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Photosensitizing Herbs as Potential Therapeutics: A Prospective Insights into their Mechanisms for the Development of Novel Drug Leads in War with Cancer and Other Human Diseases

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Abstract

In recent years, photodynamic therapy (PDT) has been accepted as an alternative option for the treatment of a wide spectrum of human ailments. It is a minimally invasive treatment that involves the interaction of a non-toxic photosensitizer. In PDT, combining photosensitizing (PS) agent that absorbs specified wavelength of light, which in turn produces free radical molecules to eliminate unwanted cells and tissues. The photosensitization process is activated by the light-induced excitation of molecules within the tissue. Bioactive principles acquired from plants documented as nature-inspired potential photosensitizers with varied properties against microbes, insects, or tumor cells. PDT is a promising method for removing diverse types of cancers but needs to be recognized in therapy as conventional chemotherapy. At present, natural compounds with PS properties are being continuously unearthed and identified. As of now, hundreds of photosensitive drugs or drug leads identified from natural sources with reduced or no toxicity to healthy tissues and no side effects encourage investigators to pursue natural PS for PDT. Although existing PS was developed years back, only a handful of them are engaged in human clinical applications. The main classes of natural photosensitizers discussed in this review are chlorophylls (hypocrellin A and B), hypericin, chlorins (Chlorin e6), and other emerging ones such as curcumin. Hence, the present review aimed to explore the efficacious PS properties of a few herbal-derived PS, preferably the potential ones in terms of specificity, and mechanism of action, inducing less or no toxicity to normal cells but their other medicinal applications.

Introduction

Nature-derived bioactive principles or drug leads from various herbs, microorganisms, animals, and mineral sources are in place for the management of human disease diagnosis, prophylaxis, and therapy, practiced since human civilization [1], [2]. However, medicinal herbs with miraculous remedial control have always shown special attention. Like every other scientific and technological advancement, the arena of therapeutic medicine and its allied sciences has also made a rapid decisive leap [3]. The combination of chemical entities and their inclusion as therapeutic drugs or drug leads indeed revolutionized the treatment options for diseases as a result, a substantial number of synthetic drugs are available to target against various human illnesses [4]. However, they exhibit a range of adverse reactions and are responsible for side effects and diseases. Another factor one should consider is the cost measure as synthetic or combinatorial medications are expensive and not affordable [5].

Natural Products (NPs) as Lead Molecules in Drug Discovery

The therapeutic effectiveness and non-toxic nature of medicinal herbs have been the current focus and gained significant interest. NPs or bioactive principles have been demonstrated as templates for new drug development [2], [6] with the adaptation of various advanced developments from synthetic integrative chemistry, and molecular modeling domains [7], [8], [9] to obtain drug leads for drug discovery. The drug leads obtained from plants are both multi- and inter-disciplinary but time-consuming, advanced more accurate rapid methods adopted including various isolation and bioassay screening. It is estimated that 20,000–55,000 species of medicinal herbs are in practice worldwide, of which 15–20% of them are terrestrial plants with enormous pharmaceutical potential [10]. According to the World Health Organization, about 25% of the medicines prescribed globally are obtained from plants, and 252 drugs (approximately 11%) are solely from plant origin

and a substantial quantity of synthetic ones is from natural precursors [11]. Despite the success made with plant-derived NPs, huge hurdles and challenges remain exist. Hence, investigators and pharmaceutical industries need to invest time and effort to improve both the quality and quantity of nature-derived compounds [12], [13].

It is widely accepted that plant-derived natural compounds are harmless because of their less toxic nature in comparison with pure chemicals [1]. It is evident that bioactive principles compromise/nullify the toxic nature of the remaining additional components of a plant, however, the whole extract exhibits less toxicity with enormous potency [14]. In the last few decades, medicinal chemists have isolated many clinically important bioactive principles/phytocompounds from various traditional medicinal plants [2], [15], [16]. The progress of medicinal drug development from herbal plant sources faces numerous hurdles such as absorption, therapeutic efficiency, and poor compliance. Despite having the above problems, still crude herbs/plants are mostly formulated in various preparations. It is well known that the finding of new novel drug leads from plant sources is time-consuming, to overcome this, the adaptation of appropriate advanced tools for plant material collection, throughput screening assays, bioactive structure, and function elucidation required for drug leads development need the incorporation of multiple advanced techniques [17], [18], [19]. It is well established that the drug leads of plant origin involve simple stepwise preparation and therefore less expensive than synthetic drugs [20], [21], [22]. In this regard, by employing, various approaches such as combinatorial and synthetic chemistry and modeling approaches are highly employed to obtain novel drug and drug lead entities from plant sources [15], [23].

PDT is an emerging alternate mode of regulatory-approved site-specific cancer treatment and it requires the introduction of a harmless photosensitizing (PS) agent that accumulates selectively more in cancer cells [24], [25], [26], [27], [28] with minimal risk to healthy tissue than surrounding cells. In PDT, combining PS absorbs specified wavelengths of light, which in turn produces free radical molecules to eliminate neoplastic cells and tissues. PDT can be employed to alleviate skin diseases, target microbial infections [29], different malignancies [30], [31], and a variety of other complications in cardiovascular, ophthalmic, and immune dysfunctions [32], [33]. There are three well-established PDT-mediated biological mechanisms involved in the destruction of tumorous tissue: cellular, vascular, and immunological [34]. Several cellular organelles such as mitochondria and plasma membrane are known sites of photosensitizer location [34], [35], [36], [37]. However, not all the PS may not localize and bind to specific intracellular organelles or locations but rather bind to the diverse structures, which may lead to the involvement of various death pathways in PDT [32], [38], [39]. In comparison to standard surgery options, the PDT approach is the non-invasive, precise target, repeated administration of regimen without total-dose limitations associated with radiotherapy, as a result, little or no scarring is found after healing [40]. However, for successful clinical outcomes, photosensitizers should meet certain requirements [41].

Although many studies in the last few decades have shown much interest in PDT for various applications based on its successful outcomes, despite its positive note, yet less interest toward plant-derived PS agents or bioactive principles, especially their phototoxic properties, which are very less tested to date. However, herbal research recently gained momentum to explore plants as sources for new phytotherapeutic agents [16], [19], [42], [43]. For years, a Food and Drug Administration (FDA) approved photoactive sensitizer such as hematoporphyrin derivative, namely Photofrin [44], was extensively employed for the clinical treatment of the vast array of cancers, which include bladder, breast [45], [46], and to kill various microbial organisms [43], [47]. However, it has some restrictions such as (i) its cutaneous tissue retention time for 4–10 weeks after uptake that leads to long-term skin photosensitivity, (ii) patients need to stay for a considerable length of time to avoid light, (iii) its insufficient low wavelength activation compromises tissue penetration, and finally, (iv) its badly defined molecular formula. Hence, the above limitations and drawbacks have encouraged the quest for new and novel sensitizers with ideal characteristic features suited to be adopted in the clinic for better outcomes [46], [48], [49].

In recent years, many established studies have enumerated various merits of ideal photosensitizers [26], [28], [50]. An ideal PS needs to be hydrophilic in nature for easy absorption, non-toxic till exposed to light, and activated by an appropriate wavelength by a tunable laser light source [51]. More importantly, a good PS should generate a good photodynamic outcome based on its cellular localization and selectivity [52], [53]. The following are some of the characteristic features such as (a) it should be a righteous unmixed chemical drug lead with selective absorption by the target, (b) induction of minimum dark effects (i.e., activated only by light irradiation), (c) high photo activity or quantum yield of free radicals species, (d) rapid clearance of PS to avoid irradiation mediated side effects, and finally, (e) stronger absorption in the long wavelength range between ~630 nm and ~800 nm [45], [46], [54], [55]. Based on the above characteristics, most of the currently available synthetic or natural photosensitizers have been identified and employed for various applications [46], [50], [56], [57].

From the available phytochemical literature, the PS metabolites were isolated from 35 families of plants, belonging to 15 various classes of phytochemicals [58]. These secondary metabolites are the products of four biosynthetic pathways such as shikimate, terpenoid,

fatty acid, and polyketide [59]. Previous studies have established that these light-activated isolates or extracts obtained from plants of various taxonomies comprised 44 families which include *Loganiaceae*, *Malpighiaceae*, *Papaveraceae*, *Phytolaccaceae*, *Piperaceae*, *Acanthaceae*, *Campanulaceae*, *Gesneriaceae*, and *Sapotaceae* [58], [60].

A spectrum of herbs-derived extracts have been isolated and tested for their chemotherapeutic properties but their PS ability for PDT is rarely examined [50], [61], [62], [63], [64]. To become a competent novel photosensitizer, it needs to meet and pass certain significant pre-requisite steps for PDT studies. In reality, till date, only a handful of FDA-approved PDT drugs in the clinic such as Photofrin®, Foscan®, and Levulan® to treat mainly skin, gynecological, gastrointestinal, and head and neck (H&N) type of cancers [65], [66]. Besides, in the last few years, quite a sizable quantity of both natural and synthetic compounds have been developed and screened both *in vitro* and *in vivo* as potential PS agents for PDT investigations [34], [56], [67], [68].

Yet, the hunt for new PS from potential natural sources is continuing by adopting crucial advanced scrutinizing steps. In this line, chlorophylls, porphyrins, furocoumarins, chlorins (Chlorin e6 [Ce6]), and a few other emerging PSs are of interest as they have exhibited superior therapeutic efficacy [69]. However, the new prospective PS should meet the eligible criteria to enhance target-specific actions for therapeutic efficiency in PDT and various other wider clinical applications.

It is conceivable that no current PS meets all the clinical requirements [68], [70]. Most of the PS have many disadvantages such as limited cell specificity or selectivity, skin sensitivity to prolonged irradiation, and unpredictable efficacy [41], [71], [72]. Other requirements include the following: (i) PS should be water soluble for intravenous injection, (ii) they should exhibit stronger absorption of light mostly in the near-infrared region, which is required for deep penetration into tissues, (iii) yield high quantum of singlet oxygen (O_2) and produce less or no toxicity in the dark, and finally, fast cleared from the body. However, chlorins (Ce6), hypocrellins, hypericin (HY), and curcumin exhibit advantageous characteristics compared to other commonly employed PS. The following cellular organelles are prime target locations for photosensitizers, which include mitochondria, lysosomes, endoplasmic reticulum (ER), plasma membrane, and Golgi, etc., [34], [36], [73]. However, not all the current PS may not localize and bind to specific intracellular organelles or locations but rather bind to diverse structures, which may reflect the involvement of various death pathways in PDT [32], [38], [39], [74].

Many PSs such as chlorophylls, furocoumarins, chlorins including hypocrellins, HY, and curcumin have gained attention in recent years because of their efficacy [50], [66]. Based on the available literature and efficacy, this review will focus on the chlorin type of natural photosensitizers and their counterparts because of their efficacious pharmacokinetic and photodynamic activities. Most compounds or molecules absorb light and acquire energy, subsequently losing the gained energy through radiationless loss/decay by an internal conversion mechanism. However, the PS molecule's internal conversion is not effective and not sufficient. Rather PS molecules transfer electrons to each other by transferring molecular O_2. In most cases, energy transfer occurs efficiently in their excited triplet states since this position allows an extended period for electron transfer. In fact, most of the current effective photosensitizers used in the clinics exhibit high quantum yields in their excited triplet state [75], [76].

In general, photosensitizers absorb light maximum at the far-red region, specifically at 668 nm, which falls within the optical window of biological tissues (600–800 nm range). Low-wavelength light fails to penetrate the tissue into deeper regions and produces no results. Similarly, very long wavelengths (800 nm and above) are also not useful as they have insufficient energy to excite tissue O_2 to become singlet and then to generate a substantial yield of reactive oxygen species (ROS) [77]. Avoiding side effects, minimal or no destruction to nearby/surrounding healthy tissue but PS-specific localization to neoplastic lesions is an essential consideration for clinical PDT. It is known that most of the PS-produced ROS do not discriminate between cancer and non-cancerous tissues. Although the selectivity may not be achieved by any natural PS extracts, it can be achieved maximally by combinatorial chemistry or by employing tunable laser light as a source and precise delivery tools technique to target the tumor area/region [76], [77]. Although many clinically approved PS, only a few under clinical trials are currently in use to treat various types of cancer. Some of the synthetic counter partners of PS are listed below:

Photolon

Photolon (1, 3, 5, 8-tetramethyl-4-ethyl-2-vinylchlorin 6 cabonic acetic-7-propionic acid sodium vapor salt), whereas, Ce6 hydrophile PS compound is linked with polyvinylpyrrolidone (PVP) in the ratio of 1:1 [78], [79]. Although, the chemical formula correlates with partially reduced porphyrin moiety, molecularly similar to Ce6, which separates pheophorbide exocyclic dimethyl amine β-ketoester by hydrolysis [80], [81]. The combination product of Photolon® by Ce6 and PVP exhibits better solubility and durability in water leading to superior bioavailability when compared to Ce6 alone [79], [82]. Unlike first-generation porphyrins, second-generation chlorins (Ce6 and derivative of Photolon®) demonstrated a higher ability to assemble in the neoplastic tissue but also cleared fast from the body and strongly absorbed in the red (between 640

and 700 nm) and thus qualify for the treatment deep sheeted and mass tumors [80], [81]. The i.v of Photolon improves the high uptake rate in target tissues which produces not only high tumorotropic but also produces less phototoxic reactions and is removed entirely after a period of PDT from the localized targets.

Previous reports have proven that Photolon has a better therapeutic outcome with increased wavelength to match its absorption peak because of its deeper penetration ability [54], [83] and proven that Photolon® prefers the following intracellular localization order such as: nucleus, mitochondria, lysosomes, and Golgi apparatus [32], [70]. A study by Ali-Seyed *et al*. [32] demonstrated that Photolon-PDT specifically induced apoptosis in CT-26 cells, this apoptotic cell death implies physiological correlates with minimal drug toxicity [84], [85].

Both natural PS Ce6 and its synthetic counterpart Photolon® share many qualities such as rapid accumulation of PS in the targets, faster clearance from the body, and producing a high quantum of singlet O_2 when compared to first-generation PS [86], [87]. Besides they are activated by near-infrared wavelengths (e.g., 664 nm), which enables molecules to enter into deeper layers of tissue [88], compared to 630-nm laser light used for photofrin or porphyrins [89]. Since Ce6 and Photolon® exhibit superior photophysical attribution for PDT such as higher molar absorption in the near-infrared spectrum and prolonged photoexcited triplet states, they are attractive PDT candidates when compared to other current porphyrin-based PDT agents. Previous studies have proven the local application of Photolon® as an ointment/patch form or by oral rinse with infra-red irradiation at 665nm exhibits therapeutic potency in xenograft tumors and clinical trials [82], [90]. To support this claim, Ce6-based photosensitizers have recently received more attention due to their high photodynamic activity and therapeutic efficacy [85] against many types of tumors such as nasopharyngeal, melanoma, and bladder [32], [78], [91].

Foscan/M-tetrahydroxophenyl chlorine (mTHPC)

Foscan (Biolitec Pharma Ltd., Dublin, Ireland/ Germany) is a plant-based chlorine derivative is a PS consisting of temoporfin [92]. When compared to porphyrins, Foscan produces an increased amount of O_2 and exhibits high target specificity due to its hydrophobic nature leading to increased amalgamation of PS in target tissues [93], [94]. However, it is an industrial pure chemical and can produce quick and significant photodynamic reactions (PDR), but its treatment period is shorter in terms of seconds to avoid a longer hospitalization period as well as in the darkroom for more than a day because light exposure including normal room light is sufficient to activate this drug and produce significant severe burn (dark toxicity). Foscan-PDT is highly effective, and this PS found a special place for primary and recurrent H&N cancer treatments [96]. The biggest disadvantage of Foscan-PDT is so painful to even under anesthesia for most patients who undergo Foscan illumination.

Mono-L-aspartyl chlorin e6 (NPe6)

This PS was promoted using various generic branded names such as MACE, LS11, and NPe6. This derivative is also called Fotolon (RUE Belmedpreparaty, Minsk, Republic of Belarus). NPe6 is herb-derived chlorine [95], [96] based effective PS bioactive principle to produce the PDR. It is important to note that, unlike Foscan, NPe6 does not cause dark toxicity after infusion for hours, which helps a longer treatment period [96], [97]. Moreover, NPe6 allows shorter periods of single-day infusion and therapy, which is highly acceptable both to patients and practitioners.

Radachlorin

Radachlorin® (Rada-Farma) and Photoditazine® (Veta-Grand) are hydrosoluble chlorines produced in Russia [98]. Normally Photoditazine® composition consists of Ce6 only whereas, Radachlorin® composition consists of Ce6 (90–95%), p6 (5–7%), and other unpublished components (1–5%). In the Russian Federation, both Radachlorin® and Photoditazine®-PDT are employed in various clinical applications for many types of malignant tumors such as bronchus, esophagus, melanoma, oral and colon, vulva, and various additional types of neoplasia [99], [100]. Radachlorin-PDT does not produce either local or systemic problems and produces good results without skin photosensitization. Radachlorin® also has a few disadvantages such as photo instability similar to other PSs such as porphyrins and phthalocyanines [101]. However, this PS can rapidly be degraded by laser light as it can be demonstrated by their decreasing absorption versus fluorescence intensity [100] when in simple solutions or complex environments.

Chlorins are promising PS agent for PDT when compared to other PS, owing to their absorption and emission spectra falling in the red to far-red wavelength range [102] as the 600–800 nm range of light penetrates deeper into the target tissues, whereas low concentration PS and low wavelength light or doses normally resulted into high phototoxicity [88]. Numerous numbers of FDA-approved chlorin-type PSs such as Talaporfin (LS11, Temoporfin [Foscan, mTHPC, 5,10,15,20-Tetra(m-hydroxyphenyl) chlorin], N-aspartyl Chlorin e6, NPe6), Photolon®, radachlorin (a mixture of three chlorins), MACE, and Photodithazine (glucosamine salt of Ce6) [103], [104] are employed in various clinical applications, which include the treatment of many types of cancer. Most of the chorines including bacteriochlorins fall in the bandwidth of red

and near-infrared permitting deeper tissue penetration for light, therefore qualifying these PS ideal candidates for PDT of neoplastic tissues [98], [105], [106].

Despite many investigations have outlined the PDT outcome of many synthetic drugs, little or inadequate attention has been paid to herbal plant extracts or plant-derived bioactive principles. Herbal extracts from curative plants are considered safer when compared to synthetic counterparts. Hence, it is appropriate to review some of the socioeconomically important medicinal plants derived from PS phytochemicals and their utilization in PDT to treat various diseases including cancer. In recent years, PDT employed plant-based photosensitive drug leads receiving paramount importance as a green approach in PDT. Besides, this review discusses their possible molecular mechanism to place them in their rightful prospective scientific discipline which will determine the scope of green PDT for the treatment of a wide range of human chronic diseases.

Chlorins

Photosensitivity and poor absorption of tissue-penetrating low-wavelength PS have led to the search for new ones with many novel characteristics, specifically the sensitizing agents absorbing longer wavelength light for deeper penetration and faster clearance from the normal tissues [106]. Cholrin type of second-generation PS agents has some superior qualities like shorter photosensitization span, red to near-infrared absorption bandwidth and yield higher quantum of O_2, and target selectivity [107]. The chlorine type of PS exhibits photophysical properties similar to the porphyrin type of macrocycles. For example, bacteriochlorins PS falls in the bandwidth of red and near-infrared permitting deeper tissue penetration for light, therefore qualifying chlorin-type PS is ideal candidate and gaining interest as the preferred choice for photodynamic diagnosis and PDT of neoplastic tissues in the clinic [98], [108].

Chlorins are the main type of nature-derived PS agents originating from chlorophyll a. It has a longer spectrum of absorption wavelength, improved target selectivity, and elicits meager photosensitive reactions. The longer spectra of wavelength between 650 and 700 nm aid deep penetration of targets. These novel characteristics motivate investigators in the field to look for more plant-derived extracts to elucidate the structure and function of many new prospective herb-derived PS [69]. It is important to note that such as porphyrin-type derivatives, chlorin PS can also exhibit two additional hydrogen atoms combined with peripheral pyrrole double bonds. This nature-derived chlorophyll displays strong absorption with appropriate O_2 production with lack of water solubility and instability are the only drawbacks, however, much effort is underway to adopt advanced purification and combinatorial chemistry techniques to attract more attention for various pharmaceutical applications [109].

Ce6

Ce6 is a nature-derived PS agent and a member of the chlorin family. It is normally obtained from Spirulina chlorophyll (*Chlorella ellipsoidea*) and other green plants [77]. Ce6 is lipophilic in nature and exhibits an asymmetric structure with three ionizable carboxylic groups in it but pH dependent [110], [111]. Ce6, (17S,18S)-18-(2-carboxyethyl)-20-(carboxymethyl)-12-ethenyl-7-ethyl-3,8,13,17-tetramethyl-17,18,22,23-tetrahydroporphyrin-2-carboxylic acid, its molecular structure, is C34H36N4O6 with a molecular weight of 596.67. Ce6 is one of the interesting classes of tetrapyrrole compounds based on their origination and photophysical properties [112]. It is well established that tetrapyrrole backbones are present in numerous biomolecules such as chlorophyll, bacteriochlorophyll, and heme and they are collectively called “pigments of life” [112]. In general, tetrapyrrole type of PS (except bacteriochlorins) tend to generate predominantly Type II (O_2) and Type I (OH) free radical species which are normally generated by PS with other structures. Although many tetrapyrrole PS agents have been employed for various PDT applications, only a few of them have exhibited their superior actions in the clinic as well as in clinical trials [32], [82]. Ce6 is highly preferred for PDT applications not only for its longer and deeper penetration of red spectra region [113] but also for its low-cost making when compared with other porphyrin-type agents and exhibiting long lifetime in their photoexcited triplet state [114]. It is evident that longer wavelength laser light always penetrates deeper than the lower one (633 nm) commonly used for Photofrin by high sensitizing efficacy and rapid elimination from the body [115] together with the higher values of interconversion coefficient (and, consequently yields high quantum of O_2 when compare to porphyrins (610–620 nm).

Hypericum

HY is a polycyclic phenanthrenedione biosynthesized by the herb *Hypericum perforatum* L belongs to the genus *Hypericum* [116]. HY is well known as St. John’s wort and is the best-described prominent representative from this genus. HY is a new class of novel PS agents exhibiting superior characteristics both *in vitro* and *in vivo* studies when compared to several other photosensitizers currently in usage and investigated [117], [118], [119], [120]. HY binds mainly to the cell membrane of multiple subcellular organelles [121], [122], [123] and metabolizes quickly *in vivo* investigations without exhibiting toxic reactions [124], [125]. It is well established that HY-PDT has shown its potential outcomes against a variety of cancer types [123], [126], [127], microbes including viruses [128], [129]. Besides, HY photosensitizer elicits superior O_2 production and a high quantum yield of fluorescence upon light irradiation [130]. The above

facts strongly support HY as a potential PS for further development and its clinical use for multiple human chronic diseases.

Besides, a secondary metabolite of *Hypericum* HY is also present in other *Hypericum* species [131], [132] and in basidiomycetes (*Dermocybe* spp.)[133],[134]orendophyticfungusgrowsin*H.perforatum* (*Thielavia subthermophila*)[135],[136],[137]. Since HY is a bioactive PS, it is applied for various clinical applications other than targetting cancer, moreover, its efficacious potentials have been assessed using various cultures of *H. perforatum* and their transgenic clones [138], [139]. Besides, *Hypericum* cultures were tested for various biotechnological applications in terms of their preservation or producing various secondary metabolites or bioactive drug leads [140], [141].

HY exhibits two broad peaks such as white light (500–600 nm) and ultraviolet (UV) light (300–400 nm) compared to many other existing second-generation PS with absorption peaks of 600 nm or above, which is suitable for deeper tissue penetration. These dual absorption peaks weaken its preference in the clinic compared to its counterparts and may be seen as a small setback. However, its current depth of UV-A light penetration is sufficient to apply for dermal and subdermal skin vasculature and may be used in other clinical practices to treat various types of carcinomas such as skin and others including nasopharyngeal, pancreatic, basal cell, bladder, and cancer [142], [143], [144], [145], [146].

Another significant plant-derived PS that was separated from the genus *Hypericum* specifically *Hypocrella bambusae* is natural hypocrellins, particularly hypocrellins A (HA) and B (HB). It is possible to convert HA to HB under certain circumstances. In fact, HY is a precursor or a parent compound of HA and HB and a soluble perylquinone derivative. Like HY, these HA, HB compounds also exhibit strong red spectra absorption peaks and have shown strong photodynamic effects on tumors [126], [127], anti-viral potency, especially against human immunodeficiency virus type I and vesicular stomatitis [128], [129].

Recent technological advancements in the isolation and synthesis of HA and HB and their mechanism of action against various cancer types offer hope for its application in PDT [6], [25], [26], [128]. More importantly, many compelling evidence suggests that apoptosis type of cell death is involved which is mostly preferred in the clinic for better PDT outcomes without having any side effects. In traditional medicine, HA and HB were both used to treat vitiligo, psoriasis, and other skin conditions. Strong photodynamic tasks, minimal dark toxic reactions, the high quantum yield of O_2, and other impressive physiochemical attributions make hypocrellins an attractive drug-lead compound in the pursuit of new and novel herb-derived PS agents [7], [8], [9], [128], [147], [148]. The above qualities led to numerous investigations for various experimental hypocrellins on the priority list as possible novel photosensitizers employed for use in PDT of various tumors and various other applications in the clinic.

Curcuma longa (*Zingiberaceae*) is mostly employed in Indian conventional medication as a therapeutic for a wide range of illnesses, which include blood, hepatic, and stomach disorders, infections, and inflammation. One of *C. Longa's* main bioactive substances is curcumin [149]. Numerous pharmacological activities, including antioxidant, anti-inflammatory, antimicrobial, antitumor, and hepatoprotective properties, have been linked to curcumin [150], [151]. In addition, curcumin is widely used in medications, food, and cosmetics. Scientists have been very interested in curcumin and curcuminoids' photoactive potential for many years [152].

According to previous investigations, curcumin fulfills all PS requirements and exhibits phototoxic effects [153], [154]. It has been determined that a daily dosage of 12 g/kg body weight of curcumin is reported as recommended and safe. The use of curcumin in anticancer research is made possible by its selectivity for the target cells. Curcumin was absorbed more preferentially or selectively by a number of tumor cell lines than by normal, healthy cells. Because of its high extinction coefficient and wide absorption spectrum between 300 nm and 500 nm, curcumin has the potential to cause significant phototoxicity even at micromolar doses [153], [154].

Mechanism of Action of PS

PDT may be a promising treatment for patients with tumors. Despite recent advancements, the mechanism of its action of many PS is poorly understood and is different from the cytotoxic effects induced by known antitumor drugs because the exact molecular mechanism of action of PDT is still subject to many research efforts. However, it is known that multiple factors play a role in governing the outcome of PDT as well as the effective mechanism of action of irradiated PS including chlorins [155], [156]. C6-PDT targets not only neoplastic cells, microvasculature, and inflammatory and immune systems of hosts. It appears clear that the combination of all these components is required to achieve long-term control of the tumor. Many well-demonstrated results have indicated that the better outcome of PDT treatment mainly depends on the type, concentration, and intracellular localization of the photosensitizer [32], [157]. In addition, light wavelength, light fluence, and fluence rate are important to ensure sufficient O_2 availability and supply [106], [155], [158]. Besides the above, it is important to ensure sufficient light reaches the target and how the PS interacts with cells subcellular localization in the target tissue/tumor

also PS should be available for a certain time interval between its application and irradiation of the target cells [159]. Besides, the conditions in which the PDR occurs as they are crucial to determining the outcome of PDT to a certain extent [34], [160].

For many PSs, mainly chlorins found mitochondria as an important sub-cellular target used in PDT because these PSs are able to induce mitochondria-mediated apoptosis and cellular damage after illumination [161]. In most cases, it is accepted that the accumulation of a PS including Ce6 in mitochondria but less with ER [162], [163] leads to the activation of the apoptotic pathway in the cell. Kessel and Poretz [164] reported that Ce6 was located in the plasma membrane and/or mitochondria and later by Ali-Seyed *et al*. [32] confirmed their findings and also reported some additional sub-cellular targets including nucleus, lysosomes, and Golgi apparatus. However, this study failed to demonstrate both Ce6 and Photolon in ER. The mechanism of action of Ce6-induced PDT (Ce6-PDT) was not clear previously because the majority of investigations concentrate on tumor cells, but its detailed mechanism is mostly started clear now. The generation of highly reactive O_2 and the formation of ROS lead to the rise of free radical stress leads to the dysfunction of mitochondria and ER function and, subsequently, to the execution of all types of death programs such as apoptosis, necrosis, and autophagy [32], [34], [164], [165]. Besides the above, chlorin-PDT induces hypoxia by altering tumor vasculature, which leads to microvascular shutdown [166], [167] and induces inflammatory and immune responses [168].

Apoptotic type of programmed cell death by anti-cancer agents is initiated by the loss of mitochondrial potential [169]. Many investigations have observed notable disorders of mitochondrial potential 3 h PDT in nearly 50% of irradiated cells. It is known that the disruption of mitochondrial potential by free radicals leads to cytochrome C release into the cytoplasm, which in turn stimulates caspase cascades, which include executioner caspase-3 at the final stage. Moon *et al*. [170] have shown Ce6-PDT both *in vitro* and *in vivo* using a rat tumor model. In this study, 3-week-old male Sprague–Dawley rats were inoculated with RK3E-ras cells, followed by the administration of Ce6 for 24 h. PDT was employed using an advanced laser diode at a light dose of 100 J/cm^2. Ce6-PDT induces apoptosis through the activation of caspase-3 and its downstream target such as PARP cleavage and the reduction of anti-apoptotic bcl-2. The *in vivo* experiments confirmed the above and demonstrated that Ce6-PDT led to a significant reduction in tumor size. These results suggest that Ce6-PDT can effectively arrest tumor growth by inhibiting cell proliferation and inducing apoptosis.

Conclusion

In summary, at present, PDT has emerged as preferred therapeutic options for multiple malignant cancers. Photosensitizer Ce6 and its synthetic counterparts have proven to be useful in designing PDT as the most promising agents for clinical use against various types of cancer. Besides, various established investigations have demonstrated that PDT under specific therapeutic windows, which are ideal and successful cancer treatment by inducing apoptotic cell death. However, one can not rule out the possibility of eliciting potential complications in Ce6-based PDT *in vivo*, which targets multiple cell types including normal cells if an inappropriate wavelength of light sources is used. Although a discussion of every perspective of chlorin PSs on their anti-cancer tested in the last few years is beyond the scope of any single review, the present review discussed mostly the anti-cancer prospects not the other important potentials like anti-microbial efficacy of this photosensitizer Ce6 and its synthetic counterparts.

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