Al-Nahrain Journal for Engineering Sciences **NJES** 26(4)365-373, 2023
http://doi.org/10.29194/NJES.26040365

Strategies of Nanocarrier-Based Therapeutic Drug Delivery

Walaa A. Salih[1*], Alaa A. Al-Taie[2]

Authors affiliations:
1*) Department of Biomedical Engineering, College of Engineering, Al Nahrain University, Baghdad, Iraq
walaa.a1812@gmail.com

2) College of Engineering, Department of Biomedical Engineering, Al Nahrain University, Baghdad, Iraq
alaa.ayyed@nahrainuniv.edu.iq

Paper History:

Received: 27th Aug. 2023

Revised: 5th Oct. 2023

Accepted: 10th Oct. 2023

Abstract

In recent years, nanoparticles have garnered considerable attention in the field of cancer treatment due to their extensive potential and wide range of uses. The research mostly focuses on the inorganic chemicals, with a specific emphasis on metals, in order to enhance the comprehension of functional nanoparticles synthesis. This undertaking is motivated by the distinctive characteristics exhibited by these materials, which provide significant advantages for both fundamental scientific inquiry and practical implementations, notably those focused on cancer. The purpose of this review is to conduct a comprehensive analysis of the diverse nanocomposites applications, with a specific emphasis on their utilization in medication delivery.

Keywords: Drug Delivery, Nanocomposites, Laser ablation

استراتيجيات توصيل العقاقير العلاجية باستخدام حاملات نانوية

ولاء احمد صالح ، الاء عايد جبر

الخلاصة:

في السنوات الأخيرة، اجتذبت الجسيمات النانوية اهتمامًا كبيرًا في مجال علاج السرطان بسبب إمكانياتها الواسعة ومجموعة استخداماتها الشاسعة. تركز الأبحاث بشكل رئيسي على المواد الكيميائية غير العضوية، مع تركيز محدد على المعادن، لزيادة فهم تركيب الجسيمات النانوية ووظائفها. يتم تحفيز هذا الجهد من خلال الخصائص المميزة التي تظهرها هذه المواد، والتي توفر مزايا كبيرة سواء للتحقيق العلمي الأساسي أو التنفيذات العملية، بشكل ملحوظ تلك المرتكزة بشكل خاص على السرطان. هدف هذا الاستعراض هو إجراء تحليل شامل لتطبيقات النانوكومبوزيت المتنوعة، مع التركيز الخاص على استخدامها في تسليم الأدوية.

1. Introduction

Cancer constitutes a significant health issue. According to the most recent Global Cancer Report published by the World Health Organization, Between the years 2008 and 2012, there was an observed increase in the incidence of cancer cases, with the number rising from 12.7 million to 14.1 million. According to estimates, there is a projected increase of 75% in the annual incidence of newly diagnosed cancer cases over the next two decades. This spike is expected to lead to an approximate annual count of 25 million new cancer cases [1]. Utilizing the GLOBOCAN 2020 projections for cancer incidence and fatality, which were meticulously generated by the International Agency for Research on Cancer .These statistics paint a stark picture: a staggering 19.3 million individuals worldwide grapple with the harrowing diagnosis of a new cancer case[2]. patients are typically treated with conventional therapies like chemotherapy, surgery and radiation therapy. Chemotherapy is classified as a form of systemic therapy that employs medications to treat or prevent cancer and affects the entire body. Since chemotherapeutic drugs are distributed throughout the body, the selectivity of the treatment towards the targeted tumor is constrained, resulting in significant risks not only to malignant cells but also to adjacent healthy tissues. Cyclophosphamide, methotrexate, doxorubicin, docetaxel, and fluorouracil are chemotherapeutic drugs. They may be employed alone or in tandem with other agents. Nanomaterials are an option when seeking for novel cancer therapy methods. For over thirty years, nanoparticles have served as pharmaceutical transporters to enhance the in vivo effectiveness of anticancer drugs. Initial research conducted in the year of 1970s utilized nanoparticles drug carriers, specifically liposomes containing anticancer drugs. Through the invention of nanostructured drug delivery devices, new anticancer chemotherapies were created [3]. Over the past two decades, the advent of nanotechnology has ushered in a transformative era in the field of clinical therapeutics. This revolution has been marked by groundbreaking advancements that have redefined the way we approach medical treatment.

In particular, the utilization of nanoscale drug carriers has emerged as a promising solution to

NJES is an **open access Journal** with **ISSN 2521-9154** and **eISSN 2521-9162**

several long-standing challenges in healthcare, offering a myriad of advantages compared to conventional chemotherapeutic agents [4]. Nanocarriers are used to enhance current cancer therapy techniques. They mitigate the adverse effects of cancer treatments[5]. The advent of anticancer nanomedicines has ushered in a promising era in cancer treatment, offering the potential to significantly reduce the risk of debilitating side effects associated with traditional chemotherapeutic drugs.

These innovative therapies represent a groundbreaking approach to combating cancer while enhancing the overall quality of life for patients[6]. In recent years, numerous clinical trials have utilized chemotherapeutic nanoparticles, including 5-fluorouracil. It is used as a cytotoxic agent for cutaneous cancer, breast cancer, and digestive cancers[5]. Due to the remarkable electrical, optical, magnetic, and chemical properties of metallic nanostructured materials, they have generated considerable scientific interest over the past few decades[7]. At the nanoscale, material properties alter. This is due to the fact that bulk materials have generally stable properties regardless of size, but as the size decreases, the proportion of surface atoms increases relative to bulk material. This generates nanoparticles with unexpected properties[8].

Due to their ability to permeate cellular walls and membranes, the biological interactions of nanoparticles differ from those of bulk materials. Nanoparticles, especially noble metals NPs such as gold or silver , are versatile agents used in a vast array of biomedical applications, including highly sensitive diagnostic assays[8].

Chemical techniques, the sonochemial method, sol gel , and laser ablation were utilized to produce the nanoparticles [9]. Nonetheless, employing these chemical reduction approaches is discouraged due to the compounds' elevated reactivity and recognized potential to engender environmental and biological hazards. In lieu of this, several methodologies for crafting nanoparticles (NPs) have emerged, including the laser ablation technique (LA)[10]. The advantages of laser ablation (LA) over chemical synthesis include its straightforwardness and the lack of solution-based chemicals. Moreover, the laser pulse has surfaced as an adaptable technique with substantial potential, given its capacity to erode diverse substances like metals, ceramics, and polymers due to its extremely high energy concentration.

Los Angeles achieved growth manipulation by fine-tuning factors such as irradiation time, duration, energy concentration, wavelength, and related parameters [11]. Figure (1) represent Schematic diagram of pulse laser ablation in liquid (PLAL) method.

2. The diverse medical applications of nanoparticles

Extensive research has been conducted on nanoparticles due to their considerable promise in the field of biomedicine. In a study done by Maksimova et al. (2007), the application of silica /gold, silica (core) and gold (shell) ,nanoparticles was explored in the photothermal therapy of spontaneous tumors in canines and felines. The laser irradiation parameters were refined through the utilization of preliminary studies conducted on laboratory rats. Using a thermal imaging device, the temperature patterns within tissue and fluid samples were analyzed .

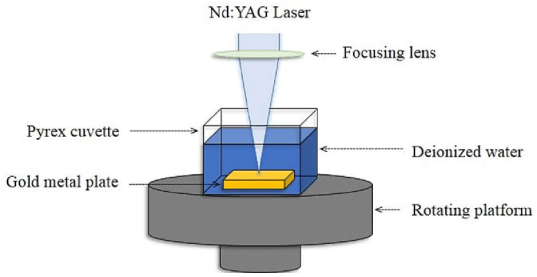

Figure (1): Schematic diagram of pulse laser ablation in liquid (PLAL) method[12].

Research findings indicate that the temperature measured on the surface is notably surpassed by the temperature observed within the volume region where nanoparticles are localized. The researchers demonstrated that the administration of plasmon-resonant gold nano-shells through local injection, coupled with the use of continuous wave (CW) semiconductor laser irradiation at a wavelength of 808 nm, results in the optical eradication of cancer cells [13]. In 2010, Zhou, Feifan, et al. made the discovery that (SWNTs) single-walled carbon nanotubes exhibit a high degree of absorption of near-infrared light. It is widely acknowledged that biological systems exhibit a high degree of transparency within this specific optical range.

The optical properties of (SWNTs) nanotubes present an opportunity for the application of targeted photothermal therapy in cancer treatment. The Cobalt-Molybdenum Catalyst "CoMoCAT" nanotubes, which possess a small absorption peak at 980 nm and have a consistent size of roughly 0.81 nm, have been identified as highly promising candidates for implementing this distinctive method. With the aim of precisely and selectively binding to the surfaces of tumor markers expressed by folate receptors, the process involves the coupling of CoMoCAT SWNTs with folate.

The tumor cells targeted with Folate SWNT were irradiated using a 980-nm laser. During both in vitro and in vivo experiments, it was observed that FA-SWNT exhibited a large reduction in photothermal destruction of normal cells that were not targeted, while simultaneously demonstrating a considerable enhancement in photothermal damage to tumor cells [14]. In a study by Kocbek, Petra, et al. in 2010, it was shown that titanium dioxide (TiO_2) and zinc oxide (ZnO) nanoparticles (NPs) demonstrate both short-term and long-term toxicity to keratinocytes in the in vitro setting. The cellular response is influenced by the type of NP, its concentration, and the duration of exposure. In contrast to titanium dioxide (TiO_2), zinc oxide nanoparticles (ZnO NPs) elicit more pronounced adverse effects on keratinocytes. The vitality of cells is minimally affected by TiO_2 concentrations up to 100 µg/ml, however exposure to ZnO at concentrations over 15µg/ml results in a

decrease in cell viability. Prolonged exposure to zinc oxide nanoparticles (ZnO NPs) induces alterations in cell-cycle distribution at a concentration of 10 µg/ml, impairs cellular morphology, and diminishes mitochondrial functionality. From this standpoint, it can be argued that TiO_2 does not exhibit any detrimental impacts. To mitigate the potential hazards of skin cancer, individuals are employing sunscreens containing zinc oxide (ZnO) and titanium dioxide (TiO_2) nanoparticles (NPs) for prolonged durations[15].

In 2014, Browning et al. made a significant finding on the influence of nanoparticles' reduced dimensions on their chemical and physical properties, often resulting in consequential alterations in their toxicity. In both domestic and industrial settings, individuals are exposed to inhalation of titanium dioxide (TiO_2) nanoparticles. Nanoparticles are increasingly prevalent in various consumer products, such as cosmetics, lotions, and sunscreens, hence leading to widespread exposure among the general public. The potential negative impacts of TiO_2 nanoparticles on human skin cells are not yet fully understood. To explore the possibility cytotoxic and clastogenic effects of TiO_2 nanoparticles during a 24-hour exposure, a human skin fibroblast cell line was employed. The clonogenic survival assay revealed that the relative survival percentages for treatments of 10, 50, and 100 µg/cm^2 were 97.8%, 88.8%, and 84.7% correspondingly. To ascertain the potential of TiO_2 nanoparticles in order to induce significant types of DNA damage, including chromatid breaks can occur, isochromatic lesions, or chromatid exchanges, the clastogenicity of the sample was assessed by the utilization of a chromosomal aberration assay. The application of treatments at 0, 10, 50, and 100 g/cm^2 resulted in the occurrence of metaphases displaying cellular damage in 3.3%, 3.0% and 2.7% of cells, respectively. No instances of chromatid swaps or isochromatic lesions were detected. The results of this study indicate that human skin cells do not exhibit cytotoxic or clastogenic effects when exposed to TiO_2 nanoparticles [16]. In a study done by Arooj Syeda, et al. in 2015, , an investigation was carried out on the photocatalytic cytotoxic effects of various nanoparticles (NPs) on human malignant melanoma (HT144) and normal Immortalised Human Colonic Epithelial Cells (HCEC) . The findings revealed that ZnO: Ag nanocomposites exhibited a higher efficacy in inducing cancer cells death compared to normal cells. When comparing nanocomposites containing low silver (Ag) content (1%, 3% and 5%) to those with high silver content (10%, 20% and 30%), it was shown that the latter exhibited a higher level of hazard. The IC50 values for ZnO:Ag at concentrations of 10%, 20% and 30% were determined to be 23.37 µg/mL, 19.95 µg/mL, and 15.78 µg/mL, respectively [17].

In 2017, Chakra, CH Shilpa et al. Outlined is a process to create a nanocomposite by merging nanoparticles of zinc oxide and titanium dioxide. A range of electron microscopy methods, spectroscopy approaches, and scatterometry were utilized to investigate the merging of particles. The techniques employed in this study encompassed X-ray diffraction, field emission electron microscopy, transmission electron microscopy, Fourier transform infrared spectroscopy, and dynamic light scattering. The effectiveness of the substances in battling cancer was assessed across four separate cell lines. The results demonstrate notable potential of the nanoparticles in fighting cancer [18].

In a study conducted in 2017, Chakra, CH et al. presented findings that showcased the antibacterial and anticancer attributes of a nanocomposite comprised of zinc oxide and titanium nanoparticles. The results revealed a synergistic impact of the nanocomposite on the antibacterial and anticancer characteristics, surpassing those of the individual nanometal constituents. The nanocomposite demonstrated superior antibacterial activities as compared to zinc oxide. Nevertheless, the antibacterial efficacy of the nanocomposite exhibited a decline in comparison to that of titanium dioxide. In contrast, the nanocomposite exhibited a reduced level of anticancer activity in comparison to zinc oxide, whereas it has shown an enhanced level of anticancer activity in comparison to titanium dioxide[19]. In the same year, El-Naggar, Noura El-Ahmady et al. conducted a study which demonstrated that the bio-AgNPs displayed in vitro anticancer effects against MCF-7 cell lines, a type of breast cancer originating from the mammary gland. Additionally, the researchers observed a moderate level of haemolysis activity (7.8%) in erythrocytes exposed to free radicals of 2,2-azobis (2-amidinopropane) dihydrochloride, commonly referred to as "AAPH". AgNPs are widely employed in several industries, including pharmaceuticals, food, cosmetics, and medicine, due to their enhanced antibacterial, anticancer, and antihemolytic properties[20]. In 2018, Samadi, Saman et al. accomplished a synthesis of composites consisting of Graphene Oxide (GO), titanium dioxide (TiO_2), and Doxorubicin (DOX). These composites were subsequently included into solutions of chitosan and Poly (Lactic Acid) (PLA) to produce nanofibrous scaffolds composed of chitosan, PLA, GO, TiO_2, and DOX. The impact of varying the proportion of PLA to chitosan, the content of TiO_2/DOX, and the content of GO/TiO_2/DOX on the release of DOX from nanofibrous scaffolds was explored using a central composite design featuring three factors and three levels. To gain deeper insights into the fabricated composites and nanofibers, XRD, SEM, and TEM analyses were employed. The mean diameter of the fibers was computed as 170 nm for the PLA/chitosan composite and 140 nm for the PLA/chitosan/TiO_2/DOX/GO composite [21].

In 2018, Sabre, Mahmoudi et al. did a study in which they used a biological mechanism to create silver nanoparticles (Ag NPs). The potential anti-cancer properties of these Ag NPs were next examined in comparison to A431 human skin cancer cells. The findings of their investigation showed that these nanoparticles significantly reduced the proliferation of cancer cells. The cytotoxicity of Typhlonectes natans (also known as T. natans) and

Ag NPs was assessed using the MTT test. In order to evaluate these compounds' suitability as therapeutic agents for the treatment of human skin cancer, the human epidermoid carcinoma A431 cell line was used. The cell viability of the A431 skin cancer cells was seen to decrease to 24.3% at a concentration of 100 g/ml T. natans-Ag NPs. T. natans-Ag NPs showed an IC50 value of 64.2 g/ml against A431 cancer cells after being exposed for 24 hours [22].

In a study demonstrated by Ghaemi, Behnaz et al. in 2019, it was shown that the application of Ag/ZnO nanoparticles (NPs) resulted by triggering the production of (ROS) reactive oxygen species in melanoma cells upon exposure to ultraviolet (UV) radiation. This led to a transformation of the Golgi structures inside these cells, causing a transition from tightly packed perinuclear ribbons to dispersed vesicle-like structures distributed throughout the cytoplasm. Collectively, the utilisation of Ag/ZnO nanoparticles (NPs) facilitates the process of stress-induced fragmentation of the Golgi apparatus and autophagy, finally resulting in the mortality of melanoma cells[23]. In 2019, Rao, Tentu Nageswara et al. showed in a study that extracting Acacia nilotica can be used to biologically synthesize Ag-doped TiO_2-NPs. It was determined that this approach was simple, safe, environmentally sustainable and economical. FTIR, XRD, FESEM, EDS and TEM were just some of the spectroscopic and microscopic techniques used to completely characterize the synthesized material. $AgTiO_2$ nanoparticles (NPs) have their anticancer and antiproliferative properties tested. Human breast cancer MCF-7 cell lines were used to examine the cytotoxic effects of $AgTiO_2$ NPs. It is hypothesized that (ROS) reactive oxygen species and oxidative stress mediate this harmful effect. As a result, Ag-doped TiO_2 nanoparticles are seen as having potential in the fields of medication delivery as well as the pharmaceutical and food industries [24].

In a paper published in 2020, Hariharan et al. showed how to dope titanium dioxide (TiO_2) nanoparticles (NPs) with silver nanoparticles (Ag NPs) at concentrations of 0.005, 0.010 and 0.015 M using a hydrothermal approach. The peak intensity seen in the XRD study increased in tandem with the increase in Ag content. The morphological and optical properties of the synthesised $AgTiO_2$ nanoparticles were also examined, and this gave proof of their efficient photocatalytic activity. $AgTiO_2$ produced at a concentration of 0.010M may have a higher level of photocatalytic activity as a result of its unique geometrical properties [25]. In a similar fashion, Nie, Chuang, et al. investigated the photothermal cytotoxicity of $AgTiO_2$ NPs in C57BL/6J mice and B16-F10 cells in 2020. They created $AgTiO_2$ NPs by using a straightforward sol-gel approach to create Ag NPs in two steps and coating them with TiO_2. Because of the oxide discovery, $AgTiO_2$ NPs notably demonstrated strong photothermal conversion efficiencies and biocompatibility in vivo and in vitro. The photothermal cytotoxicity of $AgTiO_2$ NPs was examined for cytotoxicity and therapeutic efficacy in B16-F10 cells and C57BL/6J mice. When in vitro Ag NPs-treated cells (100 mg/ml) are exposed to light irradiation, the greater temperature causes cell death. A subcutaneous melanoma tumour model was injected with $AgTiO_2$ nanoparticles (100 mg/ml), and the tumor was subsequently subjected to a 2 Wcm^2, 808 nm laser for one minute. In order to gradually shrink the tumor volume, near infrared region "NIR" laser irradiation only required one treatment. The results demonstrate that local photothermal therapy for cutaneous melanoma using biocompatible $AgTiO_2$ NPs is both effective and desirable [26]. Using a hydrothermal process, Pragathiswaran, Chelliah, et al. produced TiO_2ZnO nanocomposites that were then adorned with AuNPs in the same year. Morphology, XRD and FTIR analyses confirmed the Au nanoparticles mixed with TiO_2ZnO nanoparticles. It was discovered that TiO_2ZnOAu nanocomposites have potent anti-inflammatory, antifungal and antibacterial properties. Additionally, an in vitro cytotoxicity study utilizing the MTT assay revealed that the synthesized nanocomposites possessed significant anticancer activity against MCF7 cells. Further investigation is required prior to commencing clinical studies involving TiO_2ZnO-Au nanocomposites in order to assess their biocompatibility, biodegradability, clearance, dose, and mode of administration [27].

Nagajyothi, PC et al. In the year 2021, did an investigation to assess the influence of silver (Ag) on the surface, structure, morphology, and bioactivity of the ZnOAg nanocomposite. Four different levels of Ag (2.5%, 5%, 7.5%, and 10%) were integrated into the composite, resulting in variants named ZnO/Ag-2.5%, ZnO/Ag-5%, ZnO/Ag-7.5%, and ZnO/Ag-10%, respectively. Among these, the ZnO/Ag-7.5% composite displayed heightened anticancer efficacy against the HeLa and SKOV-3 cell lines, outperforming the other ZnO/Ag composites [28].

3. Drug delivery application

The utilization of medicine delivery has a significant influence on the management of numerous diseases, particularly cancer. In this application, a wide variety of polymers and nanoparticles have been utilized to enhance the treatment's efficacy. During the mid-1970s, Ringsdorf introduced a novel idea—linking chemotherapeutic agents covalently to a water-soluble polymer. This innovation aimed to enhance the solubility and stability of hydrophobic drugs and potentially enhance tumor specificity through the incorporation of a targeting component [29]. Aryal, Santosh et al. in 2009 conducted a synthesis and analysis of gold nanoparticles (Au NPs) coupled with doxorubicin (DOX), which were soluble in water. Equal doses of methyl thioglycolate (MTG) and thiolate methoxy polyethylene glycol (MPEG-SH) were employed for the purpose of stabilizing the gold nanoparticles, also referred to as Au NPs.

The MTG parts of the thiol-stabilized gold nanoparticles were linked to the anticancer drug DOX by using hydrazine as a bridge molecule. The unique conjugation of DOX with Au NPs holds

promise for enhancing the efficacy of photothermal cancer therapy, as well as facilitating targeted delivery of anticancer medications to the site of disease [30].

In 2013, Iannazzo, Daniela, et al. reported that it is Capability to tackle issues related to the management of anti-cancer drugs, like low solubility, ineffective distribution in the body, lack of specificity, and damage to healthy tissues, by employing drug delivery methods. Different substances, such as liposomes, microspheres, polymers, and recently, carbon nanotubes (CNTs), have been studied for transporting anti-cancer medications. The aim is to decrease the frequency of drug administration, enhance targeted delivery, and optimize the utilization of these drugs, leading to better patient adherence [31].

In a study conducted by Venkatasubbu, G. Devanand, et al. in 2013, it was discovered that the use of folic acid blended nanoparticles (FA–PEG–TiO_2) as drug carriers exhibited the ability to selectively target cancer cells while evading the reticuloendothelial system. The synthesis of titanium dioxide nanoparticles was conducted by a liquid chemical approach. The sample was subjected to a temperature of 450 ºC for a duration of three hours. The identification of anatase titanium dioxide is verified using X-ray diffraction (XRD) investigation. The nanoparticles exhibited an average size distribution of 12 nm, as determined by TEM and DLS studies. The PEGylation and folic acid transplanting were validated through the utilization of UV and FTIR spectroscopies[32].

A unique drug delivery system utilizing microencapsulation was effectively developed by Li, Puwang et al. in 2015 for the targeted administration of combination medications to the colon. This was achieved through the encapsulation of drug-loaded FA-CS nanoparticles with an enteric polymer, enabling selective drug targeting. The in vitro release investigation demonstrated that the colon was exposed to the combination drug-loaded FA-CS NPs after the dissolution of Eudragit S-100, which was facilitated by enteric coating. The findings of their study provide confirmation that nanoscale particulate materials (NPMs) hold significant potential as a means of specifically delivering anticancer medications to the colon, offering a viable approach for the chemotherapeutic treatment of colon cancer [33]. Tummala, Shashank et al in 2015 showed that the encapsulation of 5-FU into a chitosan polymer was effectively achieved by the solvent evaporation emulsification technique. The chitosan nanoparticles containing 5-FU, with a drug to polymer ratio of 1:3, demonstrated higher levels of entrapment efficiency, drug content, and cumulative drug release in comparison to other polymeric nanoparticles with varying polymer ratios[34].

In 2016, Ou, Gang, et al. published a study detailing a pharmacological intervention utilising a titanium oxide-based compound for the treatment by the photothermal therapy (PTT) process. The researchers reported significant therapeutic effectiveness alongside few adverse effects, indicating a promising therapeutic option. In the context of the in vivo mouse model, the Magnéli phase refers to a series of sub stoichiometric oxides of titanium with the general formula Ti_nO_{2n-1}, where the value of n falls within the range of 4 to 10. These oxides are generated through the high temperature reduction of titania in a hydrogen atmosphere. Specifically, Ti_8O_{15} nanoparticles are produced using the arc-melting process, which is commonly employed for the purpose of melting metals, particularly to create alloys. The heating process involves the generation of thermal energy through the initiation of an electric arc between a tungsten electrode and metallic substances positioned within a recessed area known as a crucible, located within the copper hearth.

During the vacuum arc melting process, the chamber was subjected to evacuation, followed by the introduction of argon gas. The material exhibited a near-infrared light absorption rate above 98% and shown a significantly enhanced efficacy in photothermal therapy. Furthermore, the Ti_8O_{15} nanoparticle photothermal therapy (PTT) material has remarkable biocompatibility and biosafety. This material introduces innovative applications for titanium oxides in photothermal conversion. Moreover, it identifies Magnéli-phase titanium oxide as a novel group of PTT agents[35].

In a study conducted in 2016 by Banerjee, Sovan Lal, et al. who identified that chitosan-graft-poly(acrylamide), combined with polyethylene glycol and silver nanoparticles, denoted as "Cts-g-PAAm/PEG/Ag" Nps, displayed notable antibacterial efficiency against both gram-positive and gram-negative bacteria. The assessment of cellular toxicity through in vitro cell cytotoxicity research revealed substantial harm to human cervical carcinoma cells. The nanoparticle displays potential for versatility, making it well-suited for various uses encompassing antibacterial and medical applications [36].

In an additional investigation done by Abdul Jalill in 2016 [37], the research focused on the examination of C. colocynthis, a plant species known for its presence of hazardous cucurbitacins that can cause irritation in the gastrointestinal tract. The study aimed to explore the potential therapeutic effects of C. colocynthis, specifically its anti-inflammatory, anti-tumor, and anti-diabetic properties. The aquatic extract of this plant was found to contain twenty-nine distinct components, with varying quantities of more than nine elements. The purified extract of C. colocynthis had anticancer properties when tested against the AMN3 and AMGM cell lines, but did not exhibit any significant effect on the L20B cell line. Similar patterns of behavior were observed in the treatment of pure titanium dioxide nanoparticles (TiO_2 NPs), as well as in the combined treatment of TiO2 NPs with Cucumis colocynthis aquatic extract. The combination treatment of Citrullus colocynthis aquatic extract and TiO_2 NPs exhibited an antagonistic effect on the cytotoxicity of cell lines (AMN3 and AMGM).

In a study conducted by Sağir et al. in 2016 [5], they achieved the successful encapsulation of 5-Fluorouracil within a magnetic zeolite–magnetite

nanocomposite (MZNC). This resulted in the development of a hybrid nanoparticle that exhibited fluorescent capabilities in the near-infrared optical range. MZNC has the potential to serve as a proficient carrier that can be specifically directed towards tumor locations. In 2018, Safwat et al. effectively synthesized gold nanoparticles (GNPs) by the utilization of $NaBH_4$ as a reducing agent and Cetyltrimethylammonium bromide (CTAB) as a stabilizing agent. CTAB was utilized at a pH of 8.5 to electrostatically load 5-FU. The entrapment efficiency of 5-FU was influenced by both the molar ratio of 5-FU to CTAB and the pH of the solution. The highest entrapment efficiency was seen at a pH of 11.5 and a molar ratio of 1:1. The stability of 5-FU/CTAB-GNPs against salt was observed after a storage period of four months at room temperature and four degrees Celsius. The results indicated that the nanoparticles maintained good stability under these conditions. The release of 5-FU was found to be dependent on pH, with a more rapid release observed in an acidic environment. The drug loaded GNPs formulations (5-FU/CTAB: 1:1, pH 11.5) were supplemented with gel and cream bases. The cream containing 5-FU/CTABGNPs exhibited superior ex vivo drug permeability over the dorsal skin of mice in comparison to all other formulations that were investigated. The cream formulation had the most significant in vivo anti-skin cancer efficacy, as evidenced by the smallest tumour volume and weight seen. Due to the possibility of administering anticancer drugs through topical means, there is a potential to minimize systemic side effects, enhance therapeutic efficacy, and improve patient compliance [38].

In 2018, a study conducted by Behnam, Mohammad Ali, et al. examined the use of PEGylated TiO_2NPs in the context of photothermal therapy (PTT). The objective of this technique was to induce hyperthermia and necrosis in malignant tumor cells. The confirmation of the development of a thin polyethylene glycol (PEG) coating on titanium dioxide nanoparticles (TiO_2 NPs) with the aim of enhancing their dispersibility has been established. A total of forty female mice with malignant conditions were divided into four groups of identical size. Each group was subjected to a therapy involving the administration of nanoparticles (NPs) and the use of a laser diode with specific parameters (wavelength λ= 808 nm, power P equals to 2 W, and intensity I equals to 2 W/cm^2). The treatment was applied for a duration of seven minutes, occurring only once during the entire treatment period. In contrast to mice just subjected to laser therapy, mice administered with TiO_2-PEG NPs alongside laser stimulation exhibited significantly reduced average tumor sizes. By employing thermo-gravimetric measurement and transmission electron microscopy techniques, the study aims to investigate and analyze the properties and behavior of the materials under examination [39].

In a study performed by Narmani et al. in 2020, the drug loading capabilities of nano-complexes consisting of Polyethylene glycol, Poly(methyl methacrylate), fatty acid, 5-FU, graphene, and Technetium-^{99m} (PEG-PAMMA G_4-FA-5-FU -^{99m}Tc) that were assessed. The evaluation involved analyzing the drug release characteristics, stability, effectiveness in inhibiting cancer cells, and potency in inhibiting tumor growth. The results on cellular uptake provided insights into the true efficacy of FA-targeted nanoparticles in penetrating breast cancer cells [40]. In 2021, Nazir, Samina, et al. The following is an elucidation of the production procedure employed for a nanodrug. The nanodrug was later incorporated into a polymeric matrix consisting of functionalized arabinoxylan, specifically referred to as carboxymethylarabinoxylan (CMARX), in various manifestations. The nanodrug is administered into CMARX, thereafter undergoing crosslinking with varying amounts of crosslinker (TEOS) in order to examine the range of physicochemical properties and in-vitro functions. The wetting characteristics of nanocomposite hydrogels have demonstrated significant diversity. The discovered result exhibits significant swelling and biodegradation properties, which are crucial for the controlled release of 5-FU. The augmented attributes of swelling, biodegradation, and moisture have a role in the conservation of therapeutic compounds that target bacterial and cancerous activities, hence improving the management and treatment of malignant melanoma skin cancer. The nanocomposite hydrogels have exhibited pH-responsive characteristics, exhibiting controlled and sustained release of 5-FU over a wide range of pH values. Moreover, it is noteworthy to mention that NCH-1 has substantial antibacterial activity against *S. aureus and P. aeruginosa*, alongside remarkable anticancer efficacy against U-87 cell lines [41].

4. Laser Ablation Method

For medical applications, laser ablation has been extensively used to generate metallic nanoparticles. In 2002, Tsuji, Takeshi, et al. utilized 355, 532 and 1064 nm lasers with a relatively high fluence of 36 J/cm^2 in water to produce silver nanoparticles. The spherical shape of these nanoparticles does not change (regardless of the wavelength of the ablation light), as shown by TEM and absorption spectra acquired with a spectrometer [42].

Titanium dioxide nanoparticles were synthesized in a sterile water solution by the laser ablation process developed by Barreca, F. et al. in 2010. Nd:YAG lasers with outputs of 532 nm were used to irradiate a Ti target, with operational fluences ranging from 1 to 10 J cm^2 and ablation times spanning 10 to 30 minutes. Nanoparticles with sizes of 10 nm or less and agglomerations of 100-200 nm were observed under an electron microscope, with the concentration of both increasing as the laser's intensity did. The optical bandgap values are consistent with the anatase phase, as observed by UV-vis absorbance [43].

Alnassar et al. employed pulsed laser ablation in 2013 to target titanium incorporated in Sodium Dodecyl Sulphate (SDS) solution and created TiO_2 nanoparticles. This is in reference to nano-synthesis using laser ablation as a green approach. The size of

nanoparticles was shown to depend on laser factors including pulse energy and the presence of chemically active species rather than the original colloidal characteristics. The average particle size was reduced from 185 nm to 110 nm during the re-irradiation process at an average energy of 180 J. The characterization of the NPs was investigated using a variety of techniques, including UV-vis, TEM, DLS and FTIR. The blue shift appeared to have reduced particle size, as seen by (UV-vis), and TEM analysis shows that the average particle size of 180 nm is predominantly the result of nanoparticle aggregation [44].

In 2014, M. Tajdidzadeh et al. investigated the size, stability and morphology of Ag-NPs. Using a Nd:YAG pulsed laser with 532 nm and 360 mJ/pulse, a pure Ag plate was ablated to produce Ag-NPs in organic substances like ethylene glycol (EG) and biopolymers like chitosan. The media (chitosan, EG) enabled for the production of NPs that were uniformly distributed and had an average size of around 10 nm in chitosan and 22 nm in EG. In comparison to pure water, the stability, shap, and particle size of NPs were assessed. The stability of the samples as well as their UV-visible absorption spectra was examined. The results demonstrated that chitosan produced NPs at a higher rate than other media [11], by laser ablation of silver plates outdoors using a nanosecond laser, Boutinguiza, M. et al. in 2015 increased production yield. TEM was used to study the characterization of the produced nanoparticles. The results showed that narrow size distributions of crystalline silver nanoparticles with rounded forms, ranging from a few to 50 nm, were created. The resulting nanoparticles were mostly formed through an explosive phase, which encouraged the development of assemblies of chain-like particles with continuous crystalline interfaces between particles [45].

Herbani et al. used pulsed laser ablation of submerged Au, Ag, and Cu metal particles in their research in 2018. They identified CuO nanoparticles for the Cu target because to the rapid oxidation of Cu in water, which resulted in its low durability. The formation of Au, Ag, and CuO nanoparticles could not be recognized by the human eye due to their distinctive colors—red, yellow, and the suspension of dark green colloidals, respectively. The surface plasmon frequency of Au, Ag, and CuO colloidal nanoparticles is confirmed to be at 520 nm, 400 nm, and 620 nm, respectively, by the UV-Vis spectrophotometer. According to TEM examination, all of the synthesized nanoparticles possessed crystalline morphologies and particle sizes between 20 and 40 nm [46]. In order to produce silver nanostructured, Fernández-Arias et al. used Pulsed laser ablation in liquid (PLAL) in 2019. With tools like EDS, HRTEM, XRD and UV-visible spectrophotometry, the resulting films were looked at for their makeup, surface features, crystalline arrangement, topographical features and optical properties. The coverings were made of tiny pieces of silver that ranged in size from a few nanometers to a few hundred nanometers. These films had a clear localized surface plasmon resonance (LSPR) peak at 400 nm, and they all had the same shape and look [47].

In 2021, Khashan used A Q-switch Nd: YAG laser to prepare a TiO_2 NPs suspension in deionized distilled water over a range of laser energy and ablation times. UV-visible absorption spectra obtained from a UV-Vis spectrophotometer. FTIR, XRD, and TEM were used to analyze the materials' characteristics. While TiO_2 NPs' UV-Vis spectra revealed a discernible band-to-band absorption peak in the UV range. There was evidence of an O-Ti-O bond thanks to FTIR research. In the XRD patterns, flat crystalline phases (101) and (112) of TiO_2 were seen at 2θ equals 35.4° and 38.8°, respectively. The size distribution of TiO_2 NPs has a spherical-like structure and varies based on the ablation period, as seen by TEM pictures. The size distribution of TiO_2 NPs was also demonstrated to be correlated with the laser ablation period, with longer ablation times resulting in a lower size dispersion [48].

Elsayed, et al. in 2022, Utilizing laser ablation, a successful synthesis of bimetallic nanoparticles combining colloidal ZnO and Ag was achieved. The characterized analysis of these nanoparticles encompassed techniques such as UV-Vis spectrophotometry, SEM, EDX, Raman spectroscopy, X-ray Photoelectron Spectroscopy (XPS), and Photo-Luminescence. These investigative measures unveiled that the size range of the bimetallic nanoparticles varied between 30 to 130 nm, thereby confirming the establishment of the nanocomposite structure. For potential assessment, the composite's impact was gauged on cancer cell lines HCT-116 and HELA through employment of the MTT assay (3-(4, 5-Dimethylthiazol-2-yl)-2, 5-Diphenyltetrazolium bromide). The findings demonstrated that the ZnO-Ag composite exhibited its highest impact on cell lines at a concentration of 10 μg/mL. This research implies that the bimetallic ZnO-Ag composite generated via laser ablation exhibits promising potential within the domain of cancer therapy [49].

5. Conclusion

1. The field of anticancer therapies has seen a significant impact from nanocomposites.
2. Several methods are used, with Pulsed Laser Ablation in Liquid PLAL of a metal target in a liquid solution standing out as one which is a highly versatile and promising approach.
3. PLAL approach is characterized by its procedural simplicity and does not require the use of chemical reagents in the solution. It is considered a green method due to its eco-friendliness.
4. PLAL allows for the loading of drugs and blending of polymers with nanometallic materials, thereby enhancing drug delivery capabilities.

In summary, pulsed laser ablation exhibits significant promise in the field of drug delivery applications.

6. References

[1] Stewart, B. and C. Wild, World Cancer Report 2014. World Cancer Report 2014. Geneva,

Switzerland: World Health Organization, International Agency for Research on Cancer. 2015, WHO Press.
[2] Sung, H., et al., Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians, 2021. **71**(3): p. 209-249.
[3] Felice, B., et al., Drug delivery vehicles on a nano-engineering perspective. Materials Science and Engineering: C, 2014. **41**: p. 178-195.
[4] Waheed, S., et al., Engineering nano-drug biointerface to overcome biological barriers toward precision drug delivery. Journal of Nanobiotechnology, 2022. **20**(1): p. 395.
[5] Sağir, T., et al., Preparation and in vitro evaluation of 5-flourouracil loaded magnetite–zeolite nanocomposite (5-FU-MZNC) for cancer drug delivery applications. Biomedicine & Pharmacotherapy, 2016. **77**: p. 182-190.
[6] Tagde, P., et al., Recent advances in folic acid engineered nanocarriers for treatment of breast cancer. Journal of Drug Delivery Science and Technology, 2020. **56**: p. 101613.
[7] Lin, J., et al. Synthesis and characterization of FeCo nanoparticle colloid by pulsed laser ablation in distilled water. in 33rd EPS conference on plasma phys. Rome. I. 2006.
[8] Ravishankar Rai, V. and A. Jamuna Bai, Nanoparticles and their potential application as antimicrobials. A Méndez-Vilas A, editor. Mysore: Formatex, 2011: p. 197-209.
[9] Devaraj, P., et al., Synthesis and characterization of silver nanoparticles using cannonball leaves and their cytotoxic activity against MCF-7 cell line. Journal of nanotechnology, 2013. **2013**.
[10] Hussein, S.I., Study the effect of gold nanoparticles on cancer and normal cells (in vitro study). Iraqi Journal of Cancer and Medical Genetics, 2016. **9**(2).
[11] Tajdidzadeh, M., et al., Synthesis of silver nanoparticles dispersed in various aqueous media using laser ablation. The Scientific World Journal, 2014. **2014**.
[12] Jamaludin, N., et al. Effect of laser energy and wavelength on average size of gold nanoparticles synthesized by pulsed laser ablation in deionized water. in Journal of Physics: Conference Series. 2020. IOP Publishing.
[13] Maksimova, I.L., et al., Near-infrared laser photothermal therapy of cancer by using gold nanoparticles: Computer simulations and experiment. Medical Laser Application, 2007. **22**(3): p. 199-206.
[14] Zhou, F., et al., Cancer photothermal therapy in the near-infrared region by using single-walled carbon nanotubes. Journal of biomedical optics, 2009. **14**(2): p. 021009-021009-7.
[15] Kocbek, P., et al., Toxicological aspects of long-term treatment of keratinocytes with ZnO and TiO2 nanoparticles. Small, 2010. **6**(17): p. 1908-1917.
[16] Browning, C.L., et al., Titanium dioxide nanoparticles are not cytotoxic or clastogenic in human skin cells. Journal of environmental & analytical toxicology, 2014. **4**(6).
[17] Arooj, S., et al., Novel ZnO: Ag nanocomposites induce significant oxidative stress in human fibroblast malignant melanoma (Ht144) cells. Beilstein journal of nanotechnology, 2015. **6**(1): p. 570-582.
[18] Chakra, C., K. Raob, and V. Rajendar, Nanocomposites of ZnO and TiO2 have enhanced antimicrobial and antibacterial properties than their disjoint counterparts. Dig J Nanomater Biostruct, 2017. **12**: p. 185-193.
[19] Chakra, C.S., et al., Enhanced antimicrobial and anticancer properties of ZnO and TiO 2 nanocomposites. 3 Biotech, 2017. **7**: p. 1-8.
[20] El-Naggar, N.E.-A., M.H. Hussein, and A.A. El-Sawah, Bio-fabrication of silver nanoparticles by phycocyanin, characterization, in vitro anticancer activity against breast cancer cell line and in vivo cytotxicity. Scientific reports, 2017. **7**(1): p. 10844.
[21] Samadi, S., et al., Fabrication of chitosan/poly (lactic acid)/graphene oxide/TiO2 composite nanofibrous scaffolds for sustained delivery of doxorubicin and treatment of lung cancer. International journal of biological macromolecules, 2018. **110**: p. 416-424.
[22] Saber, M.M., S.B. Mirtajani, and K. Karimzadeh, Green synthesis of silver nanoparticles using Trapa natans extract and their anticancer activity against A431 human skin cancer cells. Journal of Drug Delivery Science and Technology, 2018. **47**: p. 375-379.
[23] Ghaemi, B., et al., Supramolecular insights into domino effects of Ag@ ZnO-induced oxidative stress in melanoma cancer cells. ACS applied materials & interfaces, 2019. **11**(50): p. 46408-46418.
[24] Rao, T.N., et al., Green synthesis and structural classification of Acacia nilotica mediated-silver doped titanium oxide (Ag/TiO2) spherical nanoparticles: Assessment of its antimicrobial and anticancer activity. Saudi Journal of Biological Sciences, 2019. **26**(7): p. 1385-1391.
[25] Hariharan, D., et al., Enhanced photocatalysis and anticancer activity of green hydrothermal synthesized Ag@ TiO2 nanoparticles. Journal of Photochemistry and Photobiology B: Biology, 2020. **202**: p. 111636.
[26] Nie, C., et al., Ag@ TiO2 nanoprisms with highly efficient near-infrared photothermal conversion for melanoma therapy. Chemistry–An Asian Journal, 2020. **15**(1): p. 148-155.
[27] Pragathiswaran, C., et al., TiO2@ ZnO nanocomposites decorated with gold nanoparticles: Synthesis, characterization and their antifungal, antibacterial, anti-inflammatory and anticancer activities. Inorganic Chemistry Communications, 2020. **121**: p. 108210.
[28] Nagajyothi, P., et al., In vitro anticancer activity of eco-friendly synthesized ZnO/Ag nanocomposites. Ceramics International, 2021. **47**(24): p. 34940-34948.

[29] Ringsdorf, H. Structure and properties of pharmacologically active polymers. in Journal of Polymer Science: Polymer Symposia. 1975. Wiley Online Library.
[30] Aryal, S., et al., Doxorubicin conjugated gold nanoparticles as water-soluble and pH-responsive anticancer drug nanocarriers. Journal of Materials Chemistry, 2009. **19**(42): p. 7879-7884.
[31] Iannazzo, D., et al., Recent advances in carbon nanotubes as delivery systems for anticancer drugs. Current medicinal chemistry, 2013. **20**(11): p. 1333-1354.
[32] Venkatasubbu, G.D., et al., Folate targeted PEGylated titanium dioxide nanoparticles as a nanocarrier for targeted paclitaxel drug delivery. Advanced Powder Technology, 2013. **24**(6): p. 947-954.
[33] Li, P., et al., Microencapsulation of coupled folate and chitosan nanoparticles for targeted delivery of combination drugs to colon. Journal of microencapsulation, 2015. **32**(1): p. 40-45.
[34] Tummala, S., M.S. Kumar, and A. Prakash, Formulation and characterization of 5-Fluorouracil enteric coated nanoparticles for sustained and localized release in treating colorectal cancer. Saudi Pharmaceutical Journal, 2015. **23**(3): p. 308-314.
[35] Ou, G., et al., Photothermal therapy by using titanium oxide nanoparticles. Nano Research, 2016. **9**: p. 1236-1243.
[36] Banerjee, S.L., et al., Modified chitosan encapsulated core-shell Ag Nps for superior antimicrobial and anticancer activity. International journal of biological macromolecules, 2016. **85**: p. 157-167.
[37] Jalill, R.D.A., Antagonistic effect between Citrullus colocynthis extract and TiO2 nanoparticles in anticancer combination therapy. Iraqi Journal of Cancer and Medical Genetics, 2016. **9**(2).
[38] Safwat, M.A., et al., Fluorouracil-loaded gold nanoparticles for the treatment of skin cancer: development, in vitro characterization, and in vivo evaluation in a mouse skin cancer xenograft model. Molecular pharmaceutics, 2018. **15**(6): p. 2194-2205.
[39] Behnam, M.A., et al., The application of titanium dioxide (TiO2) nanoparticles in the photo-thermal therapy of melanoma cancer model. Iranian journal of basic medical sciences, 2018. **21**(11): p. 1133.
[40] Narmani, A., et al., Breast tumor targeting with PAMAM-PEG-5FU-99m Tc as a new therapeutic nanocomplex: in in-vitro and in-vivo studies. Biomedical Microdevices, 2020. **22**: p. 1-13.
[41] Nazir, S., et al., Nanocomposite hydrogels for melanoma skin cancer care and treatment: In-vitro drug delivery, drug release kinetics and anti-cancer activities. Arabian Journal of Chemistry, 2021. **14**(5): p. 103120.
[42] Tsuji, T., et al., Preparation of silver nanoparticles by laser ablation in solution: influence of laser wavelength on particle size. Applied surface science, 2002. **202**(1-2): p. 80-85.
[43] Barreca, F., et al., Small size TiO2 nanoparticles prepared by laser ablation in water. Applied Surface Science, 2010. **256**(21): p. 6408-6412.
[44] Alnassar, S.I., et al., Study of the fragmentation phenomena of TiO2 nanoparticles produced by femtosecond laser ablation in aqueous media. Optics & Laser Technology, 2013. **51**: p. 17-23.
[45] Boutinguiza, M., et al., Production of silver nanoparticles by laser ablation in open air. Applied Surface Science, 2015. **336**: p. 108-111.
[46] Herbani, Y., et al. Pulse laser ablation of Au, Ag, and Cu metal targets in liquid for nanoparticle production. in Journal of Physics: Conference Series. 2018. IOP Publishing.
[47] Fernández-Arias, M., et al., Synthesis and deposition of Ag nanoparticles by combining laser ablation and electrophoretic deposition techniques. Coatings, 2019. **9**(9): p. 571.
[48] Khashan, K.S., et al., Antibacterial activity of TiO2 nanoparticles prepared by one-step laser ablation in liquid. Applied Sciences, 2021. **11**(10): p. 4623.
[49] Elsayed, K.A., et al., Fabrication of ZnO-Ag bimetallic nanoparticles by laser ablation for anticancer activity. Alexandria Engineering Journal, 2022. **61**(2): p. 1449-1457.