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A Comprehensive Review of Photodynamic Therapy for Treatment of Cancer

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ABSTRACT

Photodynamic therapy (PDT) is a simply invasive therapeutic modality accepted for clinical treatment of numerous types of cancer and non-oncological disorders. We reviewed the action mechanism and principles of photodynamic therapy. The work additionally addresses photosensitizers, how they are activated, and techniques to improve photosensitized singlet oxygen emission. Significant advances have been highlighted in the framework of combating hypoxia in tumors utilizing innovative methods for instance nanoparticle-mediated photodynamic therapy. We reported the application of nanoparticles of silica in photodynamic therapy, covering their properties, their mechanisms of action, as well as ways to prepare carbon nanotubes and photosensitizers complexes. In this article we compared the properties of various nanoparticles employed in Photodynamic therapy, among them gold nanoparticles, silica-based nanoparticles, and carbon nanotubes, along with metal-organic frameworks. Finally the excellent performance of silica nanoparticles for photodynamic therapy, suggesting that encapsulated Protoporphyrin (IX) surpasses exposed protoporphyrin (IX) among silica nanoparticles is also covered in this study.

Keywords: Tumor hypoxia, Nano medicines, Photodynamic Therapy, Photosensitizer, Carbon nanotubes

1. INTRODUCTION

Photodynamic therapy can be defined as a light-based cytotoxic therapy that provides a temporal and spatial variation of the treatment with relatively little or no systematic toxicity which is why it has become more popular worldwide. Photodynamic therapy is a variant

of phototoxic therapy that involves a particular wavelength of light to excite the photosensitive (a photoactive molecule) which yields reactive molecular species or free radicals that can interact with neighboring microenvironment. In photodynamic therapy, spatial selectivity can be attained through two methods:

- By using various methodologies that include immune-conjugates or Nano constructs precisely targeting the PS to the tumor compartment
- To destroy malignant tissue while saving surrounding healthy tissue we selectively deliver light to the target area.

Both methods are crucial for the therapy of diffuse tumors such as glioblastoma in the brain. The limited depth of light penetration into the tissue is the primary barrier to the use of light-based methods such as PDT has only been frequently used in the past few years for medical procedures on easily accessible outermost layers of tissues e.g. skin, retina, and other tissues. In the deep tissues or large tumors, the transfer of light is hindered by a significant decrease in the strength as the light penetrates the tissue, which is why the efficiency of photodynamic therapy is decreasing because light becomes cytotoxic once it reaches the tissue PDT provides progress in term of cancer treatment due to treating the highly resistant surface tumors to regular therapy. Recurrence can be the result of reducing the disease that remains in the surgical [1].

Photochemistry, photobiology, and quantum physics are the new therapies used in PDT advancements and all are become popular in clinical practice. Photodynamic therapy uses new laser medicine technology in the treatment of various diseases. PDT is a highly effective technique with no adverse effects or consequences. The base of certain drug tendencies especially the basis for this is the ability of some drugs such as photosensitizers, to accumulate and stay around in the tissue of various bacteria, malignant tumors, and highly proliferative tissues. Photochemical reactions are induced by laser energy in the sensitized cell tissue, and singlet oxygen and free radicals are formed, resulting in the death of sensitized substances and their destruction without harming the healthy parts. The technique is the most organ-preserving and well-tolerated, allowing for numerous therapies if necessary, healing is a natural recovery process the last decade, with the rise of

Figure 1. New innovative strategies for PDT

domestic photosensitizers and lasers for PTD, an increasing number of researchers have investigated the methods used in a variety of sectors [2]. Scientific studies on the application of photodynamic therapy (PDT) to the treatment of festering wounds have emerged in recent years, highlighting the benefits of PDT over conventional methods, particularly its strong antimicrobial and anti-inflammatory properties as shown in figure 1. It is significant in the context of chronic infectious processes that the pathogens fail to become resistant to PDT. Prevents systemic negative consequences associated with the use of antibiotics and antiseptics by identifying topically the area of laser irradiation of sensitized tissues.

The application of antibacterial PDT has been utilized to remove specific infections in the periodontal tissues or decrease the bacterial load. To perform PDT regionally without causing harm to molecules that are nearby, cells, or organs, the cytotoxic product, which frequently includes singlet oxygen, must act locally. PDT was effective in minimizing the periodontal symptoms of redness and bleeding on probing, as reported by animal research [3].

Three primary components need to be there in tumor tissues for PDT to help combat cancer: a suitable light source, appropriate PSs, and a large amount of O_2. The decision regarding the choice of a light source has vital significance as it must offer continuous light distribution to the required area to accomplish an effective treatment result. Most PSs utilized by PDT absorb the majority of light in the visible spectrum, which falls around 400 and 700 nm. Four distinct types of light sources have been examined in PDT until now: argon-pumped lasers, metal-vapor-pumped lasers (Au- or Cu-vapor lasers), solid-state lasers (Nd: Y AG lasers, Ho: YAG lasers, KTP: YAG/dye lasers), and diode lasers. Three non-laser light sources were additionally investigated: lamp light, light-emitting diodes (LEDs), and daylight. Red light argon dye lasers to identify objects Nd: YAG lasers, red light (635 nm) LED lamps, red light lamps with spectra of 570–670 nm, green light (520 nm), blue light from light-emitting diodes (420 nm), sunlight, and so on have all been applied in medical treatments. thereby, novel techniques are used for achieving deeper penetration depth, employing near-infrared (NIR), X-ray, interstitial, and internal light [4].

2. PHOTOSENSITIZERS

A further vital component involved in PDT activity is PS. Malignant zones are usually at which PSs gather. It subsequently gets active when subjected to some specific wavelength and intensity of light. A photodynamic reaction (PDR) takes place by the lighted PS in interaction with oxygen. PS activity has a direct association with the anti-tumor functions of PDR. Considering therapy performance, a few factors are essential: PS's purity, pharmacokinetic traits, amphiphilicity, and dosimetry. PDT effectiveness can be additionally boosted by utilizing various PS molecular carriers to target distinct subcellular regions of the target cell. PS's fluorescence properties can be applied theranostically in addition to PDT. Theranostic strategies, for instance, may incorporate tumor therapy and hypoxia imaging. A few features that should be found within a suitable PS consist of low dark toxicity, easy handling, high activation capacity, and singlet oxygen formation. Likely, some PSs are photodynamically inactive in solutions that are aqueous due to their restricted dissolution and aggregation in water. This problem could stop the in vivo implementation of these PSs. The absorption and emission behaviors of PSs in DMSO solutions remain among the primary topics of most research. High singlet

oxygen quantum yield and water's ability to dissolve in an aqueous solution are important qualities for a perfect PS. To make insoluble PSs suitable in aqueous solutions, these individuals were previously mixed with liposomes, nanoparticles, or emulsions. To enhance PSs' ability to dissolve in water and singlet oxygen formation in aqueous solutions, hydrophilic substituents, such as ionic substitutes, can also be included in them. Furthermore, by transforming them using functional groups (for example, polyhydroxylate and carbohydrates), nonionic water-soluble PSs could be produced [5].

3. TUMOR HYPOXIA

Adjacent biological macromolecules and the thereby generated $^1O_2$ went through processes of oxidation that might further cause cytotoxicity, harm to cells, and even death. The implementation of PDT in cancer treatment remains limited regardless of its numerous advantages because of many intrinsic disadvantages. To enhance the hypoxia of tumors, PS, for example, will convert oxygen to extremely harmful reactive oxygen species [1] when subjected to UV irradiation shown in figure 2. As a result, furthermore, to the already present tumor hypoxia, the oxygen consumption linked to the formation of ROS will also decrease the effectiveness of PDT. In addition, if tumor hypoxia grows more severe, it will promote the dissemination of the tumors and increase the likelihood of PDT sensitivity. Hence, an important area of research aimed at boosting PDT utility is currently coming out with innovative and feasible methods of reducing tumor hypoxia [6].

Nevertheless, through transferring energy, the T1-stated PS can also sensitize O_2 to form extremely dangerous singlet oxygen ($^1O_2$); this kind of mechanism is also known as "type II PDT." Typically, in type I PDT, a PS molecule can generate a ROS molecule. On the opposite hand, when there is sufficient light and O_2, a PS molecule in type II PDT can continuously generate $^1O_2$. So, an incredible curative impact can be attained. Improper supply of oxygen to the tumor's tissues is triggered by the malignant development of cancer cells and an irregular expansion of tumor blood vessels [7]. O_2-dependent PDT is less efficient whenever the tumor microenvironment (TME) is hypoxia. PDT further

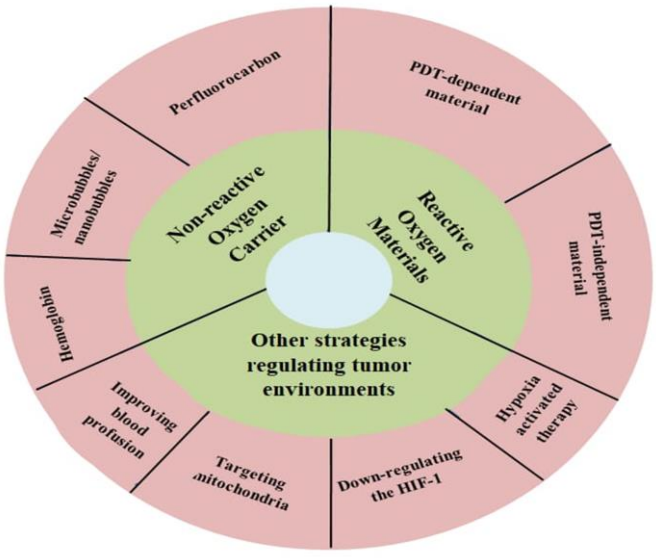

Figure 2. Tumour hypoxia and its strategies

results in an extensive hypoxia TME as it utilizes an excessive amount of oxygen, harms tumor blood vessels, and further limits oxygen delivery. Hypoxia-induced factors (HIF-1α) and the growth of tumor neovascularization may enable cancer cells to expand and recur. This is why it becomes so important from the scientific point of view to discover novel substances and procedures for the PDT of hypoxia tumors [8].

Across the world, cancer persists as one of the top causes of life expectancy. Following reports, there were approximately 18.1 new instances and 9.6 million fatalities due to cancer in 2018. It predicts that nearly 17 million individuals are expected to pass away by 2030. The requirement for improved therapies that are novel is made evident by these data. Standard therapies for cancer methods, which include radiotherapy, chemotherapy, immunotherapy, and surgery, have some disadvantages. Complicated physiology (which consists of issues with the size of the tumor, location, stage, and metastasis) renders curing some cancers difficult to accomplish. Additionally, tumor handling can be hindered by resistance which often emerges to reduce the initially administered success rates of immunotherapy, electromagnetic radiation, and chemotherapy, and numerous side effects appear during or after the treatment). It seems that there have been recommendations for improving and maximizing the successful outcome of standard treatment for cancer via alternative or extra therapies like DNA therapy, diet therapy, photodynamic therapy, insulin potentiating therapy, HAMLET (human alpha-lactalbumin made lethal to tumor cells), telomerase therapy, hyperthermia therapy, dichloroacetate, harmless radiofrequency cancer treatment, and bacteriotherapy.

A method that could potentially be able to successfully get through some of the shortcomings associated with standard cancer therapy is the employment of therapy for bacteria, as previously pointed out. Bacteria on their cells have powerful cancer-fighting abilities. Bacteria can be altered genetically to modify their metabolic pathways and adjust their capacity to produce and discharge certain chemicals, presenting another incredible property [9].

4. ADVANCEMENT AND CHALLENGES OR BACTERIA IN CANCER TREATMENT

Appropriate therapy for cancer demands an array of approaches due to its complicated characteristics. It was known as far back as nearly a century ago that bacteria experienced a long history of working as cancer-fighting agents. Therapists exploited bacteria that were alive, particularly streptococci and clostridia, for the first time in the cure of cancer. Nowadays, the majority of uses for this are involving genetically altered bacteria. Employing several approaches, bacteria can be utilized for cancer therapy. The methods mentioned above comprise related bacterial toxic effects, merger with complementary medication, bacteria with the capability to influence the expression of drugs that fight cancer, expression of antibodies specific to malignancies, the transmission of genes, interference with RNA, and pro-drug fragmentation. Various cancer models have been utilized used to assess the application of entire live, attenuated, and/or mutated bacteria alone, or in tandem with standard therapies. The most frequently used genera of bacteria in this field are Lactobacillus, Salmonella, Clostridium, Bifidobacterium, Escherichia, Pseudomonas, Caulobacter, Listeria, Proteus, and Streptococcus. Three categories of bacteria have been extensively investigated in animal models with different tumors for the possibility of serving as vectors for generating or delivering genes linked to anti-angiogenic aspects, suicide genes, cancer suppressor genes, or

carcinoma-associated antigens. These species include Clostridium Bifidobacteria and Salmonellae. While a few clinical investigations have been carried out previously and indicate partial outcomes, further study on humans must be done. Mutant bacteria can also be utilized for theranostic objectives since they can be recognized as dual medicinal and diagnostic substances applying positron emission tomography (PET) and magnetic resonance imaging (MRI) [10].

Because PDT was successfully used therapeutically for 25 years to combat cancer, this has been what is known as the "photo-antimicrobial renaissance era" while PDT initially proved to function as a promising antimicrobial treatment for drug-resistant infections in the medical sector in the early 1990s. It was recently observed that many significant multidrug-resistant bacteria are susceptible to antibacterial PDT (aPDT), regardless of their resistance to drug qualities. Adaptation to aPDT hasn't been demonstrated frequently to date, implying that while bacteria could evolve and resist the treatment, the possibility continues to be restricted. Greater effectiveness aPDT systems are continually being developed, primarily through combinatory approaches that utilize various chemical pathways and/or perspectives. Although aPDT is still not effective in treating widespread infections, it holds tremendous possibilities for curing specific infections and preventing AMR.

5. EMERGING NANO MEDICINES FOR PDT-DRIVEN CANCER IMMUNOTHERAPY

Tumors that are no immunogenic (cold) cannot generally be converted into immune-stimulating [11] by standard immune therapy. Certainly, modalities of therapy based on nanotechnologies may convert chilled tumors into warm ones, specifically the PDT mentioned previously that utilizes numerous immunostimulatory pathways to activate the immune response. To improve the success rate of PDT, novel and superior Nano medicines have been produced subsequently. These consist of Nano sized metal-organic frameworks (nMOFs), TME-responsive NPs, tumor hypoxia-reversed Nano medicines, and upconversion NPs (UCNs). Regarding developed tumors, the increased effectiveness of PDT as well as immunotherapy could result in an aggressive synergistic effect [12].

5.1. Tumor Hypoxia Reversed Nano Medicines for Cancer Immunotherapy

PDT's performance is greatly affected by tumor hypoxia, which becomes worse by the rapid proliferation of tumors which results in inadequate circulation and local consumption of oxygen. Likewise, by promoting the creation of immune-suppressive cells (such M2 type macrophages) and stimulating tumor formation and recurring, tumor hypoxia may interfere with anticancer immunity. Therefore, among the main approaches used to increase the effectiveness of PDT-driven cancer immunotherapy is to minimize hypoxia in the tumor site. Hemoglobin, catalase [13], manganese dioxide nanoparticles (NPs), oxygen-shuttle Nano per fluorocarbon (nanoPFC), hyaluronidase (HAase), and metformin (Met) are a few examples of nanomaterials and medicinal products that researchers are currently developing to alleviate tumor hypoxia [12].

6. CHALLENGES OF PHOTODYNAMIC THERAPY AGAINST CANCER

The most notable challenges for PDT include:

- The PS's unwanted diffusion around an intramuscular injection,
- A potential effect of absorption of light passing across tissues is inadequate light provided to the tumor position.

- Partial tumor eradication throughout PDT followed by tumor recovery, (incomplete or short-term impairment of the blood supply to the tumor during PDT and subsequently angiogenesis or arterial repair), or (hypoxia in the cancer surroundings that restricts the oxygen available for PDT.
- Stimulation of cancer-fighting immune responses transmitted through PDT. These inefficient factors and present attempts to improve PDT or its integration with other modalities will be described.
- Controlled diffusion of light across biological tissue
- Lowered levels of reactive oxygen species (ROS) as a consequence of the tumor's hypoxic
- Instantaneous vascular interruption which is modified,
- Malignancy recurrence after partial malignant eradication,
- Stimulation of the body's defenses against cancer [9]

7. PRINCIPLES OF PHOTODYNAMIC THERAPY

PDT enhances the chosen tissue's selective damage via the dynamic interaction of a PS, light with an appropriate wavelength, and molecular oxygen. A PS is delivered superficially or physically to the cancerous tissue, in which it aggregates primarily during the drug-light interval. The next stage in the PDT treatment is to subject the cancerous tissue to a wavelength that is suitable for light, often in the red spectral zone ($\lambda \geq 600$ nm). Reactive oxygen species [1] including singlet oxygen ($^1O_2$), superoxide radical ($O_2-\bullet$), hydroxyl radical (HO•), and hydrogen peroxide (H_2O_2) generate when lighting changes light into molecular oxygen. The PS itself is unable to interact with biomolecules. Whenever an array of metabolic processes are initiated by these carcinogenic photoproducts, the selected tissue could experience damage or probably death [14].

Its chemical responses are considered to be driven by a light-activated PS interacting with different molecules to create radicals. A photon gets absorbed whenever a PS gets sunlight, which fosters the PS to its excited singlet state, or S1, wherein an electron moves to a higher-energy orbital. The PS may go back to its ground state S0 from this unsteady and typically momentary state by transforming its energy into heat or fluorescence; this capability can be leveraged for optical monitoring and diagnosis. On the contrary, an intersystem crossing could arise, that might trigger the PS population to appear in the excited triplet state T1. The PS may exchange energy in its T1 state using a pair of distinct procedures: either through phosphorescence or by collapsing with other molecules resulting in chemically reactive species. For various kinds of organic substrates or solvents, T1 can react to move an electron or a proton, causing the development of radical anion or cation species, correspondingly. The PS usually generates PS from an interaction with a substrate that provides electrons. PS ultimately incorporates oxygen to produce superoxide anion radicals. The type I reaction is the term that we call this. Type II reactions include the immediate interaction of T1 with ground state oxygen $^3O_2$ mediated energy transfer, which results in the generation of singlet oxygen $^1O_2$, which is a highly reactive oxygen species [1]. Detailed descriptions of the precise molecular mechanisms underlying these photochemical reactions exist [15].

7.1. Principle for Antibacterial Photodynamic Therapy

The photosensitization of bacteria by external compounds that are called photosensitizers (PSs) is the backbone of APDT. Following that, exposition of the infected area to light with a resonance wavelength (typically in the visible-light range, 400–700 nm) triggers hazardous oxidative stress, and that in return

leads to cell death. Upon consuming the light, the radiation ground state PS, which exists within the bacteria as well as on their surface, gets activated to transform into its singlet state (1PS). Reactive oxygen species [1] or reactive molecular transients develop because the excited state electrons shift across into a triplet state (3PS), that possesses a longer duration of action but lower energy. In type II reactions, the excited PS reacts directly with molecular oxygen (O_2) and forms a strong connection between the 3PS and substrate is essential for the type I or type II mechanism that causes the photochemical actions. Whenever electrons from the 3PS move to a material that is in the triplet state, type I reactions release radicals. Molecular oxygen is a common type I reaction terminating substrate, that generates superoxide anion. In a physiological surrounding, O_2•– is usually not dangerous, though it can produce more destructive ROS, such as carbonate radical anions (CO_3•–) and hydroxyl radicals (•OH), that oxidize biomolecules and eventually trigger damage to cells and mortality. 3PS→O_2 energy transfer yields highly reactive singlet oxygen ($^1O_2$) as shown in figure 3. The type of PS that is distributed and the microscopic setting in which APDT is placed are believed to influence the proportion of type I to type II reactions, which are believed to take place concurrently during APDT [16].

7.2. Mechanism of Action of PDT

To carry out PDT, a few requirements need to be achieved, such as

- The most stringent probable tumor incorporation associated with a photosensitizer (PS),
- Adequate time has lapsed after infusion to allow the photosensitizer to become embedded in the cancerous tissue to the maximum degree feasible, in addition
- The introduction of the malignancy to light at a suitable wavelength is necessary to trigger optical degradation.

As tumor cells collapse through optical means, typically a pair of oxidation pathways is concerned. As a consequence of the exchange of electrons or hydrogen, photosensitive substances react to oxygen or biological molecules culminating in the formation of radicals known as free radicals. Energy flows from an oxygen molecule's triplet state of relaxation into its triplet excited mode, yielding singlet oxygen. Numerous biomolecules, particularly cholesterol, unsaturated fatty

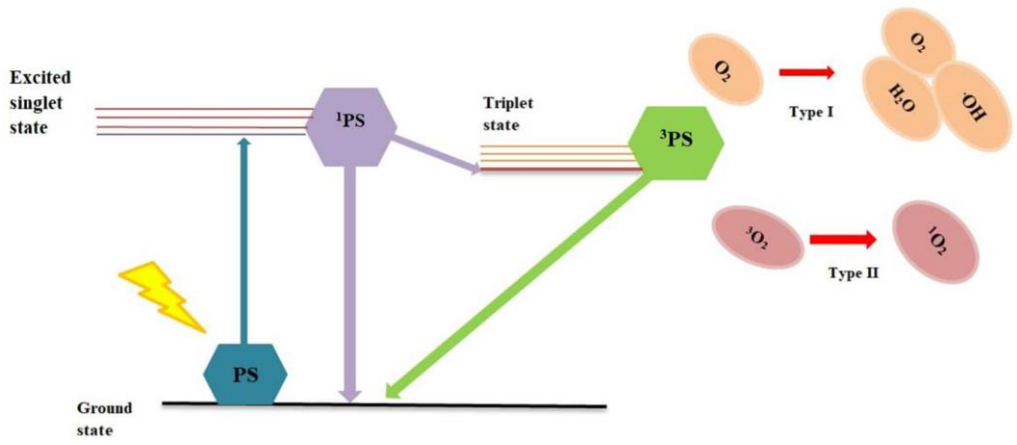

Figure 3. Products generation for aPDT in Tupe-Iand Type-II reactions

acids, and alpha-amino acids notably tryptophan 3 and metanil 6, quickly react with singlet oxygen. These molecules are the essential constituents of many different biological membranes. Consequently, through PDT, the rupture of membranes is an essential variable in the necrosis and ultimately demise of blood vessels. To provide the greatest light absorption to the therapy position, the photosensitizer is usually administered with liposomes or aqueous buffer solutions. The light source can often be powered by lasers with optical fibers attached [17].

7.3. The Mechanism of the Antitumor Effects of Photodynamic Therapy (PDT)

PDT is a confined cancer treatment that is non-intrusive. In photodynamic therapy (PDT), a photosensitizer is injected alongside a wavelength of visible light to induce a photoreaction generated by the photosensitizer. Ground-state molecular oxygen (3O2) transforms into an array of highly reactive oxygen species on stimulation of the photosensitizer. Among the most reactive of the aforementioned species is chemically extremely reactive singlet oxygen (1O2), which reacts with several biological molecules, including lipids, proteins, and nucleic acids, subsequently triggering the death of cancerous cells. That is understood that a variety of PDTs disrupt the vasculature of tumors besides cancer cells [18]. Owing to the photosensitizer's preferential aggregation in cancer cells and the reason that the irradiation is confined to the cancer site, it is fairly non-invasive, demonstrating minimized systemic adverse effects and a substantially particular cancer destruction PDT is therefore being utilized regularly for the therapy of a variety of carcinomas that can be directly subjected to radiation, which include cancers of the lung, brain, esophagus, stomach, breast, skin, bladder, and uterus [19].

7.4. Apoptosis and Necrosis

Photo-chemical processes of categories I and II can initiate distinct pathways of cell demise that are directly damaging to malignant cells. PDT-induced cell death used to be classified as type I, or apoptosis, type II, or cell death related to autophagy, and type III, or necrosis. PDT additionally harms the vessel walls and promotes the attraction and stimulation of immune cells. However, plenty of different cell death methods that could have been activated by PDT have been established over the past few decades. These outcomes indicate that our awareness of PDT-associated cancers has expanded

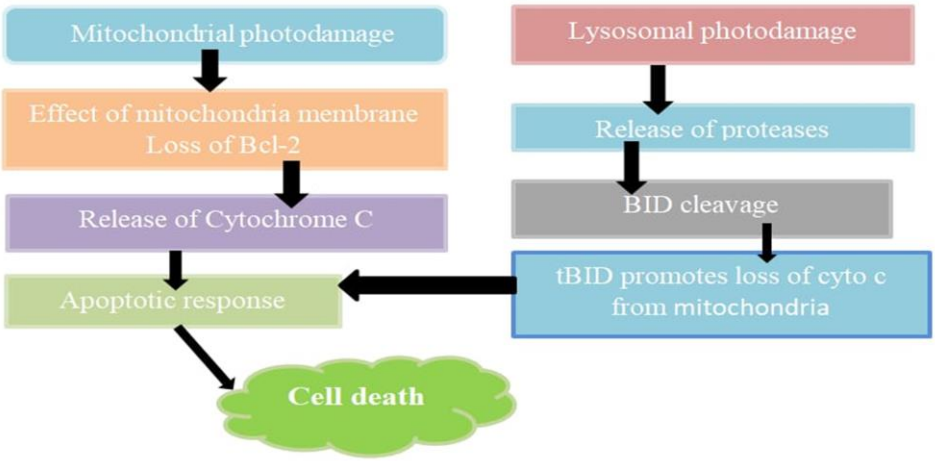

Figure 4. Cell death pathway for cancerous cells in PDT

[20], the last few years, other "non-conventional" cellular death modalities, which include regulated different kinds of necrosis, like necroptosis, ferroptosis, "standard pyroptosis, parthanatos, and mitotic catastrophe, are being demonstrated as well as the " cell death pathways of apoptosis, necrosis, and autophagy. These forms of cell death can be initiated by photodynamic responses. The results of these investigations presented new insights into the signaling mechanisms that contribute to PDT-induced death rates as shown in figure 4. Furthermore, we must reconsider the results we obtained on cancers PDT and modify existing information whenever necessary owing to the emergence of new analytical methods for understanding together certain aspects of the cell death pathway [20].

8. GOLD NANOPARTICLES BASED PHOTODYNAMIC THERAPY

Nanotechnology is also building in roads into biomedical study, and because of its adaptability and potential for functionalization, it could recover and speed tissue regeneration [21]. The resonance wavelength's light stimulates surface plasmons, thereby providing gold nanoparticles (AuNPs) their particular nanoscale aspects. The modification of photon energy into heat whenever applied to a wavelength of NIR laser is one of the aforementioned characteristics. The internal temperature within the cells of a tumor might increase to the extent of hyperthermia, which can result in programmed cell death. Scientific research tends to refer to this treatment method as PTT.

Proper characterization of physicochemical and optical characteristics can be guaranteed by the carefully constructed architecture of AuNPs. Moreover secure and established to be non-toxic as well as biocompatible is the gold core. AuNPs' surface may easily be transformed for specific purposes, and ligands, pharmaceuticals, as well as biodegradable films are capable of being used. For the majority of the relatively large-molecular-weight medicines in availability today, the size of AuNPs provides an enhanced penetration and retention effect (EPR). Utilizing AuNPs, medicines, and imaging molecules may possess greater solubility as well as effective pharmacokinetics [22]. Tumor-specific nanoparticle buildup and administration of drugs can be achieved through passive, active, or any combination of each of the targeting modalities. Cancerous cells are destroyed gradually by the EPR effect, which is ubiquitous in many sick regions. Targeting actively can be accomplished when AuNPs are mixed with numerous tumor-targeted substances, such as antibodies (Abs). Although AuNPs possess a higher surface-to-volume ratio in comparison to free-drug compounds, they may substantially decrease the lowest effective dose relative to different methods of targeting because of their enhanced drugs and/or prodrug load capability [38].

8.1. Characterization of Gold Nanoparticles

Applying distinctive UV-visible spectra, the generation of gold nanoparticles was demonstrated. The intensity of absorption at 540 nm rises as the quantity of plant extract goes up, as Figure 9Aa indicates. Additionally, the production of GNPs has been identified by microscopic analysis. During an incubation period of 24 hours of $HAuCl_4$ with five milliliters of Aloe vera leaf extract, a TEM investigation was carried out utilizing the nanogold solution [23].

9. PHOTODYNAMIC THERAPY BASED ON METAL-ORGANIC FRAMEWORKS (MOFs)

A newly developed porous nanocarrier referred to as nanoscale metal-organic frameworks (NMOFs) that contain organic-inorganic hybrid approaches, has received growing recognition in the therapeutic sector

as show in figure 5. MOFs provide multiple distinct advantages in drug incorporation and delivery as opposed to standard nanocarriers. First of all, most MOFs have a response-degradation pathway that allows medicine to penetrate malignancies and discharge their therapeutic effects. For instance, due to its low pH, ZIF-8, a kind of pH-responsive MOF that belongs to the zeolitic imidazolate frameworks (ZIF) family, might break down in cancerous cells and discharge its cargos. Furthermore, MOFs displayed limited systemic adverse effects as well as excellent drug-loading properties especially compared to different drug carriers including liposomes, micelles, dendrimers, and inorganic carriers. Lastly, MOFs show substantial potential for determining the cause of cancer. The high degree of specificity, strength, repeatability, and versatility of MOFs and their resulting hybrids as nanosensors is beneficial for the early identification of cancers [23].

9.1. Characteristics of MOFs

A particular kind of interesting therapeutic carrier is a medium-size porous filter (MOF), that features substantial porosity, large surface area, flexible pore size, effortless functionalization, robust biocompatibility, and biodegradable properties MOFs possess plenty of potential for administering medications due to their distinctive characteristics [23].

10. CARBON NANOTUBES-BASED PHOTODYNAMIC THERAPY

Carbon-based nanohorns Nasocones, or CNHs, typically appear as horn-shaped, single-walled entities. CNHs comprise an average length of about 40 to 50 nm, a diameter of 2 to 5 nm, and a pitch that is approximately 120°. Sometimes, they appear as 50–100 nm spherical clusters. The effect of EPR can best build up in a cancerous location with a diameter in this range. Single-walled nano horns are made by arc discharge (AcD) or laser ablation (LA) employing metal-free catalysts and pure graphite rods; single-walled nanotubes are generated using metal contaminants. The capacity to be generated at room temperature offers CNHs a further benefit over CNTs.

The additional features unique to CNHs are comparable to those of CNTs. CNHs can absorb NIR light, which may

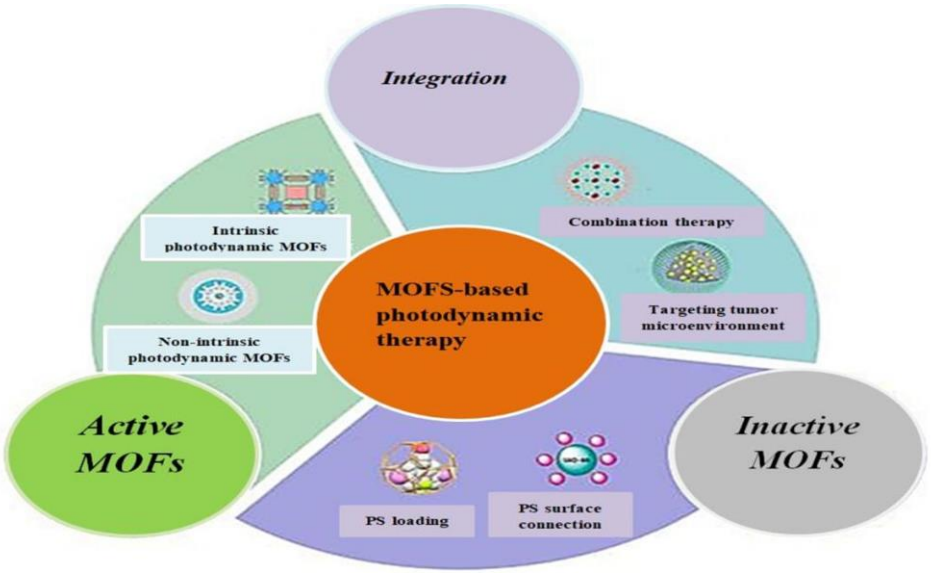

Figure 5. The Frameworks of MOFs based photodynamic therapy

profoundly impact photo thermal events. This feature enhances their physiological uses, especially in PTT. The SWNHs were previously utilized by Whitney *et al.* to boost the temperature when subjected to near-infrared light, this destroys cancerous cells. CNHs have shown the effectiveness associated with their PTT via utilizing it in combination with NIR irradiation to harm cancer cells in vivo [24]. Employing PTT tumor ablation generated by CNHs, tumors may be destroyed while presenting a danger to healthy cells. A few days after medical treatment, hair reappeared in the volunteers who were administered heat or CNH before experiencing a malignant recurrence. The present research offered information on the efficacy of CNTs and CNHs in PTT alongside additional uses in medicine [25].

11. SILICA NANOPARTICALS BASED PHOTODYNAMIC THERAPY

Due to the advantages they offer, such as chemical stability and tenability, silica-based nanoparticles have become the focus of numerous studies. Mesoporous silica is differentiated from other types of silica substances by its number of mesopores that provide the substance an extensive surface area. Alternative silica materials comprise physiologically altered silica but Stöber silica, which is rigid and thick. MSNs constitute a renowned PS method of delivery. The pharmaceutical transferring and distribution qualities of MSN delivery mechanisms can be affected by multiple variables that include pore geometry, pore size, and drug integration techniques [26].

11.1. The Procedure of Photodynamic Therapy Based on MSNs

PS-loaded silica nanoparticles were re-reported as an appropriate platform for singlet oxygen generators, enhancing PS's modest solubility and sensitivity for cancer cells and boosting the administration of photoactive pharmaceuticals. The PS could be attached covalently to the inside or outer layer or physically coated, compared to the silica nanoparticles. In short, the incorporation of PS into the nanostructure results in increased photostability, but additionally hinders the movement of oxygen species, particularly singlet oxygen externally and molecules of oxygen within [27]. It has been proven by experiments that the $^1O_2$ yield of nanoparticles with applying PS outside has been greater compared to that of nanoparticles with PS inside out. In this study's completion, 50 nm MSNs' outside surface was linked to several PSs. First, three commercially available PSs were identified as appropriate singlet oxygen sources: Thionine (Th), Rose Bengal [28], and Chlorine 6 (C6). Thionine (Th) was used extensively in PDT and has been recognized as a suitable singlet oxygen creator. Functional groups (amine in Thio- and carboxylic in Rose Bengal along with Chlorine 6) have already been found in the molecular frameworks of these ethnic backgrounds [29].

12. COMPARISON OF CHARACTERISTICS OF SINPS WITH OTHER NANOPARTICALS

The two types of in vitro and in vivo investigations are looking toward silica nanoparticles, which are proven to be promising for PDT purposes. It was successfully found that encasing photosensitizers in silica nanoparticles performs exceptionally well since silica is non-toxic, inert to chemicals, and translucent to sunlight. The existence of hydroxyl groups on the outermost layer of silica promotes chemical functionalization. Furthermore, the blend of stable silicon nanoparticles and photosensitizers has been effectively absorbed by tumor cells, causing them to the decomposition it at the same time to remove it as silicic acid [30]. Although silicon nanoparticles (SiNPs) had

excellent qualities, they were thoroughly investigated as a developing fluorescent nanomaterial for a variety of applications in biology and medicine. Whenever it concerns fluorescence and photobleaching resistance, SiNPs generally outshine standard organic dyes such as fluorescein isothiocyanate (FITC). Another proof point of the low level of toxicity and superior compatibility of SiNPs is that they're able to be biodegraded in vivo by the kidney and liver [31]. In addition, specific investigations have shown that the SiNPs can be used to perform fluorescence imaging which uses two-photon excited (TPE). By deploying two near-infrared (NIR) laser photons instead of a single visible photon, TPE fluorescence imaging may provide enhanced temporal selectivity and deep tissue penetration despite minimizing the disruption triggered by auto-fluorescence from biological tissues.

Due to that, SiNPs possess the ability to be utilized as fluorescent probes in medicinal and medical diagnostics. The development of SiNPs nanohybrids having multifaceted synergistic medicinal properties remains worth researching for obtaining improved treatment since right now, nanocomposites made from silicon nanoparticles (SiNPs) tend to be confined to a single medicinal modality. The current research utilized mesoporous silica nanoparticles (MSN) to serve as a nano platform. Particularly, SiNPs, as well as the photosensitizer 5,10,15,20-tetrakis (1-methyl 4-pyridinio) porphyrin tetra (p-toluenesulfonate) (TMPyP), were initially incorporated in the MSN while afterward improved with folic acid (FA) to produce the mesoporous silica nanocomposite for intended two-photon-excited fluorescence imaging-guided photodynamic therapy (PDT) and chemotherapy. When loading doxorubicin (DOX), a cytotoxic medication, for chemotherapy, the implanted TMPyP might produce singlet oxygen that carries out PDT beneath exposure to light. In addition, the near-infrared (NIR) laser excitation permitted the nanocomposite to achieve targeted two-photon fluorescence cellular image processing, thus preventing the disruption of biological auto-fluorescence, owing to the two-photon promoted fluorescence of SiNPs.

13. CONCLUSION

Photodynamic therapy (PDT) is an innovative novel therapy for cancer that targets cancer cells via light and photosensitizers (PSs). This article covered some aspects associated with photodynamic therapy (PDT), a potentially efficient cancer treatment that targets cancer cells through the integration of radiation using photosensitizers (PSs). The investigation highlighted Photodynamic therapy's challenging circumstances and modifications, in particular how employing nanoparticles might enhance Photodynamic therapy's efficiency for deep malignancies such as osteosarcoma. We examined the mechanisms of action of Photodynamic therapy, encompassing the physics of Photodynamic therapy's, the mechanisms of the anticancer consequences of, Photodynamic therapy photosensitizer stimulation, and singlet oxygen production. The usage of silica, carbon nanotubes, metal-organic frameworks (MOFs), gold, and carbon nanoparticles in photodynamic therapy (PDT) was investigated in this work . A comprehensive overview of their uses in the treatment of cancer has been offered through the production and characterization of different nanoparticle-based Photodynamic therapy methods, notably silica nanoparticles, carbon nanotubes, metal-organic frameworks, and gold nanoparticles. Despite their excellent photophysical properties and biocompatibility, silicon nanoparticles surpassed gold nanoparticles in the research investigation and, therefore, are effective for PDT.

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15. CONFLICT OF INTEREST

The authors have declared that there is no conflict of interest.

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17. REFERENCES

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