NANOTECHNOLOGY-BASED DRUG DELIVERY SYSTEMS AND THE IMPACT OF GOLD NANOPARTICLE SIZES IN BREAST CANCER THERAPY
EYAD MAJED ALASHQAR
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Declaration

I hereby declare that all information, documents, analysis, and results in this thesis have been collected and presented according to the academic rules and ethical guidelines of the Institute of Graduate Studies, Near East University. I also declare that as required by these rules and conduct, I have fully cited and referenced information and data that are not original to this study.

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Abstract

NANOTECHNOLOGY-BASED DRUG DELIVERY SYSTEMS AND THE IMPACT OF GOLD NANOPARTICLE SIZES IN BREAST CANCER THERAPY

Study Background: Nanotechnology emerges as a promising avenue, offering unparalleled potential in creating personalized drug delivery systems to combat this disease. This thesis explores the current advancements and the significant impact of nanotechnology on enhancing cancer therapy targeted drug delivery systems. Its precise manipulation of multifunctional nanoparticles allows for the customization of size, shape, and surface attributes, revolutionizing how drugs are administered for enhanced effectiveness against cancer. More specifically, it examines various size ranges of gold nanoparticles for breast cancer therapy. Nanoparticles, especially gold nanoparticles, offer numerous advantages due to their unique physicochemical properties, notably the capacity to specifically aim therapeutic drugs at cancer cells while minimizing their toxicity.

Method: This study aims to examine the effectiveness of various size ranges of Au gold nanoparticles used in the treatment of breast cancer according to a set of various parameters. The Multi-Criteria Decision Making (MCDM) technique, Fuzzy Preference Ranking Organization Method for Enrichment of Evaluations (PROMETHEE) will be used to assess results.

Result: The results of this study using the fuzzy PROMETHEE technique indicated that 1-5 nanometer size range of the DOX Au gold nanoparticle is the first ranked and best-performing gold nanoparticle especially in its success rate, low cost with loading efficiency and lowest cytotoxicity, with a net outranking flow of 0,1474, followed by DOX Au gold nanoparticle with size range 5-20 nanometers with a net outranking of 0,0724, and then DOX Au gold nanoparticle with size range 20-50 nanometers with a net outranking flow 0,0001. The DOX Au gold nanoparticle with size range >100 nanometers is ranked next with a negative net outranking flow

of -0,0767 and the lowest-ranked DOX Au gold nanoparticle for the breast cancer therapy is with size range 40-70 nanometers and a negative outranking flow of -0,1432.

Conclusion: A revolutionary era in the therapy of cancer has begun with the application of nanotechnology. Gold nanoparticles are now being widely used in clinical therapies for a wide range of cancer types and especially breast cancer. When compared with conventional drugs, nanoparticles based on drug delivery systems provide improved stability, tumor specificity, pharmaceutical kinetics, biological compatibility and success rate. Additionally, they are essential in reducing systemic toxicities and combating medication resistance. These unique benefits have made gold nanoparticle more widely used in targeted drug delivery systems and chemotherapies. The results of this decision-making approach on the evaluation of gold nanoparticles with different size ranges used for breast cancer therapy will aid in optimizing highest results on breast cancer patients and the medical field of treating cancer. The Fuzzy PROMETHEE offers the ideal size range of gold nanoparticle.

Keywords**:** Nanotechnology, drug delivery, nanoparticles, breast cancer, fuzzy PROMETHE

Özet

NANOTEKNOLOJİ TABANLI İLAÇ DAĞITIM SİSTEMLERİ VE ALTIN NANOPARÇACIK BOYUTLARININ MEME KANSERİ TEDAVİSİNDE ETKİSİ

Giriş:

Nanoteknoloji, bu hastalıkla mücadele için kişiselleştirilmiş ilaç dağıtım sistemleri oluşturmada benzersiz bir potansiyel sunan, umut verici bir yol olarak ortaya çıkmaktadır. Bu tez çalışması ile, mevcut gelişmeler ve nanoteknolojinin kanser tedavisini hedef alan ilaç dağıtım sistemlerini geliştirme üzerindeki önemli etkisi araştırılmıştır. Çok işlevli nanopartiküllerin boyut, şekil ve yüzey özellikleri bakımında hassas manipülasyonu kansere karşı ilaçların etkinliklerinin arttırılması ve uygulanma biçiminde devrim yaratmıştır. Daha spesifik olarak, meme kanseri tedavisi için çeşitli boyut aralıklarındaki altın nanopartiküllerini incelenmiştir. Nanopartiküller, özellikle de altın nanopartikülleri, benzersiz fizikokimyasal özelliklerinden dolayı ve özellikle terapötik ilaçları kanser hücrelerine spesifik olarak hedefleyerek bunların toksisitesini en aza indirme kapasitesi.ile meme kanseri tedavi sürecinde çok sayıda avantaj sunmaktadır.

Yöntem: Bu çalışma, meme kanseri tedavisinde kullanılan çeşitli boyut aralıklarındaki Au altın nanopartiküllerinin çeşitli parametrelere göre etkinliklerinin incelenmesini amaçlamaktadır. Sonuçların değerlendirilmesinde Çok Kriterli Karar Verme (MCDM) tekniği, Bulanık Değerlendirmelerin Zenginleştirilmesi için Tercih Sıralaması Organizasyon Yöntemi (PROMETHEE) kullanılmıştır.

Bulgular: Bulanık PROMETHEE tekniğinin kullanıldığı bu çalışmanın sonuçları, DOX Au altın nanopartikülünün 1-5 nanometre boyut aralığının, özellikle başarı oranı, yükleme verimliliği ile düşük maliyeti ve en düşük sitotoksisite açısından 0,1474 net üstünlük akışıyla birinci sıradaki ve en iyi performans gösteren altın nanopartikülü olduğunu göstermiştir. 5-20 nanometre boyut aralığına sahip DOX Au altın nanoparçacığı ise 0,0724 net üstünlükle ikinci sırada yer almıştır. Ve ardından 0,0001 net üstünlük değeri ile 20-50 nanometre boyut aralığına sahip DOX Au altın nanoparçacığı üçüncü sırada yer almıştır. Boyut aralığı >100 nanometre olan DOX Au altın nanoparçacığı, -0,0767'lik negatif net sıralama değeri ile dördüncü sırada yer almış ve meme kanseri tedavisi için -0,1432'lik net sıralama değeri ile 40-70 nanometre boyut aralığındaki DOX Au altın nanoparçacığı son sırada yer almıştır.

Sonuç: Nanoteknolojinin uygulanmasıyla kanser tedavisinde devrim niteliğinde bir dönem başlamıştır. Altın nanopartikülleri artık çok çeşitli kanser türleri ve özellikle meme kanseri için klinik tedavilerde yaygın olarak kullanılmaktadır. Geleneksel ilaçlarla karşılaştırıldığında, ilaç dağıtım sistemlerine dayanan nanopartiküller gelişmiş stabilite, tümör spesifikliği, farmasötik kinetik, biyolojik uyumluluk ve başarı oranı sağlar. Ayrıca sistemik toksisitelerin azaltılmasında ve ilaç direnciyle mücadelede de önemlidirler. Bu benzersiz faydalar, altın nanopartikülünün hedefe yönelik ilaç dağıtım sistemlerinde ve kemoterapilerde daha yaygın olarak kullanılmasını sağlamıştır. Meme kanseri tedavisinde kullanılan farklı boyut aralıklarına sahip altın nanopartiküllerinin değerlendirilmesine ilişkin bu karar verme yaklaşımının sonuçları, meme kanseri hastalarında ve kanser tedavisinin tıbbi alanında elde edilen sonuçların optimize edilmesine yardımcı olacaktır. Bulanık PROMETHEE, altın nanoparçacıklarının ideal boyut aralığını sunmaktadır.

Anahtar Kelimeler: Nanoteknoloji, ilaç dağıtımı, nanopartiküller, meme kanseri, Bulanık PROMETHEE

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List of Abbreviations

AHP	Analytical Hierarchy Process
API	Active Pharmaceutical Ingredient
BSA	Body Surface Area
DDS	Drug Delivery System
EPR	Enhanced Permeability and Retention Effect
FDA	Food and Administration
FLU	Fluticasone
FNNs	Fuzzy Neural Networks
FST	Fuzzy Set Theory
HIV	Human Immunodeficiency Virus
HPMC	Hydroxyl Propyl Methylcellulose
IgG	Immunoglobullin
IV	Intravenously
LDDS	Localized Drug Delivery Systems
MCDM	Multicriteria Decision Making Models
MEMS	Microelectromechanical systems
MNZ	Metronidazole
NDDS	Nano-drug Delivery Systems
NP	Nanoparticle
PDD	Physical Drug Delivery
pH	Potential Hydrogen

PLA	Polylactic Acid
PLG	Poly (lactide-co-glycolide)
PLGA	Polylactic-glycolic Acid
PROMETHEE	Preference Ranking Organization Method for Enrichment Evaluation
PVP	Polyvinylpyrrolidone
SAMs	Self-assembled monolayers
SF	Silk Fibrin
SPIONs	Superparamagnetic Iron Oxide Nanoparticles

CHAPTER I

1. Introduction

1.1 Background of the study

Nanotechnology has revolutionized cancer treatment through advanced drug delivery methods, presenting unprecedented levels of precision and efficacy. Essentially, nanotechnology operates by crafting and adapting materials at a nanoscale level, imbuing nanoparticles with specific functionalities. In the realm of cancer therapy, these minute particles act as specialized carriers for medications, allowing targeted delivery to tumor sites while minimizing damage to surrounding healthy cells (Mosleh-Shirazi, et al. 2022) [1]. The innovative application of nanotechnology in delivering cancer medications has tackled numerous significant hurdles. Firstly, these nano-sized drug carriers navigate the body's complex barriers, like cellular membranes and circulation, to precisely target tumor sites. Secondly, they enhance the drug's stability and solubility, extending its lifespan in circulation and boosting its therapeutic impact. Targeted delivery involves tailoring nanoparticles to exclusively target cancer cells while bypassing healthy ones (Xu, et al. 2023) [2]. These specialized particles can selectively attach to cancer cells when triggered by specific ligands, enabling precise medication delivery. Combining multiple medications or therapeutic agents simultaneously, made possible by nanotechnology, leads to improve the outcomes. Additionally, customizing nanocarriers with surface modifications enables them to selectively bind to and identify cancer cells, facilitating drug accumulation at tumor sites. Ongoing research focuses on refining nanocarrier structures, exploring new combinations of medications, and incorporating advanced imaging and diagnostic technologies. This continual evolution in nanotechnology for drug delivery in cancer therapy holds promise for more personalized and effective treatments, promoting hopes for better patient outcomes and improved quality of life (Raheem, et al 2023) [3].

1.2 Statement of the Problem

Breast cancer is a worldwide health concern and for this reason it is necessary to constantly researching on therapeutic approaches to improve the results for the patients. Gold nanoparticles (AuNPs) have made an important step for a revolutionary treatment for cancer therapy due to their unique physical and chemical properties through targeted drug delivery systems. However, the size-dependent effects of gold AuNPs present several challenges that require further investigation and need to be addressed. This study aims to explore the size-dependent properties gold nanoparticles in order to understand their full-fledged potential on the treatment outcomes in breast cancer therapy.

Problems encompass issues such as low solubility, a key obstacle in formulating effective therapies, as it impacts the drug's bioavailability. Consequently, poor solubility stands as a primary hurdle faced by companies and scientists when dealing with newly identified chemical entities. Low bioavailability poses a significant issue in drug effectiveness, the cytotoxicity is another criterion that should be taken into account and cost may prove to be very expensive. By examining the outlined problems, this thesis intends to examine the size-dependent effects of gold nanoparticles in breast cancer therapy. The progress of effective and personalized treatments for breast cancer patient is essential.

1.3 Purpose of the Study

The purpose of this study is to access how nanotechnology and specifically drug delivery systems can enable healing of breast cancer in the most effective ways. Drug delivery system can help in various purposes in enhancing the therapies on cancer. To begin with, small carriers for drug at a nano-scale, offer a targeted approach to delivering treatment, particularly in combating cancer cells, while minimizing harm to healthy tissue.

To be precise, the aim of this study is to examine different size range of the gold NP and examine which of these size ranges are the most effective in breast cancer therapy. Criteria such as cytotoxicity, the cost, the loading efficiency and the success rate are chosen.

1.4 Research Questions/Hypotheses

Based on previous research, the present thesis was initially based on the following interrelated set of research question:

a. Does the size range of gold nanoparticles (AuNPs) affect the therapy for breast cancer patients?

In order for researchers to find the best treatment for breast cancer for various patients, they must research various size ranges of gold nanoparticles to achieve best possible personalized treatments for each patient.

The above initial research question led to the generation of the main hypotheses:

a. The size range of gold nanoparticles affects the success rate of breast cancer therapies.

1.5 Significance of the Study

In the past few years, nanotechnology has made remarkable strides, especially in medicine, notably in creating advanced drug delivery systems tailored for cancer treatment. These systems have shown promise in boosting treatment effectiveness, reducing toxicity, improving patient adherence, enabling precise targeting, facilitating combination therapies (Jahan, et al. 2023) [4]. At its core, advancements in drug delivery technology are fundamentally transforming cancer therapy, enhancing its effectiveness, precision in targeting, and customization for individuals.

The significance of this study is to advance and develop the breast cancer therapy through targeted drug delivery system with the use of gold nanoparticles. The size range of gold nanoparticles has unique properties in order to develop breast cancer therapy reducing side effects and increasing therapeutic efficacy. Its significant lies in advancing the field of medicine and more specifically breast cancer therapy providing more customized and precision on targeting breast cancer treatments with low cytotoxicity effects and improving the results and quality of life of patients.

This is a very important study comparing the size of gold nanoparticles for the treatment of breast cancer and contributing to existing literature review. The study findings will have an important impact on patients' outcomes by enhancing the therapeutic effects of breast cancer therapy through the size range of gold nanoparticles within the drug delivery system. It will contribute to the nanomedicine field and provide innovative solutions to current challenges, resulting in improved patient care, enhanced quality of life, and decreased healthcare costs.

1.6 Limitations

This thesis focused on treating breast cancer with the usage of drug delivery systems and specifically with the gold nanoparticles. A major limitation of this research is that there many criteria that can be used, but for the purpose of this thesis the following are used cytotoxicity, success rate, loading efficiency and cost. These are chosen based on the existing recent research that is examined especially for breast cancer therapy and are considered the most important ones for the research questions that are set. In the future, other criteria like the surface charge, the drug loading and release, the photothermal properties and the biocompatibility can be further examined.

Although great progress has been made, drug delivery systems for breast cancer treatment still face limitations. Tumour heterogeneity, where the diverse molecular characteristics of different breast cancer subtypes pose a challenge in devising an effective drug delivery system. Thus, the heterogeneity of cancer must be a key to the appropriate treatment as well as the personal characteristics of a patient (Afzal, et al., 2021) [5].

Chapter one reviewed the background, the purpose and the significance of the study by stating also the problem the limitations and the research questions that accompany this thesis. Next, Chapter 2 discusses thoroughly the literature review on nanotechnology discussing in the various approaches and the methods of nanotechnology based on drug delivery. It further explains the nanoscale drug delivery mechanism and the advantages of the use of drug delivery system. In Chapter 3 there is a focus of drug delivery systems and their usage in cancer therapy. More specifically, different types of targeted delivery systems in cancer therapy are examined, the

rotation and techniques used. Furthermore, the dosage of drug delivery and systemically administered drugs are discussed, rounding off with the advantages and disadvantages. Chapter four is stating the methodology that is used which is the drug delivery system in clinical trials and their benefits and limitations are also defined. Ethical consideration and informed consent are also included in this chapter as well as the fuzzy logic and its application along with fuzzy PROMETHEE. Multicriteria decision making model (MCDM) is also a very crucial point of discussion for choosing the right methodology and criteria in order to collect systematic data. In Chapter 4 an analysis of data takes place according to the criteria chosen in the collection of data in chapter 3 and a general review of the results is reviewed. To round off, Chapter 5 is the conclusion of the current thesis and the future challenges that are stated for any further research in the field of drug delivery systems usage in breast cancer therapy.

CHAPTER II

2. Literature Review

2.1 Introduction

Nanotechnology is the engineering and manufacturing of materials at the atomic and molecular scale. In its strictest definition from the national nanotechnology initiative, nanotechnology refers to structures roughly in the 1−100 nm size regime in at least one dimension (see Figure 1) (Bayda, et al. 2019) [6]. Despite this size restriction, nanotechnology commonly refers to structures that are up to several hundred nanometers in size and that are developed by bottom-up or top-down engineering of individual components. This can be achieved through various methods, including lithography, etching, deposition, and other techniques used in microelectromechanical systems (MEMS) and nanotechnology (Ebad-Sichani, et al. 2023) [7]. Nanotechnology is important for a wide range of applications, including the production of microelectronic devices, sensors, drug delivery systems and medical devices. It also plays a key role in the development of new materials and technologies, such as nanostructured catalysts, solar cells, and batteries (Vasilev, 2021) [8]. Nanofabrication involves the use of specialized equipment and techniques to create nanoscale structures and devices with high precision and accuracy. These structures and devices can be used in a wide range of applications, including electronics, energy, medicine, and materials science (Malik, et al. 2023) [9].

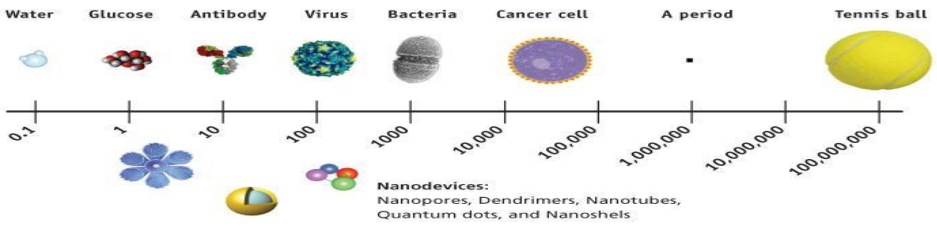


Figure 1: Nanofabrication scale 1 to 100 nm [164]

2.2 Applications of Nanotechnology

There are various and widespread applications of nanotechnology. To begin with, one major application of nanotechnology is electronics and photonic. Nanotechnology is used to make transistors, sensors, and lasers, among other components for electrical and photonic devices. Another application is biomedical and healthcare, where nanotechnology is utilized to make tissue engineering scaffolds, drug delivery systems, biosensors, and other diagnostic and therapeutic devices. Energy, materials and devices for energy production, storage, and conservation, such solar cells, batteries, and fuel cells, can be made using nanotechnology processes. Furthermore, science materials with unique characteristics, such as superconductors, nanocomposites, and functionalized surfaces, are created with nanofabrication and nanotechnology. Materials and equipment for environmental monitoring and remediation, such as air pollution sensors and water filtration systems, are made using nanotechnology (Zhu, et al 2022) [10]. Through nanotechnology, protective coatings and sensors, materials and devices with better qualities are used in security and defense applications. In biology, numerous instruments and devices for research and diagnostic usage are made using nanotechnology. It may be used, for instance, to build nanoscale sensors for identifying particular proteins or microfluidic devices for handling and analyzing tiny amounts of biological fluids (Tovar-Lopez 2023) [11]. This thesis is going to focus on the drug delivery systems by using Au gold NPs in breast cancer treatment.

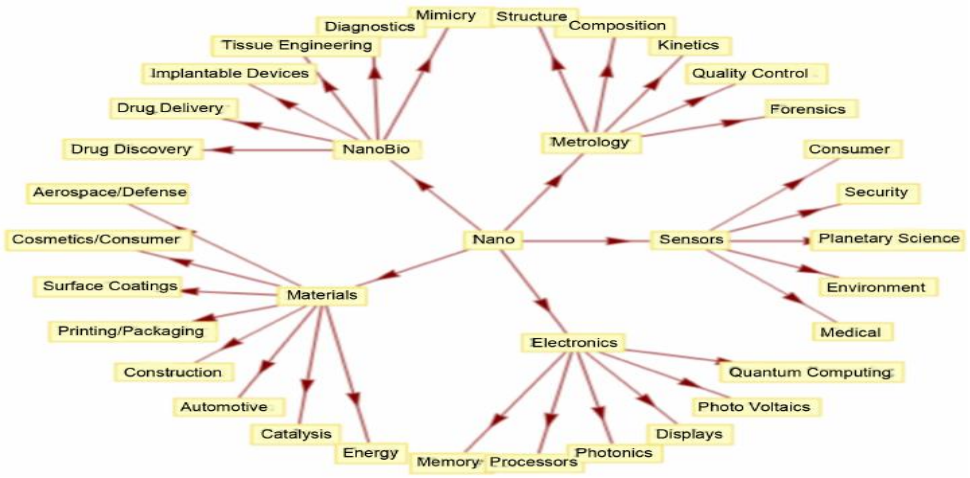


Figure 2: Nanotechnology in various fields [165]

2.3 Approaches of Nanotechnology

Over the past two decades, nanotechnology has become a major attention of researchers, showing the abilities in improving electron transfer efficiency in materials, generating high energy densities that lead to pulse energy, enabling accurate clinical diagnosis and detection, and enhancing material properties. This technology has also contributed to the environmental remediation, control, and development of new therapeutic methods. However, this technology is still continuous developing in manufacturing and manipulation techniques which have paved the way for the production of highly sensitive devices based on nanostructures. There are three approaches that are used in manipulating and fabricating Nanostructures, nanomaterials, and nanocomposites: top-down, bottom-up, and hybrid approaches (Kumar, et al., 2017). [12]

2.3.1 Top-Down Approaches

Top-down approaches to nanotechnology are starting with a bulk material and gradually reducing the size of the structure using diverse methods including etching, lithography, and milling. These approaches are in contrast to bottom-up approaches, which include constructing structures one atom or one molecule at a time. Top-down approaches may be used to construct a variety of nanostructures, including nanotubes, nanoparticles, and nanowires, and they are effective for producing objects with clearly defined forms and patterns. They are frequently used in the creation of nanoscale parts and microelectronic devices (Kumar, et al. 2017) [13].

There are some examples for top-down approaches, such as photolithography, utilizing light the pattern is transferred to a photoresist material, which is then used as a mask to etch the pattern into a substrate in the process of photolithography. Electron-beam lithography patterns a substrate with the help of a focused electron beam. High resolution can be achieved, but the process is slower and more costly than photolithography. Lithography can be further divided into photolithography, which uses a light-sensitive polymer that is exposed to light to transfer a customized shape onto the polymer, and soft lithography, which uses a mold to create nanostructures out of poly (dimethylsiloxane). Also, lithography is the most typical top-down manufacturing methods, because it has cost effectiveness, high quantity, high resolution, and versatility (Chen, Y. 2015) [14].

2.3.2 Bottom-up Approach

A bottom-up approach identifies and analyzes individual parts or lower-level systems before combining them to create higher-level systems or more intricate structures. In disciplines including biology, engineering, and computer science, this method is frequently employed. For instance, in computer science, a bottom-up strategy can start with discrete computer hardware parts such as capacitors, transistors, and resistors and then combine them to produce bigger parts for example circuit boards. Then, these parts may be connected together to create even bigger systems (such as servers and computers) (Khan, et al. 2022) [15].

In biology, studying how cells and molecules work and interact with one another, a bottom-up approach is frequently applied. Biologists can comprehend better how individual cells and molecules contribute to the overall functioning of an organism by learning the characteristics and activities of those particular cells and molecules (Xavier, et al. 2014) [16]. While in the economy field, economists occasionally employ a bottom-up approach to assess consumer and corporate behavior and how it affects the overall performance of an economy. This can aid in locating the variables that promote economic stability and growth. Overall, by dissecting complicated systems into smaller, more manageable bits and examining how those pieces interact, the bottom-up approach is a helpful tool for comprehending them (Saul, 2018) [17].

2.3.3 Hybrid Approach

Hybrid nanotechnology or nanofabrication approaches involve combining elements of both top-down and bottom-up approaches to achieve specific goals. For example, self-assembly and photolithography working together may produce very complex and accurate microstructures. Self-assembled monolayers (SAMs), for instance, can be utilized as a photolithographic template to create features with nanometer-scale dimensions (Parviz, et al 2003) [18]. Another technique is an electric current is used to deposit metal ions from a solution onto the substrate while employing a template to direct the formation of the film or coating. This technique is known as electrodeposition combined with template-assisted methods. The form, size, and composition of the final film or coating may be precisely controlled using this procedure, which can also be used to create a variety of materials, such as semiconductors, and metals (Ruiz-Gómez, et al. 2022)

[19]. There is also another technique is the use of 3D printing technologies in conjunction with chemical processes to synthesize materials or things is referred to as "3D printing mixed with chemical synthesis including polymers, metals, and ceramics, and it allows for the exact control of the form, size, and composition of the final material or item (Aguirre-Cortés, et al. 2023) [20].

2.4 Applications of Hybrid Materials

Hybrid materials significantly matter in the daily life and as an alternative to designing new materials, their features allow the development of innovative industrial applications. These applications can be applied in many fields such as electronics, optics, mechanics, energy, biology and medicine. Hybrid materials are divided into organic and non-organic. Following, the applications described below are chosen for medicine (Das, et al., 2021) [21]. Researchers are attracted to explore new and smart nanocomposite materials through the use of hybrid organic-inorganic nanomaterials. These materials display interesting properties, including notable catalytic activity, stimulated optical features, and diverse physical properties. Organic nanoparticles, such as liposomes, polymers, polymer formulations, and micelles, have been extensively studied for these applications in drug delivery system, imaging technologies, and gene delivery. In addition, inorganic nanoparticles have gained attention because of their distinct physical and chemical properties, which are affected by the material composition and size, inorganic NPs are incomparable with conventional polymer/ lipid-based nanoparticles (Khalid, et al., 2020) [22].

2.4.1 Biomedical Applications

Hybrid materials are utilized to make a variety of medical equipment and treatments in the biomedical field. Hybrid materials may be utilized to construct targeted, regulated, and sustained drug delivery systems. Drug delivery systems are one example of a hybrid material's biomedical use. For instance, medications may be delivered to particular parts of the body, such cancer cells, using hybrid materials consisting of polymers and nanoparticles (Cai, et. al 2021) [23]. Another example of hybrid material's biomedical is biosensors, using hybrid materials and it is possible to

make extremely sensitive and selective biosensors, which have a variety of uses. As an example, hybrid materials comprised of metal nanostructures and polymers have been created for use in biosensors for detecting certain biomarkers in blood and other bodily fluids (Soto, & Orozco, 2022) [24].

2.5 Nanotechnology in Healthcare and Medicine

The word of nanomedicine is utilized to describe the use of nanotechnologies in medicine and healthcare. In order to prevent, monitor, diagnose and cure illnesses, nanomedicine employs technology at the nanoscale and nano-enabled procedures. Nanotechnologies have a great deal of potential in the field of medicine, including in drug delivery systems, diagnostic tools, imaging, tissue-engineered constructs, pharmaceutical therapeutics, and implants (see figure 3). They have also advanced the treatment of many diseases, including cancer, musculoskeletal conditions, diabetes, cardiovascular disease, and bacterial and viral infections (Haleem, et al. 2023) [25].

Figure 3: Aids in medication delivery to the tumor complex via a nanomedicine platform [166]

2.6 Applications of Drug Delivery

Numerous industries have been transformed by nanotechnology, and medication delivery is one such one that is quite promising. The engineering and manipulation of materials at the nanoscale, which generally ranges from 1 to 100 nanometers, is the focus of the field of nanotechnology. At this size, materials display special qualities that can be used to develop revolutionary drug delivery systems with improved accuracy and efficiency (Sahu, et al. 2023) [26].

Nanotechnology in the context of drug delivery is concentrated on the creation of nanoscale drug delivery systems, also known as nanocarriers or nanoparticles. These nanocarriers are intended to encapsulate medications, protect them from deterioration, and deliver them with improved accuracy to specific areas in the body. Drug delivery refers to the procedures and equipment used to deliver therapeutic substances to predefined target organs and tissues. Traditional drug delivery techniques frequently have issues with poor solubility, constrained bioavailability, fast degradation, and lack of selectivity. With the use of nanotechnology, which opens up new possibilities for effective pharmaceutical administration, these limitations can be overcome (Tiwari, et al 2012) [27]. In medication delivery based on nanotechnology, scientists create and refine nanoscale carriers, also known as nanoparticles. Lipids, polymers, metals, and inorganic compounds can all be used to create these nanoparticles. They have distinct physicochemical characteristics, including the capacity to encapsulate and shield medicinal molecules, a high surface area-to-volume ratio, and variable size and shape (Sim, et. al 2021) [28].

Since of its high selectivity towards the target region, nanotechnology application is crucial in the field of drug delivery, since it can minimize the damaging side effects of medications on healthy cells. Nanotechnology is employed for drug delivery due to its low cost of products, improved patient comfort, efficiency, low plasma fluctuation, and high solubility. In order to deliver drugs to the target area, the nanoparticle (NP) plays a critical role and can conjugate with various pharmaceuticals employing a range of methods (Rizvi, et al. 2018) [29]. The NP surface is built with ligands to increase cell affinities and co-polymers to increase immune cell protection. The drug-conjugated nanoparticles will ultimately be able to recognize the location, unite with the target, and enter the cell by receptor-mediated endocytosis. NPs can then release medications under control to treat illnesses (Wanigasekara, et. al 2016) [30].

Nanotechnology-based drug delivery has transformed the practice of medicine by increasing the efficacy and efficiency of therapeutic interventions. Here are some of the important uses for delivering drugs in nanotechnology, such as targeted drug delivery; drugs can be precisely directed to target cells, tissues, or organs utilizing nanotechnology. Drugs can be carried by nanoparticle and delivered directly to the target spot, by reducing adverse effects and enhancing therapeutic results. Selective drug delivery is made possible by the ability of these nanoparticles to identify and attach to particular biomarkers or receptors on target cells (Hsu, et al. 2023) [31].

Combination therapy is made possible by the simultaneous delivery of several drugs or therapeutic agents made possible by nanotechnology. Synergistic effects can be created, improving treatment results, by encapsulating several medications into a single nanoparticle or creating multifunctional nanoparticles. When treating complicated illnesses like cancer, where numerous pathways or targets must be targeted, combination treatment can be especially successful (Gurunathan, et al. 2018) [32]. In nanomedicine for diagnostic and theranostic purposes, nanoparticles can be created to act as diagnostic tools in addition to being for drug delivery. Because of the ability of these nanomedicines to contain imaging agents like contrast agents or fluorescent dyes, non-invasive imaging and real-time disease progression monitoring are made possible (Zhu, et al 2021) [33].

2.7 Smart Drug Delivery Systems for Cancer Therapy

Anticancer drugs often face difficulties due to their lack of specificity and toxicity concerns. And their therapeutic effects are obstructed further by problems, including drug resistance and insufficient concentrations at tumor sites. Although additional options exist, including radiation and surgery, their limited applicability underscores the need for new anticancer treatments. By enhancing the distribution, behavior and efficacy of therapeutic drugs within the body, nano-drug delivery systems (NDDS) provide viable platforms for anti-cancer therapy (Kenchegowda, et al., 2022) [34]. An important component of NDDS is smart drug delivery systems, which allow controlled release, targeted precision, and biological barrier traversal. As a result, for smart drug delivery system, the systemic adverse effects will be reduced and therapeutic enhancing will be increased (Wang, et al., 2022) [35].

2.8 Strategies of Smart Drug Delivery System for Cancer Therapy

In the field of cancer therapy, smart nanoparticles have proven to be an outstanding platform. This technology has been designed to release a therapeutic cargo specifically at tumor sites in response to both internal factors such as pH, enzymes and redox gradients, and external factors such as temperature, ultrasound, magnetic field and electric field, and has been subject to extensive investigation. These nanoparticles, which respond to stimuli, enable drug release on demand. This precision not only reduces non-target side effects by preventing the drug from leaking into the bloodstream, but also ensures more precise therapeutic enhanced. However, an intelligent drug delivery system holds great promise in this field (Li, & Kataoka. 2020) [36].

2.8.1 Endogenous stimulus-responsive Drug Delivery System

Biological features that distinguish tumor tissues from normal tissues include low pH levels, high expression of certain enzymes, high redox potential, and hypoxia. By taking advantage of these contrasts, drug delivery systems (DDS) that are sensitive to pH, enzymes, and redox conditions are created. These systems are designed to load smart drugs and enable their timely and site-specific release, increasing the effectiveness of treatment (Mi., 2020) [37].

2.8.2 Drug Delivery System Responsive to Exogenous Stimuli

The ability to precisely control drug release by external agents in these systems makes them promising for overcoming inter-patient variability. Temperature-responsive polymers play a crucial role in the design of these drug delivery systems since many of these particular induce heat generation. An increase in temperature can accelerate drug release from heat-sensitive materials. Exogenous stimuli-responsive drug delivery systems in cancer therapy offer advantages of adjusting their position and strength, using stimuli such as light, magnetic fields, or electric fields. Another benefit is the flexibility in applying or removing exogenous stimuli. Furthermore, these systems can integrate multiple external catalysts into a single nano-platform, providing multifunctional advantages (Raza, et al., 2019) [38].

2.8.3 Smart Receiver-Based Drug Delivery System

Precision targeting is critical in drug delivery systems, particularly smart drug delivery systems (DDS). Tumor targeting drug delivery uses two fundamental approaches: passive targeting and active targeting. Whereas passive targeting has always been the emphasis, there is rising dispute regarding its effectiveness following years of investigation, this mostly back to the effect of enhanced permeability and retention (EPR). Researchers observed that positive and negative influences have different impacts on the formation of nanoparticles (NPs) within malignant tumors. Notably, they discovered that with time, receptor-mediated targeting contributes more and more to the EPR effect. Furthermore, it is becoming clear that NP transport through the gaps in cancer blood artery endothelial cells is essential for improving permeability and effective retention (EPR). The interaction between drug delivery systems (DDSs) and non target locations is a common topic of discussion when it comes to active targeting. These issues involve both nonspecific and selective interactions, in which receptors may be expressed similarly yet differently in target and nontarget regions. There have been several techniques suggested to solve these problems. One reversible protective strategy for the target molecule is the creation of nanoparticles that react to the acidity of tumors (Wang, et al., 2022) [39].

2.9 Nanoparticles Drug Delivery Mechanism

NP can be utilized to enhance drug delivery because they have advantageous features that can be leveraged to circumvent the body's defense mechanisms. In an effort to improve the effectiveness, safety, and tolerance of ingested medications, several nanoparticle formulations have been used in drug research. Better pharmacokinetic and pharmacodynamic, high solubility, and controlled release features have all been demonstrated by formulations based on nanoparticles. Effective nanoparticle delivery systems might be made via a number of processes such as shape, particle size, and surface charge all these are essential factors for nanoparticles (Lôbo, et al, 2021) [40].

2.9.1 Surface Charge

The zeta potential of nanomaterials, which represents the electrical potential of particles that is impacted by its composition, is typically utilized to express and assess surface charge. Nanomaterial surface charge is essential for drug loading. Several techniques, including encapsulation, covalent conjugation, and hydrophobic contact, all these techniques can be utilized for loading drugs (Joudeh, et al. 2022) [41].

2.9.2 Particle Size

The most crucial aspects of nanomaterials are their size distribution and particle size because they govern their physical and chemical properties. Biological destiny, toxicity, in vivo distribution, and targeting capacity of these nanomaterials for drug delivery systems are determined through their size distribution and hydrodynamic size. They can control medication loading, stability, and release Although the importance of nanoparticle drug delivery systems has been emphasized, these systems are useless if the medication is not delivered or is not distributed efficiently. The surface area to volume ratio of tiny particles increases. This would suggest that more drugs are present on the particle's surface than on the surface of a bigger molecule. A quicker rate of medication release would result from being close or at the surface. Large surface area to volume ratio nanoparticle systems might be advantageous, but toxicity must constantly be regulated (Prabhakar, et. al 2020) [42].

2.10 Advantages and Disadvantage of Nanotechnology in Drug Delivery

Drugs are often ingested or administered intravenously, circulate throughout the body, and may have a negative impact on tissues, organs, and cells. Because of their vulnerability to absorption across the intestinal epithelium, peptide and protein drugs are inadequately absorbed after oral administration. And high dosages are required for traditional drug delivery to achieve the required bioavailability. The following are some benefits of utilizing nanoparticles as a drug delivery. The prolonged and controlled release of the medication throughout transportation and localization, modifying the medication's organ distribution and subsequent clearance to maximize therapeutic efficacy, and minimize adverse effects (Saeed Jan, et al. 2023) [43].

Medicine can enter the system without causing a chemical reaction, which is crucial for keeping the medicine stable. It is also simple to modify medication degradation and controlled release properties. Since there is no drug wastage, the medication is more bioavailable at a given location in the proper dosage for a longer length of time (Wen, et al. 2015) [44]. It extends the half-life of a drug's systemic circulation by lowering immunogenicity, decreases the frequency of administration. Increases the solubility of poorly water-soluble medicines, and releases medications steadily. In contrast to traditional methods, it increases the therapeutic performance of the medicine while giving the patient compliance and comfort (Singh, et al. 2011) [45].

Table 1 below shows the various types of drug delivery systems, the materials used for each drug delivery system and their active pharmaceutical ingredient (API). Each type of drug delivery system discusses in the last column its significance of it being used for treating a type of illness.

Table 1: Types of Drug Delivery Systems

Types of Drug delivery systems	Materials	Active Pharmaceutical Ingredient (API)	Significance of the study
ORAL			
Silk Nanoparticles	Silk and fibrin	Celecoxib and curcumin	Since a controlled drug release was accomplished by adjusting the drug loading, silk fibroin nanoparticles were seen to promote the anti-inflammatory activities of celecoxib or curcumin and might be used for oral osteoarthritis therapy [46].
Electrospun fibers	Polylactic acid	Metronidazole	During the periodontitis therapy, metronidazole (MNZ) and PLA nanofibers were employed to limit microbiological proliferation and prevent bacterial development. [46]
OCULAR			
Nanocomposite hydrogel	Hyaluronic acid	Latanoprost	The controlled release and controlled breakdown capabilities of the hyaluronic acid nanocomposite hydrogels make them viable drug delivery systems for numerous eye illnesses. In vitro, they also regulated the release of latanoprost. [46]
Hydrogel contact lens	Silicone	Ofloxacin/ Chloramphenicol	The Silicone hydrogel contact lenses are an alternate ocular delivery method for the treatment or prevention of corneal infections that may be utilized to manage medicine administration to the eye. [46]

PULMONARY Porous particles	Poly(lactide-co-glycolide) (PLGA) Nanopolymeric	Celecoxib	Using supercritical fluid technique, large porous celecoxib-PLGA microparticles demonstrated sustained drug delivery and antitumor effectiveness without significantly increasing toxicity. [46]
Nanoparticles	Particles consisting of hydroxyl propyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP)	Fluticasone	According to in vitro antibacterial experiments, HPMC-PVP-FLU nanoparticles had a better impact on Gram-positive bacteria than unprocessed FLU and a positive control. [46]
IMPLANT Silk disc implants	Silk fibrin	IgG antibody or human immunodeficiency virus (HIV) inhibitor 5P12-RANTE	SF was created as insertable discs that are capable of encasing either IgG antibody or the HIV inhibitor 5P12-RANTES. The protein that was generated after the prolonged release of the water vapor annealing for 31 days might prevent HIV infection in human colorectal tissue as well as blood. [46]
Bone biomaterials implant	Hydroxyapatite	Doxorubicin-loaded cyclodextrin	After implantation, the hydroxyapatite-cyclodextrin-doxorubicin chemotherapy method improved the drug's ability to target tumor cells while safeguarding the more delicate healthy cells. [46]

SYSTEMIC			
Polylactide scaffold hydrogel injections	Cholesterol modified poly (ethylene glycol)–polylactide	Chondrocytes	The hydrogel offers an alternative to surgical cartilage repair and acts as a potential chondrocyte carrier for cartilage tissue creation. [46]
Functionalized plant chloroplast	Lyophilized lettuce cells (ACE2/ANG-(1–7))	Lyophilized lettuce cells (ACE2/ANG-(1–7))	The clinical progress of the first oral protein treatment to prevent/treat the underlying pathophysiology for this condition looks promising given the effective reduction of pulmonary arterial hypertension with no harm. [46]
VAGINAL			
Organogel	Palm oil and hyaluronic acid	Maraviroc	This demonstrates the possible use of an organogel made of hyaluronic acid and palm oil for the vaginal administration of anti-HIV microbicide. [46]
Vaginal rings	Silicone matrix polymer	Dapivirine	Women who received a dapivirine-containing vaginal ring on a monthly basis had a lower chance of contracting HIV-1, with subgroups showing higher effectiveness. [46]
TOPICAL			
Hydrogel	Polyvinyl alcohol and carbopol	Diclofenac diethylamine	The study emphasized the benefit of the transdermal hydrogel experiment over the hydrogel containing tiny drug particles. [46]
Electrospun fiber	Polylactic acid and collagen	Collagen and silver sulfadiazine	The electrospun fibers had the potential to be used in the treatment of chronic wounds, because they were nontoxic to cells and offered ideal substrates for the growth and cell attachment of newborn epidermal keratinocytes. [46]

CHAPTER III: Nanotechnology-Based on Drug Delivery in Cancer Therapy

3.1 Drug Deliver in Cancer Therapy

Nanotechnology has been utilized in medicine more over the past few decades, including applications for tumor targeting, diagnostics, and therapy that are more efficient and safer. Drug delivery methods based on NPs have demonstrated a number of benefits in the treatment of cancer, including a good pharmacokinetics, such as, decrease in adverse effects, reduced drug resistance, and accurate targeting of cancer cells. The size and characteristics of nanoparticle are utilized in medication delivery systems, which are often chosen or created by depending on the pathophysiology of tumors. In terms of mechanics, Nanocarriers in cancer therapy work by situating the target material after absorption and acting as carriers for cancer cells (Yao, et al. 2020) [47].

A range of biomolecules, such as peptide, protein, and nucleic acid-based medicines, have replaced traditional small chemical medications as the preferred drug delivery methods and therapeutic modalities during the past twenty years. Millions of patients are currently receiving their cancer therapies through the use of drug delivery systems, which have sparked the development of treatments as well as substantial advancements in in current therapies (Varanko, et al. 2020) [48]. Several drug delivery systems, including liposomal systems, polymers drug conjugates, local chemotherapies that have been approved by healthcare organizations and are now being used in hospital and clinics. Delivery of anticancer drugs is a crucial component of cancer treatment that aims to improve the efficacy of cancer treatments by lowering their negative effects. They impact both cancerous cells and healthy cells, thus traditional cancer therapies like radiation therapy and chemotherapy can have serious adverse effects. Targeting tumor cells more accurately with drug delivery techniques aims to maximize therapeutic effect, while limiting harm to healthy tissue (Xiao, et al. 2022) [49].

3.2 Targeted Delivery in Cancer Therapy

In most parts of the world, cancer is still one of the top causes of mortality. Regular screening has led to an early prognosis of the disease, and a deeper comprehension of the mechanism of tumor growth has created a wealth of novel therapeutic opportunities. Following surgical excision, the residual cancer cells in the majority of solid tumors are treated using a range of techniques for instance radiation, chemotherapy, immunotherapy and many more (Debela, et al. 2021) [50]. However, chemotherapy is still the recommended course of action if the disease has spread as there are few alternative options. Chemotherapy frequently fails, because cancer-killing drug have a hard time getting to the tumor in sufficient quantities without endangering the rest of the body. Additionally, some drugs may harm healthy cells. However, a technique known as targeted drug delivery offers promise. It aims to deliver the appropriate dosage of medication straight to the tumor, potentially improving cancer treatment by lowering adverse effects and increasing efficacy (Amjad, et al. 2023) [51].

By using targeted drug delivery, healthcare providers can increase the therapeutic efficacy of drugs, while minimizing side effects and reducing systemic exposure to medicines. Targeted drug delivery aims to deliver pharmaceuticals or therapeutic agents to a specific region inside the body with the lowest possible risk of adverse effects on healthy tissue (Tewabe, et al. 2021) [52]. When a human organ or a cell area is affected by tumor, drugs can be assigned on their own or by a drug delivery system. The essence of particular targets or their ligands are monitored by different manners of delivery the drug to the affected target with the use of various delivery systems associated with ligands. Solid or hematologic tumor must develop other ways personalized to every cancer type (Elumalai, et al. 2023) [53]. There are three approaches of targeting drug delivery on tumor; the passive, active, and physical targeting. To begin with, an overview will take place on passive targeting, including the two types, EPR effect and localised delivery. Secondly, a discussion on the active targeting will proceed, including the vascular endothelium. To conclude, physical targeting will be examined describing magnetic field (Yu, et al. 2016) [54].

3.2.1 Passive Targeting

In passive targeting cancer therapy, depends on physiological characteristics of target tissue. This allows drug- loaded liposomes and nanoparticles to accumulate in tumors, and these tumors often contain leaky blood vessels due to the enhanced permeability and retention effect (EPR). EPR effect and localized delivery these are approaches of drug targeting (Bazak, et al. 2014) [55].

Tumors demonstrate a phenomenon referred to as the enhanced permeability and retention (EPR) effect, which holds promise in cancer treatment. This effect elucidates how specific nanoparticles possess a tendency to accumulate more in tumor tissues than in normal tissues due to distinctive characteristics of the vasculature within tumors (Wu, 2021) [56]. Leveraging the impact of EPR, researchers have explored an alternative approach for delivering traditional anticancer drugs. The biodistribution of nanoparticles in the bloodstream plays a crucial role in achieving high levels of accumulation in solid tumors. Several nano-carrier systems have been developed, incorporating those designed for delivering anticancer drugs, to treat cancer based on the enhanced permeability and retention principle (Subhan, et al 2023) [57].

3.2.1.1 Localized Drug Delivery

The significance of localized drug delivery systems (LDDS) is growing, offering patient's friendly and non-invasive alternatives for cancer treatment with minimal doses to reduce toxicities. LDDS entails directly delivering drugs to the specific tumor site, eliminating systemic side effects and concentrating drug levels at the target location. However, Transmucosal and transdermal drug delivery systems are commonly employed for localized administration. However, not all tumors, such as lung cancer, are suitable for this approach. In contrast, for prostate cancer treatment, this strategy can prove effective (Hussein, et al. 2020) [58].

3.2.2 Active Targeting

In the realm of cancer treatment, "active targeting delivery" denotes a specific approach to administering therapeutic drugs. This method aims to selectively target cancer cells, while minimizing the impact on healthy cells. It involves the application of certain compounds, known as ligands, onto the surface of cancer cells. These ligands identify and bind to receptors or markers that are overexpressed in cancer cells (Rana, et al 2023) [59]. In contrast, passive targeting exploits the enhanced permeability and retention (EPR) effect associated with malignancies. Active targeting entails the design of drug delivery vehicles equipped with ligands or antibodies attached to their surfaces, such as liposomes or nanoparticles. The selection among these ligands is predicated on their capacity to identify and attach to particular receptors or antigens that exhibit greater abundance in cancerous cells relative to normal cells (Subhan, et al. 2021) [60].

3.2.2.1 Tumor Vascular Endothelium

One of the drug delivery technique, referred to as "active targeting on vascular endothelium," employs therapeutic compounds crafted to selectively engage with and accumulate in the endothelial cells lining blood arteries. A promising strategy involves targeting malignancies through their vascular endothelium, utilizing easily accessible targets and genetically stable endothelial cells that resist developing resistance to therapeutic drugs (Glassman, et al 2020) [61]. The vascular endothelium of solid tumors differs anatomically from normal tissues, displaying functional receptors on the cell surface. Targeting the tumor vasculature with different effector molecules, including cytotoxic pharmaceuticals, antiangiogenic chemicals, immunostimulatory agents, and radiolabeled cytotoxic medications, is possible after particular angiogenic targets have been identified. The vascular endothelium is widely accessible throughout the circulatory system, offering a variety of therapy options for cancer. This encompasses endothelial cells as well as certain tissue components that can function as medication delivery or carrier systems. Numerous physiological activities depend on vascular endothelium (Glassman, et al. 2020) [62].

3.2.3 Physical Targeting

To enhance drug delivery methodologies, various techniques from diverse technological and scientific domains have been adapted to develop physical drug delivery (PDD) systems. Essential to this endeavor is a purpose-built system enabling the manipulation of drug dispersion within a living organism via diverse physical processes (Rodriguez, et al. 2012) [63]. Employing a spectrum of physical modulation strategies aids in surmounting the outlined constraints and challenges in administering medications physically. These PDD systems encompass distinct categories like electrical, ultrasound, magnetic, and photo systems, each employing unique physical modulation techniques. However, conducting an exhaustive analysis of all available resources proves impractical due to the extensive breadth of this field (Adepu, et al 2021) [64].

3.2.3.1 Magnetic Field Targeting

The core of magnetic drug delivery relies on external magnetic forces directing particles within the body. Superparamagnetic iron oxide nanoparticles (SPIONs) are commonly employed for this purpose (Wahajuddin, et al. 2012) [65]. Unlike traditional ferromagnetic materials, these particles aren't inherently magnetic but become magnetized only when exposed to an external magnetic field. Once the field is removed, their magnetic orientation dissipates, returning to a random state. SPIONs' responsiveness to magnetic fields is crucial for their application in thermal ablation, imaging, and hyperthermia treatment involving magnetic nanoparticles (Liu, et al. 2019) [66].

Consequently, there has been a persistent need to create SPIONs that are more effective. A particle's magnetic moment is often inversely correlated with its size. As a result, a number of techniques have been created to make superparamagnetic iron oxide nanoparticles larger. Using an external local magnetic field, a therapeutic agent enclosed or bonded in a magnetic drug carrier is injected intravenously as part of the magnetic targeting strategy (Dulińska et al. 2019) [67]. The therapeutic agent may then be localized and targeted preferentially in tumor tissue. Materials like cobalt, magnetite, iron, and nickel are frequently used as magnetically sensitive drug carriers. Microspheres, nanospheres, magnetic liposomes, and colloidal iron oxide solutions (ferromagnetic fluids) are a few examples of these drug carriers (Rarokar, et al. 2023) [68].

3.3 Drug Delivery Rotation in Cancer Treatment

The process of occasionally altering the treatment plan or the particular medications used to target cancer is known as rotation of drug delivery in cancer therapy. This strategy is used to accomplish a number of important goals such as overcoming resistance; as time passes, cancer cells may become resistant to some drugs, which will decrease their efficacy. It may be more difficult for cancer cells to adapt and become resistant when various medications or pharmacological classes are alternated (Spoială, et al. 2023) [69].

Certain cancer cells could react more favorably to a certain medication despite being less responsive to. Clinicians may be able to target a wider variety of cancer cell subpopulations and maximize therapy success by switching up their drugs regimen, thus enhancing efficiency. Some cancers may spread or develop into secondary tumors during treatment (Wang, et al. 2019) [70].

Rotating drugs can help target both the primary tumor and potential metastatic sites, preventing metastasis. Continuous exposure to high doses of a single drug can lead to drug saturation or the development of tolerance and these rotating drugs can help avoid this problem Oncologists usually decide on a patient's course of therapy after considering their requirements and therapeutic responses. The kind and stage of the malignancy, the patient's general health, and the particular medications that are available all have a role in the rotation strategy that is used (Mansoori, et al. 2017) [71].

3.4 Nanoparticles

With diameters ranging from 1 to 100 nanometers, nanoparticles are very small particles. They can be created using drug encapsulation and drug delivery to particular target organs. Lipids, polymers, metals, or inorganic compounds can all be utilized to create nanoparticles. They can improve solubility, protect drugs from degradation, and lengthen drug circulation in the body. These drug delivery techniques using nanotechnology include benefits including increased medication stability, controlled release, focused distribution, and fewer adverse effects. Prior to wide-scale clinical application, however, it is crucial to stress that intensive research and development are currently being conducted to improve these strategies and guarantee their efficacy and safety (Joseph, et al. 2023) [72].

3.5 Techniques Used in Drug Delivery for Cancer Therapy

The treatment of cancer involves the employment of several advanced medication delivery techniques. Cancer treatments have been developed using a broad variety of nanocomposites based on synthetic polymers, proteins, organic and inorganic compounds, and lipids. When a drug is encapsulated in a carrier as opposed to being administered directly, there are several benefits that include improved pharmacokinetics, increased drug solubility, decreased toxic side effects, drug's pharmacodynamics characteristics, targeted drug delivery, and the drug's prevention of the drug from degrading in the bloodstream (Edis, et al. 2021) [73]. Comprehensive collection of various drug delivery molecules with varying surface features, structures, physicochemical characteristics, and sizes, together with targeting techniques, has been created thus far. There are many types of nanoparticles as used drug delivery system in cancer therapy such as, carbon nanotubes, liposomes, dendrimers, gold nanoparticle, and polymeric micelles and some of them will be discussed in the following section. These types of nanoparticles are used for cancer drug delivery due to their large area of surface, adjustable features and small sizes. These anticancer drugs are also targeted, delivered, and encapsulated by using these types (Ezike, et al. 2023) [74].

3.5.1 Polymeric Nanoparticles

Polymeric nanoparticles are crucial for the regulated administration of anti-cancer drugs. By enhancing bioavailability, stability, and target specificity, NP can provide effective therapeutic solutions that mitigate adverse effects and get around the drawbacks of traditional therapy approaches. Drug delivery techniques based on nanoparticle have the ability to accomplish a number of goals. By dispersing hydrophobic substances in aqueous environments, they can increase the time that the pharmaceuticals remain in the bloodstream, preserve their stability, and improve the poorly soluble medications (Dristant, et al. 2023) [75].

3.5.2 Carbon Nanotubes

In recent years, carbon nanotubes have emerged as an innovative conduit for delivering both large and small medical compounds. These nanotubes can be tailored by incorporating specific compounds to alter their biological or physical traits. Beyond their role as carriers for diverse therapeutic compounds, carbon nanotubes have demonstrated utility in inducing photothermal cancer cell death, leveraging their substantial surface area and precise dimensional control (Murjani, et al. 2022) [76]. Carbon nanotubes stand out as a prominent nanomaterial widely employed in drug delivery, electronics, energy storage, and solar cells. Moreover, they offer a promising avenue in medical fields like cancer treatment, where they serve as drug delivery systems, ensuring targeted drug delivery to tumors while sparing healthy tissues. Unlike conventional chemotherapy, where medications affect both tumor cell and normal cell, targeted delivery reduces adverse side effects and allows for more effectiveness and focused dosages of chemotherapy agents, potentially revolutionizing traditional cancer treatments (Madani, et al. 2011) [77].

3.5.3 Polymeric micelles

Moreover, in the ongoing treatment of cancer, consistent administration of anticancer drugs is essential to uphold the optimal drug concentration at tumor sites. Prolonged use of these drugs can lead to enduring side effects and potentially trigger drug resistance. Polymeric micelles play a crucial role here, serving as a highly valuable tool in maintaining the stability of medications within aqueous environments (Wang, et al. 2023) [78]. These micelles protect the enclosed medications, facilitating targeted accumulation and sustained circulation within solid tumors. In addition, their ability to protect medications from external influences is vital for maintaining consistent blood flow and facilitating the controlled discharge of loaded drugs at tumor sites (Lu, et al. 2018) [79]. Drugs can be integrated into the micelle interior through either interaction with the polymer's hydrophobic segment or attachment to the polymer backbone using reversible connections, which can be triggered under specific conditions to release the active drug. Moreover, polymers have been modified to micelles by adding polyethylene glycol (PEG) to increase the circulation duration and avoid denaturation, using low temperatures or pH-sensitive polymer conjugates, and adding targeted ligands. PEG is the most widely used and efficient stealth polymer in the field of drug delivery using polymers (Pacheco, et al. 2023) [80].

3.5.4 Liposomes

Liposomes are spherical vesicles that consist of one or more lipid bilayers that are widely utilized in nanomedicine for cancer therapy and drug delivery, because of their capacity to retain medications at low levels. Both hydrophilic and hydrophobic medications can be included in them as chemical and physical characteristics (Abbasi, et al. 2023) [81]. Furthermore, the pharmacological advantages of liposomes are increased, and the effectiveness of anticancer medications is enhanced by the liposomes' increased flexibility and capacity to chemically change through the cross-linking of various molecules, polymers, and ligands. It has benefits that can be used to nanomedicines and improve the body's ability to detect, sustain, and identify anti-cancer cell agents (Rommasi, et al. 2021) [82]. PEG is a very hydrophilic polymer with very low toxicity that is frequently used to improve the stability and pharmacokinetics of drugs as well as drug carriers. Nowadays, PEG-lipid is widely used to modify the liposome surface (PEGylation) for the purpose of administering drugs. This technique has been used in the past to create

PEGylated liposomes, which are effective drug delivery vehicles enclosed in liposomes. In particular, doxorubicin-loaded liposomes show notable pharmacological activity with little toxicity. It has been widely used in clinical settings and approved for use as cancer therapies (Nakamura, et al 2012) [83].

3.5.5 Nanogels

Crosslinked hydrogel nanoparticles having a three-dimensional network structure are known as nanogels, and they are capable of encasing drugs. They can react to environmental cues like pH, temperature, or enzymes, which enables regulated drugs release. Nanogels have great drug loading capacity, good stability, and anti-drug degradation properties. Nanogels have become a focal point in discussions about drug delivery systems, particularly for targeted and precise drug administration (Maravajhala et. al 2012) [84]. Their effectiveness is underscored by remarkable qualities such as brilliant drug loading capacity, adaptability, responsiveness to environmental stimuli, and nanoscale properties. Chitosan, a natural polysaccharide derived from the deacetylation of chitin, boasts a unique chemical structure that lends itself to various chemical modifications. Despite its molecular intricacies, chitosan stands out as a distinctive biopolymer, being both biodegradable and biocompatible. Incorporating chitosan into nanogel formulations not only enhances their biodegradability but also contributes to their overall biocompatibility, proving advantageous in biomedical applications like drug delivery and regenerative medicine (Kayra, et al 2023) [85].

3.5.6 Dendrimers

High-branched synthetic molecules with a known structure are called dendrimers. On their surface, they have a lot of functional groups that can be altered to transport drugs. Dendrimers are advantageous for targeted drug delivery because they have a high drug-loading capacity, precise control over size and surface chemistry, and the power to overcome cellular barriers (Svenson, et. al 2012) [86]. In real-world medical applications, nanocarrier-based drug delivery systems, such as dendrimers, play a pivotal role in ensuring precise and controlled drug release. These microcarriers protect adjacent healthy tissue from harm, while effectively delivering the adaptable therapeutic payload to the specific target site. By changing the drug release pattern, these nanoparticles enhance the overall bioavailability of the drug. Commonly used drug carriers include polylactic-glycolic acid (PLGA), an FDA-approved biodegradable polymer. The exceptional degradation properties of PLGA allow for the gradual release of both hydrophilic and hydrophobic drugs. In addition, PLGA can modify its surface properties, facilitating enhanced interactions with specific cells or tissues, and readily binds to specific target molecules (Alkahtani, et al., 2021) [87].

3.5.7 Quantum Dots

Semiconductor nanocrystals called quantum dots have special optical characteristics. They can be functionalized with drugs or chemicals that target certain organs by coating them in biocompatible materials. For imaging and targeted drugs delivery, quantum dots have been investigated. They offer real-time monitoring of drug release and localization in the body (Wagner, et. al 2019) [88].

Table 2: Advantages and Disadvantages of Nanoparticles

Nanoparticles	Advantages	Disadvantages
Nanogels [89]	Improving the therapeutic efficacy, reducing the adverse effects of drugs, and easy degradability by enzymes, and high biocompatibility and biodegradable formulation.	Surfactant or monomers present in nanogel may cause adverse effects in the formulation, limited drug-loading efficiency and suboptimal regulation of drug release.
Quantum Dots	Enhanced stability, reduced toxicity, precise targeting, high specific surface area, and small size and unique physicochemical properties. [90]	Poor solubility, low bioavailability, poor absorption in the body, and probable adverse effects of drugs. [91]
Liposomes [92]	Reduced toxicity, resistance to chemical deterioration, delivery of hydrophilic, amphipathic, and hydrophobic medications, and enhanced effectiveness.	The short half-life, fusion and leaking of the encapsulated medication, potential for adverse responses to liposomal ingredients.
Dendrimers	Enhanced drug efficacy, and the high penetrability of biological barriers and cell membranes, reduced drug toxicity, high loading capacity of the drug. [93]	Poor solubility, stability bioavailability or patient compliance, limited drug loading. [94]
Carbon Nanotubes	Enhanced the solubility in water, increased dispersion, enhancing their delivery efficiency, and reduced toxicity. [95]	Insolubility and tendency of carbon nanotubes, the presence of impurities, in-uniformity in shape and structure, large surface area leads to protein misfolding. [96]

3.6 Dosage of Drug Delivery in Cancer Therapy

The dose of cancer medicine prescribed to a patient depends on a number of factors for instance the patient's overall condition, the type of cancer, the specific drug being taken, and the recommended treatment plan for the treatment tumors. There are crucial points to take into consideration before treatment such as cancer's specific characteristics, specifically its stage and location, will impact the treatment strategy (Krzyszczyk, et al. 2018) [97]. The type of cancers changes based on the condition, whilst the different cancer types may require different dosages of drugs. Drug type with the choice of cancer medication mostly determines the dosage. There are differences in the dosage regimens for chemotherapy, radiation therapy, targeted therapy, and immunotherapy (Anand, et al. 2022) [98]. Important considerations include the medical history of the patient's, state of health. To avoid harmful side effects, patients with cancer disease may need to have their dosage adjusted. Doses of anticancer drugs are usually calculated based on a standardized criterion, which is body surface area (BSA). Although many physiological functions are proportional to body surface area, drug clearance in general is only partially related to this parameter. Thus, after administration of equivalent drug doses based on body surface area, wide variation in plasma drug concentrations can be found between patients, with the result that some patients experience minimal toxicity while others may exhibit symptoms of severe toxicity (Arshad, et al. 2021) [99].

3.7 Systemically Administered Drugs

One of the challenges issues in cancer therapies is the way to affect the result of cancer treatment by applying anticancer medications optimally and carefully, even though the use of pharmaceuticals in the management of cancer has significantly impacted the fate of most forms of malignancies. However, adhering to appropriate pharmacological practices in the implementation of treatment plans while using anticancer drugs is critical and has to be addressed. Most cancer treatments include the delivery of drugs orally, systemically, or topically. Drug distribution that is localized to the tumor site or its immediate surroundings is referred to as locally regional distribution (Wen, et al. 2015) [100].

Systemic exposure is therefore avoided or much reduced, since the antineoplastic agent's concentration at the tumor site is increased. The exposure of healthy organs or tissues to the medication being supplied is one of the main majors of this kind of drug administration (Saito, et al. 2023) [101]. Evidently, resolving this issue should be the goal of any new strategy to improve anticancer medication delivery systems. Nonetheless, systemic delivery of cytotoxic anticancer medications will remain essential for the development of cancer therapies (Ioele, et al. 2022) [102].

3.8 Advantages and Disadvantages of Drug Delivery in Cancer Treatment

The use of drug delivery systems in cancer treatment offers many advantages, enhancing efficacy while reducing side effects and improving treatment efficacy. These advantages precisely target cancer cells, increasing the drug concentration at the tumor site and increasing the effectiveness of treatment. Another advantage is the reduced toxicity of the drug (Dang, et al. 2020) [103]. Compared to traditional chemotherapy, it reduces exposure to healthy tissues and organs, reducing the toxicity of the drug and reducing side effects for the patient. In addition, improved bioavailability enhances the therapeutic effect of the drug by supporting stability, solubility, absorption and controlled release, ensuring preferred delivery to the tumor site while preventing degradation (Senapati, et al. 2018) [104].

NP with optimal size and surface properties are designed to prolong the presence of cancer drugs in the bloodstream, thereby enhancing the distribution of these treatments throughout the body. Drug delivery systems in cancer therapy offer many advantages as examined, however, disadvantages are also evident. Some of these disadvantages are instability in the circulation, poor bioavailability, and lack of biodegradation, inadequate tissue distribution and potential toxicity raise concerns over their safety, limited targeting, resistance development, complexity and cost, and biocompatibility concerns (Li, et al. 2023) [105]. Targeting cancer cells using medication delivery systems remains challenging. This is because there is a real struggle in achieving absolute specificity of the target. Some medications might unexpectedly harm nearby healthy cells, reducing their effectiveness. Moreover, cancer cells can develop resistance to specific drugs delivered through these methods, diminishing the overall effectiveness of treatments (Cheng, et al. 2021) [106].

CHAPTER IV: Methodology

4.1 Clinical Research Methodology

Clinical trials research has seen rapid growth in both the number of studies and breadth of study areas. Clinical trials research is the preferred instrument and methodological approach that supports evidence-based research and practice, because it seeks to evaluate treatments and therapies to determine the best possible way to diagnose and treat disease in patients. Obtaining reliable and validated data requires a systematic approach in planning, executing, and sampling for a clinical research project (Selker, et al 2019) [107]. It is crucial for researchers to possess a comprehensive understanding of various study methodologies. Over time, there has been a significant surge in the number and diversity of clinical trials conducted, especially on an international scale. Consequently, there is an increased demand for infrastructure and personnel support to sustain this growth. While various techniques are employed in clinical research, recent studies show that clinical trials stand as the most advanced methodology for evaluating therapeutic treatments such the usage of various drug delivery systems (Gross, et al., 2022) [108].

4.2 Drug Delivery System in Clinical Trials

Clinical trials focused on drug delivery systems involve meticulous investigation and validation of methodologies to administer pharmacological substances to patients. These trials aim to mitigate side effects, enhance patient adherence, and support drug's effectiveness. They encompass diverse strategies, encompassing innovative medication delivery mechanisms, administration, and formulations techniques (Salahshoori, et al., 2023) [109].

Typically, drug delivery system clinical trials progress through several phases: Phase I involves assessing safety, dosage, and potential adverse effects in a small group of healthy volunteers. Phase II expands the trial to evaluate safety and efficacy in greater detail, offering initial insights into efficacy and optimal dosage. Phase III broadens the study to validate the system's efficacy across a larger population, monitoring adverse effects and comparing it with established

therapies. Phase IV involves ongoing post-marketing monitoring to track real-world functionality and safety, focusing on medication efficacy, patient acceptance, adherence, and ease of use. Varied delivery systems, including oral tablets, injections, patches, implants, or targeted mechanisms, undergo rigorous testing to optimize their therapeutic impact (Mahan, 2014) [110].

Crucial to these trials is the collection and analysis of data to ascertain system feasibility and market acceptance. The ultimate goal is to devise patient-friendly, safe, and efficient drug delivery methods that significantly influence the treatment landscape across various illnesses. Clinical trial participants are exploring whether different methods of drug delivery are safe, effective, and actually get the job done. Clinical trials aim to find out whether a particular method of delivering drugs can make them more available, reduce side effects, get them to the right place, or make treatments work better. Medical experts plan, conduct and evaluate how well treatments work and how safe they are for real patients, using different tools and methods (Varala, et al. 2023) [111].

4.3 Ethical Considerations and Informed Consent

Before any clinical trial, it is necessary to make sure participants fully understand what the trial entails and its potential risks and benefits. Experiments must follow ethical rules and principles. It is important that participants remain anonymous and all data will be received confidentially. It is very important before any participant takes part in an experiment or clinical trial, they must sign the informed consent (Arellano, et al. 2023) [112].

4.4 Collecting and analyzing data

Collecting data involves using various methods such as surveys, physical check-ups, laboratory tests, and imaging techniques (Kiani, et al 2022) [113]. For the purpose of this thesis, the collection of data is done through literature research of existing data collected through clinical trials. Thus, the data will be secondary data and these data were analyzed thoroughly and examined by the researchers. By statistically analyzing the gathered information, researchers interpreted findings and measure the impact of treatments through delivery drug system specified on breast cancer.

4.5 Benefits and Limitations of Clinical Trials Research

Clinical trials play a crucial role in benefiting both present and future patients, significantly advancing clinical practices and an understanding of treating illnesses. Rigorous and systematic testing of new drugs or interventions with minimized bias enhances researchers' confidence in interpreting study outcomes. The phased approach in clinical trials minimizes participant risk, incrementally builds evidence, and assesses feasibility throughout each phase of the study. Notably, the reduced risk stems from the reliance of phase III and IV studies on the safety and efficacy data established in phases I and II. Conducted in a controlled and meticulous manner, clinical trials enable researchers to accurately quantify the effects of medications on patients, ensuring a certain level of certainty (Mello, et al. 2018) [114]. Additionally, adherence to internationally recognized standards and methodologies allows for replication of clinical studies across diverse populations, validating outcomes. For the purpose of this thesis, it is important to note that secondary data were used from existing research projects. Table 3a and 3b contains data gathered from various research projects in order to be able to present various results based on the usage of drug delivery systems used for breast cancer.

4.6 Fuzzy Logic and its Applications

Fuzzy logic serves as a versatile solution for managing control system issues across various platforms, from extensive data collection and control systems to expansive networked multi-

channel computers and compact embedded microcontrollers. Its applicability extends for both hardware and software domains and a fusion of the two. Essentially, fuzzy logic offers a straightforward method to derive precise outcomes from uncertain, imprecise, or incomplete input data. Leveraging a fuzzy logic based approach aids in addressing decision-making challenges by enhancing speed and accuracy in problem resolution. Currently, fuzzy logic stands out as a rapid and highly effective means of constructing intricate control systems. The reason behind its efficiency is straightforward: fuzzy logic adeptly generates accurate outputs based on provided or estimated data, mirroring the human decision-making process. This adaptability makes it an ideal fit for applications requiring such. Fuzzy logic effectively addresses a significant gap in engineering design methodologies, bridging the space between purely logic-driven approaches such as "specialized systems" and entirely mathematical strategies like "linear control design" when it comes to system design. There are many applications for fuzzy logic such as: medical diagnosis, treatment planning, personalized medicine, drug dosage adjustment, fuzzy logic has a various application for example, fuzzy image processing, fuzzy logic-based anesthetic depth control, and fuzzy logic in neural networks (Singh, et al. 2014) [115].

In medical diagnosis, fuzzy logic is useful, because it can deal with information that might not be precise or clear. For example, when symptoms are not well-defined, fuzzy logic can help categorize them into likelihood levels, aiding in the diagnosis of certain diseases. When it comes to treatment planning, fuzzy logic assists in creating care plans based on not-so-precise information, individual differences, and unclear situations. It allows adjustments in medication doses or treatment plans based on how a patient responds and their unique characteristics. Fuzzy logic plays a role in personalized medicine by evaluating genetic data, medical history, and environmental factors to recommend personalized treatment plans. When estimating patients' ideal medication doses, fuzzy logic considers factors like age, weight, and specific medication sensitivities, contributing to more accurate and personalized dosing strategies (Awotunde, et al., 2014) [116].

4.6.1 Fuzzy Image Processing

Fuzzy image processing endeavors to replicate human reasoning within computer vision tasks by offering an intuitive approach to draw conclusions from incomplete data. Its uniqueness lies in how it diverges from conventional computer vision methods. Instead of being a singular solution to a specific task, it defines a fresh category of image processing techniques. This innovative methodology serves as a complement to traditional logic, enriching the repertoire of any computer vision tool (Castillo, et al., 2017) [117].

4.6.2 Fuzzy Logic-Based Anesthetic Depth Control

In hospitals, most surgeries involve using manual anesthesia methods, which have simple on/off switches. But these methods struggle to find a balance between safety and making the experience comfortable for patients. That is where fuzzy logic control comes in. The research presented by Singh, G., Kumai, P., & Goyal, D. (2014) [118] explores a more objective way to give anesthesia during surgeries. They are using fuzzy logic, where the inputs like pulse rates and blood pressure are taken from patients under anesthesia and fed into the system. The output from this fuzzy logic system represents the right amount of anesthesia needed for the patient (Samira, et al. 2018) [119].

4.6.3 Fuzzy logic in Neural Networks

Fuzzy logic, a mathematical method, enables variables to show their membership degrees within a set, using truth values between 0 and 1. This versatile technique effectively deals with imprecision and uncertainty across diverse real-world situations. On the other hand, artificial neural networks are inspired by the human brain's structure and learning capabilities. They are comprised of interconnected neurons arranged in layers, capable of learning and adjusting iteratively through input-output data relationships. Artificial neural networks and fuzzy logic merge to form a robust computational model called fuzzy neural networks, or FNNs. Fuzzy neural networks, or Fuzzy Logic Networks, are designed to handle complex and uncertain data by leveraging fuzzy logic's ability to handle imprecise input and neural networks' capacity to

process and interpret information. Fuzzy neural networks aim to create a more dependable and adaptable computing system by harnessing the strengths of both fuzzy logic and neural networks. Components like input data fuzzification, a foundation of fuzzy rules, neural network structure, and output defuzzification constitute the core elements of a fuzzy neural network (FNN) (Perfiljeva, & Novak. 2023) [120].

4.7 Multi-Criteria Decision Making Model (MCDM)

Multi-criteria decision-making (MCDM) serves as a method to evaluate multiple factors or criteria in order to determine the optimal choice among decision-making challenges. Those approaches applicable across various industries like finance and engineering design. Known for its innovative nature, MCDM has garnered acclaim for its precise decision-making capabilities. Its inception can be traced back to Benjamin Franklin's exploration of moral algebra, marking an early milestone in this field. Empirical and theoretical researchers have extensively explored MCDM techniques, assessing their adaptability in mathematical modeling to construct frameworks that organize decision-making complexities and extract preferences from the available array of alternatives. Those approaches considers a multitude of qualitative and quantitative factors that require fine-tuning to pinpoint the best possible solution. For example, cost or success rate, alongside procedure quality, often stands as a predominant factor in numerous decision-making scenarios. Moreover, expert panels assign different weights to these criteria, considering the respective significance of each criterion within its specific context (Taherdoost & Madanchian 2023) [121].

In recent decades, several authors have introduced or modified various MCDM techniques, differing notably in algorithm complexity, criteria weighting methods, representation of preference evaluation criteria, susceptibility to data ambiguity, and the approach to data aggregation. Moreover, these methodologies are anticipated to exhibit distinct advantages and disadvantages, specific to each type of MCDM, which will be individually elucidated. For instance, while the Analytical Hierarchy Process (AHP) faces constraints due to criteria and choice interdependencies, it remains user-friendly (Ayan, et al. 2023) [122]. Conversely, employing fuzzy set theory (FST) permits the utilization of imprecise inputs but demands intricate development. Broadly, all MCDM approaches offer an advantage by accounting for

disproportionate and conflicting impacts of various actions. Conversely, these techniques, owing to the inherent nature of the problems they address, yield solutions that necessitate compromises among multiple objectives, hindering the attainment of an optimal solution. The applications of MCDM span diverse fields such as medicine, finance, engineering, and economics (Al Mohamed, et al. 2023) [123].

4.8 Fuzzy PROMETHEE

Decision making is an important aspect of top management across different levels, and it is common to encounter conflicts of interest or interference during this process. One method that has proven useful in such situations is preference ranking organization methods for enrichment evaluation (PROMETHEE). In particular, Fuzzy PROMETHEE is a hybrid model of fuzzy logic and the PROMETHEE approach. In Fuzzy PROMETHEE, elements of the decision matrix (a matrix that contains the selected alternative sets, criteria, and the weights for criteria) can be defined using fuzzy sets. And, MCDM analysis is applied using PROMETHEE.

PROMETHEE is used for identifying the most qualified applicants during the admissions process (Nasution, et.al. 2019) [124]. This decision support model is specifically designed for scenarios involving multiple criteria, and it effectively addresses the challenges of decision making. Decision-making systems incorporating PROMETHEE technology excel at identifying high-performing students whose attributes match their abilities and values, achieved through comprehensive analysis of criteria and careful consideration of options (Nasution, et al., 2019) [125].

Cancer manifests itself through various symptoms that cause cells to grow with no control on it, which leading to serious damage and often loss of life to patients. This study by Albarwary et al. (2021) [126] evaluated the nanoparticles (NPs) applications in cancer treatment via using the fuzzy PROMETHEE method. These NPs play a pivotal role in targeting specific sites, managing toxicity levels, delivering anticancer drugs directly to affected areas, and regulating their release, all aimed at ensuring patient safety. Different types of NPs, including gold, liposomes, polymeric micelles,

nanogels, and dendrimers, have been used for drug delivery purposes. Comprehensive evaluations, including charge, price, size, shape, molecular attachments, pH temperature, and responsiveness, among other aspects of these nanoparticles, are performed to ensure their safety and efficacy. Leveraging this wealth of NP information, the PROMETHEE trial demonstrates the most effective means of administering anticancer drugs. Treatments such as surgery, radiation, and chemotherapy are frequently used in cancer treatment, chemotherapy, although widely used against tumors and cancer cells, lacks a consistent distinction between malignant and healthy cells, leading to risks and lasting adverse effects on patients (Ozsahin, et al 2017) [127]. In this thesis, gold nanoparticles will be thoroughly examined, specifically focusing on their various size ranges for breast cancer therapy, as presented in Table 3b.

Table 3a: Different Nanoparticles Used for Breast Cancer (Detailed)

NP	Therapeutic Agent Drug	Toxicity	Doses (mg/m2)	Targeted Delivery	Size Range of NP	Cost	Adm.	Success Rate
Liposomes [128]	Doxorubicin with paclitaxel	Cardiotoxicity, bone marrow suppression, gastrointestinal issues, hypersensitivity	50–150 mg/m^2, 3 times per week	Active	40- 180 nm	Paclitaxel ($18 / 6mg) Dox ($ 258 /50mg)	IV	31-78 %
Micelles [129] [130]	Paclitaxel	Nausea, vomiting, diarrhea, muscle/joint	80-175 mg/m^2 once per week for	Passive	10-100 nm	Paclitaxel ($18 / 6mg)	IV	30-76.9 %

		pain	3 weeks					
Nanogels [131][132][133]	Docetaxel	Fluid retention syndrome, hypersensitivity reactions, neutropenia	60-100 mg/m^2 once per 3 weeks	Passive	100-200 nm	Docetaxel ($54/10mg)	IV	41-72%
Dendrimer [134][135][136]	Tamoxifen	Nausea, vomiting, rash, fatigue	20–40mg every day	Passive	1- more than 100 nm	Tamoxifen ($18/20mg)	IV and Oral	82%
Gold [137][138][139]	Doxorubicin	Myelotoxicity, nausea, vomiting	10-40mg	Passive	1-80 nm	50$/5mg	IV	85%

Table 3b: Different size shapes for Au Gold nanoparticle

Drugs	Alternatives (size of NPs)	Cytotoxicity	Success rate	Loading efficiency	Cost	Side Effect
Aim /Weights	-	Min/H	Max/VH	Max/M	Min/M	Min/H
DOX Au Nps	1-5nm	Low[140] 28%[141]	>98% [142] 84%[141] >98%[143]	93.4%[143]	Low[140] $5-100 [144] ($72) [145]	Autophagosome formation Vesicle-entrapped NPs, endocytosis of NPs, Dose >14day can cause organ damage[146] (VH)
DOX Au Nps	5-20nm	low[140] 54.5%	55.10% [147] 79.2 ± 0.69% [148]	89%[143]	($72) [145]	Vesicle-entrapped NPs, endocytosis of NPs, toxic effect detected within 24 h of Nps exposure, NPs are exacerbated at 72hrs exposure[149]. (H)
DOX Au Nps	20 -50nm	High[140] 73.4% 83.3%[141]	93%[150]	75.8%[151]	High[152] ($216)	impaired renal excretion and physiological barriers[153] (M)

DOX Au Nps	40-70nm	moderate[140] 57.25% [154]	76.34%,[142]	83.64 ± 2.47[155]	High [156] $455-$795[157]	Accumulation of NPs in organs and tissues[158] (L)
DOX Au Nps	>100nm	Very 93.1%[141]	83.56 ± 0.78%[148]	35.81 ± 1.76[155]	($345)[159]	↑ toxicity, volume of drug distribution, ↓lifetime, critical dose drug (M)

VH: Very High, H: High, M: Moderate, L: Low

Triangular fuzzy numbers are employed to represent linguistic values, where VH (Very High) is defined as (0.75, 1, 1), H (High) as (0.5, 0.75, 1), M (Medium) as (0.25, 0.5, 0.75), and L (Low) as (0, 0.25, 0.5) [161,162]. The Yager index is utilized for defuzzification, and average values are applied to numerical data when necessary. Additionally, the Gaussian preference function is chosen for criteria assessment.

CHAPTER V

5. Result and Discussion

The full-ranking results for the different size range of Au gold nanoparticles are examined for treating breast cancer and multi criteria method is used including criteria and parameters such as the cytotoxicity, loading efficiency, the side effect, the cost and the success rate (shown in Table 3b). These criteria are chosen as the most important ones for breast cancer therapy as examined in previous research data. As previously mentioned, the data used in this thesis is secondary data.

The results of the fuzzy PROMETHEE analysis for the selected alternatives and parameters are presented in Table 4. DOX Au NPs with size range 1-5 nm ranks top, with a net outranking flow 0,1474. As a result, DOX Au NPs with size range 1-5 nm is the best-performing size range for breast cancer treatment based on selected criteria. It has a high success rate, a 98% which is considerably high for treating breast cancer and has the lowest cytotoxicity with (28%) for the breast cancer patient, causing autophagosome formation vesicle-entrapped NPs, endocytosis of NPs and may cause organ damage. It has a low cost with loading efficiency 93.4%.

DOX Au Nps with size range 5-20nm ranks second with net outranking flow of 0,0724. It has a success rate of 55%, the cytotoxicity is low with 54.5%, the cost is low and the side effects are high. DOX Au Nps with size range 20-50nm follow the rank with a net flow of 0,0001 respectively. It has high cytotoxicity with loading efficiency 76% and with moderate side effects. The success rate is between 40-60%, however the cost is high with $216.

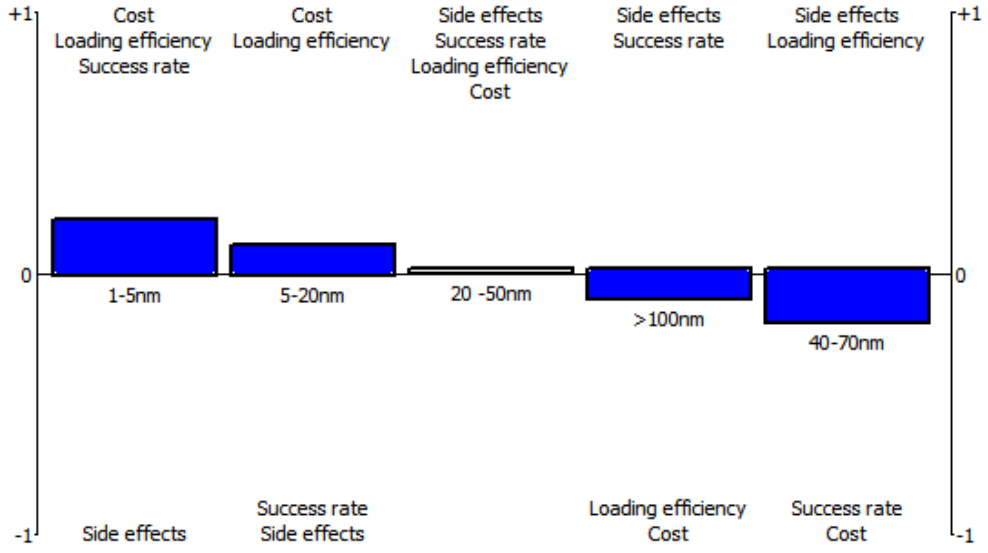
The DOX Au Np with size range >100nm ranks fourth, with a negative net outranking flow of -0,0767. The cytotoxicity is very high with 93% with moderate loading efficiency. The side effects of size range >100nm are moderate and may cause high toxicity. However, the cost is high ($345), with a high success rate. The ranking result reveals that the size range 40-70nm is the lowest-ranked DOX Au Nps for breast cancer therapy, with a net outranking flow of -0,1432. The cytotoxicity is moderate, with high loading efficiency, whilst the side effect is low. It has a moderate success rate and the cost is high with $795.

Table 4: Fuzzy PROMETHEE for Different Size range of Au gold NP Used for Breast Cancer Treatment

Rank	Alternatives	Net Outranking Flow	Positive Outranking Flow	Negative Outranking Flow
1	1-5nm	0,1474	0,1499	0,0025
2	5-20nm	0,0724	0,1110	0,0385
3	20 -50nm	0,0001	0,0746	0,0745
4	>100nm	-0,0767	0,0374	0,1141
5	40-70nm	-0,1432	0,0035	0,1467

Figure 4 shows the PROMETHEE evaluation results according to the parameters chosen for breast cancer treatment. The size range 1-5 nm has the highest success rate followed by the size range 5-20nm. In the third rank the size range 20-50nm of gold nanoparticle stands and it is followed by the size range of >100nm. The size range 40-70nm has the lowest success rate and highest price, ranking last.

Figure 4: PROMETHEE Evaluation Results



The PROMETHEE network in figure 5 shows the distance between different size range of DOX Au NPs from the most effective alternative to the least effective alternative based on the selected parameters

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Figure 5: PROMETHEE network

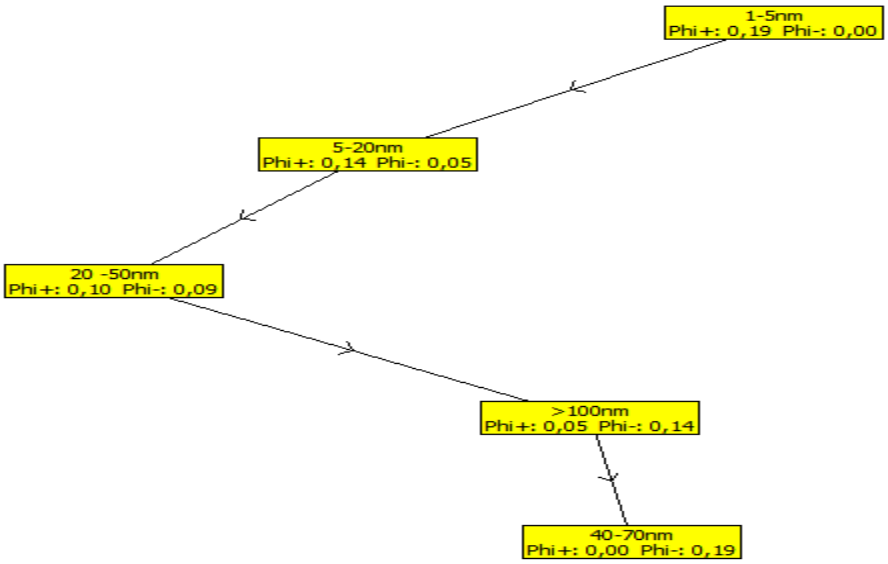


Figure 6 shows the action profile of the positive and negative points about 1-5nm, having a positive ranking on loading efficiency, cost, and side effect, whilst there are no negative.

Figure 6: Action Profile for 1-5nm

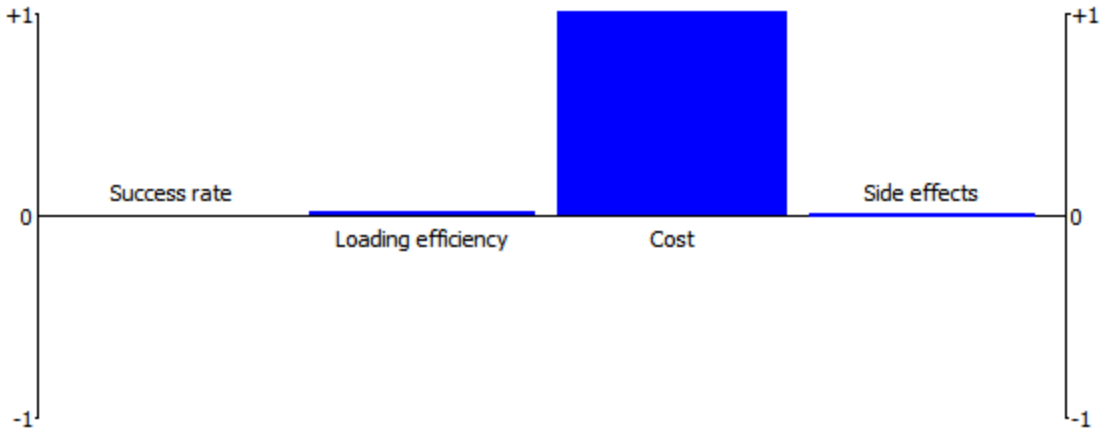


Figure 7 shows the action profile of positive points on 5-20nm, having a positive ranking only on the cost.

Figure 7: Action Profile for 5-20nm

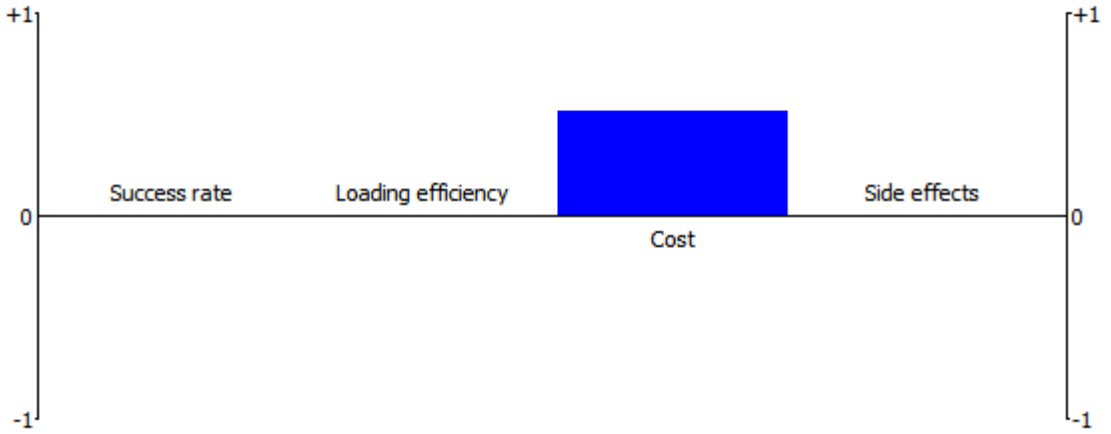


Figure 8 shows that there are no either positive or negative points of action profile in 20-50nm of gold nanoparticle compared to other alternatives. The success rate, loading efficiency, cost, and side effect all of them are on the line.

Figure 8: Action Profile for 20-50nm

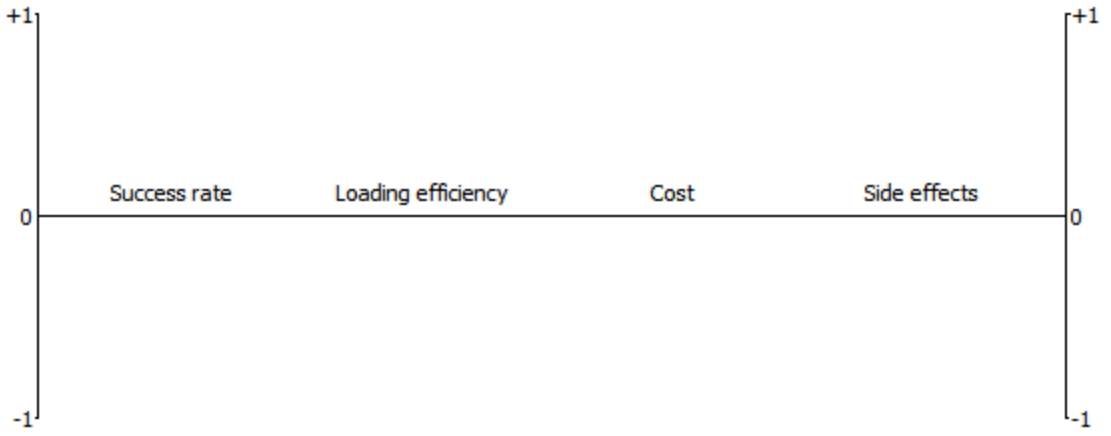


Figure 9 shows the action profile of positive and negative points about >100nm, having a positive ranking in loading efficiency, whilst has a negative ranking in cost. The success rate and side effect are just on the line.

Figure 9: Action profile for >100nm

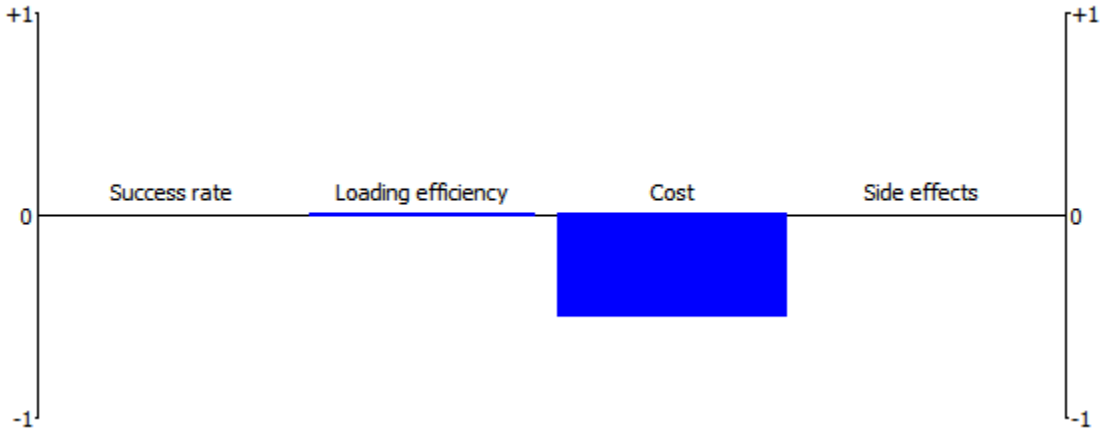
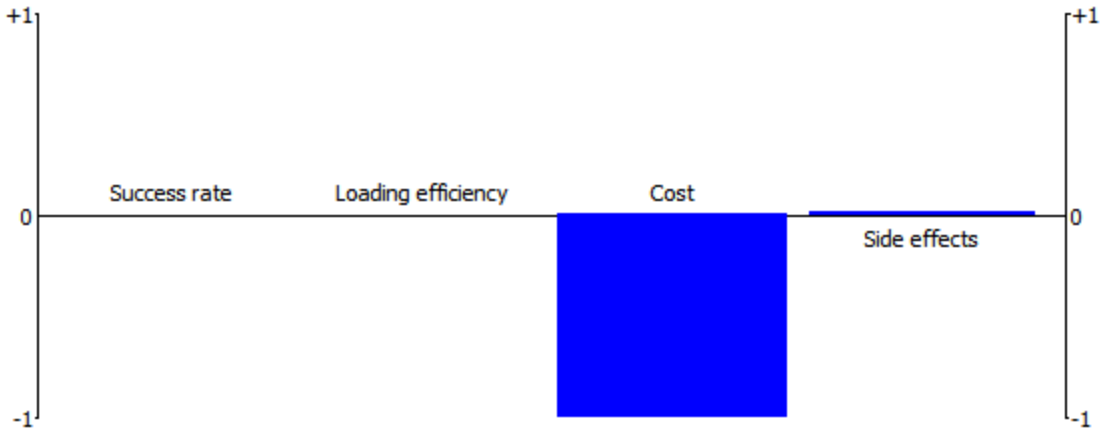


Figure 10 shows the action profile of positive and negative points of 40-70nm, which has a positive ranking on the side effect, while has a negative ranking on cost. The success rate and loading efficiency are just on the line.

Figure 10: Action Profile for 40-70nm



5.1 Future Challenges

Recent advancements have enhanced the manner in which medicinal compounds sourced from plants interact with the body to combat illnesses. However, several hurdles impede the effectiveness of these enhancements. One of the primary obstacles involves precisely directing the medication to specific areas within the body. Achieving precise targeting is crucial for enhancing the delivery of medication. Even though focusing on particular regions is considered safer and more efficient, ensuring that the drug effectively reaches these sites remains a challenge. These drugs are susceptible to rapid degradation by the body's enzymes, and their negative charge hampers cell absorption when administered in higher doses (Badar et al. 2022) [160]. Consequently, these drugs often struggle to reach their intended destinations and are minimally absorbed, if at all, by the body. The use of compounds in medication delivery systems poses a significant challenge due to their toxicity. Specific nanoparticles employed in these systems can pose risks to both the environment and human health. (Sharma, et al. 2021) [161].

5.2 Conclusion

Technological advancements are poised to revolutionize the global healthcare landscape, promising enhanced precision and efficacy in treatments, alongside cost reduction and streamlined management. Despite the potential of these advancements to significantly aid individuals, many groundbreaking treatments remain inaccessible due to their high costs. Embracing these innovative treatments instead of awaiting cheaper alternatives could immensely benefit all, particularly those lacking convenient healthcare access. The development of automated, cost-effective systems for producing and delivering medicine will play a pivotal role in ensuring universal access to necessary healthcare services.

A revolutionary era in the therapy of cancer has begun with the application of nanotechnology. Gold nanoparticles are now being widely used in clinical therapies for a wide range of cancer types and especially breast cancer. When compared with conventional drugs, nanoparticles based on drug delivery systems provide improved stability, tumor specificity, pharmaceutical kinetics, biological compatibility and success rate. Additionally, they are essential in reducing systemic toxicities and combating medication resistance. The results of this decision-making approach on the evaluation of gold nanoparticles with different size ranges used for breast cancer therapy will aid in optimizing highest results on breast cancer patients and the medical field of treating cancer. The Fuzzy PROMETHEE offers the ideal size range of gold nanoparticle. The results indicate that the most effective size range for gold nanoparticles in breast cancer treatment, when used with DOX, is 1-5nm, followed by 5-10nm and 20-50nm. This study can be extended via adding more criteria for the specific aim of the decision makers.

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APPENDICES

Appendix A

Ethical Approval Document

There is no ethical approval document that can be presented.

Prof. Dr. Dilber Uzun Ozsahin

Assist. Prof. Dr. Berna Uzun Supervisor

Appendix B

Curriculum Vitae

EYAD ALASHQAR

BIOMEDICAL ENGINEER

Riyadh, Saudi Arabia
eyadmajed23@gmail.com
+966543542167

PROFILE

I am a strongly motivated, skillful, and self-organized engineer. As a postgraduate, I am seeking an entry- level position in biomedical engineering. I have sound theoretical knowledge and practical experience in medical devices.

SKILLS

- Medical equipment maintenance
- Collaboration
- Communication skills
- Problem-Solving

EDUCATION

Near East University

2016 - 2020
Bachelor's degree in Biomedical Engineering

Near East university

2021 - 2024
Master in Biomedical Engineering

STRENGTHS

- Quick learner
- Attention to detail
- Team worker
- Critical thinking
- Excellent organization
- Decision making

EXPERIENCE

2019-2020 **Riyadh**

Salehyia Healthcare Company

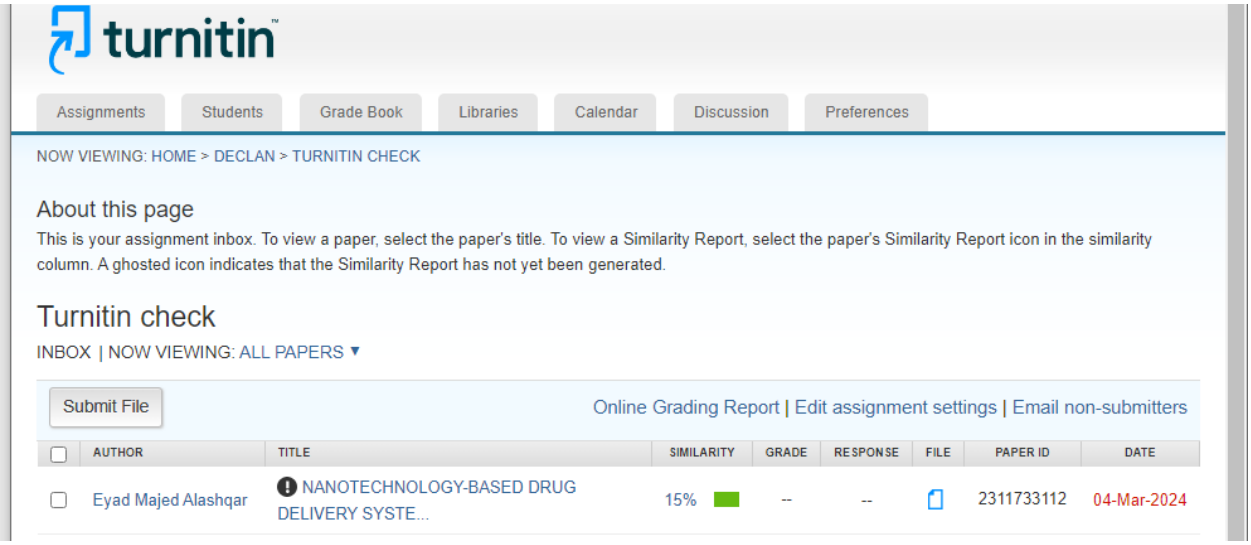
Assisted in the maintenance and calibration of medical equipment, including patients' monitors and laboratory instrumentation, and the delivery of medical devices to hospitals.

LANGUAGES

Arabic ● ● ● ● ●
English ● ● ● ●
Turkish ● ● ●

Appendix C

Similarity Report



Supervisor

Prof. Dr. Dilber Uzun Ozsahin

Assistance Supervisor

Assist. Prof. Dr. Berna Uzun