973
- Mao, J. J., Pillai, G. G., Andrade, C. J., Ligibel, J. A., Basu, P., Cohen, L., Khan, I. A., Mustian, K. M., Puthiyedath, R., Dhiman, K. S., & Lao, L. (2022). Integrative oncology: Addressing the global challenges of cancer prevention and treatment. *CA: A Cancer Journal for Clinicians*, 72(2), 144–164. https://doi.org/10.3322/caac.21627
- Mutair, Y., Mushtaq, G., Al-Daoud, F., Al-Qassim, M., & Hariri, M. (2024). Early-age breast cancer during active conflict in Syria: A crosssectional study. *Journal of Liaquat University of Medical & Health Sciences*, 23(03), 191–196. https://doi.org/10.22442/jlumhs2024v23i03
- Qiu, Y., Shi, Y., Chao, Z., Zhu, X., Chen, Y., & Lu, L. (2025). Recent advances of antibody-drug conjugates in treating breast cancer with different HER2 status. *Therapeutic Advances in Medical Oncology*, 17, 17588359241311379. https://doi.org/10.1177/17588359241311379
- Sabnis, A. J., & Bivona, T. G. (2019). Principles of resistance to targeted cancer therapy: Lessons from basic and translational cancer biology. *Trends in Molecular Medicine*, 25(3), 185–197. https://doi.org/10.1016/j.molmed.2018.12.002
- Tanaka, T., Decuzzi, P., Cristofanilli, M., Sakamoto, J. H., Tasciotti, E., Robertson, F. M., & Ferrari, M. (2009). Nanotechnology for breast cancer therapy. *Biomedical Microdevices*, *11*, 49–63. https://doi.org/10.1007/S10544-009-9307-4
- Torres Quintas, S., Canha-Borges, A., Oliveira, M. J., Sarmento, B., & Castro, F. (2024). Nanotherapeutics in women's health: Emerging nanotechnologies for triple-negative breast cancer treatment. *Small*, 20(41), 2300666. https://doi.org/10.1002/smll.202300666
- Viale, G., Basik, M., Niikura, N., Tokunaga, E., Brucker, S., Penault-Llorca, F., & de Giorgio-Miller, V. (2023). Retrospective study to estimate the prevalence and describe the clinicopathological characteristics, treatments received, and outcomes of HER2-low breast cancer. *ESMO Open*, 8(4), 101615. https://doi.org/10.1136/esmoopen-2023-101615