Review

Natural Product-Based Photosensitizers for Photodynamic Therapy: Translational Potential and Pharmaceutical Strategies for Clinical Translation

Renato Sonchini Gonçalves * and Emmanoel Vilaça Costa

Posted Date: 31 March 2026

doi: 10.20944/preprints202603.2420.v1

Keywords: photodynamic therapy; natural products; photosensitizers; drug delivery; nanoformulation; translational research; reactive oxygen species; hypericin; chlorin; curcumin

 doi:10.20944/preprints202603.2420.v1

Review

Natural Product-Based Photosensitizers for Photodynamic Therapy: Translational Potential and Pharmaceutical Strategies for Clinical Translation

Renato Sonchini Gonçalves [1,*] and Emmanoel Vilaça Costa [2]

[1] Department of Engineering and Exact Sciences, Setor Palotina, Federal University of Paraná (UFPR), Palotina 85950-000, PR, Brazil
[2] Postgraduate Program in Chemistry, Federal University of Amazonas (UFAM), Manaus 69080-900, Brazil
* Correspondence: renato.sonchini@ufpr.br; Tel.: +55-98-985-149-235

Abstract

Photodynamic therapy (PDT) is a clinically established, minimally invasive modality that relies on the interaction between a photosensitizer (PS), light, and molecular oxygen to generate cytotoxic reactive oxygen species (ROS). Despite decades of development, the clinical performance of many photosensitizers remains limited—not primarily due to insufficient photodynamic activity, but rather to unfavorable physicochemical and biopharmaceutical properties that impair in vivo efficacy. Natural products represent a structurally diverse and biologically relevant source of photosensitizers with intrinsic photochemical potential. However, their translation into clinically viable PDT agents has remained disproportionately limited. This discrepancy highlights a critical and often underappreciated bottleneck: pharmaceutical incompatibility. In this mini-review, we provide a pharmaceutics-centered perspective on natural product-based photosensitizers, shifting the focus from molecule discovery toward translational feasibility. We critically examine the key barriers that restrict clinical progression—including poor aqueous solubility, aggregation-induced quenching, instability, and suboptimal biodistribution—and assess the formulation strategies that enable their resolution. Particular emphasis is placed on nanotechnology-enabled delivery systems, targeted carriers, and hybrid platforms that enhance solubility, stability, and tissue selectivity. Representative compounds are discussed within a translational context, highlighting the contrast between advanced candidates such as hypericin and chlorophyll-derived chlorins and more limited systems such as curcumin. Collectively, this work demonstrates that the success of natural photosensitizers in PDT is determined less by intrinsic photodynamic efficiency and more by their compatibility with pharmaceutical engineering strategies. This perspective provides a concise framework to guide the rational development of clinically relevant natural photosensitizer systems.

Keywords: photodynamic therapy; natural products; photosensitizers; drug delivery; nanoformulation; translational research; reactive oxygen species; hypericin; chlorin; curcumin

1. Introduction

Photodynamic therapy (PDT) is a clinically established, minimally invasive therapeutic modality that relies on the interplay among a photosensitizer (PS), light of an appropriate wavelength, and molecular oxygen to generate cytotoxic reactive oxygen species (ROS) [1–3]. Upon light activation, the photosensitizer undergoes electronic excitation and transfers energy or electrons to surrounding substrates, leading to the formation of singlet oxygen and other reactive species that induce localized oxidative damage [4,5]. This mechanism enables selective destruction of malignant or infected tissues while minimizing systemic toxicity, making PDT particularly attractive for oncology, dermatology, and antimicrobial applications [3,6]. Figure 1 illustrates the translational pathway of natural product-

 doi:10.20944/preprints202603.2420.v1

based photosensitizers in photodynamic therapy, highlighting key pharmaceutical barriers and the formulation strategies that enable their progression toward clinical application.

Despite these advantages, the clinical performance of currently available photosensitizers remains suboptimal [3,7]. First- and second-generation synthetic PSs are often associated with significant limitations, including poor aqueous solubility, aggregation in physiological environments, prolonged skin photosensitivity, and insufficient selectivity toward target tissues [7,8]. Moreover, many clinically used PSs exhibit suboptimal absorption profiles, limiting light penetration and therapeutic efficacy in deeper tissues [1,9]. These challenges highlight the need for novel photosensitizing agents with improved photophysical and biopharmaceutical properties [8].

In this context, natural products have emerged as a promising and underexplored source of photosensitizers [10,11]. Owing to their structural diversity, evolutionary optimization, and inherent biological activity, natural compounds such as porphyrin derivatives, anthraquinones, and curcuminoids have demonstrated significant potential in PDT applications [1,3]. Many of these molecules possess intrinsic chromophoric systems capable of light absorption and ROS generation, as well as additional pharmacological effects that may enhance therapeutic outcomes [2,11]. However, despite encouraging preclinical results, only a limited number of natural product-based photosensitizers have advanced toward clinical application [8,10].

A critical barrier to the translation of natural photosensitizers is not solely related to their photochemical performance, but rather to their pharmaceutical limitations [8,10]. Poor water solubility, chemical instability, aggregation-induced quenching, rapid metabolism, and inadequate biodistribution significantly hinder their therapeutic efficacy *in vivo* [7,11]. Furthermore, variability in natural sources and challenges in large-scale production complicate standardization and regulatory approval [12]. These issues underscore the importance of adopting a pharmaceutics-oriented perspective when evaluating the clinical potential of natural PDT agents [13].

Recent advances in drug delivery and formulation science have begun to address these limitations [13,14]. Nanoformulation strategies, including liposomes, polymeric nanoparticles, lipid-based carriers, and supramolecular systems, have shown considerable promise in enhancing the solubility, stability, and tumor-targeting capability of natural photosensitizers [8,15]. In addition, rational chemical modification and hybrid systems are being explored to optimize photophysical properties and improve therapeutic performance [10]. These approaches are reshaping the translational landscape of natural product-based PDT [14,15].

In this context, a critical question emerges: which natural product-based photosensitizers are most likely to become clinically viable PDT drugs, and what pharmaceutical strategies are enabling this transition? Addressing this question requires moving beyond descriptive cataloging toward a critical assessment of translational potential, considering both molecular properties and formulation-driven performance [3,10].

This mini-review aims to provide a pharmaceutics-centered perspective on natural product-based photosensitizers for PDT. We discuss the key physicochemical and biopharmaceutical barriers that limit their clinical translation and highlight advanced formulation strategies designed to overcome these challenges [13,14]. Furthermore, we critically evaluate the most promising natural compounds based on their translational readiness and therapeutic potential. By integrating photochemical and pharmaceutical insights, this review outlines a strategic framework to guide the development of clinically relevant natural photosensitizer systems.

The literature discussed in this review was selected based on relevance to photodynamic therapy and translational potential. Peer-reviewed articles were identified through major scientific databases, focusing on studies reporting natural product-based photosensitizers with demonstrated photodynamic activity, particularly those evaluated in *in vivo* models or advanced formulation systems. Emphasis was placed on compounds with well-characterized photophysical properties and evidence of improved performance through pharmaceutical strategies, including nanoformulation and targeted delivery approaches.

 doi:10.20944/preprints202603.2420.v1

Importantly, we argue that the primary limitation in the clinical translation of natural product-based photosensitizers is not insufficient photodynamic activity, but rather their incompatibility with pharmaceutical requirements for effective in vivo performance. This shift in perspective—from molecule-centered discovery to formulation-driven viability—enables a more rational and predictive assessment of translational potential and redefines the priorities for future development in photodynamic therapy.

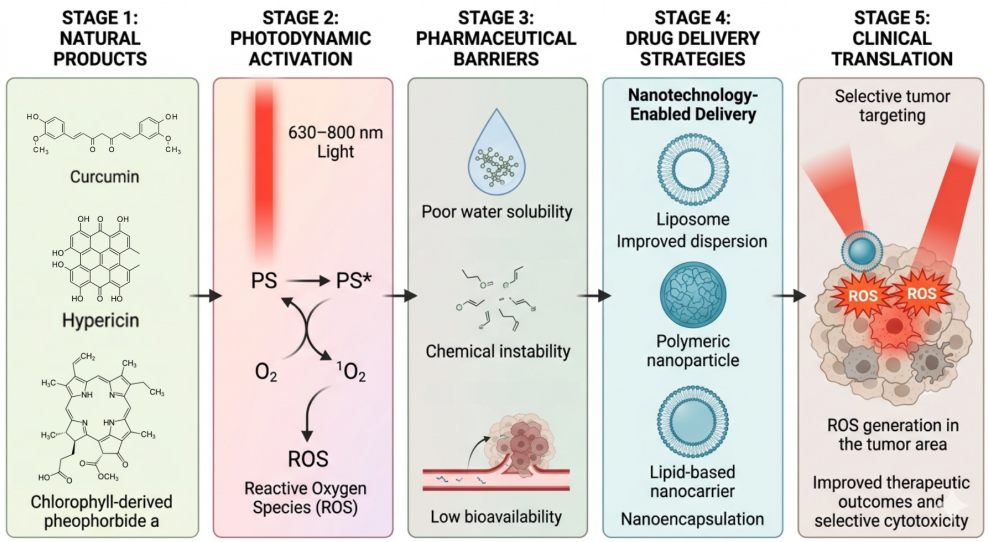

Figure 1. Schematic workflow of natural product-based photosensitizers in photodynamic therapy (PDT). Natural compounds such as curcumin, hypericin, and pheophorbide a act as photosensitizers that, upon light irradiation (630–800 nm), generate reactive oxygen species (ROS), including singlet oxygen ($^1O_2$). However, their clinical performance is limited by poor aqueous solubility, aggregation, chemical instability, and low bioavailability, resulting in insufficient tumor accumulation. Nanotechnology-enabled delivery systems, such as liposomes, polymeric nanoparticles, and lipid-based nanocarriers, improve solubility, stability, and tumor accumulation, thereby enhancing ROS generation at the tumor site and ultimately leading to improved therapeutic outcomes and selective cytotoxicity.

2. What Defines a Clinically Viable Photosensitizer?

Photodynamic therapy (PDT) relies fundamentally on the properties of the photosensitizer (PS), which determines not only the efficiency of reactive oxygen species (ROS) generation but also the overall therapeutic outcome. While numerous natural products have demonstrated photodynamic activity *in vitro*, only a small fraction exhibit characteristics compatible with clinical translation. Therefore, defining the key attributes of a clinically viable photosensitizer is essential to guide the identification and development of promising candidates. Figure 2 illustrates the fundamental photophysical and photochemical processes involved in photodynamic therapy, including Type I and Type II reaction pathways and their dependence on oxygen availability.

 doi:10.20944/preprints202603.2420.v1

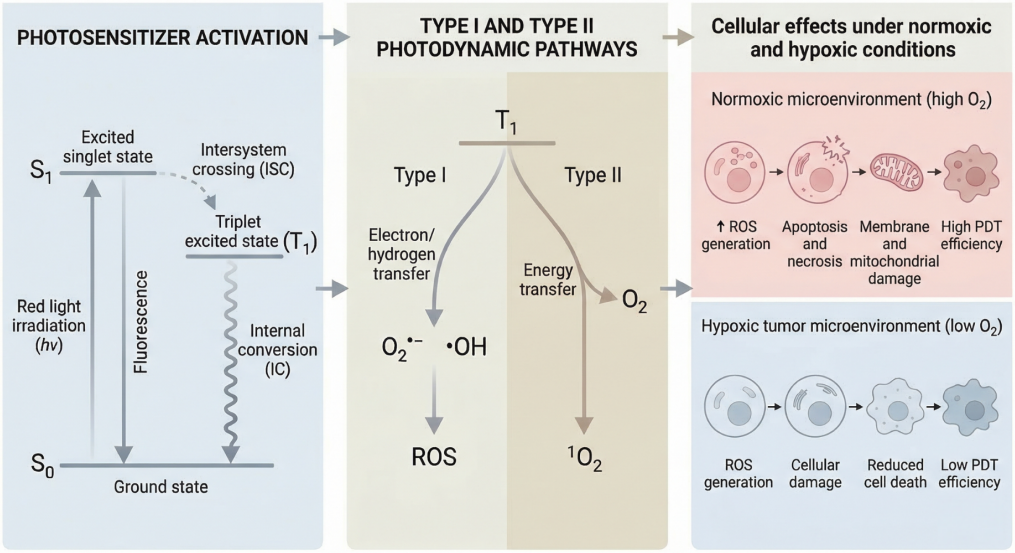

Figure 2. Photodynamic therapy (PDT) mechanism from photosensitizer activation to cellular response under different oxygen conditions. (Left) Upon red light irradiation ($h\nu$), the photosensitizer (PS) transitions from the ground state (S_0) to the excited singlet state (S_1), followed by intersystem crossing (ISC) to the triplet excited state (T_1). The excited states may undergo radiative (fluorescence) or non-radiative decay, including internal conversion (IC). (Center) The triplet state (T_1) drives photodynamic reactions through two main pathways: Type I reactions involve electron or hydrogen transfer to generate reactive oxygen species (ROS), such as superoxide ($O_2^{\bullet -}$) and hydroxyl radicals (•OH), whereas Type II reactions involve energy transfer to molecular oxygen (O_2), producing singlet oxygen ($^1O_2$). (Right) The biological outcome depends on oxygen availability. Under normoxic conditions, efficient ROS generation leads to membrane and mitochondrial damage, resulting in apoptosis or necrosis and high PDT efficacy. In contrast, hypoxic tumor environments limit ROS production, reducing cellular damage and therapeutic effectiveness.

An effective PS must possess appropriate photophysical properties, particularly strong absorption within the so-called therapeutic window (600–800 nm), where tissue penetration of light is maximized. Compounds absorbing at shorter wavelengths, although often photochemically active, are limited by shallow penetration depth and reduced applicability in treating deeper lesions. In addition, a high quantum yield of ROS generation, especially singlet oxygen, is critical to ensure sufficient cytotoxicity upon light activation. Photostability is another essential requirement, as rapid photobleaching can significantly reduce treatment efficacy.

Beyond photochemistry, biopharmaceutical properties play a decisive role in clinical performance. Ideal photosensitizers should exhibit adequate aqueous solubility or be readily incorporated into pharmaceutical formulations without aggregation. Aggregation-induced quenching is a well-known limitation of many hydrophobic compounds, leading to reduced ROS generation and compromised therapeutic activity. Furthermore, favorable pharmacokinetics, including sufficient circulation time and selective accumulation in target tissues, are essential to maximize therapeutic selectivity while minimizing off-target effects.

Safety is another critical consideration. A clinically viable PS should display minimal dark toxicity and low systemic adverse effects, while enabling controlled activation exclusively at the irradiated site. Rapid clearance from healthy tissues is desirable to reduce prolonged photosensitivity, a common drawback of several first-generation photosensitizers. For natural products, additional challenges include batch-to-batch variability, potential impurities, and difficulties in standardization, all of which must be addressed to meet regulatory requirements.

From a pharmaceutical development perspective, scalability and reproducibility are key determinants of translational success. Natural compounds must be obtainable in sufficient quantities, either through extraction, semi-synthesis, or total synthesis, with consistent quality and purity. Moreover,

 doi:10.20944/preprints202603.2420.v1

compatibility with advanced drug delivery systems—such as liposomes, polymeric nanoparticles, and lipid-based carriers—is increasingly recognized as a critical factor, as formulation strategies often dictate *in vivo* performance more than intrinsic molecular properties.

Taken together, these considerations highlight that the translation of natural photosensitizers into clinically viable PDT agents depends on a complex interplay between photophysical efficiency and pharmaceutical feasibility. Importantly, many natural compounds fail not because of insufficient photodynamic activity, but due to unfavorable biopharmaceutical characteristics that limit their *in vivo* applicability.

Based on these criteria, natural product-based photosensitizers can be broadly categorized according to their translational readiness: (i) advanced candidates with demonstrated *in vivo* efficacy and formulation compatibility; (ii) promising preclinical compounds with favorable photochemical properties but significant pharmaceutical limitations; and (iii) exploratory molecules requiring substantial optimization. This classification provides a rational framework to critically assess the most promising natural photosensitizers and to identify the key strategies required to advance them toward clinical application.

3. Promising Natural Product-Based Photosensitizers

The natural product-based photosensitizers summarized in Table 1 can be broadly classified according to their translational readiness, reflecting not only their photodynamic performance but also their pharmaceutical feasibility. While several compounds exhibit promising photochemical properties, only a limited number demonstrate characteristics compatible with clinical development. This section critically discusses the most relevant candidates, emphasizing the factors that position them along the translational spectrum.

Table 1. Translational assessment of natural product-based photosensitizers for photodynamic therapy (PDT).

PS	Origin	Key advantage	Main barrier	Limitation	Strategy	Status
Hypericin	*H. perforatum*	Strong ROS generation; red absorption	Aggregation due to poor solubility	Biopharmaceutical	Liposomes; polymeric nanoparticles	Advanced
Chlorins	Chlorophyll-derived	Red absorption; clinically validated scaffolds	Hydrophobicity; formulation dependence	Formulation-driven	Semisynthetic optimization; delivery systems	Clinically mature
Curcumin	*C. longa*	High safety; pleiotropic activity	Instability; low bioavailability; blue-light activation	Photophysical + PK	Nanocarriers; micelles; hydrogels	Clinically explored
Hypocrellin	*H. bambusae*	High phototoxicity; low dark toxicity	Poor solubility; limited penetration	Photophysical + delivery	Nanoparticles; molecular conjugation	Preclinical
Berberine	*Berberis* spp.	ROS generation; anticancer activity	Low bioavailability; suboptimal excitation	PK + photophysical	Targeted nanoparticle delivery	Preclinical
Emodin	Various plants	Consistent phototoxicity	Limited validation; shallow penetration	Photophysical	Topical systems; nanoformulations	Exploratory
Riboflavin	Vitamin B_2	Excellent safety profile	Blue-light dependence; low penetration	Photophysical	Local delivery; combination approaches	Niche

3.1. Clinically Advanced and Translationally Relevant Candidates

Among natural product-derived photosensitizers, hypericin and chlorophyll-derived chlorins represent the most advanced candidates in terms of clinical relevance and translational potential. Hypericin, a naturally occurring anthraquinone isolated from Hypericum perforatum, exhibits strong absorption in the red region and high efficiency in generating reactive oxygen species. These properties, combined with its intrinsic fluorescence, make hypericin particularly attractive for both therapeutic and diagnostic applications. However, its clinical translation has been significantly constrained by poor aqueous solubility and a strong tendency to aggregate, which reduces photodynamic efficiency

 doi:10.20944/preprints202603.2420.v1

in biological environments. Recent advances in nanoformulation and carrier-based delivery systems have partially addressed these limitations, enabling improved bioavailability and tissue targeting.

Chlorophyll-derived chlorins, including chlorin e6 and related semisynthetic derivatives, constitute the most clinically mature class of natural-origin photosensitizers. Their strong absorption in the red region allows deeper tissue penetration compared to many other natural compounds, and their photodynamic efficiency has been validated in multiple preclinical and clinical contexts. Importantly, several clinically approved photosensitizers are derived from chlorophyll scaffolds, highlighting the translational viability of this class. Nonetheless, their performance remains highly dependent on formulation strategies, particularly to overcome hydrophobicity and optimize biodistribution.

3.2. Clinically Explored but Limited Candidates

Curcumin represents one of the most extensively studied natural compounds in photodynamic therapy, largely due to its well-established safety profile and broad biological activity. Its ability to generate reactive oxygen species under light irradiation has been demonstrated in numerous studies, particularly in antimicrobial and dermatological applications. However, curcumin suffers from significant limitations that hinder its broader clinical application in PDT. Its absorption is primarily in the blue region of the spectrum, which restricts tissue penetration and limits its use to superficial conditions. In addition, poor chemical stability and low bioavailability further compromise its therapeutic potential. To overcome these barriers, a wide range of formulation strategies, including nanocarriers, hydrogels, and micellar systems, have been developed, leading to improved photodynamic performance in localized applications. Despite these advances, curcumin remains more suitable for niche or superficial indications rather than deep-tissue oncological PDT.

3.3. Emerging Preclinical Candidates

Several natural products, including hypocrellin A/B, berberine, emodin, and riboflavin, have demonstrated promising photodynamic activity at the preclinical level, but their translational progression remains limited. Hypocrellins, which belong to the perylenequinone family, exhibit high phototoxicity and low dark toxicity, making them attractive candidates for PDT. However, their poor solubility and suboptimal absorption characteristics necessitate advanced formulation approaches to achieve meaningful *in vivo* performance.

Berberine, an isoquinoline alkaloid, has shown consistent photodynamic activity and anticancer effects in experimental models. Nevertheless, its low bioavailability and unfavorable excitation profile restrict its clinical applicability. Similarly, emodin and aloe-emodin display reproducible phototoxic effects and potential anticancer activity, particularly in superficial or skin-related applications, but lack robust translational validation and standardized formulation strategies.

Riboflavin occupies a distinct position among natural photosensitizers due to its excellent safety profile and established use in antimicrobial and pathogen inactivation applications. However, its excitation in the UV–blue region limits its effectiveness in deep tissue PDT, confining its application primarily to surface or extracorporeal settings.

Collectively, these observations highlight that the translational success of natural photosensitizers is not solely determined by their intrinsic photodynamic properties, but rather by their compatibility with pharmaceutical development strategies. While compounds such as hypericin and chlorophyll-derived chlorins have progressed due to favorable photophysical profiles combined with formulation adaptability, many other natural products remain constrained by biopharmaceutical limitations. This reinforces the notion that overcoming pharmaceutical barriers is a critical determinant in advancing natural product-based photosensitizers toward clinically viable PDT therapies.

4. Pharmaceutical Barriers Limiting Clinical Translation

Despite the promising photodynamic properties reported for many natural compounds, their clinical translation remains fundamentally constrained by pharmaceutical limitations rather than photochemical inefficiency. Poor aqueous solubility, aggregation-induced quenching, chemical instability,

 doi:10.20944/preprints202603.2420.v1

and suboptimal pharmacokinetics collectively impair *in vivo* performance and prevent the achievement of therapeutically relevant concentrations at target sites. These constraints are not peripheral challenges but represent the central bottleneck in the development of clinically viable natural photosensitizers.

One of the most significant challenges is poor aqueous solubility, which is particularly common among hydrophobic natural compounds such as hypericin, chlorophyll derivatives, and anthraquinones. Limited solubility not only hinders formulation development but also leads to aggregation in physiological environments. This aggregation often results in aggregation-induced quenching, reducing the efficiency of reactive oxygen species generation and ultimately diminishing photodynamic activity.

Closely related to this issue is chemical and photochemical instability. Many natural photosensitizers are prone to degradation under physiological conditions or upon light exposure, leading to reduced therapeutic efficacy and inconsistent performance. For example, curcumin is well known for its rapid degradation and poor stability, which significantly limits its clinical applicability despite extensive research interest.

Another major limitation is suboptimal pharmacokinetics and biodistribution. Effective PDT requires sufficient accumulation of the photosensitizer in target tissues, particularly tumors or infected sites. However, many natural compounds exhibit rapid metabolism, poor membrane permeability, or nonspecific distribution, resulting in inadequate therapeutic concentrations at the target site and increased off-target effects.

The mismatch between absorption wavelength and tissue penetration further constrains clinical application. Photosensitizers that absorb in the UV or blue region, such as riboflavin and curcumin, are limited to superficial treatments due to the low penetration depth of short-wavelength light. In contrast, effective treatment of deeper tissues requires absorption in the red or near-infrared region, which is not inherently present in many natural compounds.

From a formulation perspective, lack of standardization and reproducibility represents an additional barrier, particularly for compounds derived directly from natural sources. Variability in extraction methods, purity, and composition can lead to inconsistencies in therapeutic performance and complicate regulatory approval. Furthermore, large-scale production of natural photosensitizers with consistent quality remains a significant challenge.

Finally, limited compatibility with conventional drug delivery systems can further hinder translation. Many natural compounds require advanced formulation approaches to achieve acceptable solubility, stability, and targeting, increasing development complexity and cost. Without appropriate delivery strategies, even highly potent photosensitizers may fail to demonstrate meaningful *in vivo* efficacy.

Taken together, these barriers highlight that the primary limitation in advancing natural product-based photosensitizers is not the lack of photodynamic activity, but rather the inability to effectively translate these compounds into pharmaceutically viable systems. Addressing these challenges requires an integrated approach combining molecular optimization with advanced formulation and drug delivery strategies.

5. Formulation and Drug Delivery Strategies to Overcome Pharmaceutical Barriers

The pharmaceutical limitations discussed above have driven the development of a wide range of formulation and drug delivery strategies aimed at improving the clinical applicability of natural product-based photosensitizers. These approaches focus on enhancing solubility, stability, biodistribution, and target specificity, ultimately enabling more efficient and controlled photodynamic therapy. The main limitations and corresponding strategies are summarized in Table 2.

 doi:10.20944/preprints202603.2420.v1

Table 2. Key pharmaceutical limitations and enabling strategies for natural product-based photosensitizers in photodynamic therapy.

Photosensitizer	Main limitation	Enabling strategy
Hypericin	Poor solubility, aggregation	Nanoformulations, liposomes, polymeric carriers
Chlorin derivatives	Hydrophobicity, formulation dependence	Semisynthetic optimization, delivery systems
Curcumin	Instability, low bioavailability, blue-light absorption	Nanocarriers, hydrogels, micelles
Hypocrellin A/B	Poor solubility, limited penetration depth	Nanoparticles, conjugation strategies
Berberine	Low bioavailability, suboptimal excitation	Targeted nanoparticle delivery
Emodin / Aloe-emodin	Limited validation, shallow-light activation	Topical systems, nanoformulations
Riboflavin	Blue-light dependence, limited tumor use	Local delivery, combination approaches

Figure 3 illustrates the impact of nanotechnology-based delivery systems on the performance of natural product-based photosensitizers, highlighting improvements in solubility, stability, tumor targeting, and photodynamic efficacy. One of the most extensively explored approaches is the use of liposomal delivery systems, which are particularly effective for hydrophobic photosensitizers. Liposomes provide a biocompatible environment that improves aqueous dispersibility while protecting the photosensitizer from premature degradation. In addition, their structural similarity to biological membranes facilitates cellular uptake and enhances accumulation in target tissues. Liposomal formulations have shown significant success in improving the performance of compounds such as hypericin and chlorin derivatives.

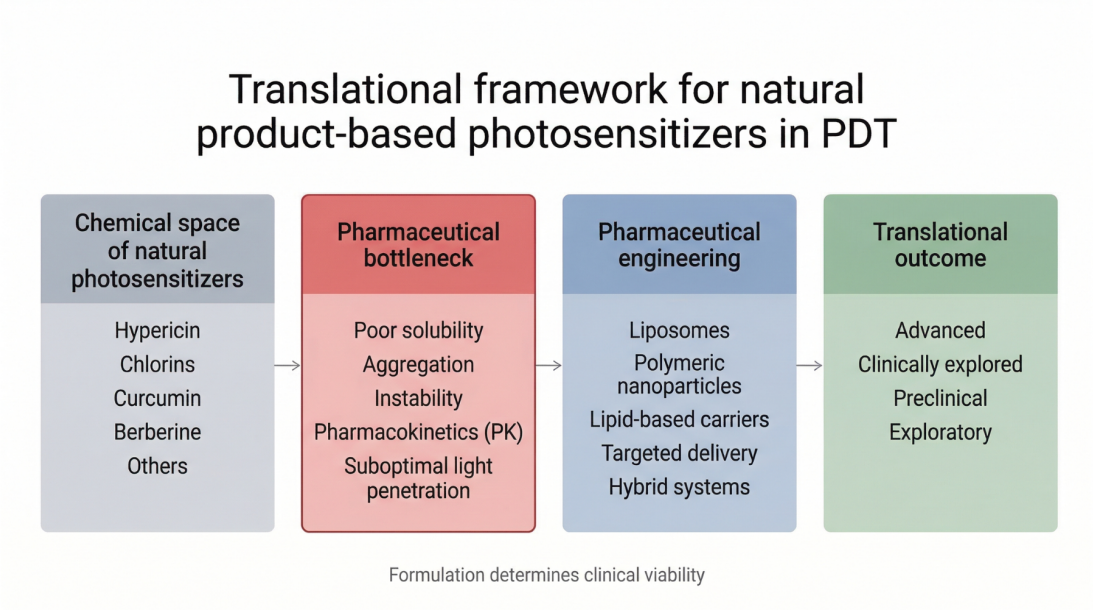

Figure 3. Translational framework for natural product-based photosensitizers in photodynamic therapy (PDT). Natural photosensitizers occupy a broad chemical space but face critical pharmaceutical constraints that limit clinical translation. Key bottlenecks include poor aqueous solubility, aggregation, instability, suboptimal pharmacokinetics, and limited light penetration. Advanced formulation and drug delivery strategies—such as liposomes, polymeric nanoparticles, lipid-based carriers, and targeted systems—enable the mitigation of these barriers. The extent to which these pharmaceutical limitations are addressed ultimately determines translational progression, ranging from exploratory and preclinical stages to clinically investigated and advanced applications.

 doi:10.20944/preprints202603.2420.v1

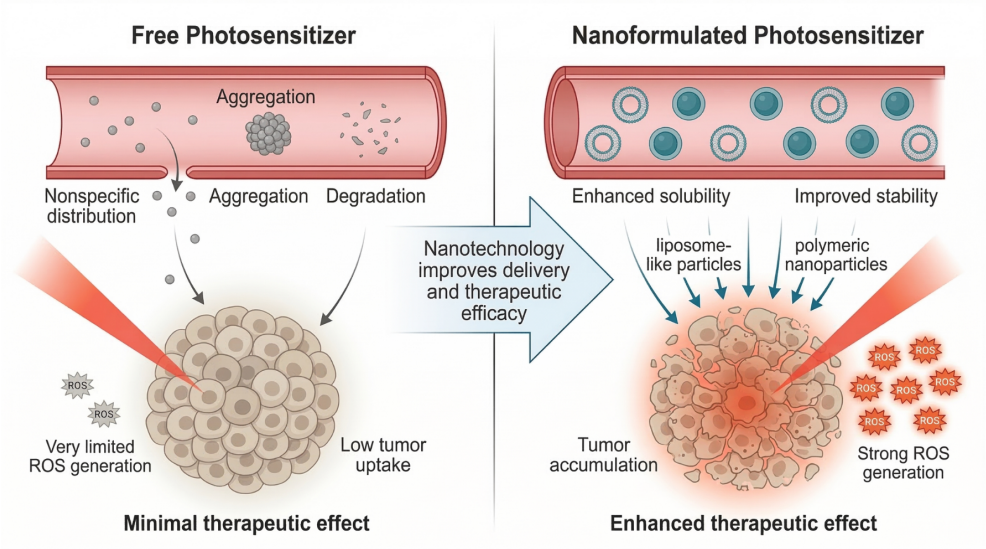

Figure 4. Impact of drug delivery systems on the performance of natural product-based photosensitizers in photodynamic therapy (PDT). Free photosensitizers exhibit poor aqueous solubility, aggregation, chemical instability, and nonspecific distribution, resulting in low tumor accumulation and limited reactive oxygen species (ROS) generation upon light activation. In contrast, nanoformulated systems, such as liposomes and polymeric nanoparticles, improve solubility and stability, enhance tumor accumulation, and promote increased ROS production, including singlet oxygen ($^1O_2$), ultimately leading to improved therapeutic efficacy.

Another important strategy involves polymeric nanoparticles, which offer high versatility in terms of composition, surface modification, and controlled release properties. These systems can be engineered to optimize circulation time, reduce nonspecific distribution, and enable passive or active targeting. For natural photosensitizers with poor bioavailability, polymeric carriers have demonstrated the ability to significantly enhance therapeutic efficacy by improving both stability and tissue accumulation.

Lipid-based nanocarriers, including solid lipid nanoparticles and nanostructured lipid carriers, represent an additional promising platform. These systems combine the advantages of lipid compatibility with improved stability and scalability, making them particularly attractive for pharmaceutical development. They have been widely investigated for compounds such as curcumin, where they contribute to enhanced stability and improved photodynamic performance.

Inclusion complexes based on cyclodextrins provide a complementary approach for improving solubility and reducing aggregation of hydrophobic photosensitizers. By encapsulating the active molecule within a hydrophobic cavity, cyclodextrins enhance aqueous dispersibility without requiring extensive chemical modification. This strategy has been particularly useful for compounds prone to aggregation-induced quenching.

More advanced systems include stimuli-responsive and targeted delivery platforms, which are designed to release the photosensitizer in response to specific environmental triggers such as pH, redox conditions, or enzymatic activity. These systems can also be functionalized with targeting ligands, such as antibodies or peptides, to enhance selective accumulation in tumor tissues. Such approaches are especially relevant for improving the selectivity and reducing off-target effects of PDT.

Finally, hybrid strategies combining natural photosensitizers with additional therapeutic modalities are gaining increasing attention. These include systems that integrate photodynamic therapy with photothermal therapy, chemotherapy, or immunotherapy, leading to synergistic effects and improved treatment outcomes. In many cases, the success of these approaches depends heavily on the design of multifunctional delivery systems capable of co-delivering multiple agents.

Collectively, these formulation and drug delivery strategies demonstrate that the limitations of natural photosensitizers can be effectively addressed through pharmaceutical design. Importantly,

 doi:10.20944/preprints202603.2420.v1

these advances reinforce the concept that successful translation of natural PDT agents relies not only on molecular properties, but also on the development of optimized delivery systems capable of maximizing therapeutic performance *in vivo*.

6. Translational Outlook and Future Perspectives

Despite significant advances in the development of natural product-based photosensitizers for photodynamic therapy, their clinical translation remains limited. Bridging the gap between promising preclinical findings and successful clinical application requires a more integrated approach that combines photochemical optimization with pharmaceutical design and translational considerations.

One of the key future directions lies in the rational design and optimization of natural photosensitizers, including semisynthetic modification and hybrid molecule development. Structural modifications aimed at shifting absorption toward the red or near-infrared region, improving photostability, and enhancing ROS generation efficiency may significantly expand the therapeutic applicability of natural compounds. In addition, combining natural scaffolds with synthetic moieties offers a promising strategy to balance biological activity with optimized photophysical properties.

Another important avenue is the continued advancement of nanotechnology-based delivery systems, which are expected to play a central role in the clinical translation of natural photosensitizers. The development of multifunctional nanocarriers capable of improving solubility, protecting against degradation, and enabling targeted delivery will be essential to maximize therapeutic efficacy while minimizing systemic toxicity. In particular, stimuli-responsive and actively targeted systems hold great potential for enhancing treatment selectivity in complex biological environments.

The integration of photodynamic therapy with other treatment modalities represents a further promising direction. Combination therapies, including photodynamic–photothermal therapy, chemo-photodynamic therapy, and immuno-photodynamic approaches, have demonstrated synergistic effects in preclinical models. These strategies may overcome some of the intrinsic limitations of PDT, such as hypoxia and limited light penetration, while enhancing overall therapeutic outcomes.

From a translational perspective, standardization, scalability, and regulatory considerations remain critical challenges. The variability associated with natural product extraction, as well as the complexity of advanced delivery systems, can hinder reproducibility and complicate regulatory approval. Future research should prioritize the development of standardized production methods and well-characterized formulations to facilitate clinical evaluation.

Finally, advances in precision medicine and imaging-guided therapy may further enhance the clinical potential of natural photosensitizers. The use of theranostic platforms combining diagnostic and therapeutic capabilities, as well as patient-specific treatment planning, could improve treatment accuracy and clinical outcomes.

Overall, the future of natural product-based photosensitizers in photodynamic therapy will depend on the successful integration of molecular design, pharmaceutical engineering, and clinical strategy. By addressing current limitations through interdisciplinary approaches, these compounds may evolve from promising experimental agents into clinically relevant therapeutic tools.

7. Conclusions

Natural products constitute a rich and underexplored source of photosensitizers for photodynamic therapy; however, their limited clinical translation reflects a fundamental mismatch between intrinsic photodynamic activity and pharmaceutical viability. As highlighted throughout this review, most natural photosensitizers fail not because they cannot generate reactive oxygen species, but because they cannot be effectively delivered, stabilized, or distributed in vivo.

This paradigm shift repositions pharmaceutical engineering as the central determinant of translational success in PDT. Advances in nanotechnology-enabled delivery systems, targeted carriers, and multifunctional platforms demonstrate that clinically relevant performance can be achieved when formulation strategies are integrated early in development.

 doi:10.20944/preprints202603.2420.v1

Future progress in this field will depend on prioritizing compounds that meet strict translational criteria and on designing systems that bridge the gap between molecular activity and therapeutic applicability. Ultimately, the clinical success of natural photosensitizers will not be defined by the discovery of new molecules, but by the ability to transform a limited set of viable candidates into pharmaceutically optimized therapeutic platforms.

Author Contributions: Conceptualization, data curation, methodology, investigation, writing—original draft, writing—review and editing, visualization, supervision, project administration, R.S.G.; conceptualization, data curation, methodology, formal analysis, writing—review and editing, E.V.C.

Funding: This review received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study.

Conflicts of Interest: The author declares no conflicts of interest.

References

1. Dolmans, D.E.J.G.J.; Fukumura, D.; Jain, R.K. Photodynamic therapy for cancer. *Nat. Rev. Cancer* **2003**, *3*, 380–387.
2. Castano, A.P.; Demidova, T.N.; Hamblin, M.R. Mechanisms in photodynamic therapy: part one—photosensitizers, photochemistry and cellular localization. *Photodiagnosis Photodyn. Ther.* **2006**, *3*, 279–293.
3. Agostinis, P.; Berg, K.; Cengel, K.A.; Foster, T.H.; Girotti, A.W.; Gollnick, S.O.; Hahn, S.M.; Hamblin, M.R.; Juzeniene, A.; Kessel, D.; et al. Photodynamic therapy of cancer: an update. *CA Cancer J. Clin.* **2011**, *61*, 250–281.
4. Henderson, B.W.; Dougherty, T.J. Mechanisms of photodynamic therapy. *Photochem. Photobiol.* **1992**, *55*, 145–157.
5. Castano, A.P.; Demidova, T.N.; Hamblin, M.R. Mechanisms in photodynamic therapy: part two—cellular signaling, cell metabolism and modes of cell death. *Photodiagnosis Photodyn. Ther.* **2004**, *2*, 1–23.
6. Hamblin, M.R. Antimicrobial photodynamic inactivation: a bright new technique to kill resistant microbes. *Curr. Opin. Microbiol.* **2016**, *33*, 67–73.
7. Allison, R.R.; Sibata, C.H. Photosensitizers in clinical PDT. *Photodiagnosis Photodyn. Ther.* **2004**, *1*, 27–42.
8. Lucky, S.S.; Soo, K.C.; Zhang, Y. Photodynamic therapy: from the basic to the clinical. *Drug Discov. Today* **2015**, *20*, 565–574.
9. Huang, Z. A review of light penetration in tissue and its implications for photodynamic therapy. *Photodiagnosis Photodyn. Ther.* **2008**, *5*, 90–99.
10. Zhao, X.; Liu, J.; Fan, J.; Chao, H.; Peng, X. Natural products for photodynamic therapy: a review of recent advances. *Chem. Soc. Rev.* **2021**, *50*, 4185–4219.
11. Majumdar, P.; Nomula, R.; Zhao, J. Natural compounds as photosensitizers for photodynamic therapy. *J. Mater. Chem. B* **2019**, *7*, 7024–7041.
12. Harvey, A.L.; Edrada-Ebel, R.; Quinn, R.J. The re-emergence of natural products for drug discovery in the genomics era. *Nat. Rev. Drug Discov.* **2015**, *14*, 111–129.
13. Patra, J.K.; Das, G.; Fraceto, L.F.; Campos, E.V.R.; Rodriguez-Torres, M.D.P.; Acosta-Torres, L.S.; Diaz-Torres, L.A.; Grillo, R.; Swamy, M.K.; Sharma, S.; et al. Nano based drug delivery systems: recent developments and future prospects. *J. Nanobiotechnol.* **2018**, *16*, 71.
14. Huang, L.; Huang, X.; Yang, X.; Hu, J.; Zhu, Y.; Yan, P.; Xie, Y. Novel nano-drug delivery systems for natural products and their application. *Pharmacol. Res.* **2024**, *201*, 107100.
15. Chilakamarthi, U.; Giribabu, L. Photodynamic therapy: past, present and future. *Chem. Rec.* **2017**, *17*, 775–802.

 doi:10.20944/preprints202603.2420.v1

disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.