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Nanotechnology in PDT - New Possibilities and Applications

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Abstract: The revolution in the field of nanotechnology that we are witnessing has had a huge impact on biomedicine, including PDT. For PDT to be both effective and safe, it is essential that PS is delivered at therapeutic concentrations to target cells (such as cancer cells) while being absorbed only in small amounts by non-target cells, thereby minimizing undesirable effects. Side effects in healthy tissues. Nanomaterials are attracting increasing attention due to their tunable, enhanced physicochemical, and biological properties compared to their conventional bulk counterparts.

Keywords: photodynamic therapy; photosensitizer; nanotechnology; quantum dots.

1. Introduction

Nanocarriers that, when combined with drugs, enhance tissue penetration are crucial in the field of photodynamic therapy. The fact is that the most effective photosensitizers are hydrophobic molecules with a strong tendency to aggregate [1-4], which reduces their efficiency. In this case, the most optimal is the monomeric form, which guarantees its photoactivity [5]. Photosensitizers generally do not bind or migrate preferentially to cancer cells, making it difficult to precisely target diseased tissues with photodynamic therapy [6]. Therefore, significant efforts have been made to design delivery systems that can have a very beneficial effect on the overall mechanism of PDT-induced cancer cell death. Many nanostructures have been used in PDT, including plasmonic gold nanoparticles, mesoporous silica nanoparticles, carbon nanotubes, graphene, and upconversion nanoparticles [2]. An interesting group of nanoparticles is fullerenes [7], titanium dioxide [8], and some types of quantum dots [9], where the nanoparticle itself serves as a photosensitizer thanks to having an extinction coefficient of significant size in the appropriate area of the electromagnetic spectrum, absorbing light and photochemically producing ROS.

2. Materials and Methods

If nanoparticles are biodegradable, their composition will be limited to lipids and some polymers. If it is the opposite, they will remain in the body for a long time and cause side effects [2]. Lipid-based nanoparticles, such as liposomes, micelles, and nanoemulsions, are used as carriers for photosensitizers. Constructed of lipids or amphiphilic polymers, they self-assemble into carriers capable of delivering photosensitizers [10]. These nanocarriers have many advantages, including a significant increase in photochemical efficiency and the ability to localize to tumor areas after intravenous injection, thanks to the so-called EPR effect [11].

Liposomes are artificially created, nanometer-sized vesicles made of natural phospholipids and cholesterol. They were discovered in 1961 and have since become a versatile tool in biology, biochemistry, and medicine [12]. Liposomes consist of a hydrophilic head and two hydrophobic phospholipid chains, which allow them to transport both hydrophilic and hydrophobic substances [13]. Photosensitizers in liposomes can be delivered to cells in two main ways: by combining the liposomes with cell membranes and releasing their contents into the cytosol, or by uptake by phagocytic cells, which then release them inside the cell [14]. The use of liposomes as carriers of photosensitizers improves the effectiveness and safety of photodynamic therapy. For example, in experiments on rats with human brain glioma, it was found that liposomes increase the uptake of photosensitizer in tumor tissues, especially compared to traditional methods of administration [15]. However, liposomes have a short circulation time in the body, which makes it difficult to achieve an appropriate ratio of photosensitizer in the tumor to that in normal tissues. To improve this aspect, liposome modifications have been used, including both passive and active targeting. Passive targeting exploits liposomes' natural tendency to accumulate in cancer tissues, driven by features such as rapid angiogenesis and increased vascular permeability [16]. Liposomes with a longer circulation time have been developed, allowing them to preferentially accumulate in tumors [17,18]. However, modified liposomes may exhibit reduced interaction with cells, thereby affecting their effectiveness [19,20]. To enhance targeting, liposomes can also be modified to bind to cancer cells through active mechanisms. This means that molecules on the liposome surface can bind to specific markers on cancer cells, which increases the interaction of liposomes with target cells [21]. Lipoplexes are structures formed from positively charged liposomes and other particles, most often containing negatively charged polynucleic acids. They are widely used in gene therapy to deliver nucleic acids such as DNA and small interfering RNA [22]. Research suggests that lipoplexes can improve the effectiveness and specificity of photosensitizers such as chlorine e6. However, when complexed with positively charged liposomes, ce6 showed increased cellular uptake *in vitro* and selective targeting of tumor tissues *in vivo*, resulting in prolonged retention in tumor cells [23]. The use of positively charged liposomes proved crucial, as the ce6 complexation efficiency was over 90% for these liposomes, in contrast to neutral and negatively charged liposomes, which achieved less than 12% [24]. Nanoemulsions, consisting of oil-in-water dispersions, can enhance the preferential delivery of photosensitizers to the tumor site, thereby reducing the toxic side effects of photodynamic therapy [25]. The use of nanoemulsions in photodynamic therapy may involve the local application of photosensitizers to the skin or other mucous membranes. An example is the use of nanoemulsions to transport mTHPC (meta-tetrahydroxyphenylchlorin) to increase skin absorption [26]. Another approach is to develop a magnetic nanoemulsion that combines PDT with magnetohyperthermia to destroy cancer cells synergistically [27]. 5-Aminolevulinic

acid (ALA) is a precursor of the natural photosensitizer, protoporphyrin IX, in the heme biosynthesis cycle [28]. When exogenous ALA is applied to areas with tumors or other undesirable tissues, the heme cycle's feedback inhibition is bypassed, leading to the accumulation of excess PPIX after several hours. Because ALA is often applied topically, various methods have been studied to increase its absorption through the skin [29]. For example, a nanoemulsion with 30 nm egg lecithin particles was used to enhance ALA delivery to the skin [30]. This preparation, known as BF-200 ALA, is being clinically studied for the treatment of actinic keratosis [31]. Nanocells are a technology developed to improve drug delivery to solid tumors [32]. These nano cells consist of a nuclear nanoparticle surrounded by a lipid envelope associated with the inhibition of angiogenesis. The main advantage of this technology is the precise delivery of drugs to the tumor site, which reduces toxicity and increases treatment effectiveness. When the nanocell reaches the tumor area, its outer shell releases an agent that inhibits angiogenesis, thereby cutting off the blood supply to the tumor cells. At the same time, the internal nanoparticle releases the chemotherapy drug, which can freely reach cancer cells because the nano cell is already enclosed within the tumor. This strategy not only ensures effective drug delivery but also reduces toxicity because the drugs are isolated from healthy cells. So far, this technique has only been tested with chemotherapy drugs, but there is potential to develop nano cells capable of carrying photosensitizers [33]. Porphysomes are an interesting combination of a lipid nanostructure and a potential photosensitizer. They can act multifunctionally, including self-quenching of fluorescence, and exhibit unique photothermal and photoacoustic properties. These particles, composed of a pyropheophoride and a cationic phospholipid, may be promising for cancer therapy [34, 35]. Polymer nanoparticles represent a promising tool in photodynamic therapy (PDT) via drug delivery. PDT drugs in the form of polymer nanoparticles offer several key advantages over traditional PDT drugs. First, they enable more PS to be delivered to the target area. Secondly, polymer nanoparticles are flexible in terms of surface modification. Third, polymer nanoparticles are resistant to degradation in biological environments. Fourth, they allow loading with multiple components, such as tumor-cell-targeting ligands and contrast agents. It is also worth noting that polymer nanoparticles are the appropriate size, making them well-suited to the characteristics of cancer tissues [36]. Research on polymer nanoparticles for PDT therapy uses various types of polymers, both synthetic, such as PLGA, HPMA, and PAA, and natural, such as chitosan or alginate, and proteins, such as albumin or collagen. The choice of the appropriate type of polymer depends on the specific therapeutic goals and requirements. Poly(D, L-lactide-co-glycolide) polymer, known as PLGA, is a material widely studied in the field of drug delivery due to its suitability and ability to degrade in the body [37]. The study utilized various photosensitizers (PS) such as porphyrins, chlorite, hypericin, and phthalocyanines loaded into PLGA nanoparticles and evaluated their effectiveness in PDT. It was found that hypericin-loaded PLGA nanoparticles showed higher photodynamic activity than the free drug in NuTu-19 ovarian cancer cells [38]. A similar effect was observed in another study, in which PLGA nanoparticles loaded with meso-tetra(4-hydroxyphenyl)porphin (m-THPP) were more effective than the free drug against EMT-6 breast cancer cells [39]. Treatment with PLGA nanoparticles allowed for lower drug doses and shorter time intervals between drug administration and irradiation compared to free m-THPP. ZnPc has also been loaded into PLGA nanoparticles and successfully applied in PDT [40]. Polyacrylamide, or PAA, is a useful substance for systemic use because it dissolves readily in water, preventing aggregation. PAA is non-toxic and does not cause biological reactions [41]. PAA nano-

particles, even those with non-biodegradable cross-linking agents, have been used in PDT [42]. Studies have shown that this polymer can effectively play a role in photodynamic therapy when loaded with photosensitizers such as methylene blue (MB) [43] and Photofrin [44]. In one study, PAA nanoparticles loaded with m-Tetra(hydroxyphenyl)chlorin (m-THPC) were effective in killing C6 glioma cells in rats. An important aspect of these particles is that they achieve results comparable to those of the free drug [45]. Moreover, methylene blue-coated PAA nanoparticles were effective in eliminating bacterial infections, especially Gram-positive bacteria [46]. N-(2-Hydroxypropyl)methacrylamide (HPMA) is a biocompatible copolymer that can passively accumulate in tumor areas and be tailored to contain special targeting ligands [47]. Studies have shown that HPMA copolymer-based drugs combining photodynamic therapy (PDT) and chemotherapy were more effective than using these therapies alone in Neuro2A neuroblastoma and human ovarian cancer [48]. Dendrimers and hyperbranched polymers have been used for the delivery of difficult-to-transport substances, such as 5-ALA, due to their hydrophilic nature. An example is the ALA dendrimer 18m-ALA, which can efficiently deliver ALA to mouse skin cells and human skin cancer cells. Importantly, these dendrimers turned out to be more effective in porphyrin production than free ALA alone [49]. In Kataoka's laboratory, dendrimers containing zinc porphyrin and zinc phthalocyanine were developed [50]. These nanoparticles were introduced into human lung cancer cells, and after uptake, they concentrated in lysosomes and were released when irradiated with light. Studies on tumor-bearing mice have shown that these nanocarriers show a better response to photodynamic therapy (PDT) compared to drugs alone. Additionally, Liao *et al*. created a connection between PS ce6 and a hyperbranched polymer called HPEE. HPEE-ce6 nanoparticles showed significantly greater efficacy in killing oral cancer cells than ce6 alone [51]. Natural polymers such as albumin and chitosan have also been found to be useful in PDT. Albumin loaded with the photosensitizer pheophorbide. was incubated with Jurkat cells for 24 hours. The results showed that treatment with these nanoparticles resulted in higher cell-killing efficiency and lower toxicity in the dark, compared to VFRGT `fre alone. W3SAEZfeophorbida [52]. Another study used polysaccharide nanoparticles to encapsulate 5,10,15-triphenyl-20-(3-N-methylpyridinium-yl)porphyrin [53]. It turned out that the inclusion of a photosensitizer in these nanoparticles significantly increased their ability to kill HeLa cells in the presence of light, and the effect was almost four times stronger than in the case of a phosphatidylcholine-lipid emulsion [24]. In contrast, chitosan, a biodegradable polymer loaded with the photosensitizer m-THPP, was able to kill 14C cancer cells under light exposure after 6 h of incubation, and its effectiveness was comparable to that of free m-THPP [54]. In another study, chitosan nanoparticles that contained conjugated PPIX were created. These PPIX-eGC conjugates, when injected into mice with squamous cell carcinoma and irradiated with light, showed efficacy in tumor destruction, unlike the free photosensitizer [55].

2.1. Pegylated polymers.

Additionally, polymer nanoparticles can be coated with a PEG (polyethylene glycol) layer, which prolongs their circulation time in the blood and facilitates their accumulation in tumor tissues, thereby increasing their effectiveness in drug delivery [56]. Studies have shown that the addition of PEG to PLL and ce6 conjugates improves the selectivity and efficacy of photodynamic cancer therapy in OVCAR-5 ovarian cancer cells [57]. Another study used PEG-coated PLA nanoparticles loaded with hexadecafluoro ZnPc and then tested them in EMT-6 tumor-bearing mice [58]. The results showed that these nanoparticles were more effective in

photodynamic therapy than the same substances prepared in a traditional way, which is a promising result. To further improve the effectiveness of polymer nanoparticles in cancer therapy, special ligands can be attached to their surfaces, allowing them to "actively" bind to cancer cells. For example, in *in vitro* studies on the human breast cancer cell line MDA-MB-435, PAA nanoparticles were loaded with Photofrin and iron oxide and then targeted to cells using the F3 ligand. These nanoparticles concentrated in the cell nuclei and, when exposed to light, led to their destruction [44].

Micelles are so-called colloidal dispersions, microscopic structures consisting of surfactant molecules that spontaneously form in solution. These structures form due to the amphiphilic properties of molecules with hydrophobic and hydrophilic regions. Micelles are used in the transport of drugs, especially those that are sparingly soluble in water (hydrophobic). Within these structures, hydrophobic drugs can be placed physically or chemically bonded to the hydrophobic core of the micelles. Micellar nanocarriers have many beneficial properties as drug delivery systems. These include improved drug bioavailability, enhanced ability to cross physiological barriers (the EPR effect), and beneficial changes in drug distribution in the body [59,60]. There are two main categories of micelles: polymeric micelles, formed by block copolymers with hydrophilic and hydrophobic fragments, and micelles prepared from water-soluble polymers conjugated to lipids.

Polymer micelles can be classified into various classifications, such as diblock copolymers, such as PEG-b-poly(caprolactone) (PEG-PCL), which are effective in delivering photosensitizing substances. Studies have shown that PEG-PCL micelles containing the photosensitizer PPIX were compared with PPIX alone in terms of response to photodynamic therapy [61]. PEG-PCL micelles have also been used in the encapsulation of other substances, such as phthalocyanines [62], chlorite [63,64], and pheophorbides [65], suggesting their great potential as carriers for hydrophobic photodynamic sensitizers.

Encapsulation of dendrimers containing photosensitizing substances can also be improved by the use of PEG-PLL micelles [66-68]. Another biocompatible and biodegradable block copolymer is PEG-b-poly(D, L-lactide) (PEG-PLA), which has been used in nanotechnology research on the properties of PPIX delivered by micelles. A group of researchers also conducted experiments using PEG-PLA micelles to encapsulate mTHPC for therapeutic purposes in the treatment of head and neck cancer [69,70].

Micelles can also respond to changes in body pH, enabling selective release of photosensitizing substances at the target site, especially in tumor areas and inflamed tissues with reduced pH [71].

PEG-lipid micelles resemble the structure of amphiphilic copolymers, but in PEG-lipid micelles, the hydrophobic part is represented by a lipid and not by a hydrophobic polymer block. In which the lipid part contains a hydrophobic photosensitizing substance (PS), and PEG prevents the rapid removal of these particles by the reticuloendothelial system (RES) [72]. Studies have shown that PEG-PE (polyethylene glycol-phosphatidylethanolamine) micelles can significantly increase the solubility of photosensitizing agents such as tetraphenylporphyrin (TPP) and can be modified with monoclonal antibodies, thereby improving their ability to reach target sites in the body and the effectiveness of photodynamic therapy against cancer. This approach was tested in a mouse model of Lewis lung cancer with promising results [73].

Methylene blue (MB) is a heterocyclic aromatic chemical compound with photodynamic ability. It is used to treat methemoglobinemia by intravenous administration, but its clinical use is limited due to difficulty in penetrating the cellular region of tumors.

Encapsulating MB inside silica nanoparticles (SiNPs) is a way to use it as a therapeutic vector and protect it from degradation. In a study by Tang and other researchers [52], ORMOSIL nanoparticles were used to encapsulate MB. Three types of nanoparticles with diameters below 200 nm were compared: polyacrylate (PAA), sol-gel silica, and ORMOSIL. The results showed that PAA nanoparticles had the most effective singlet oxygen ($^1O_2$) delivery and positive photodynamic effect on C6 glioma tumor cells in rats. Sol-gel SiNPs had the highest capacity to store MB, although they supplied $^1O_2$ less efficiently.

Roy *et al*. [74] investigated the use of ORMOSIL nanoparticles as a PS carrier, overcoming many of the limitations associated with "unmodified" SiNPs. The results of *in vitro* studies showed that ORMOSIL nanoparticles with HPPH were able to be effectively taken up by cancer cells and deliver the drug to the cytoplasm. After exposure to light with a wavelength of 650 nm, significant damage to photosensitized cancer cells was observed. *Studies have shown that encapsulation of photosensitive compounds such as methylene blue (MB), porphyrins (PPIX), m-THPC, and Pc4 in ORMOSIL nanoparticles or other types of silica nanoparticles improves the efficiency of singlet oxygen ($^1O_2$) generation compared to free photosensitive compounds [75,76].

Additionally, in a study by Zhou *et al*. [77], porous silica nanospheres with embedded photosensitizers such as hematoporphyrin (HA) showed greater light stability and higher $^1O_2$ generation capacity than free HA. *In vitro* experiments showed that these nanoparticles disrupted mitochondrial membrane potential, suggesting their effectiveness in inducing apoptosis [77].

Covalent conjugation of photosensitivity (PS) inside nanoparticles has a significant advantage because this combination prevents the release of PS during circulation in the body. Prasad and co-workers [78] pioneered the covalent incorporation of PS molecules into ORMOSIL nanoparticles by synthesizing iodobenzylpyrosilane (IPS) with vinyltriethoxysilane in a microemulsion core. These nanoparticles, approximately 20 nm in size, retain their spectroscopic and functional properties, which enable the efficient generation of singlet oxygen ($^1O_2$). They are also monodisperse and stable in aqueous suspension and can be readily taken up by cancer cells *in vitro*, exhibiting phototoxicity proportional to their cellular uptake. This highlights their potential in both diagnostics and photodynamic therapy of cancer [44].

Qian *et al*. [79] encapsulated PPIX in 25 nm diameter ORMOSIL nanoparticles using a similar method to Prasad. They demonstrated the effectiveness of photodynamic therapy on HeLa cells, where cellular structures were damaged after exposure to light with a wavelength of 532 nm at a low dose. The study by Simon *et al*. [80] also demonstrated the synthesis and properties of PPIX in ORMOSIL nanoparticles, with intracellular accumulation of PPIX SiNPs taking place in the cell cytoplasm. Higher production of reactive oxygen species (ROS), leading to cell destruction, was found to be correlated with the presence of PPIX SiNPs in both HCT 116 and HT-29 colon cancer cells [80].

Gold Nanoparticles (AuNPs) are used in photodynamic therapy (PDT) in two main ways: as drug delivery platforms and as surface plasmon-enhanced agents that exploit nonlinear optical fields generated at very short distances from metal nanoparticles [81-83].

Conjugation of PS molecules with AuNPs is an effective way to improve the targeting effect and effectiveness in cancer treatment.

It is possible to modify AuNPs covalently or noncovalently with PS. Moreover, the small size of AuNPs can be an advantage, allowing them to penetrate tissues and leak into the

tumor microenvironment. In this way, modified AuNPs can serve as both diagnostic and therapeutic tools for cancer [84].

It is worth noting their low toxicity [82]. Moreover, AuNPs are biocompatible and have versatile surfaces, adaptable sizes, and unique optical properties [83]. The use of a polyethylene glycol (PEG) coating allows for maintaining the stability of AuNPs in physiological conditions [84,85]. AuNPs can serve as drug carriers in cancer PDT therapy, enabling efficient drug release via diffusion across the cell membrane through noncovalent adsorption of PS to AuNPs [86]. Using noncovalent delivery of Pc4 with PEG-gold nanoparticles, Cheng et al. observed surprisingly effective drug release and tumor penetration *in vivo* [80]. Moreover, pegylated AuNP-PS conjugates can be effectively excreted through the renal and hepatobiliary systems [81]. AuNP-modified porphyrin-brucine conjugates have been shown to significantly improve PDT compared to free PS [87, 88]. *In vitro*, PDT from hematoporphyrin-nanogold nanocomposites proved to be much more effective than hematoporphyrin alone [87]. Furthermore, nanocomposites with larger gold particles (45 nm) were more effective than those with smaller particles (15 nm), suggesting that larger particles can transport more PS molecules to cancer cells [81].

Semiconductor nanoparticles are materials of very small size. These nanoparticles exhibit unique quantum properties and can be used in various fields, including photodynamic cancer therapy (PDT). One example is the use of semiconductor nanoparticles such as ZnO, CdSe, and GaAs as carriers of photosensitizers in PDT.

(A) Semiconductors such as ZnO absorb UVA or blue light, which leads to the formation of ROS, which is beneficial in PDT.

(B) CdSe-core quantum dots (QDs) that are covered by a zinc sulfide-bonded passivation layer and a thiol-containing biocompatible layer. Photosensitizers (PS) can be covalently attached to QDs, which enables resonance energy transfer (FRET) between QDs and PS. QD emission can be used to excite PS, which increases the effectiveness of PDT [84].

2.2. Zinc oxide and titanium dioxide.

Both zinc oxide (ZnO) and titanium dioxide (TiO_2) have the ability to produce reactive oxygen species (ROS) after light absorption. The main active substance that is generated by these reactions is the hydroxyl radical (HO·), although superoxide anion and singlet oxygen ($^1O_2$) may also be produced. Traditionally, these materials have been studied for their excitation by ultraviolet (UV) light, but increasingly, experimentation is being conducted with visible light, particularly blue light [89-91].

An example of the use of ZnO is the work of Zhang *et al*. [92], where ZnO nanorods loaded with the drug daunorubicin were used to kill liver cancer cells synergistically. UV irradiation significantly increased cytotoxicity compared to the drug alone [90]. TiO_2 has been widely studied as a potential photosensitizer in photocatalysis, especially in wastewater disinfection [91]. However, there are also reports of its use in anticancer therapy. For example, TiO_2 nanoparticles with incubated C6 glioma cells or Ls-174-t colon cancer cells exposed to UV or UVA radiation induced significant damage to cancer cells [92,93]. Wang *et al*. [94] showed that TiO_2-PDT (photodynamic therapy) could also be effective *in vivo*, in which TiO_2 nanoparticles were injected around the tumor and then irradiated with UVA light, leading to significant tumor necrosis and prolonged survival in mice [94].

Quantum dots (QDs) are microscopic semiconductor crystals whose size determines their band gap, i.e., the energy difference between the highest valence band and the lowest

conduction band. QDs have a broad absorption spectrum, but their fluorescence is narrow and can be controlled by changes in size. Typical materials used to produce QDs include cadmium selenide (CdSe), cadmium sulfide, indium arsenide, and indium phosphide. QDs can generate reactive oxygen species (ROS) upon irradiation with UV or visible light, which may have potential for photodynamic therapy (PDT). Some studies have shown that QDs can be used to enhance excitation energy transfer to conventional photosensitizers, thereby improving their efficiency. In other experiments, QDs generate ROS themselves, especially in the presence of oxygen, which may be related to their triplet state. Additional passivation layers on the QD surface can control ROS generation. QDs can be trapped in cells and exhibit phototoxicity towards cancer cells. They can also be used for targeted treatment using cell receptors [95]. Samia *et al*. used CdSe QDs combined with a silicon photosensitizer (Pc4) [96], achieving efficient excitation energy transfer via FRET. They also found that QDs themselves generate $^1O_2$ directly, which may be related to their triplet state [97]. It is also possible to control ROS generation by passivating the QD surface [98]. Research on QDs has demonstrated their ability to target cancer cells through the folate receptor. QDs can be used for effective PDT and also as part of therapeutic systems based on FRET energy transfer [99,100].

Fullerenes are carbon nanostructures with a closed cage composed of carbon atoms (C60, C70, C84, etc.). These molecules are characterized by 12 pentagons and a variable number of hexagons, forming a structure resembling a football [101]. Fullerenes have a unique structure that ensures a high molar absorption coefficient and high triplet efficiency. In organic solvents or hydrophobic environments, fullerenes are very efficient at producing photoexcited 1O2, whereas in aqueous environments they switch to type 1 photochemistry, producing HO • [102]. Pure C60 is poorly soluble in water, forming nanoaggregates, which limits its photodynamic effectiveness. However, if we modify it by adding hydrophilic or amphiphilic functional groups, the modified C60 will become more photostable and more effective as a photosensitizer. There are various fullerene structures used in PDT that offer advantages over traditional photosensitizers. Additionally, fullerenes can form self-assembled nanoparticles, enabling their use as drug carriers with targeted effects on tissues [103]. Fullerenes as photosensitizers for photodynamic therapy (PDT) have some unique advantages but also limitations. First, their extreme hydrophobicity and tendency to aggregate make them difficult to formulate as PDT drugs. However, there are various fullerene drug delivery strategies, such as liposomes [104], micelles [105], dendrimers [106], pegylation [107], cyclodextrins [108], and self-nanoemulsifying systems [109]. Second, the main absorption of fullerenes occurs in the blue and green regions of the visible spectrum, not in the infrared, where light transmission through tissue is maximum. One of the paradoxes is that fullerenes act as antioxidants or quenchers of reactive oxygen species (ROS) in the dark [110], while under the influence of light, they become producers of ROS and other pro-oxidants. The explanation for this phenomenon appears to be related to the C60 hydration mechanism, which inactivates the hydroxyl radical via a shell of "ordered water" associated with the fullerene nanoparticle. The water jacket can slow or trap hydroxyl radicals long enough for them to react with one another to form less reactive ROS, e.g., hydrogen peroxide [111,112].

Shi *et al*. [112] developed a nanocomposite with PEGylated C60 fullerene-coated iron oxide nanoparticles that had increased biocompatibility and solubility, were superparamagnetic, and exhibited strong photodynamic properties. A novel photodynamic anticancer drug, hematoporphyrin monomethyl ethers, was associated with a nanoparticle that exhibited potent photodynamic activity *in vitro* on cultured B16-F10 cells and *in vivo* in a

murine tumor model, demonstrating a 23-fold increase in drug uptake by tumor cells in the tumor. Moreover, the nanocomposite also acted as a T2 contrast agent for *in vivo* magnetic resonance imaging [113].

A new hybrid GO-C60 complex containing methoxy polyethylene glycol and single-replacement C60 was developed to combine photodynamic and photothermal therapy using the step-coupling method. The hybrid is soluble in various media, such as physiological solutions. The addition of C60 to GO did not affect its photothermal properties but facilitated the generation of singlet oxygen ($^1O_2$) from C60 in the near-infrared in aqueous solution. This hybrid can also induce the production of reactive oxygen species in HeLa cells. Due to the synergistic effect of GO and C60, the GO-C60 hybrid outperforms both components in inhibiting cancer cells, indicating its great potential [114].

2.3. Carbon nanotubes and graphene.

Carbon nanomaterials are among the most intensively studied materials due to their unique properties, including large specific surface area, high carrier mobility, high electrical conductivity, flexibility, and optical transparency, which favor their extensive applications in the biomedical field [115]. An important issue regarding substances used in PDT is their delivery to organs/cancer tissue/cells. There are many strategies for targeted drug delivery, but a satisfactory multifunctional carrier is needed. One possibility is carbon nanotubes and graphene.

Carbon nanotubes (CNTs) are a one-dimensional form of carbon that has a perfect cylindrical shape. CNTs can be considered as a sheet of graphene (a hexagonal lattice of carbon atoms) folded along specific directions corresponding to the chirality of the CNT. Folding a single layer of graphene forms a single-wall nanotube (SWCNT), whereas folding multiple layers of graphene forms a multi-wall nanotube (MWCNT). The similarity between CNTs and graphene extends beyond their geometric structure to their properties. Strong carbon-carbon bonds are responsible for high mechanical strength [116]. In terms of electrical properties, CNTs exhibit a semiconductor or metallic character. SWCNTs have a relatively large theoretical surface area, averaging ~1315 m2g−1 [117] (about half that of graphene) but varying with SWCNT quality, reaching a maximum of 1587 m^2g^{-1} [118]. CNTs have a very high length-to-diameter ratio: the diameter is typically 0.4–2.5 nm, while the length can be as much as 20–1000 nm for SWCNTs, and for MWCNTs, the diameter ranges from 1.4–100 nm, and the length from 1–500 μm [119]. Due to their tubular shape, CNTs have an internal volume that can accommodate specific substances. Moreover, curvature makes CNTs more reactive than pure graphene, thereby facilitating their chemical functionalization [120]. Zhu *et al*. designed a novel photodynamic therapy (PDT) agent using a protein-binding ssDNA aptamer, a photosensitizer, and a single-wall carbon nanotube (SWNT) [120]. The PDT method is based on covalently linking a photosensitizer to an aptamer and then immobilizing it on the SWNT surface so that the photosensitizer can be activated only by light after binding to the target. Zhu *et al*. selected the human α-thrombin aptamer and covalently linked it to chlorine e6 (Ce6). SWNT was excellent at quenching singlet oxygen production (SOG) [120]. In the presence of a target, binding of target thrombin will disrupt the interaction between DNA and SWNTs, causing the DNA aptamer to fall off the SWNT surface and restoring SOG. Controlled $^1O_2$ generation (SOG) with high selectivity and localization leads to more effective and reliable PDT and fewer side effects [121]. Erbas *et al*. tested the use of non-reactively functionalized carbon nanotubes as carriers for potential photosensitive substances with the Bodipy group in

PDT [121]. A sensitizer noncovalently attached to SWNTs has been shown to generate singlet oxygen upon excitation at 660 nm with a red LED array; this work highlights the potential of SWNTs as a viable alternative carrier of bioactive agents, including photodynamic therapy sensitizers [122].Sundaram *et al*. conducted research that resulted in the conjugation of a single-wall carbon nanotube (SWCNT) with hyaluronic acid (HA) and chlorine e6 (Ce6), which was coated on the walls of the SWCNT. The obtained nano biocomposite was characterized by UV-Vis spectroscopy, Fourier transform infrared spectroscopy (FTIR), X-ray diffraction (XRD) analysis, particle size analysis, and zeta potential measurement [122]. The study results showed that the newly obtained nanobiocomposite improved the ability of PDT to deliver the photosensitizer and induce cell death in colon cancer cells [123].

Graphene has a unique two-dimensional structure and excellent physicochemical properties, which make it the most promising nanomaterial in the 21st century [124,125]. Graphene and its derivatives, such as graphene quantum dots (GQD), graphene oxide (GO), and reduced graphene oxide (rGO) (so-called graphene-based nanomaterials, GBNM), are widely used in biomedical applications due to their superior properties compared to traditional materials. For example, GQDs exhibit excellent photoluminescence properties [126], high photostability [127], and good biocompatibility [128]. GO and rGO have large surface areas, sharp edges, and excellent photothermal conversion effects [129,130]. These unique properties play an important role in the application of GBNM in many biomedical fields.

Zhou *et al*. loaded GO with hyaluronic acid (GO-HA), a hydrophobic, non-porphyrin photosensitizer isolated from the parasitic fungus Hypocrella bambuase found in the People's Republic of China [1]. The optimal loading was 1 mg/mg according to fluorescence, and GO-HA had a slightly lower $^1O_2$ quantum yield compared to the free substance. The stability of GO-HA in aqueous solution was much higher than that of HA, and the toxicity in the dark was lower but comparable to phototoxicity towards HeLa cells [125].

Huang *et al*. conjugated GO with folic acid and then loaded ce6 (80% loading). These nanocarriers delivered Ce6 to MGC803 cells containing the folate receptor, and this internalization could be blocked by free folate, suggesting a receptor-dependent process. *In vitro*, PDT led to significant cell killing [132].

Jin *et al*. loaded ce6 onto PEG-functionalized GO[133]. They not only investigated the killing of PDT using a 660 nm laser but also found significant synergism when PDT was combined with a previously reported photothermal effect induced by GO excitation at 808 nm [133].

A study conducted by Yu *et al*. developed a novel nanocomposite that uses photodynamic therapy (PDT) in combination with immunotherapy to fight cancer [134-135]. This nanocomposite is composed of GO, HPPH (photosensitizer), HK peptide (target ligand), and PEG (hydrophilic shell) GO(HPPH)-PEG-HK. Researchers conducted many experiments to evaluate the effectiveness of this nanocomposite. We first investigated the specific targeting ability of GO(HPPH)-PEG-HK in vivo against 4T1 tumors and metastatic 4T1 cells in the lung. The fluorescence intensity and accumulation of the nanocomposite in the 4T1 tumor and the metastatic lung tumor were significantly higher compared to the control group. The accumulated amount of the nanocomposite increased with increasing time. These results demonstrated that GO(HPPH)-PEG-HK nanocomposite could specifically target cancer cells after intravenous administration. They then tested the therapeutic efficacy of the nanocomposite in mice bearing 4T1 tumors. They found that tumor volume was significantly reduced compared to the control group, suggesting the therapeutic efficacy of the

nanocomposite. The next step was to investigate whether PDT using this nanocomposite could activate the body's immune response against cancer. The investigators performed a tumor xenograft 10 days after PDT treatment. It turned out that the antitumor immunity of the mice was enhanced, and the tumor volume was significantly reduced. Moreover, cancer cells with lung metastasis were also inhibited by host immunity [134].

Yu *et al*., inspired by the promising results, prepared a prophylactic vaccination with necrotic 4T1 cells using GO(HPPH)-PEG-HK-based PDT [134]. Healthy mice were inoculated with necrotic 4T1 tumor cells. 7 days later, the tumor cells were inoculated into mice to examine the mice's immune memory. These results demonstrate that tumor-targeted PDT using GO(HPPH)-PEG-HK can effectively ablate primary tumors and destroy residual tumor cells, thereby preventing distant metastasis by activating host antitumor immunity and suppressing tumor recurrence by stimulating immune memory [135].

There are many other nanoparticles with a wide range of applications in biomedicine, the development of which may be of key importance, making them useful systems for photodynamic therapy as photosensitizers. Figure 1 shows a list of the most frequently used nanomaterials in combination with PDT.

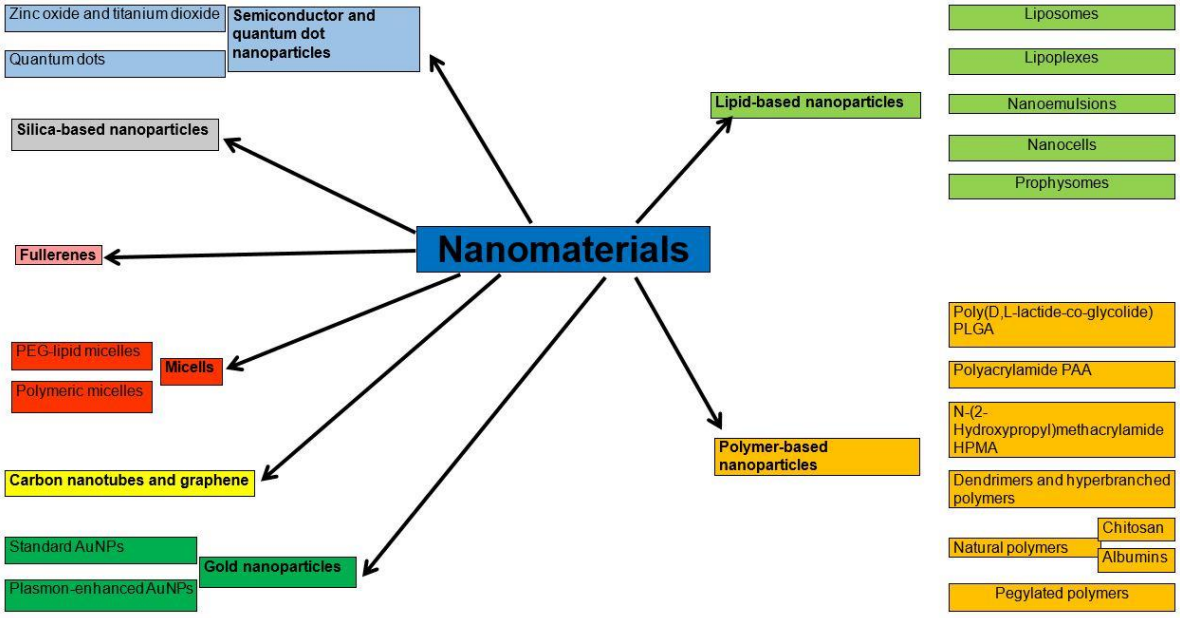

Figure 1. List of the most frequently used nanomaterials in combination with PDT—figures prepared independently by the authors.

3. Development of New Light Sources to Improve the Effectiveness of PDT

Lasers are commonly used in photodynamic therapy (PDT) for the treatment of both superficial and interstitial lesions. A unique feature of lasers is the generation of monochromatic light with a very narrow and coherent wavelength band. Lasers provide high optical power and wavelength that can be controlled to match a specific photosensitizer. Because lasers generate a narrow, concentrated beam of light, optical fibers are often used in combination with lasers for endoscopic or intra-institutional applications. In the treatment of superficial lesions, to uniformly irradiate a relatively large target tissue, the laser can be combined with lenses that disperse the light stream [136,137].

All light sources convert input energy into light. In the case of an incoherent light source (e.g., a light bulb), light is generated by spontaneous emission, and photons are emitted

randomly by excited atoms. This results in radiation in all directions, with wavelength scattering and no relationship between individual photons. The main components of a laser are the active medium (i.e., the gain source), the resonant chamber, and the energy source. The characteristics of the material in the active medium enable light amplification through stimulated emission. It may be a solid (such as glass, crystal, fiber, or powder), a gas (including atomic, ionic, molecular, or eximeric), or a liquid (organic dye). The active medium is inside the resonance chamber. The simplest resonance chamber consists of two mirrors directed at each other. The pump or energy source supplies energy via electric current or light of a different wavelength, which excites the active medium. The excited active medium emits spontaneous fluorescence during relaxation, which is neither coherent nor well-concentrated under normal conditions. However, in a laser resonance chamber, the emitted fluorescence is reflected by the chamber's mirrors, passing through the active medium multiple times, resulting in stimulated emission of photons at each passage. The light amplification process produces coherent light (i.e., high monochromaticity and high directional purity) because the stimulated emission is in phase with the stimulating light. Part of the amplified light is extracted from the chamber through a partially transparent mirror. Many different types of lasers have been used for PDT, which will be described next. Currently, semiconductor lasers are the most common light source for clinical PDT. Lasers operating in pulsed and continuous modes are being used, and the advantages of each in PDT are still being explored [138].

Dye lasers. In dye lasers, the lasing agent is an organic dye molecule (e.g., rhodamine or a red ketone), which emits light in the 600–650 nm spectral range. This is done to match the wavelength to the absorption wavelength of a specific photosensitizer. The dye material is usually a liquid and constantly circulates to avoid overheating. Due to circulation, only part of the dye is responsible for lasing in the chamber. The energy source is a pump laser, usually argon, Nd-YAG, copper, or potassium titanyl phosphate (KTP). A pump power of at least tens of watts is needed. These pump lasers require high-voltage power sources, high current, and water cooling, which makes them less portable. Surgical laser systems can be adapted to work with dye lasers. The pump laser's emission wavelength should match the dye's absorption wavelength. Typically, a lasing dye produces light in a wide spectral range. The wavelength of the output light can be selected using customizable optical filters in the ray path and the geometry of the resonance chamber. The dye laser can be tuned to different wavelengths, enabling it to be used with a variety of photosensitizers and making it a versatile light source. However, they are large, not very portable, require frequent servicing, and have a high economic cost. Most clinical applications have shifted to semiconductor lasers [139].

Semiconductor lasers. Semiconductor lasers are semiconductor devices in which electron-hole recombination leads to the generation of light. The compact solid-state unit contains the active medium and the resonance chamber. The energy source is electric current. There are many common applications for low-power semiconductor lasers, such as laser pointers and optical disc readers. Most clinical applications of PDT use high-power semiconductor lasers. Semiconductor lasers are lighter, more compact, more portable, more stable, and cheaper than dye lasers. Standard electrical power and air cooling sources can be used for a semiconductor laser with power up to 8 watts. High power can be achieved by combining or "stacking" laser diodes. However, the generated beam is larger and has a larger angular size compared to the dye laser. However, the output laser can be coupled to optical fibers, but in some cases, the fiber core may be larger. Semiconductor lasers are fixed-wavelength devices, so a separate laser source is required for each photosensitizer that absorbs

at a unique excitation wavelength. Clinical semiconductor lasers can deliver irradiance of up to 1 W/cm². Semiconductor lasers with output wavelengths in the range of 415–690 nm are typically used in PDT [140].

4. Conclusions

When creating nanoparticles for PDT, scientists ask themselves certain questions and assumptions regarding whether the photosensitizer should be enclosed in the nanoparticle or covalently bound to it. The answer to this question gives rise to further questions directed and conditioned by this answer. If the photosensitizer is noncovalently closed, it is likely to be released more easily and, therefore, better absorbed by the cells. However, there is a danger and risk that it may be released prematurely, which will prevent it from accumulating adequately at its final destination.

Author Contributions

Conceptualization, D.A.; M.B.; K.W.; K.D.; D.L.; A.M.; and D. B.-A.; methodology, D.A.; M.B.; K.W.; K.D.; D.L.; A.M.; and D. B.-A.; software, D.A.; M.B.; K.W.; K.D.; D.L.; A.M.; and D. B.-A.; validation, D.A.; M.B.; K.W.; K.D.; D.L.; A.M.; and D. B.-A.; formal analysis, D.A.; M.B.; K.W.; K.D.; D.L.; A.M.; and D. B.-A.; investigation, D.A.; M.B.; K.W.; K.D.; D.L.; A.M.; and D. B.-A.; resources, D.A.; M.B.; K.W.; K.D.; D.L.; A.M.; and D. B.-A.; data curation, D.A.; M.B.; K.W.; K.D.; D.L.; A.M.; and D. B.-A.; writing—original draft preparation, D.A.; M.B.; K.W.; K.D.; D.L.; A.M.; and D. B.-A.; writing—review and editing, D.A.; M.B.; K.W.; K.D.; D.L.; A.M.; and D. B.-A.; visualization, D.A.; M.B.; K.W.; K.D.; D.L.; A.M.; and D. B.-A.; supervision, D.A.; All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

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