Recent Developments of Porphyrin Photosensitizers in Photodynamic Therapy

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Abstract

In the modern era, chemotherapy, radiation therapy, biomarker testing, immunotherapy, sonodynamic therapy, hormone therapy, photothermal therapy, photodynamic therapy, and many more therapies are available for cancer. Photodynamic therapy (PDT) is a potential, innovative and non-invasive way of treating cancer. The main component of PDT is photosensitizers (PS), role in the practical applications of PDT. When these PS are exposed to appropriate light or laser irradiation, they absorb the energy and enter an excited state. They eventually transmit the energy to the neighbouring molecules, generating reactive oxygen species (ROS), especially singlet oxygen ($^1O_2$) into the model animals and patients. The most used and popular sensitizers, such as photofrin, hematoporphyrin (Hp), aminolevulinic acid (ALA), Porphyrin, and its derivatives, were developed regularly from first-generation to third-generation PS. After the second-generation PS highly focused on Porphyrin and its derivatives with modification and complexation to boost the efficiency of PDT against cancer cells. This review focuses on the PDT development of porphyrins with nanoparticles as third-generation PS with selectivity, toxicity and biocompatibility. In addition, porphyrin-based nanomedicines are discussed in terms of current challenges and future prospects.

Keywords: Photodynamic therapy, porphyrin, photosensitizers, ROS, singlet oxygen.
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I. INTRODUCTION

Photodynamic therapy (PDT) is more controlled and can selectively target cancer cells while protecting normal tissues. PDT is a site-specific, innovative and non-invasive way of treating cancer cells with photosensitizers (PS) and light to produce the reactive oxygen species (ROS), especially singlet oxygen ($^1O_2$)[1-4]. In PDT initial phase is the injection of PS into the organism, and the subsequent stage is the tissue-localized sensitizer is exposed to appropriate wavelength light, triggering a series of biological events via various photophysical processes. As a result of the formation of singlet oxygen and reactive oxygen species, cells die. Most of the studies focused on Porphyrin and its derivative components as PS with the ability to produce ROS and singlet oxygen for PDT applications[5, 6]. A porphyrin molecule contains tetrapyrrole rings linked by four methine bridged bonds surrounded by substituent groups in square planar geometry[7-10]. The porphyrin macrocycle obeys Huckel's rule (4n+2) p-electrons; it contains 18 p-electrons aromatic system. A large range of porphyrin derivatives may be developed by substituting several functional groups onto porphin macrocycles at the meso-position or the β–position[11, 12]. Additionally, free base porphyrins should be coordinated with metals to get metalloporphyrins as complex. According to their different properties and functions, Porphyrin and its derivatives have been used in multiple applications. Porphyrin-based compounds have significant benefits over porphyrin monomers in that they may significantly enhance the roles of porphyrins for wide-range applications[13-20]. Three different kinds of PS were used in PDT. These are first, second, and third-generation PS. Photofrin and hematoporphyrin (Hp) and hematoporphyrin derivatives (HpD) were used in first-generation photosensitizers. ALA and benzoporphyrin derivatives were used in the second generation, third generation PS generally the porphyrins and their derivative combinations with nanoparticles.

This review is focused on the efficiency of porphyrins and its derivatives with nanoparticles as highly efficient third-generation photosensitizers. The nanoparticles increase the water-soluble property of Porphyrin, and it absorbs light or laser irradiation to cause the tumor cells effectively with high phototoxicity and excellent biocompatibility.

II. Photodynamic therapy (PDT) mechanism

The mechanism of PDT as presented in **figure-1** the photochemical reactions in PDT illustrated by modified jablonski diagram[3, 21]. The photosensitizers when absorbs the energy from light or laser irradiation it can be transferred to singlet ground state (S_0) to singlet excited states(S_1 and S_2). This excited Photosensitizers relax back from S_2 to S_1 via internal conversion, otherwise relax back from S_1 to S_0 with the emission of fluorescence photons or the energy transferred from singlet excited state (S_1) to triplet excited state (T_1) through the intersystem crossing. Furtherly, the energy of photosensitizers in the T_1 state can be relaxed by a phosphorescent photon or transmitted to surrounding molecules by photochemical reactions via type-I and type-II pathways. In the type-I approach, Photosensitizers in the T_1 state perform an electron- or hydrogen-transfer process to create free radicals, which then interact with water or oxygen molecules to produce hydroxyl radicals ($OH^{\cdot}$) or superoxide anions ($O2^{-\cdot}$). Otherwise in extreme oxygenated condition, T1 state photosensitizers participate in an energy transfer process with the local $^3O_2$, resulting in the generation singlet oxygen ($^1O_2$) with high cytotoxicity[21-23].

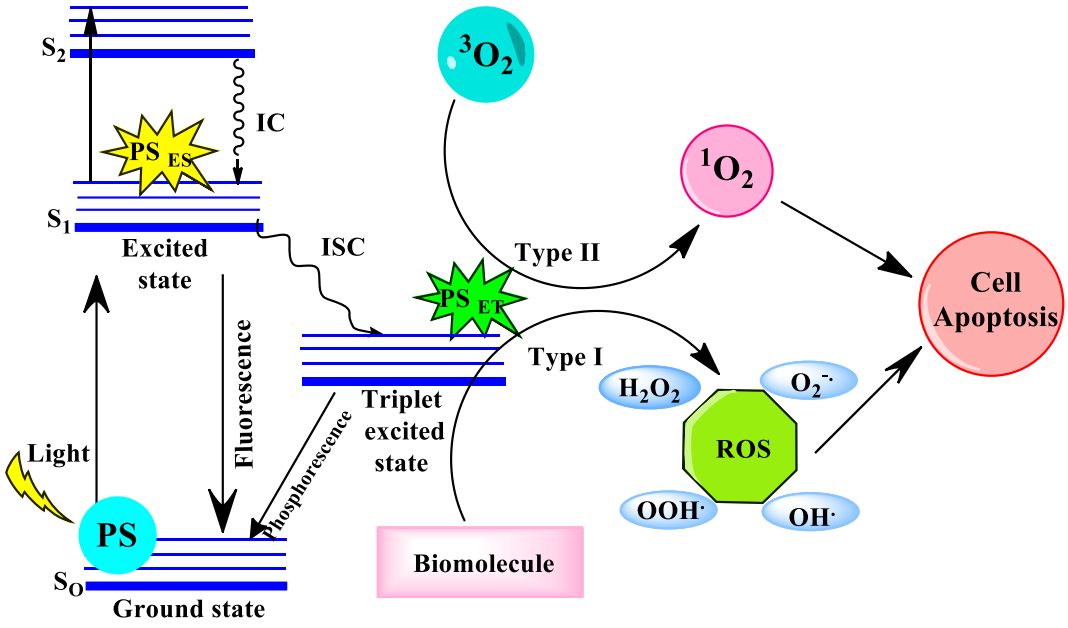

Figure 1. Schematic representation of photodynamic therapy mechanism

III. Photosensitizers and its developments

Photosensitizers (PS) are chemicals that, when exposed to light, produce reactive oxygen species (ROS) that can harm the cell structures of pathogenic mammalian cells or microbes, ultimately causing cell death. Generally, the red light penetrates tissues or cells profoundly, and there is less skin photosensitivity in this range of the spectrum, especially PS that is stimulated by longer wavelengths of light, particularly in the red and far red, which can be used to treat spots deeper in the body[24]. Hematoporphyrin derivative (HpD), has been marketed as photofrin. It was the first PS

to be authorized clinically for PDT to treat bladder cancer[25].Once Photofrins were approved for PDT therapy, researchers worldwide became very interested in developing efficient PS[26].

The following criteria should be satisfied by an ideal PS.

1. Singlet oxygen production is regarded as the significant cytotoxic agent responsible for the PDT-induced killing of cancers; it must be able to generate it effectively.
2. Long wavelength absorption should be high (700 nm to 800 nm). Porphyrin-based photosensitizers have a "Soret" band at 400 nm and a Q-band between 600 and 800 nm. PDT only uses Q-band. Aromatic compounds with 22-, 20-, and 18-p electrons are porphyrins, chlorins, and bacteriochlorins. A prominent Soret band in porphyrins absorbs light at 600 to 650 nm. Chlorins have Q-bands between 630 and 700 nm and long-wavelength bacteriochlorins absorb between 700and 800 nm, depending on the substituents at the peripheral locations. PS in this wavelength range can heal giant and deeply seated cancers.
3. It shouldn't be poisonous in the dark, cause very little skin photosensitivity, and only aggregate in tumor tissue (preferential tumor retention, fast tumor accumulation and rapid clearance from other organs).
4. In PDT processes, a PS's dispersion is essential and is affected by its chemical composition. A PS with a hydrophobic matrix and amphiphilic water solubility is beneficial.
5. When dissolved in injectable solvents, it needs to be stable and simple to use (formulation).
6. It prepared chemically pure and simple methods with high quantum yield[2, 24, 27-30].

The PS is based on three types, and these are first, second, and third generation PS.

A. First generation Photosensitizers

Hematoporphyrin (Hp) and its derivatives were the first photosensitizers introduced in PDT. Since early as 1942, Auler and Banzer demonstrated that Hp accumulates in cancers of many animal species and that these tumorsare eliminated when exposed to light. In reality, however, the 1960s marked the beginning of PDT's evolution as a legitimate diagnostic and therapeutic tool[31-34].

Table-1: Photosensitizers of First Generation and their targets.

Year	Author	Photosensitizer	Wavelength	Target
1990	Schmidt-Erfurth U, Miller J, Sickenberg M, et al.[35]	Hematoporphyrin (HpD)	630nm	Infected persons with subfoveal choroidal neovascularization
1992	Jin ML, Yang BQ, Zhang W, et al.[36]			Advanced gastrointestinol cancer suffered patients 142
2004	Stylli SS, Howes M, MacGregor L, et al.[37]			Tissue samples of brain tumor
2005	Stylli SS, Kaye AH, MacGregor L, et al.[38]			High grade glioma patients

2006	Clarke CP, Knight SR, Daniel FJ, et al.[39]			Malignant mesothelioma patients are 100
1992	Peterson, C.M., Reed, R., Jolles,C.J., et al.[40]	Photofrin	630nm	OVCAR3 Nude mice (Ovarian)
1997	Nauta, J.M., van Leengoed, H.L., Witjes, M.J., et al.[41]			Male Wistar rats (Oral cancer / dysplasia)
2015	Wang, X., Hu, J., Wang, P., et al.[42]		635nm	4T1 BALB/c female mice (Breast cancer)
2016	Sun BO, Li W, Liu N, et al.[43]		625nm	23 infected persons with subfoveal choroidal neovascularization
2017	Qiu H, Kim MM, Penjweini R, et al.[44]		635nm	Radiation-induced fibrosarcoma mice

Photosensitizing ability of Hp and other tetrapyrroles was recognized as the photosensitivity syndrome before PDT. When porphyrins are found systemically throughout the body, they trigger a phototoxic response in any body parts that are in the sun. Epidermal swelling, redness, and blistering are all signs of the moderate version of the photosensitivity syndrome; however, the severe form may be dangerous[45-48]. The chemical modification and its purification lead to the development of HpD derivatives, which show high selectivity of tumor tissues and cause less intense skin photosensitivity than the Hp[49-51]. The HpD derivatives photofrin compounds, and their targeting ability are listed in Table –1. Afterward, a combination of HpD-isolated porphyrin dimers and oligomers was commercialized under the name Photofrin[52].There is less chemical purity (a mixture of over 60 molecules) with certain limitations and drawbacks. Its maximum absorption is a relatively short wavelength – 630 nm cannot effectively penetrate the tumor tissues.The disadvantages of first-generation PS encouraged the development of second-generation PS[26, 53, 54].

B. The second-generation photosensitizers

Only a couple of the several hundred compounds with potential photosensitizing characteristics had been employed in clinical studies. Even fewer chemicals have been formally licensed for use in clinical anti-cancer PDT. Due to the drawbacks of first-generation PSs, substantial research has been done to improve PS molecule effectiveness by modifying the peripheral functioning of the porphyrin[26, 55] or by altering the porphyrin core[56, 57]have been developed by following synthetic photosensitizers such as 5-aminolevulinic acid, benzoporphyrin derivatives,chlorins, texaphyrins, thiopurine derivatives[58, 59]. The various works based on a first generation PS leads to the development of following non-porphyrinoid PS compounds as a metalloporphyrins (Lutrin and Lutex)[60, 61], purpurins (Purlytin)[62, 63], pheophorbides (Tookad)[63-65], phenothiazines (methylene blue, and toluidine blue)[66-70] , protoporphyrin IX precursors (Hexvix, Metvix, and Levulan)[71, 72], chlorins (Foscan)[63, 73, 74],porphycenes[64, 75, 76], phthalocyanines and naphthalocyanines[77-81], cyanines (merocyanine 540)[82], Xanthenes (Rose Bengal)[83-85], hypericin[86-88] and dipyrromethenes[89, 90].Other photosensitizers are based on chlorine structure such as temoporfin, mono-aspartyl chlorin e6 (NPe6) and hexylpyropheophorbide (HPPH) in**Table-2**[91]

Table-2: Photosensitizers of Second Generation and their targets.

Year	Authors	Photosensitizer	Wavelength	Targets
1993	Richter AM, Waterfield E, Jain AK, et al.[92]	Benzoporphyrin derivative monoacid ring A (BPD-MA), vertoporfin	689 nm	Subjects with non-facial PWS
2009	Tournas JA, Lai J, Truitt A, et al.[93]			Tumor tissue in a mouse tumor model
2010	Spernvak J A, White III W H, Ethirajan M, et al.[94]	HPPH	-	Mice and Rat tumor models
2010	Clichici S, Filip A, Daicoviciu D, et al.[95]	TSPP	-	Wistar male rats bearing 256 Walker carcinosarcoma
2012	Nanashima A, Abo T, Nonaka T, et al.[96]	N-aspartyl chlorin e6, Npe6	660 nm	7 patients with bile duct carcinoma
2013	Decker C, Schubert H, May S, et al.[97]	Temoporfin or m-THPC (Foscan)	652 nm	Rat model employing a radioactive lipid label and (14)C-temoporfin
2013	Duchi S, Sotgin G, Lucarelli E, et al.[98]	Meso-tetrakis (4-sulfonatophenyl) porphyrin	-	Osteisarcoma cells
2014	Diez, Valle R, Slof J, Galvan J, et al.[99]	Aminolevulinic acid (5-ALA)	635 nm	Patients with suspected malignant gliomas
2014	Rapp M, Kamp M, Steiger HJ, et al.[100]			9 patients with deep-seated contrast enhancing brain tumors

The second generation PS are distinguished by a greater purity, a larger yield of singlet oxygen production and improved penetration to deeply positioned tissues and their maximum absorption in the wavelength range between

650 – 800 nm. Second generation PS shows the less side effects as a consequence of faster removal of the PS from the body and a stronger selectivity for primary tumors. The major drawback of the second generation PS is that they are insufficiently soluble in water, which severely restricts intravenous administration and requires the development of novel drug delivery techniques. The drawback of second generation PS leads to the invention design of third generation PS[101, 102].

C. The third generation photosensitizers

The synthesis of third-generation PS is based on producing compounds with a greater affinity for tumor tissue, minimizing harm to nearby, healthy tissues. Developing a pharmacological process that would allow the parenteral injection of photosensitizers is another obstacle to the general clinical use of photodynamic therapy in cancer. The bioavailability of PS is higher in the photodynamic technique and is being successfully improved by the development of new drug-delivery technologies[103].The development of third-generation PS is distinguished by conjugating andmodifying second-generation PS with targeting entities or moieties, such as antibodies, carbohydrates, amino acids, or peptides, or by encapsulating into carriers like liposomes, micelles, and nanoparticles (NPs). The main goals in developing third-generation PS are to lessen adverse effects on surrounding cells and enhance the pharmacokinetics and specific tumoral accumulation of these PS via encouraging the bioconjugation of PS with a targeting moiety based on the unique characteristics of malignant tumor cells, such as cell surface receptors that different from those of normal cells. Such targetingmoieties immobilizations onto PS targeted at tumor cell antigens accomplish precise attachment to tumor tissues and death through a photodynamic technique without harming healthy cells. Each element fundamentally influences how the PDT response is modulated. For instance, the linkers improve the hydrophobic/hydrophilic character and enhance cellular absorption by tumour cells by reducing interactions between PS and the targeting moieties[104, 105].

Generallythirdgeneration PS developments highly focused on the encapsulation of secondgeneration with NPs, as it was very tiny, with diameters ranging from 1 to 100 nm, and some of them are capable of carrying numerous theranostic drugs. Additionally, NPs may inhibit the early release of PS, which in turn can reduce the nonspecific aggregation in healthy cells. PS-NPs show high efficiency in targeting tissue penetration of tumor cells without harmful effects on normal cells[106, 107]. Importantly, NPs provide PSs with amphilicity which allows them to navigate the bloodstream unharmed[108].When attached to PSs, the tiny size of NPs accelerates passive diffusion into cancer cells viaEPR(enhanced permeability and retention) effect[109].Recently researchers attracted in the PDT field due to the multifunctionalproperties of Nps with PSs, the unique properties of NPs as optical properties, shape, size, and porosity tunability. We have given detailed information and the development of thirdgeneration PS in **Table – 3** and this review article.

Table – 3: Photosensitizers of third generation and their targets.

Year	Author	Photosensitizer	Wavelength	Target
2009	Ruirui Zhang, Chuanliu Wu, Lili Tong, et al.[110]	Hematoporphyrin (HP) with silica core-shell nanocomposite	-	Highly metastasizing human ovarian cancer cells
2013	Nagahara A, Mitani A, Fukuda M, et al.[111]	ICG-loaded nanospheres coated with chitosan	800-805 nm	Infectious pathogens

2013	Lee HM, Jeong YI, Kim do H, et al.[112]	Chlorin e6+ChitoUDCA nanoparticles	200-400 nm	HuCC-T1 human cholangiocarcinoma cells
2015	Xing Zhu, Hao Wang, Longbin Zheng, et al.[113]	Chlorin E6 (Ce6)+Upconversion nanoparticles	980 nm, 405 nm	THP-1 macrophages
2018	Dongjian Shi, Jinfeng Zeng, Wendi Yang, et al.[114]	TPPS+Gold nanoparticles	635 nm	HepG2 cells and L929 cells
2020	Xiaolong Liang, Min Chen, Pravin Bhattarai, et al.[115]	Perfluorocarbon+Porphyrin Grafted Lipid (PGL) Nanoparticles	NIR Region	Mice bearing the HT-29 colon tumor cells
2021	WioletaBorzęcka, Patrícia M. R. Pereira, Tito Trindade, et al. [116]	Silica nanoparticles+Glycosylated porphyrins	-	HT-1376 and UM-UC-3 bladder cancer cell lines of human
2021	N. Bridged Magaela , RefilweMatshitse , TebelloNyokong, et al.[117]	Nitrogen doped graphene quantum dots nanohybrids+Sn(IV)Porphyrin	428 nm	MCF-7 human breast cancer cells.
2022	WioletaBorzęcka, Patrícia M. R. Pereira, Rosa Fernandes, et al.[118]	Spherical and rods shaped mesoporous silica nanoparticoes+ S-Glycoside Porphyrins	-	Human bladder cancer cell lines, HT-1376 and UM-UC-3
2022	Yu-Xin Li, Yamin Liu, Hui Wang, Dan-Wei Zhang, et al.[119]	Water-Soluble Porphyrin-Based Nanoparticles	655 nm	Mice B16F10, MCF-7, and HeLa cell lines
2022	Hiromi Kurokawa, HidemiShigekawa and Hirofumi Matsui, et al.[120]	Gold nanoparticles+Modified Porphyrin derivative(HpD)	870 nm	RGK-KO cancer cells

Zhang et al. Prepared mesoporous silica as a core-shell with Fluorescein isothiocyanate (FITC) dye as a multifunctional and unique core-shell nanocomposite for PDT and fluorescence imaging with high efficiency. Mesoporous silica covalently bonded with hematoporphyrin (HP) and silica core separates the FITC dyes from the surroundings. PS employed with cellular experiments of HO-8910 cells has shown that these nanocomposites are efficient in fluorescence imaging and PDT treatments; the mesoporous shell simultaneously enables O_2 to penetrate

readily; it may interact with the molecules of the photosensitizer to generate ROS. The mesoporous silica shell provides a high pore volume for efficient photosensitizationsimultaneously, the mesoporous silica nanovehicle serves as both a nanoreactor and a carrier for the photosensitizers, facilitating the photo-oxidation process efficiently. These multifunctional nanovehicles have special features that make it possible to target and treat patients with high resolution in cell imaging experiments and PDT treatments[110, 121].Nagahara at el. Designed Indocyanine Green(ICG) loaded coumarin nanospheres coated with chitosan irradiated with laser at 800-805nm, this ICG nanospheres shows the antibacterial activity in PDT. In this study ICG loaded nanospheres specifically targeted the porphyromonasgingivalis (*P. gingivalis*) bacterial activity with laser irradiation at 805 it shows efficectively on periodontal pathogens[111]Chlorin e6(Ce6) was more effective anionic characteristics than other photosensitizers like protoporphyrin IX (PpIX) and 5-aminolevulinic acid (ALA); because of this H. M. Lee at el. Was selected the Ce6 for his study; even though Ce6 is more water-soluble than PpIX, it is still hydrophobic and challenging to disintegrate in water. The fabrication of nanoparticles with Ce6 via the generation of ion complexes and hydrophobic interaction. Ce6 was integrated into the ChitoUrsodeoxycholic acid (UDCA) nanoparticles through the creation of ion-complexes. HuCC-T1 human cholangiocarcinoma cells were used to examine the PDT capability of Ce6-incorporated ChitoUDCA nanoparticles. The final results indicated the efficient absorption into cancer cells, ROS generation, and phototoxicity of ChitoUDCA NPs with Ce6 is greater than Ce6 PS molecules without the fabrication of UDCA NPs. This study shows the greater phototoxicity and targeted delivery ability against HuCC-T1 human cholangiocarcinoma cells[112].Zhu at el. Prepared the silica coated upconversion fluorescent nanoparticles with chlorine e6 (Ce6) to produce a supramolecular complex UCNPs-Ce6 employed in NIR light against THP-1 macropages in PDT treatment. Then evaluated that UCNPs-Ce6 mediated PDT promotes cancer cell death through the mitochondrial caspase pathway via bursts of ROS[122].Zeng et al. first synthesizedthe stabilized Gold nanoparticles (Au NPs) with coating of quaternized chitosan-sulfydryl (QCS-SH). Then, employing electrostatic interaction and ligand exchange to attach the PS agent meso-tetrakis(4-sulphonatophenyl)porphyrin (TPPS) onto the surface of Au NPs to create TPPS/ QCS-SH/Au NPs. Layer-by-layer deposition of anionic derivative of Porphyrin PS and positively charged Au NPs for dual mode study of PDT and Photo Thermal Therapy (PTT) treatment against the tumor cells. This study shows the TPPS/QCS-SH/Au NP's high stability, biocompatibility, effective $^1O_2$ production and excellent photothermal conversion. Under the laser irradiation at 635nm, the antitumor activity of TPPS/QCS-SH/Au NPs evaluated in detail in vitro, with results indicating that the combination of PTT/PDT therapy had much greater antitumor efficiency with lower cytotoxicity than employing single laser irradiation individually[114]. Liang et al. made a high loading porphyrin content as 38.5% self-supplemented PDT nanocarrier prepared by the ultrasonic dispersion of perfluorooctylbromide (PFOB) liquid into the prepared porphyrin grafted lipid (PGL) NPs followed by entrapping oxygen. Porphyrins and alkyl chains in PGL NPs are arranged to decrease fluorescence loss, making the particles extremely luminous and ensuring their high efficiency for generating singlet oxygen. As a result of the strong hydrophobic contact between PGL and PFOB molecules, the PFOB liquid was stabilised within the NPs at an ultrahigh loading concentration of 98.15%, which allowed for more effective oxygen delivery. The obtained O2@PFOB@PGL NPs were able to function as a major oxygen reservoir and efficiently regenerate oxygen into the hypoxictumors without external stimulation, leading to increased singlet oxygen generation, hypoxia relief, and subsequent down-

regulation of cyclooxygenase-2 (COX-2) expression, as shown by both in in vitro and in vivo experiments. Therefore, O2@PFOB@PGL NPs used for hypoxia-relief effectively suppress tumor development and liver metastasis in a mouse model of HT-29 colon cancer. O2@PFOB@PGL NPs have the potential to act as a bimodal contrast agent, improving both fluorescence and CT imaging with low dark cytotoxicity, biocompatibility, and excellent antitumor activity [115].Borzeckaet al. improve the efficiency of PDT treatment by encapsulatethe S-glucosylated and S-galactosylated porphyrins with amorphous silica nanoparticles (SNPs). The spherical shaped galacto and gluconanoformulations have been generated. The galacto- and gluco-nanoparticles (NPs) have been stable under the experiment environments and able to create a significant quantity of singlet oxygen ($^1O_2$). In vitro experiments, these two nanoformulationsdeal effectively with HT-1376 and UM-UC-3 human bladder cancer cell lines. The above experiment results exhibit that these photoactive nanoformulations are three to five times more effective than non-encapsulated/free porphyrins, as shown by photodynamic therapy (PDT) findings. These porphyrin-silica nanoformulations may prove to be effective nanocarriers for the transport of PS in PDT for cancer [116].Nyokong at el. Decided to synthesis the Sn (IV) porphyrin complex-2 while combine with nitrogen-doped graphene quantum dots that have been coated with biotin (2-B-NGQDs) and analysethe PDT activity and pytophysicochemical properties. The Sn (IV) porphyrin complex-2 was conjugated to B-NGQDs via an ester bond. Conducts the dark toxicity and PDT experiments with NGQDs and B-NGQDs using MCF-7 breast cancer lines. All of the compounds exhibited cell viability over 90% for dark toxicity, but 2-B-NGQDs exhibited particularly significant PDT activity at a dose of 40 g/mL, with cell viability of just 22%. This study results compared to pure complex-2, we find that the biotin-decorated, nitrogen-doped graphene quantum dots with porphyrin complex-2 actually boosts its PDT activity efficiently [117]. Borzeckaet al. choose to prepared the differenshaped Mesoporous silica nanoparticles(MSNPs) with the attachment of PSs as S-glycoside porphyrins(Pors). As a model PS 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin (TPPF20, PS0) was chosen. Again choose the5,10,15,20-tetrakis(4-10-thio-glucosyl-2,3,5,6-tetrafluorophenyl)porphyrin(SGlc-Por, PS1) and 5,10,15,20-tetrakis(4-10-thio-galactosyl 2,3,5,6-tetrafluorophenyl)porphyrin (SGal-Por,PS2) phtosensitizers for cancer cells targeting. Borzecka at el. Highly focused on glucose and galactose moieties porphyrin PSs for the crucial targeting of tumor cells. MSNPs attachedwith PSs via S-glycosidic linkage to form MSNP-PS1 and MSNP-PS2 show the antitumor activity against the bladder cell lines HT-1376 and UM-UC-3. The best results obtained for MSNP-PS2, MSNP-PS1 showed the lowest uptake and revealed the best phototoxicity in both cancer cells. MSNPs show the production of high-efficiency singlet oxygen, higher phototoxicity in both cancer cell lines compared to Mesoporous silica nanorods (MSNRs)[118].Li et al.designed the water soluble anionic porphyrin P1 with carboxylic groups as photosensitizers and tetrahedral cation T-NH2 with hydrophobic tetraphenylmethane core decorated by four pyridinium units combines through the electrostatic interaction between these two components. This nanoparticles shows high stability due to their multivalent electrostatic attraction. NPs displays enhanced production of reactive oxygen species singlet oxygen (1O2) in both aqueoous solutions and 10% Fetal bovine serum (FBS) solutions. NPs are exhibits the enhancement of phototoxicity against tumor cells in vitro and increased in vivo antitumor activity compared to free porphyrins[119]. Matsui at el. was synthesized porphyrin attached Au compound (Au-HpD), exhibits the cancer-specific accumulation and cytotoxicity. The intracellular Au-HpD accumulation is higher in cancer cells than in normal cells. The laser irradiation at 870nm in the presence of Au-HpD cancer cells

shows some significant morphological changes such as nuclear fragmentation indicative of cell apoptosis and chromatin condensation. After the laser irradiation on cancer cells, thetumor cells get a strong effect of Au-HpD nanoparticles is not affected the normal cells. It inhibits the cancer cells activity efficiently and shows high antitumor activity against the cancer cells. Use of (NIR) light is expected to induce cancer-specific cell death in deep regions of the organism. Au-HpD is used in the treatment of different tumors in combination therapy in the presence of NIR light[120].

IV. CONCLUSIONS

This review summarized developments in porphyrin-based nanomedicines for cancer treatment and their diagnostic applications. PDT publications have been increasing exponentially in recent years due to the advancement of material science, which has led to PSs capable of detecting and affecting only diseased cells. Several clinical trials were conducted in recent years, indicating the benefits of PDT remain attractive and promising. Compared to surgery, PDT may have better outcomes for smaller lesions than for larger or deeper lesions. The search for novel treatment modalities that obliterate cancer specific tumors without affecting normal tissues is still in high demand despite ongoing, in-depth research. With the introduction of nanotechnology and engineered nanomedicines, we have an unprecedented opportunity to diagnose and treat cancer by improving drug delivery. Concerning cancer treatment regimes, porphyrin PSs are the next generation of PSs that can be conjugated to various NP moieties, allowing them to provide multiple phototherapy and diagnostic functions. While porphyrin-based nanomedicines have many merits, their most significant drawback remains the limited light penetration into deep tumors, which remains the most significant challenge for PDT. Moreover, porphyrin-based nanomedicines do not exhibit specific cellular localization, posing a challenge in treating cancer metastases. Last but not least, more clinical research based in vivo studies on porphyrin-based nanomedicines are needed to understand their potential pharmacological benefits.

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