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REVIEW

Strategies for the development of photosensitizers

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ABSTRACT

Conventional photosensitizing agents have inherent limitations regarding their effectiveness, selectivity, and potential adverse effects, which can hinder their clinical application in oncological practices. This study delves into innovative strategies aimed at the development of advanced photosensitizers that promise improved performance for clinical use. We present a comprehensive analysis of a range of molecules with diverse chemical structures, including novel nanomaterials and conjugated systems. These compounds demonstrate remarkable photostability and possess a high capacity for selectively targeting tumor tissues, which is crucial for enhancing therapeutic outcomes. In addition to discussing the improved properties of these next-generation photosensitizers, we provide an in-depth examination of their mechanisms of action, highlighting how they induce cytotoxic effects in cancer cells while minimizing harm to adjacent healthy tissues. The potential toxicity of these compounds has been scrutinized, considering both acute and long-term effects, with a focus on strategies to mitigate adverse side effects. Our research advocates for the importance of continued investigation into the development and optimization of photosensitizers, emphasizing their multi-disciplinary applications. By integrating insights from chemistry, pharmacology, and oncology, we aim to increase the overall effectiveness of photodynamic therapy. Furthermore, we explore the potential of these agents to extend their applicability beyond traditional treatment settings, suggesting their integration with other therapeutic modalities, such as chemotherapy and radiotherapy, which could lead to synergistic effects and significantly improve patient outcomes in cancer treatment.

Keywords: porphyrins, synthesis, reactive oxygen species, photodynamic therapy

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Introduction

Conventional photodynamic therapy (PDT) has been widely accepted and supported by numerous medical organizations all over the world [1]. This treatment is based on the unique ability of certain substances, known as photosensitizers (PS), to specifically accumulate in target tissues. When these tissues are exposed to light at a wavelength appropriate to PS, the cells start to generate reactive oxygen species (ROS) and other powerful radicals and leads to the process of necrosis or apoptosis [2]. This process also triggers an immune response, causing localized inflammation and changes in blood vessels permeability in the affected area [1].

The evolution and implementation of PDT as a treatment for various pathologies presents a significant challenge, primarily due to the complexity involved in developing effective pharmaceutical agents [1,4]. Despite the limitations of the first generation of photosensitizing drugs, novel compounds have been developed, although many of them have failed in clinical trials [5,6]. However, there has been an increasing emphasis on the development of soluble forms of PS These not only reduce the time needed for administration but also simplify the treatment planning process. There is a particular focus on developing novel targeted delivery systems for PS, such as nanoparticles and monoclonal antibodies (mAb). Some of these PS are being investigated for use in intraoperative photodynamic imaging, where they could be used to visualize tumors during surgical procedures. The development of newer generations of photosensitive drugs with specific physicochemical properties presents the possibility of their use in therapeutic applications that combine imaging and treatment methods in the field of oncology [5,6].

The objective of this review article is to systematically explore the development of advanced photosensitizers that overcome the limitations of conventional agents in terms of effectiveness, selectivity, and potential adverse effects, which can restrict their clinical application in oncology.

Porphyrin-based compounds for photodynamic therapy

Porphyrin-based compounds hold significant promise for PDT. These compounds, with their tetrapyrrole structure, are actively being investigated and integrated into clinical practice [1]. Over the past several decades, porphyrins have been extensively studied for their application as agents in PDT. A significant breakthrough occurred in 1942 when it was observed that hematoporphyrin (Hp) accumulates selectively in tumor tissues [7]. Further research has validated the specific effects that porphyrins have on cancer cells [8,9]. The mechanism behind this selective accumulation can be partly attributed to low-density lipoprotein (LDL) receptors, which are highly expressed in rapidly proliferating tumor cells. The lipophilic nature of porphyrins allows them to bind to the LDL receptor's core, which is structured for apolipoprotein B, facilitating their entry into the cell [10]. Research indicates that tumor cells generally exhibit a lower pH level, typically ranging from 5.85 to 7.68, in contrast to normal tissues that usually have a pH between 7.0 and 8.0 [10]. The porphyrin molecule maintains a delicate equilibrium between protonation and deprotonation, which enables porphyrins to passively diffuse through cell membranes. This diffusion process becomes increasingly effective as the pH decreases. Consequently, a drop in pH contributes to a higher accumulation of porphyrins specifically within tumor tissues. In a tumor with a pH of 6.5, approximately 44% of the porphyrins are in a neutral state, compared to only about 3% in healthy tissue with a pH of 7.4. Neutral molecules are better able to pass through cell membranes than

charged ones, emphasizing the importance of pH in maintaining the presence of porphyrin-protein conjugates within cells and affecting their concentrations in tumors (Fig. 1).

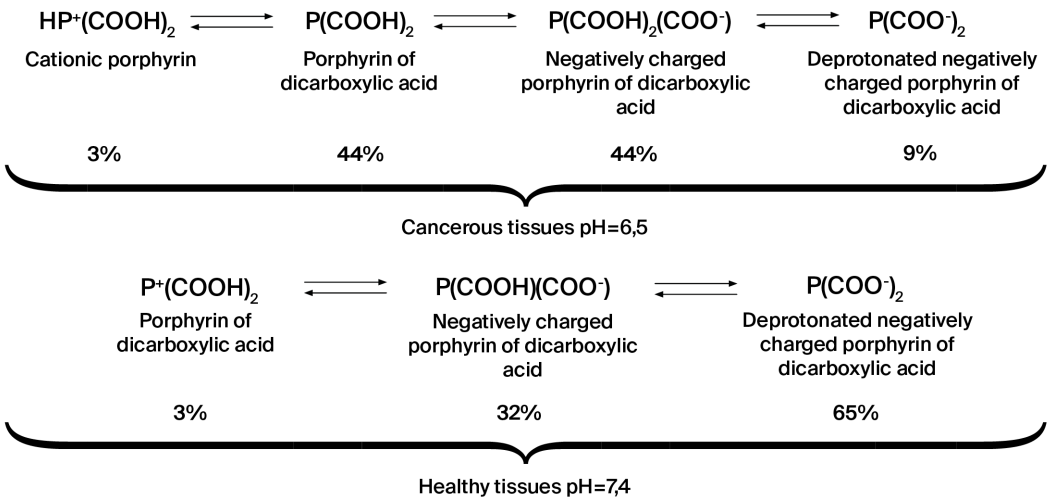

FIG. 1. Acid-base balance in the porphyrin structure in healthy and malignant tissues

Typical Classification of Porphyrin-Based Photosensitizers

The demand for novel pharmaceutical products arises from the need to improve the effectiveness of existing medications. Currently, PS, which are derived from the porphyrin family, are divided into three generations (Fig 2).

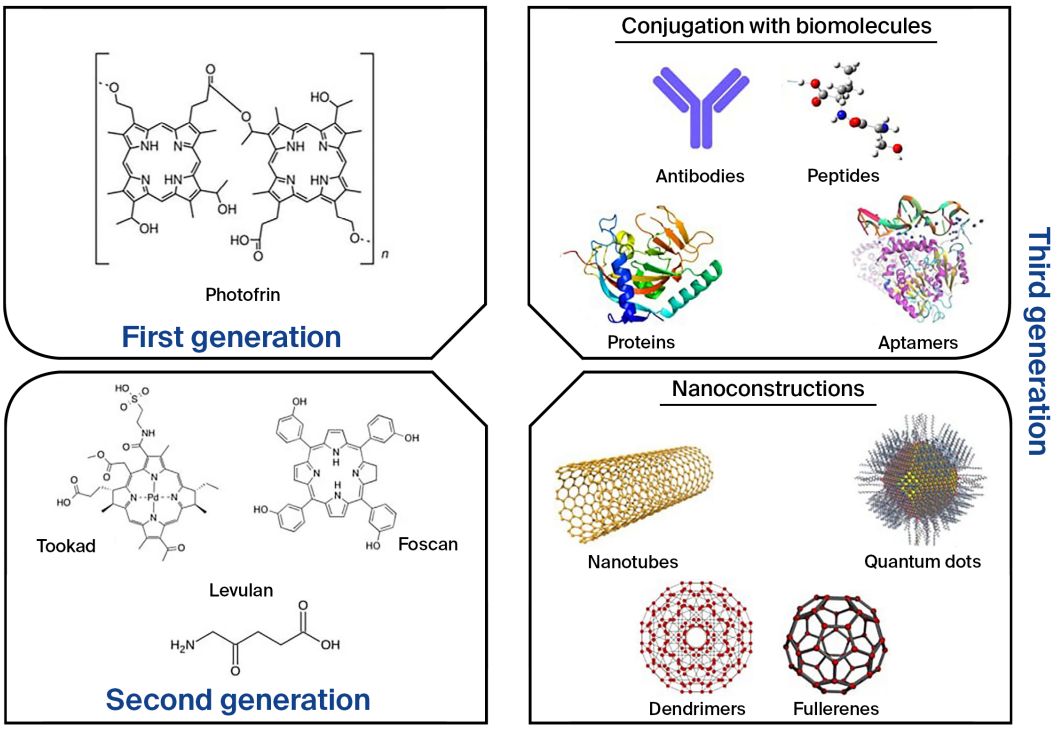

FIG. 2. Generations of tetrapyrrole photosensitizers

The first generation of PS is characterized by Hp [11]. This compound has a sophisticated chemical composition, featuring two highly reactive rings. This complexity makes it difficult to achieve purity, as Hp can exist as a mixture of various forms, including monomeric porphyrins, dimers, and high-molecular-weight oligomers. Attempts to purify Hp using a 5% solution of sulfuric and acetic acids at room temperature for 15 minutes resulted in the formation hematoporphyrin derivative (HpD) I. Prior to administration, HpD I underwent an alkaline treatment, and its pH was adjusted to 7.4 using hydrochloric acid to produce HpD II [12].

Hp play a crucial role in the landscape of PDT, particularly through their predominant use in the formulation known as Photofrin, as recognized in Canada by Axcan Pharma. Notably, these products are characterized by a significant red absorption peak at a wavelength of 630 nanometers but possess low extinction coefficients. A low extinction coefficient indicates that the photosensitizer does not absorb light very efficiently, meaning it requires higher concentrations or longer exposure times to achieve the desired activation for therapeutic or experimental purposes [13]. The effectiveness of Photofrin in cancer treatment is due to its exceptional affinity for LDL, which enhances its selectivity for cancer cells. Research has shown that this substance accumulates primarily in the membranes of mitochondria, the endoplasmic reticulum, and the Golgi apparatus in cancerous tissues [14]. When exposed to laser light at the specific wavelength of 630 nm, Photofrin triggers the production of ROS, a highly reactive form that induces apoptosis by releasing cytochrome C from mitochondria, ultimately leading to the programmed death of cancer cells. In Russia, a similar substance to Photofrin, known as Photogem, was created at Moscow State University in 1990. This substance is a blend of single-molecule and multi-molecule derivatives of Hp, and it has been approved for medical use, demonstrating similar effects to Photofrin in terms of its potential for targeting tumors [15].

Advancements in the field have led to the development of second-generation photosensitizing agents. It is shows higher photostability, so they are more resistant to decomposition under the influence of light, which leads to a longer-term preservation of therapeutic activity. The improved photostability also allows the use of lower doses of these compounds, which reduces the risk of possible toxicity and makes treatment safer for patients. Modern second-generation photosensitizers often have a wider light absorption range, which allows using different wavelengths of illumination to activate their activity [13]. This expands the application possibilities by allowing the use of light sources more suitable for clinical conditions and providing deeper penetration of light into tissues. This enhancement significantly increases the therapeutic impact on tumors, primarily facilitated through the conjugation of these agents with various targeting molecules such as antibodies, proteins, and carbohydrates. As a result, second-generation agents exhibit a higher capacity for ROS generation, thus optimizing their therapeutic effectiveness in the intricate microenvironment of tumors [16].

The innovation continues with third-generation PS, which are engineered to be encapsulated in various carrier media, enhancing their selectivity for tumor cells. Modern carrying agents include liposomes, micelles, gold nanoparticles, and other formulations that enable targeted delivery [17]. Among these, chlorin e6 (Ce6) has surfaced as a leading candidate for research and development in the realm of new pharmaceuticals [18,19]. By combining Ce6 with biocompatible amphiphilic polymers such as polyethylene glycol (PEG) and polylactic acid (PLA), stable nanoparticles (e.g., chlorin e6-conjugated methoxy-poly(ethylene

glycol)-poly(d,l-lactide) (mPEG-PLA-Ce6) are created [20]. Extensive studies reveal that these nanoparticles yield a significantly enhanced level of ROS production in both two-dimensional cellular monolayer, three-dimensional multicellular tumor spheroids and in vivo animal experiment of solid hypoxic tumor cells compared to free Ce6, showing improved cellular uptake and cytotoxic effects [21]. Recent advancements in immunogenic phototherapy highlight the use of advanced structures like core-shell nanoparticles to effectively target colorectal cancer cells while increasing oxygen levels in the tumor tissue [21]. These engineered particles, comprising gold nanoparticles coated with manganese dioxide (MnO_2) and hyaluronic acid, produce ROS when stimulated with infrared radiation, culminating in tumor cell death and fostering dendritic cell development, which is critical for a robust immune response against cancer. This method increases oxygen levels in the tumor tissue via a MnO_2 that catalyzes hydrogen peroxide (H_2O_2) breakdown and generates ROS, enhancing the photodynamic effect under laser irradiation at a wavelength of 635 nm [22].

The expanding field of theranostic medicine is currently experiencing the emergence of multifunctional nanobiomaterials. An example includes conjugated nanoparticles like polyethylene glycol-copper bismuth sulfide-Ce6-folate (PEG-Cu_3BiS_3-(Ce6)-folate), where the nanoparticles are designed to target folate receptors highly expressed in certain tumor cells [23]. Preclinical studies have underscored the promising synergistic effects of these nanoprobes in both photothermal therapy and PDT, showing significant therapeutic efficacy in glioma xenograft models. Another noteworthy PS, meta-tetra-(hydroxyphenyl)chlorin (mTHPC), known for its tendency to aggregate in biological fluids, has been tackled by creating polymer micelles to preserve its potent properties [24]. Through encapsulation in micellar structures conjugated with targeting molecules, mTHPC can achieve efficient cellular uptake in cancer cells expressing the epidermal growth factor receptor, significantly enhancing phototoxicity.

In summary, the evolution of PS from the initial generation through advanced formulations highlights a remarkable trajectory toward enhanced specificity, efficacy, and multifunctionality in cancer treatment, thereby holding substantial promise for future therapeutic applications.

Strategies for the development of next-generation photosensitizers

Porphyrins can be integrated with biological molecules through bioorthogonal chemical methods, such as phosphoramidite chemistry, solid-phase synthesis, and post-synthetic modifications like amidations and hydrazide-carbonyl reactions [25]. When it comes to the conjugation of porphyrins with oligonucleotides, there are two main approaches: the modification of porphyrin molecules using phosphoramidites and the post-synthetic conjugation [25,26]. The incorporation of porphyrins into oligomers enhances their solubility and allows them to interact with nucleic acids. This process also creates a chiral center due to the helical structure of deoxyribonucleic acid (DNA). DNA-porphyrin constructs have a wide range of applications, including the detection of specific nucleotide sequences, the staining of nuclei, and their use as antimicrobial chemotherapeutics [27].

Solid-phase synthesis is a method that can be used to modify porphyrins by integrating them into a sugar ring through the use of phosphoramidite chemistry [25]. This process involves replacing the nucleoside at the first

position of the sugar ring with a porphyrin, or linking porphyrins to nucleosides through amino functionalization of the third carbon of the sugar. This results in the formation of duplex structures containing zero to three porphyrin units using solid-phase techniques.

The post-synthetic modification of porphyrin is a novel approach in synthetic chemistry that allows for the direct conjugation of these molecules with nucleic acid bases or other specific positions within the molecule [25]. This is achieved through the use of functional linkers after the initial synthetic process, which opens up opportunities for modifying oligonucleotides after synthesis [26].

Particularly promising in this regard is the area of peptide conjugation. Peptides offer a wider range of functional reactive groups than oligonucleotides, making them an attractive target for post-synthetic modifications. There are four main methods for conducting these reactions: Staudinger ligation, copper-assisted alkyne-azide cycloaddition (CuAAC), strain-promoted alkyne–azide cycloaddition, and olefin metathesis [28]. The Staudinger ligation reaction is a rapid and highly specific process that relies on the complex interaction between azides and phosphine compounds. In 2010, N. Umezawa et al. used this technique was to synthesize 5,10,15,20-tetrakis-(3-azidophenyl)-porphyrin by combining 3-azido-benzaldehyde with an equivalent amount of pyrrole [29]. The CuAAC method has demonstrated excellent selectivity and a wide range of applications in various pH and temperature environments for the coupling of peptides with porphyrins. Porphyrin-peptide conjugates generated through the CuAAC process have shown promise for applications in PDT, tumor imaging, and targeted drug delivery. However, the use of CuAAC for the conjugation of porphyrins and peptides is limited by the inherent toxicity of copper-based catalysts towards living cells [30].

Eggleston's team also investigated the strategy of using Staudinger ligation for peptide crosslinking to produce conjugates based on Cell-Penetrating Peptide with Triphenylphosphine (CPP-TPP) [31]. This conjugate demonstrated the highest phototoxicity among other conjugation methods (such as CuAAC and thiol-maleimide), due to the presence of an extended triazole-based linker between the hydrophobic porphyrin and the polycationic peptide. Phototoxicity was assessed in a monolayer culture of human breast cancer cells, and the concentration of porphyrin needed to induce 50% cell death after 5 min of light exposure was approximately 40 nM. To further investigate the effect, a protein toxin called saporin, which inactivates ribosomes with a mass of 30 kDa, was used in conjunction with the CPP-TPP conjugate. These experiments demonstrated that cell viability decreased significantly (about 3-fold) when saporin was added, compared to exposure to the CPP-TPP conjugate alone. It's worth noting that the decrease in viability with saporin alone was negligible (approximately 10%) [31].

The process of native thiol–maleimide chemical ligation entails the selective coupling of thiol side chains from peptides containing cysteine residues with modified maleimides, culminating in the creation of novel PS belonging to the porphyrin family [32,33]. Liu et al. employed this methodology to combine protoporphyrin IX (PpIX), a photosensitizing agent, with a carrier molecule known as lipopolysaccharide and an antimicrobial peptide known as YI13WF, renowned for its capacity to eradicate bacteria [34]. Initially, the PpIX molecule underwent modification by the addition of a bismaleimide moiety. Subsequently, the modified PpIX was subjected to reaction with YI13WF in the presence of diisopropylamine and dimethyl sulfoxide, resulting in the formation of PpIX- YI13WF. The fluorescence and antimicrobial characteristics of the resulting compound were subsequently evaluated. It has been discovered that

when subjected to a concentration of 0.5 mM and illuminated with an energy density of 30 J/cm^3, the conjugate effectively eliminates 99.9% of gram-negative bacteria [34].

With regard to amino group ligation, one common method for labeling peptide amino groups is the combination with carboxylic acid derivatives, which results in the formation of stable amide or thiourea conjugates [35]. For example, porphyrin with pyridine units can react with poly-l-lysine to form a mono-amino-porphyrin thiourea conjugate that exhibits low toxicity in darkness at a concentration of 10 mM (Inhibitory Concentration 50% > 250 μg) [36]. In the presence of porphyrins, α-polypeptides can adopt secondary structures such as α-helices.

The field of antibody conjugation has been a subject of intense research since the late 1980s and early 1990s [37]. This research has led to the development of photoimmunoconjugates, such as the conjugation of Hp with a mAb that targets a protein expressed by myosarcoma M1 cells. The mAb is covalently attached to the carboxyl group on the lysine side chain of Hp. The mAb-M1-Hp conjugate demonstrates remarkable efficacy in the treatment of myosarcoma when administered at a low dose of 0.268 mg/kg, surpassing the efficacy of higher doses ranging from 2,5-5 mg/kg [38].

A benzoporphyrin derivative has been conjugated to a tumor-targeting mAb that binds to the epidermal growth factor receptor through a thiol–maleimide linkage [39]. In experimental studies conducted on Syrian golden hamsters bearing carcinomas, it has been demonstrated that administering this specific conjugate in combination with radiation therapy leads to substantial tumor necrosis. One example of such a conjugate involves linking a Ce6 derivative to a mAb specific for CA125 [40]. This antibody is then converted into polyglycolic acid through a carbodiimide reaction and subsequently modified with hydrazines. The resulting chlorin–polyglycolate–hydrazine subsequently reacts with the aldehyde group on the mAb, forming stable hydrazones.

In 2011, K. Smith et al. combined isothiocyanate-functionalized cationic porphyrins with tumor-specific antibodies and differentiation cluster receptor antibodies, such as CD104, CD146, and CD326 [41]. Low-dose conjugates, with a concentration of 10 nM/kg demonstrated comparable efficacy to high-dose Photofrin, which was administered at a dosage of 8.3 mM/kg. Furthermore, meso-tripyridyl-mono(4-carboxyphenyl) porphyrins have been synthesized in combination with amino forms of serum albumin and mAb against carcinoembryonic antigen (CEA). Ultraviolet–visible spectroscopic analysis has shown that the porphyrin labeling reaches its peak when the ratio of porphyrin to protein is 30:1, measured in terms of molar amounts [42]. For porphyrin-mAb-CEA conjugates and porphyrin–mAb complexes targeting CD104, the maximum values of the drug-to-ligand ratio have been recorded at 0.81 and 0.79, respectively [43].

A novel bifunctional linker was synthesized using a site-specific cysteine conjugation method [44]. The linker consists of bromopyridine and a cyclic acetylene, and it was designed to be used in PDT. Trastuzumab, an approved mAb for breast cancer treatment, had its eight free thiol groups reacting with bromopyridine, resulting in the formation of novel bonds between the antibody and the linker. When exposed to light at a wavelength of 625 nm, the conjugate demonstrated efficacy against HER2+ cell lines. This conjugate represents a significant advancement in the field of PDT, as it opens up new possibilities for the development of more effective treatments [44].

One such example is β-Mannose-Ce6 , which has shown comparable antitumor activity to β-glucocerebroside against human glioblastoma cells of

U251 line [45]. Additionally, it surpasses the photosensitizing capacity of first-generation agents like Talaporfin sodium (a photosensitizing agent consisting of Ce6 and L-aspartic acid). β-Mannose-Ce6 exhibits a more rapid rate of absorption compared to Talaporfin sodium, and its primary localization is within organelles such as the Golgi apparatus and mitochondria [45].

Metalloporphyrins have been identified as potential candidates for the development of future generation PS. A series of metalloporphyrin-indomethacin conjugates linked by PEG were synthesized and investigated: indomethacin-conjugated porphyrin, palladium porphyrin complex (PdPor), platinum porphyrin complex (PtPor), zinc porphyrin complex (ZnPor) [46]. Generation of ROS was assessed using 2',7'-dichlorofluorescein as a probe. Due to the effect of heavy atoms, metalloporphyrin complexes exhibited a higher quantum yield of singlet oxygen than that of porphyrin with a free base: PtPor > PdPor > ZnPor > Porphyrin. The MTT (3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide) analysis using HeLa cells confirmed the low cytotoxicity of porphyrin–indomethacin conjugates in the dark. When irradiated, PtPor demonstrated the highest therapeutic activity among these conjugates. The results showed that conjugates are mainly localized in the lysosomes of HeLa cells [46].

Conclusion

The recent advances in structural chemistry, in particular the development of new porphyrin derivatives and their combinations with other active substances, hold great potential for improved selectivity and efficacy. By modifying the structure of porphyrins by incorporating functional groups, for example, we can enhance their interaction with target cells and increase their responsiveness to light. Additionally, metallized porphyrins provide a novel application opportunity, as the addition of metal ions alters the electronic properties of the molecule and enhances its photodynamic properties. It is important to note that the successful clinical application of porphyrin PS depends on a comprehensive approach that includes optimizing the chemical structure, understanding the mechanism of action at the cellular level, developing effective delivery methods for targeted delivery to tumor tissues, and studying the interactions between PS and biological systems. These aspects require a multidisciplinary approach and an interdisciplinary research methodology in order to develop safe and effective therapeutic agents for PDT. Despite current challenges, research into porphyrins continues, presenting new opportunities for PDT and other biomedical applications. Advances in technology and development of photosensitizing agents, coupled with a better understanding of cellular biology and tumor genesis, could lead to significant improvements in cancer treatment and other medical conditions.

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