REVIEW ARTICLE

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A mini-review on metal-based breakthroughs in photodynamic therapy

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Abstract

This work aims to present Photodynamic Therapy (PDT) as an emerging approach for combating cancer, highlighting its effective therapeutic potential and distinctive attributes. Photodynamic therapy (PDT) stands as a groundbreaking approach in cancer treatment, rooted in Tappeiner's revelation of oxygen-dependent photosensitizers' impact on tumor cells under light. PDT operates by leveraging specific drugs (photosensitizers) and light wavelengths to produce Reactive Oxygen Species (ROS), culminating in targeted tumor cell elimination. This review outlines the mechanisms underlying PDT, elucidating its roles in cellular demise, vascular disruption, and triggering immunological responses against cancer cells. Notably, ongoing research concentrates on augmenting photosensitizer efficacy, with a strong focus on advancing metal complexes and nanomaterials. Transition metal coordination complexes and emerging nanomaterials like Metal-Organic Frameworks (MOFs) present promising avenues, demonstrating precise targeting, heightened ROS generation, and enhanced safety profiles within PDT. The strategic utilization of these innovations offers substantial benefits, including increased solubility, selective tumor accumulation, and optimized light absorption, heralding a transformative era in cancer care. PDT emerges as a minimally invasive, targeted therapeutic approach, with continual advancements poised to revolutionize its efficacy and safety, promising a brighter horizon for cancer treatment. This abstract encapsulates the central themes of the content, outlining the significance of PDT, its mechanisms, ongoing advancements, and the potential impact of innovative approaches involving metal complexes and nanomaterials in reshaping cancer therapy.

Key words photodynamic therapy, photosensitizers, metal-organic framework, reactive oxygen species

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Introduction

Tappeiner's accidental discovery revealed the oxygen-dependent nature of photosensitizers (PS) when exposed to light on tumor cells, leading to the pioneering concept of the photodynamic effect [1]. This discovery has since become a cornerstone of cancer treatment. As represented in the **Figure 1**, the Photodynamic therapy involves a specialized drug, the photosensitizing agent, and specific light wavelengths. Upon irradiation, photosensitizers generate Reactive Oxygen Species (ROS), effectively eliminating nearby tumor cells [2]. Photodynamic therapy offers a remarkable advantage in that can be safely repeated multiple times without causing detrimental effects like immunosuppression or myelosuppression. Moreover, it remains applicable post-surgery, chemotherapy, or radiotherapy, the treatment's selectivity ensures patient tolerance, and its painless and outpatient-friendly protocols contribute to its ease of administration. Looking ahead, the ongoing integration of Photodynamic therapy with various imaging techniques, including luminescent imaging, positron emission tomography, magnetic resonance imaging, computed tomography, photoacoustic imaging, and ultrasonography, holds immense promise for future clinical trials [3].

Although it has achieved noteworthy success, the currently employed clinical photosensitizers exhibit certain shortcomings. In response, a growing body of research has been dedicated to enhancing their performance through the introduction of metal ions. Addressing the imperative for improved PDT efficacy, considerable focus is being directed towards innovative designs of PS frameworks. This study aims to consolidate the understanding of PDT while outlining forthcoming progress aimed at augmenting therapeutic efficiency within clinical trials [4].

Principle of photodynamic therapy

Photodynamic therapy (PDT) involves the combination of non-toxic dyes known as photosensitizers (PS) and visible light of the correct wavelength to be absorbed by the PS which in the presence of oxygen leads to the generation of reactive oxygen species (ROS) that can damage cellular constituents leading to cell death. There are three main mechanisms by which PDT mediates tumor destruction [5- 6].

Cellular demise: Apoptosis and necrosis

As given in the following **Figure 1**, with the light irradiation of the Photosentizers, the generation of ROS is initiated. These oxygen-derived radicals infiltrate the body's tumor cells, inducing their demise through a combination of apoptosis and necrosis pathways [7].

Impairing vascular dynamics

The oxygen radicals produced exert their impact on tumor vasculature, disrupting its integrity and leading to a deficiency in oxygen and nutrient supply to the affected cells. Consequently, a hypoxic environment ensues within the tumor, ultimately culminating in cellular death.

Provoking immunological response

Photodynamic therapy has the potential to elicit an inflammatory reaction that activates an immune response targeting the malignant cells. This triggered immune cascade serves as a potent mechanism for eliminating cancerous cells, further enhancing the therapeutic efficacy of the treatment.

Advancements in the photodynamic therapy

The technique of PDT requires three main essential components for its effective therapeutic action, the photosensitizer light wavelength ranges from 600 to 850 nm. This range is called the "phototherapeutic window", and is predominantly used in PDT, and oxygen. The photosensitizers have a greater influence on the other two elements of PDT in providing a therapeutic effect as they get into the body cells and produce ROS [8].

Photosensitizers

Photosensitizers are safe molecules upon administration, accumulate within tumor cells, and upon exposure to specific wavelengths of light, trigger the generation of oxygen radicals. Phototfrin marked a historic milestone, becoming the first globally approved PS for esophageal and lung cancer treatment, and its application extended to diverse malignant and non-malignant conditions [9]. However, the treatment effectiveness faces challenges due to insufficient light penetration and skin photosensitivity caused by Photofrin. Sequentially, 5-aminolevulinic acid (Levulen), Temoporfin (Foscon), Verteporfin (Visudyne), Telaporfin (Foscon), and LUZ111 (Redaporfin) emerged as successive PSs for clinical PDT use [10]. Yet, these PSs share common limitations, including intricate synthesis/purification processes, limited water solubility, photostability concerns, inadequate cancer selectivity, and slow body clearance, leading to reduced ROS generation efficiency during PDT. This underscores a pressing need for enhancing existing compounds and designing novel Photosensitizers with more efficient architectural configurations [11].

Currently, Photodynamic therapy and photosensitizers exhibit diverse molecular structures, categorized into three generational tiers. The initial generation encompasses water-soluble PSs such as porfimer sodium and Heamatoporphyrin derivative (HpD) [12]. Evolving in the second generation, the PS derivatives derived from chlorins, bacteriochlorins, and phthalocyanines exhibit enhanced efficacy in cancerous regions due to their potent absorbance properties, enabling greater light penetration. The third generation includes PS molecules with heightened tumor selectivity, achieved by either amalgamation with targeting entities or encapsulation with carriers. Notably metal-complexes-based PSs, notably those containing metals like Sn, Lu, and Pd, represent a staple in the clinical development of PDT, showcasing improved efficacy and selectivity [13].

(A) Metal complexes in photosensitizers: Recently significant attention has been directed towards the potential utilization of transition metal coordination complexes and organic fluorophores as effective Photosensitizers in PDT. Transition metal complexes, exemplified by ruthenium (II) and iridium (III) complexes, alongside polymetallic counterparts, have emerged as notable contenders in the realms of therapeutics and bioimaging [14]. Renowned for their structural adaptability, exceptional photostability, sizeable Stokes shifts, prolonged emissions duration, and elevated singlet oxygen yields, these complexes also boast attributes such as extensive two-/multi- photon absorption, noteworthy cellular uptake, and precise organelle targeting capabilities. The convergence of these favorable properties has garnered considerable interest among researchers, signaling a promising avenue for exploration [15, 16]. The integration of transition metal complexes into Photosensitizers extends the duration of excited state interactions with molecular oxygen. This effect seems from the substantial atomic mass and larger atomic dimensions of these complexes. Notably, their straightforward synthesis results in Photosensitizers characterized by exceptional selectivity and specificity. Furthermore, the presence of metal ions

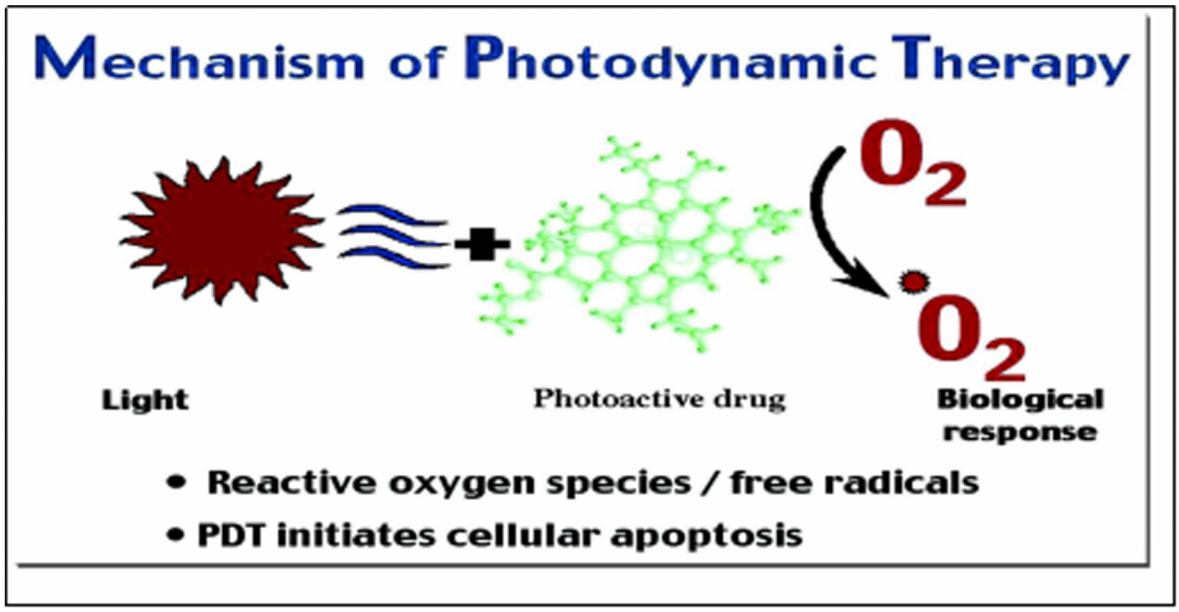

Figure 1. Mechanism of photodynamic therapy.

contributes to improved PDT efficacy, as evidenced by heightened light absorption at relatively longer wavelengths and a substantial molar extinction coefficient [17].

(B) Nanomaterials in the photosensitizers: Introducing a new frontier in nanomaterials, Metal-Organic Frameworks (MOFs) have emerged, boasting an array of merits encompassing high porosity, expensive specific surface area, modifiable pore dimensions, and facile functionalization. These attributes render MOFs adept carriers for encapsulating Photosensitizer or enhancing Photosensitizer accumulation within targeted cells during PDT. In parallel, the ascent of organic fluorophore-based Photosensitizer brings forth attributes of low toxicity, commendable biocompatibility, and enduring triplet lifetimes. Significantly, the fluorescence emitted by these PSs during PDT enables real-time treatment monitoring. In recent times, propelled by nanotechnology's progression, a tapestry of supramolecular nanoparticles, liposomes, metal-organic frameworks, and 2D nanosheets [18] has been woven, intricately enhancing the safety and efficacy of the Photosensitizer. This burgeoning array of nanomaterials revolutionizes aspects such as biocompatibility, precision targeting, controlled release, and pharmacokinetics. Yet, amidst this advancement, the biosafety evaluation of metal-complex-functionalized nanomaterials remains an essential endeavor [19]. A comprehensive scrutiny of the long-term consequences – ranging from biocompatibility and pharmacokinetic profiles to systemic toxicities, biological metabolic pathways, and immunogenicity – must be meticulously undertaken in animal models before embarking on the path of further clinical exploration and application. With a forward gaze, the strategic utilization of metal-complex-functionalized nanomaterials unfurls a vista of prospective applications, poised to redefine the diagnosis and treatment landscape across various diseases, notably within the realm of cancer therapy [20].

Discussion

Photodynamic Therapy (PDT) marks a revolutionary approach in cancer treatment, originating from Tappeiner's inadvertent revelation regarding photosensitizers' reliance on oxygen when exposed to light on tumor cells. This serendipitous finding paved the way for PDT's development—a therapeutic strategy employing photosensitizing agents and specific light wavelengths to induce targeted cell death in cancerous tissues.

PDT functions through multifaceted mechanisms, principally utilizing photosensitizers that, upon exposure to tailored light wavelengths, instigate the production of Reactive Oxygen Species (ROS). These ROS infiltrate tumor cells, triggering cellular demise through a complex interplay of apoptosis and necrosis pathways. Beyond cellular destruction, PDT disrupts tumor vasculature, leading to oxygen and nutrient deprivation within the tumor microenvironment, ultimately causing cellular demise. Furthermore, PDT has the remarkable capability to incite an immune response, bolstering its therapeutic efficacy by marshaling the immune system against malignant cells.

Recent strides focus intensely on refining photosensitizer efficacy and specificity. Notably, metal-complex-based photosensitizers, typified by transition metal coordination complexes, demonstrate extraordinary adaptability and amplified efficacy. These compounds exhibit heightened selectivity and specificity, significantly augmenting the overall effectiveness of PDT. The ongoing evolution spans three generational tiers, striving relentlessly for amplified efficacy and heightened tumor selectivity. Transition metal coordination complexes have emerged as pivotal players in PDT. These complexes, exemplified by ruthenium (II) and iridium (III) complexes, extend excited state interactions with molecular oxygen, enhancing PDT efficacy by elevating light absorption at longer wavelengths and exhibiting substantial molar extinction coefficients. Their integration into photosensitizers amplifies therapeutic effectiveness and specificity.

The integration of cutting-edge nanomaterials, such as Metal-Organic Frameworks (MOFs) and organic fluorophore-based photosensitizers, has reshaped PDT paradigms. MOFs, characterized by high porosity and customizable pore dimensions, facilitate targeted photosensitizer delivery, significantly boosting efficacy. Organic fluorophore-based photosensitizers ensure low toxicity and remarkable biocompatibility, enhancing treatment precision and pharmacokinetics. These nanomaterials pave the way for meticulous targeting, controlled release, and improved treatment efficacy.

As summarised in **Table 1** tabulation, recent strides in

Table 1. Tabulation of the significance of recent advancements in PDT.

Recent advancements	Benefits
Photosensitizer evolution	A. Enhanced light penetration leading to increased efficacy in cancerous regions. B. Improved tumor selectivity through amalgamation or encapsulation methods. C. Augmented selectivity and specificity, especially in metal-complex-based pss.
Metal complexes in ps	A. Notable attributes such as structural adaptability and prolonged emissions duration. B. Significant interest among researchers due to favorable properties. C. Enhanced pdt efficacy, evidenced by increased light absorption and substantial molar extinction coefficient.
Nanomaterial integration	A. High porosity, specific surface area, and modifiable pore dimensions in mofs. B. Enhanced photosensitizer accumulation within targeted cells during pdt. C. Low toxicity, commendable biocompatibility, and enduring triplet lifetimes in organic fluorophore-based pss. D. Improved safety and efficacy of pss through precise targeting, controlled release, and enhanced pharmacokinetics.

PDT present a spectrum of benefits, including enhanced light penetration in cancerous tissues, refined tumor targeting, and augmented therapy potency. Nonetheless, challenges persist, such as the complexity of synthesizing photosensitizers, their limited solubility, and concerns related to photostability and cancer cell selectivity. Thorough safety assessments are imperative before clinical translation to ensure sustained safety and therapeutic efficacy.

Conclusion

In contrast to conventional cancer treatments such as surgery, radiotherapy, or chemotherapy, photodynamic therapy stands out as a synergistic medical approach for cancer treatment due to its minimally invasive nature, precision targeting, and manageable systemic impact [21]. The remarkable photodynamic response achieved at a low light fluence rate enables swift treatment procedures, making PDT integration into self-contained medical devices like compact endoscopic capsules a viable option to enhance therapeutic capabilities [22]. Utilizing metal-based compounds in PDT offers a distinct advantage, with increased solubility, extended circulation, selective tumor accumulation, and mitigation of tumor hypoxia, heightened ROS production, and optimal light absorption in the visible and near-infrared spectra for enhanced tissue penetration. This progress stands as a testament to innovation's power to transcend limitations and catalyze a revolution in cancer treatment, echoing the words of Victor Hugo: "Even the darkest night will end and the sun will rise." Through PDT, we embrace a future where precision and efficacy converge to reshape the trajectory of cancer care, illuminating the path toward brighter horizons [23, 24].

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Availability of data and materials

Data and materials are available on request from the authors.

Ethical policy

Not applicable.

Author contributions

SDK conceptualized, designed, conducted research, and wrote the first draft. KJ provided supervision and revision of the draft.

Competing interests

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