Nanocarriers

Subjects: Nanoscience & Nanotechnology

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Nanocarriers are added as colloidal nanosystems loaded with therapeutic agents (anticancer agents or any macromolecules, such as proteins or genes), which allow drugs to selectively accumulate at the site of cancerous tumors. As a result of their unique nanometer range, 1–1000 nm (drug administration is preferable in the 5–200 nm range), they are used for cancer treatment. The main and most promising nanocarriers in the literature are iron oxide, gold, polymers, liposomes, micelles, fullerenes (carbon nanotubes, graphene), dendrimers, quantum dots, and nanodiamonds.

Keywords: nanocarriers ; immune system ; nanobiotechnology ; cancer

1. Introduction

Cancer is a major cause of global morbidity and mortality. It is a disease caused by a variety of factors, and its formation depends on several genetic and epigenetic aspects [1]. Malignant tumors have a specificity that affects other healthy cells in the body [2]. In order to develop more effective methods of diagnosis and treatment without harming the patient, various resources have been widely explored, and current treatment methods used for cancer control include chemotherapy, surgery, radiation, and biological therapies (immunotherapy and hormone therapy) [3][4][5].

However, these therapies have certain disadvantages and, being invasive, have side effects before and after treatment, making the patient uncomfortable. For example, the use of chemotherapeutic drugs can affect the normal and healthy growth of good cells and bring opportunities for tumor recurrence. In addition, resistance to various drugs may develop, and poor biodistribution results in a low concentration of these chemotherapeutic agents at the tumor site, which may reduce the therapeutic effect of anticancer drugs [6][7][8][9]. In this context, it is necessary to research and develop alternative beneficial and effective therapies for the drug delivery system.

Nanotechnology can increase the pharmacological properties of compounds commonly used in the treatment and diagnosis of cancer, which is why it has emerged as an innovative possibility for therapeutic intervention in cancer and in the distribution of drugs [10][11]. This can usually be achieved by different routes of administration, such as oral, nasal, transdermal, intravenous, etc. These nanocarriers can improve the effectiveness of the drug and reduce side effects. They can be encapsulated or used in combination with other drugs [12][13]. In addition, nano-scale transporters can protect drugs or any macromolecules (proteins, peptides, etc.) from degradation, reduce renal clearance, and provide sustained or controlled release kinetics, thereby increasing drug efficacy at steady-state therapeutic levels [14][15][16][17]. Their half-life in the blood improves the therapeutic index, solubility, and stability of the capsules, compared to conventional treatment methods (such as tablets, capsules, and injections) [18][19].

2. Classification of Nanocarriers

Nanocarriers can be classified into three categories based upon the materials that they are made from (**A**) lipid-based nanoparticles, (**B**) inorganic nanoparticles, and (**C**) polymeric nanoparticles (**Figure 1**).

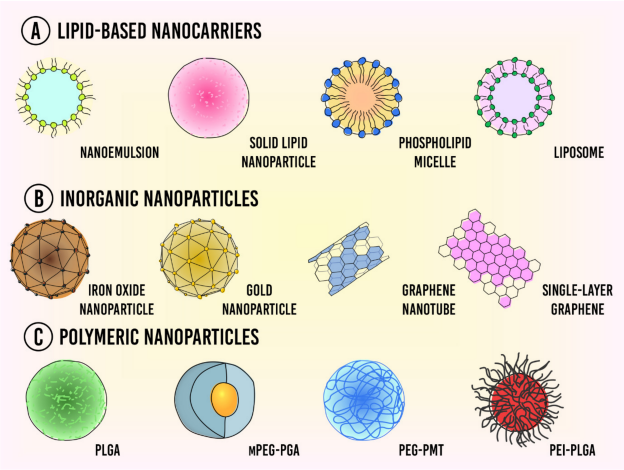

Figure 1. Types of nanocarriers used for drug delivery in cancer therapy. (**A**) Lipid-based nanocarriers; (**B**) Inorganic nanoparticles; (**C**) Polymeric nanoparticles.

2.1. Lipid-Based Nanocarriers

Liposomes were the first nanotransporters advanced by Bangham [20] in 1965, and they include the first nanotransporter (DaunoXome ™) that was clinically approved by the FDA (Food and Drug Administration) for the transport of chemotherapeutic drugs in 1996 [21]. Lipid-based nanocarriers have emerged as a very promising, emerging, and rapidly developing tool for the delivery of various drugs with low solubility, bioavailability, and stability in recent decades [22][23]. Lipid nanocarriers allow the therapeutic load to be directed to the deep layers of the skin or even reach the blood circulation, making them a promising cutting-edge technology. Lipid nanocarriers refer to a large panel of drug delivery systems [24][25]. Lipid vesicles are the most conventional, and they are known to be capable of transporting lipophilic and hydrophilic active agents [26]. Others are designed with the objective of achieving a higher encapsulation rate and greater stability, such as solid lipid nanoparticles and nanostructured lipid nanocarriers [27]. The formulation of a liposomal drug improves the biodistribution and pharmacokinetics of a drug. This means that a higher concentration of the drug can be achieved within the tumors, while reducing the concentration of the drug in normal tissue [28][29]. Lipid-based nanocarriers include liposomes, nanoemulsions, solid lipid nanoparticles, and phospholipid micelles.

2.2. Polymeric Nanocarriers

Polymeric nanocarriers are synthesized from different types of natural and synthetic polymers that generally have good biocompatibility and biodegradability [30]. The advantages of these polymer nanomaterials compared to other nanocarriers include stability in various microenvironments, slow release of drugs due to polymer degradation, and their diversity in the types of polymers and types of drugs to be encapsulated [31][32]. The hydrophobicity and hydrophilicity within the polymer structure can be controlled to suit a variety of drug molecules [33]. Commonly used natural polymers include gelatin, dextran, albumin, chitosan, and alginate, and synthetic biodegradable polymers include polylactic acid (PLA), polyglycolic acid (PGA), copolymer of lactic acid and glycolic acid (PLGA), poly (ε-caprolactone) (PCL), polyalkylcyanoacrylate (PACA), poly (ethylene glycol) (PEG), poly (D,L-lactide-co-glycolide) (PLG), polyethyleneimine (PEI), poly (L-lysine), poly (Tian Particular acid), and others [34][35][36]. Gao (2021) [37] evidences the activity of reactive oxygen species (ROS)-responsive polymers for drug delivery systems, which may include polymers containing thioether, poly (thioketal), polymers containing selenium, tellurium, arylboronic acid/ester, aryl oxalate, and ferrocene; these are being widely investigated for anticancer therapy. The properties of polymerized NPs can be beneficial for the treatment of several potentially fatal diseases, including cancer, neurodegenerative diseases, cardiovascular diseases, and even viral infections and osteoporosis [38][39].

2.3. Inorganic Nanoparticles

Among the nanocarriers that are being developed for the diagnosis and treatment of cancer are inorganic nanoparticles, which may consist of iron oxide, silica, gold, and graphene, among other compounds [40]. There is greater difficulty in translating these types of nanomaterials (NMs) to clinical application, due to their lower biocompatibility and the lack of understanding of possible complications caused by their deposition in different organs, such as greater stability, less hydrophobicity, and non-microbial storage [41][42]. Despite these difficulties, the physical properties attributed to the constituent materials of inorganic nanoparticles make it possible to apply them in a variety of processes, for example, magnetic nanoparticles can be used for magnetic resonance imaging (MRI) or with magnetic targeting, while gold and silver NM can be used for imaging or heating during targeted treatment [43][44].

Similar to organic nanoparticles, inorganic NMs are also being studied as targeted drug delivery systems [39][40]. These important nanoparticles have gained attention in preclinical studies due to their potential for diagnosis and therapy in anticancer systems, with a variety of applications including tumor imaging, drug administration, and improvement in radiotherapy. Recent advances in nanotechnology demonstrate the importance of inorganic nanoparticles, given that they are internalized by cells through the endocytosis process [45] and can be composed of different materials, some of which are gold, oxide iron, and graphene [39][40][41][42][43][44].

Iron oxide nanoparticles (IONPs), composed of magnetite (Fe_3O_4) or maghemite (γ-Fe_3O_2), were initially developed and used as contrast agents for the detection of primary tumors and metastasis by magnetic resonance [45][46]. Due to the reduced nanometric size, usually varying between 10 and 20 nm, and their responses to magnetic fields, they have been developed to be associated with different drugs and to work as a drug delivery system [39][40][41][42][43][44][45][46][47]. Iron oxide nanosystems, once functionalized, have a wide field of biomedical application, being used preferentially for the treatment and diagnosis of cancer [48]. Studies demonstrate advantages in the use of IONPs for the greater uptake of intratumoral drugs, as shown in a study by Alphandéry et al. (2019) [47], which observed that the association of doxorubicin (DOX) with IONPs increased the accumulation of intratumoral drugs, when compared to free drug treatment against ovarian cancer models [49]. In another study, IONPs conjugated to vinblastine led to decreased viability of MCF-7 breast cancer cells when compared to treatment alone [50]. These processes can be improved when these NMs receive a targeting molecule, as in Nagesh et al. (2016) [51], which combined superparamagnetic iron oxide nanoparticles (SPIONs) with docetaxel, a chemotherapy, and an antibody against a specific membrane antigen present in prostate cancer (PSMA), and increased uptake and antitumor effectiveness compared to free drugs [51]. Associated with the drug delivery system, IONPs can also be used together.

Therapies can also be based on increasing local temperature, as in a study by Estelrich et al. (2016) [52], which used photothermal therapy with IONPs, resulting in the destruction of tumor cells (MCF-7 and MDA-MB-231) [52], or as contrast agents for imaging carcinomas, such as in Patel et al. (2016) [53]. The latter study used SPIONs associated with the anti-mesothelin antibody, which is a protein expressed in the membrane of different adenocarcinomas such as pancreas, lung, liver, sarcomas, to identify pancreatic carcinoma in xenographic models by MRI, which obtained very significant results when compared with the commonly used contrast agent (T2) [53].

Another group of inorganic nanoparticles that has been developed for the treatment of cancer are those composed of gold. Gold nanoparticles are being studied as an important mechanism for drug delivery, demonstrating better tumor targeting and, thus, reducing the adverse effects caused to patients by decreasing the doses of drugs used to treat various types of cancer [16]. In addition to the chemical properties of its surface, physical properties can also be exploited to act as contrast agents in imaging and as enhancers of anticancer therapy by increasing local temperature, leading to photothermal destruction of tumors [39][54]. A system proposed by Lee et al. (2017) [55], composed of doxorubicin linked to oligonucleotides and gold nanoparticles for therapy in cancer, has demonstrated promise in reducing colorectal cancer tumors [55]. In another study, the importance of the photothermal properties of gold nanoclusters covered by silica (AuNC $\cong$ SiO_2) was demonstrated, showing the potential of these nanoparticles in the treatment of prostate cancer [56].

Graphene nanofibers, composed of a single layer of carbon atoms hybridized in sp^2, have been used in biomedicine as imaging agents, anticancer therapy, and drug delivery systems [44]. The easy functionalization processes, excellent electrical conductivity, strong mechanical resistance, and high surface area make graphene an important agent to explore to compose the theragnostic NM used against cancer [44][57]. A study by Santos et al. (2018) [57] demonstrated the potential of the association of graphene oxide nanofibers with the methylene blue photosensitizing agent in the removal of xenographic breast tumors 4T1 through the combination of photodynamic and photothermal therapies [57]. As well as the potential for direct treatment against tumor cells, Deng et al. (2020) [58] evidenced the activation of antitumor macrophages in vitro and in vivo by means of graphene oxide nanofibers combined with polyethylene glycol (PEG), which is associated with near-infrared light irradiation (NIR) [58].

3. Conclusions and Future Prospects

Years of research have investigated therapeutic alternatives for treating cancer, including surgery, radiation therapy, chemotherapy, hormonal therapy, and target therapy, which are provided according to their type, stage, and location. Currently, it is known that the common therapeutic approaches applied to the treatment of this disease, despite promoting a good prognosis for the patient, cause damage to healthy tissues, incomplete eradication of tumor cells, and adverse effects on patients. Observing these various problems associated with current treatments, new therapies have been sought that are non-invasive and have low systemic toxicity, such as nanobiotechnology. The nanotechnology field has established recently promoted cancer treatment methods. Several nanocarriers studied in this field have allowed

researchers to overcome the limitations of conventional therapies, thus increasing their efficiency in guiding the delivery of these therapeutic agents.

The studies reinforced the concept that nanocarriers can be developed to promote the recruitment of immune cells and overcome the anergy of tumor-specific T cells by blocking immunosuppressive pathways. The use of nanocarriers is a promising strategy, because it is possible to have a modular response in the TME, activate an accurate CTL response, and improve antitumor efficacy. In this context, immunotherapy combined with nanoparticles will have a significant impact on clinical performance to enhance the immune system in cancer therapy. However, there is still a need for studies to gain a deeper understanding of the mechanisms underlying the immune system and the safety profiles of nanoparticles, to ensure effective delivery of nanocarriers to the target tissue and avoid toxicity.

References

1. Vanza, J.D.; Patel, R.B.; Patel, M.R. Nanocarrier centered therapeutic approaches: Recent developments with insight towards the future in the management of lung cancer. J. Drug Deliv. Sci. Technol. 2020, 60, 102070.
2. Anselmo, A.C.; Mitragotri, S. Nanoparticles in the clinic: An update. Bioeng. Transl. Med. 2019, 4, e10143.
3. Shi, Y.; Lammers, T. Combining Nanomedicine and Immunotherapy. Accounts Chem. Res. 2019, 52, 1543–1554.
4. Beik, J.; Abed, Z.; Ghoreishi, F.S.; Hosseini-Nami, S.; Mehrzadi, S.; Shakeri-Zadeh, A.; Kamrava, S.K. Nanotechnology in hyperthermia cancer therapy: From fundamental principles to advanced applications. J. Control. Release 2016, 235, 205–221.
5. Lv, Y.; Tao, L.; Bligh, S.A.; Yang, H.; Pan, Q.; Zhu, L. Targeted delivery and controlled release of doxorubicin into cancer cells using a multifunctional graphene oxide. Mater. Sci. Eng. C 2016, 59, 652–660.
6. Guido, C.; Maiorano, G.; Cortese, B.; D'Amone, S.; Palamà, I.E. Biomimetic Nanocarriers for Cancer Target Therapy. Bioengineering 2020, 7, 111.
7. Bahrami, B.; Farsangi, M.H.; Mohammadi, H.; Anvari, E.; Ghalamfarsa, G.; Yousefi, M.; Jadidi-Niaragh, F. Nanoparticles and targeted drug delivery in cancer therapy. Immunol. Lett. 2017, 190, 64–83.
8. Ehsanimehr, S.; Moghadam, P.N.; Dehaen, W.; Shafiei-Irannejad, V. Synthesis of pH-sensitive nanocarriers based on polyacrylamide grafted nanocrystalline cellulose for targeted drug delivery to folate receptor in breast cancer cells. Eur. Polym. J. 2021, 150, 110398.
9. Rizvi, S.A.; Saleh, A.M. Applications of nanoparticle systems in drug delivery technology. Saudi Pharm. J. 2018, 26, 64–70.
10. Fang, X.; Cao, J.; Shen, A. Advances in anti-breast cancer drugs and the application of nano-drug delivery systems in breast cancer therapy. J. Drug Deliv. Sci. Technol. 2020, 57, 101662.
11. Kawasaki, E.S.; Player, A. Nanotechnology, nanomedicine, and the development of new, effective therapies for cancer. Nanomed. Nanotechnol. Biol. Med. 2005, 1, 101–109.
12. Yu, X.; Trase, I.; Ren, M.; Duval, K.; Guo, X.; Chen, Z. Design of Nanoparticle-Based Carriers for Targeted Drug Delivery. J. Nanomater. 2016, 2016, 1–15.
13. Brigger, I.; Dubernet, C.; Couvreur, P. Nanoparticles in cancer therapy and diagnosis. Adv. Drug Deliv. Rev. 2012, 64, 24–36.
14. Cryer, A.M.; Thorley, A.J. Nanotechnology in the diagnosis and treatment of lung cancer. Pharmacol. Ther. 2019, 198, 189–205.
15. Gurunathan, S.; Kang, M.-H.; Qasim, M.; Kim, J.-H. Nanoparticle-Mediated Combination Therapy: Two-in-One Approach for Cancer. Int. J. Mol. Sci. 2018, 19, 3264.
16. Liu, D.; Yang, F.; Xiong, F.; Gu, N. The Smart Drug Delivery System and Its Clinical Potential. Theranostics 2016, 6, 1306–1323.
17. Ventola, C.L. Progress in nanomedicine: Approved and investigational nanodrugs. Pharm. Ther. 2017, 42, 742–755.
18. ud Din, F.; Aman, W.; Ullah, I.; Qureshi, O.S.; Mustapha, O.; Shafique, S.; Zeb, A. Effective use of nanocarriers as drug delivery systems for the treatment of selected tumors. Int. J. Nanomed. 2017, 12, 72–91.
19. Grodzinski, P.; Kircher, M.; Goldberg, M.; Gabizon, A. Integrating Nanotechnology into Cancer Care. ACS Nano 2019, 13, 7370–7376.
20. Bangham, A.; Horne, R. Negative staining of phospholipids and their structural modification by surface-active agents as observed in the electron microscope. J. Mol. Biol. 1964, 8, 660–IN10.

21. Forssen, E.A.; Ross, M.E. Daunoxome® Treatment of Solid Tumors: Preclinical and Clinical Investigations. J. Liposome Res. 1994, 4, 481–512.

22. Akbarzadeh, A.; Rezaei-Sadabady, R.; Davaran, S.; Joo, S.W.; Zarghami, N.; Hanifehpour, Y.; Samiei, M.; Kouhi, M.; Nejati-Koshki, K. Liposome: Classification, preparation, and applications. Nanoscale Res. Lett. 2013, 8, 102.

23. Kulkarni, J.; Cullis, P.R.; van der Meel, R. Lipid Nanoparticles Enabling Gene Therapies: From Concepts to Clinical Utility. Nucleic Acid Ther. 2018, 28, 146–157.

24. Maeki, M.; Kimura, N.; Sato, Y.; Harashima, H.; Tokeshi, M. Advances in microfluidics for lipid nanoparticles and extracellular vesicles and applications in drug delivery systems. Adv. Drug Deliv. Rev. 2018, 128, 84–100.

25. Pattni, B.S.; Chupin, V.V.; Torchilin, V.P. New developments in liposomal drug delivery. Chem. Rev. 2015, 115, 10938–10966.

26. Sapra, P.T.A.T.M.A.P.; Tyagi, P.; Allen, T.M. Ligand-Targeted Liposomes for Cancer Treatment. Curr. Drug Deliv. 2005, 2, 369–381.

27. Shamant, B.S.; Moin, A.; Gowda, D.V.; Rashmi, R.; Hiremath, R. Lipid based drug delivery systems in arthritis and allied conditions. World J. Pharm. Sci. 2016, 4, 61–68.

28. Shrestha, H.; Bala, R.; Arora, S. Lipid-Based Drug Delivery Systems. J. Pharm. 2014, 2014, 1–10.

29. Ansari, M.T.; Ramlan, T.A.; Jamaluddin, N.N.; Zamri, N.; Salfi, R.; Khan, A.; Sami, F.; Majeed, S.; Hasnain, M.S. Lipid-based Nanocarriers for Cancer and Tumor Treatment. Curr. Pharm. Des. 2020, 26, 4272–4276.

30. Beck-Broichsitter, M.; Merkel, O.; Kissel, T. Controlled pulmonary drug and gene delivery using polymeric nano-carriers. J. Control. Release 2012, 161, 214–224.

31. Ahuja, R.; Panwar, N.; Meena, J.; Singh, M.; Sarkar, D.P.; Panda, A.K. Natural products and polymeric nanocarriers for cancer treatment: A review. Environ. Chem. Lett. 2020, 18, 2021–2030.

32. Vijayan, V.M.; Muthu, J. Polymeric nanocarriers for cancer theranostics. Polym. Adv. Technol. 2017, 28, 1572–1582.

33. Sun, Q.; Zhu, Y.; Du, J. Recent progress on charge-reversal polymeric nanocarriers for cancer treatments. Biomed. Mater. 2021, 16, 042010.

34. Avramović, N.; Mandić, B.; Savić-Radojević, A.; Simić, T. Polymeric Nanocarriers of Drug Delivery Systems in Cancer Therapy. Pharmaceutics 2020, 12, 298.

35. Alsehli, M. Polymeric nanocarriers as stimuli-responsive systems for targeted tumor (cancer) therapy: Recent advances in drug delivery. Saudi Pharm. J. 2020, 28, 255–265.

36. Desai, P.; Date, A.; Patravale, V.B. Overcoming poor oral bioavailability using nanoparticle formulations—Opportunities and limitations. Drug Discov. Today Technol. 2012, 9, e87–e95.

37. Gao, F.; Xiong, Z. Reactive Oxygen Species Responsive Polymers for Drug Delivery Systems. Front. Chem. 2021, 9, 66.

38. Dhas, N.; Ige, P.P.; Kudarha, R. Design, optimization and in-vitro study of folic acid conjugated-chitosan functionalized PLGA nanoparticle for delivery of bicalutamide in prostate cancer. Powder Technol. 2015, 283, 234–245.

39. Shin, D.H.; Tam, Y.T.; Kwon, G.S. Polymeric micelle nanocarriers in cancer research. Front. Chem. Sci. Eng. 2016, 10, 348–359.

40. Izci, M.; Maksoudian, C.; Manshian, B.B.; Soenen, S.J. The Use of Alternative Strategies for Enhanced Nanoparticle Delivery to Solid Tumors. Chem. Rev. 2021, 121, 1746–1803.

41. Paul, W.; Sharma, C.P. Inorganic nanoparticles for targeted drug delivery. Biointegration Med. Implant. Mater. 2020, 334–373.

42. Torchilin, V.P. Multifunctional, stimuli-sensitive nanoparticulate systems for drug delivery. Nat. Rev. Drug Discov. 2014, 13, 813–827.

43. Mura, S.; Nicolas, J.; Couvreur, P. Stimuli-responsive nanocarriers for drug delivery. Nat. Mater. 2013, 12, 991–1003.

44. Oh, N.; Park, J.-H. Endocytosis and exocytosis of nanoparticles in mammalian cells. Int. J. Nanomed. 2014, 9, 51.

45. Behbudi, G. Mini review of Graphene Oxide for medical detection and applications. Adv. Appl. NanoBio-Technol. 2020, 1, 63–66.

46. Alphandéry, E. Iron oxide nanoparticles for therapeutic Applications. Drug Discov. Today 2019, 25, 141–149.

47. Li, M.; Kim, H.S.; Tian, L.; Yu, M.K.; Jon, S.; Moon, W.K. Comparison of Two Ultrasmall Superparamagnetic Iron Oxides on Cytotoxicity and MR Imaging of Tumors. Theranostics 2012, 2, 76–85.

48. Duncan, R.; Gaspar, R. Nanomedicine (s) under the microscope. Mol. Pharm. 2011, 8, 2101–2141.
49. Carneiro, M.L.B.; Peixoto, R.C.; Joanitti, G.A.; Oliveira, R.G.; Telles, L.A.; Miranda-Vilela, A.L.; Bocca, A.L.; Vianna, L.M.; Da Silva, I.C.; De Souza, A.R.; et al. Antitumor effect and toxicity of free rhodium (II) citrate and rhodium (II) citrate-loaded maghemite nanoparticles in mice bearing breast cancer. J. Nanobiotechnol. 2013, 11, 4.
50. Alphandéry, E. Biodistribution and targeting properties of iron oxide nanoparticles for treatments of cancer and iron anemia disease. Nanotoxicology 2019, 13, 573–596.
51. Nagesh, P.K.B.; Johnson, N.R.; Boya, V.K.; Chowdhury, P.; Othman, S.F.; Khalilzad-Sharghi, V.; Hafeez, B.B.; Ganju, A.; Khan, S.; Behrman, S.W.; et al. PSMA targeted docetaxel-loaded superparamagnetic iron oxide nanoparticles for prostate cancer. Colloids Surf. B Biointerfaces 2016, 144, 8–20.
52. Estelrich, J.; Brusquets, M.A. Iron oxide nanoparticles in photothermal therapy. Molecules 2016, 408, 1567.
53. Patel, A.; Sant, S. Hypoxic tumor microenvironment: Opportunities to develop targeted therapies. Biotechnol. Adv. 2016, 34, 803–812.
54. Javid, A.; Ahmadian, S.; Saboury, A.A.; Kalantar, S.M.; Rezaei-Zarchi, S. Chitosan-Coated Superparamagnetic Iron Oxide Nanoparticles for Doxorubicin Delivery: Synthesis and Anticancer Effect Against Human Ovarian Cancer Cells. Chem. Biol. Drug Des. 2013, 82, 296–306.
55. Lee, C.-S.; Kim, H.; Yu, J.; Yu, S.H.; Ban, S.; Oh, S.; Jeong, D.; Im, J.; Baek, M.J.; Kim, T.H. Doxorubicin-loaded oligonucleotide conjugated gold nanoparticles: A promising in vivo drug delivery system for colorectal cancer therapy. Eur. J. Med. Chem. 2017, 142, 416–423.
56. Siddique, S.; Chow, J.C.L. Gold Nanoparticles for Drug Delivery and Cancer Therapy. Appl. Sci. 2020, 10, 3824.
57. Dos Santos, M.S.C.; Gouvêa, A.L.; de Moura, L.D.; Paterno, L.G.; de Souza, P.E.N.; Bastos, A.P.; Damaceno, E.A.M.; Veiga-Souza, F.H.; Azevedo, R.B.; Báo, S.N. Nanographene oxide-methylene blue as phototherapies platform for breast tumor ablation and metastasis prevention in a syngeneic orthotopic murine model. J. Nanobiotechnol. 2018, 16, 1–17.
58. Deng, X.; Liang, H.; Yang, W.; Shao, Z. Polarization and function of tumor-associated macrophages mediate graphene oxide-induced photothermal cancer therapy. J. Photochem. Photobiol. B Biol. 2020, 208, 111913.