International Journal of Nanomedicine Dovepress

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Advancing Photodynamic Therapy with Nano-Conjugated Hypocrellin: Mechanisms and Clinical Applications

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Abstract: Hypocrellin-based photodynamic therapy (PDT) is developing as a viable cancer therapeutic option, especially when enhanced by nanoconjugation. This review investigates the methods by which nano-conjugated hypocrellin enhances therapeutic efficacy and precision when targeting cancer cells. These nanoconjugates encapsulate or covalently bind hypocrellin photosensitizers (PSs), allowing them to accumulate preferentially in malignancies. When activated by light, the nanoconjugates produce singlet oxygen and other reactive oxygen species (ROS), resulting in oxidative stress that selectively destroys cancer cells while protecting healthy tissues. We look at how they can be used to treat a variety of cancers. Clinical and preclinical studies show that they have advantages such as increased water solubility, improved tumor penetration, longer circulation times, and tailored delivery, all of which contribute to fewer off-target effects and overall toxicity. Ongoing research focuses on improving these nanoconjugates for better tumor targeting, drug release kinetics, and overcoming biological obstacles. Furthermore, the incorporation of developing technologies such as stimuli-responsive nanocarriers and combination therapies opens exciting opportunities for enhancing hypocrellin-based PDT. In conclusion, the combination of hypocrellin and nanotechnology constitutes a significant approach to cancer treatment, increasing the efficacy and safety of PDT. Future research will seek to create conjugates including hypocrellin, herceptin, and gold nanoparticles to induce apoptosis in human breast cancer cells in vitro, opening possibilities for therapeutic applications.

Keywords: hypocrellin, cancer, photodynamic therapy, photosensitizer, nanoparticles

Introduction

Globally, cancer continues to be a leading cause of death primarily due to late detection and ineffective chemotherapy treatments.[1] Approximately out of the 20 million newly reported cases, 10 million deaths were estimated in 2023 based on available data.[2,3] Globally, roughly 1 in 5 men and 1 in 6 women will develop a tumor at some point in their lives, contributing to about 1 in 6 deaths.[4] Numerous ecological and lifestyle aspects, including as infrared (IR) radiation, endogenous reactive oxygen species (ROS), carcinogenic compounds, and complex pathways involving topoisomerase and nuclease activities, influence the genesis of cancer.[5] Conventional treatment options for cancer include chemotherapy, immunotherapy, radiation therapy, targeted therapy, endocrine therapy, and surgery.[6] Regrettably, the existing therapeutic interventions exhibit notable limitations, include toxicities and side effects that make dose administration difficult.[7,8] Hence, there is a pressing necessity for the development of innovative and more efficacious therapeutic approaches to enhance clinical outcomes. A minimally invasive therapeutic method for cancer and several non-cancerous illnesses is called photodynamic therapy (PDT).[9] PDT entails the elimination of undesirable cells or tissues through the induction of ROS production during photoactivation, wherein a photosensitizing agent is stimulated by light of specific wavelengths.[10] When exposed to light, photosensitizers (PSs) and non-toxic dyes, interact with oxygen to produce ROS. These ROS can harm cellular components and cause cellular death.[11] Over the years, numerous elements have been identified as playing roles in the biochemical processes of cancer, encompassing oxidative stress, ROS, and electron

Received: 7 July 2024
Accepted: 3 October 2024
Published: 1 November 2024

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transport.[12,13] The dual advantages of PDT, characterized by the selective accumulation of PSs within tumor tissue and targeted light irradiation, render it a promising therapeutic avenue for combating malignancies. The efficacy of PDT is significantly influenced by the PS, which serves as a crucial determinant.[14]

Hypocrellins are considered a promising new generation of PSs for use in PDT.[11] Hypocrellins, which comprise the following four substances- "hypocrellin A (HA), hypocrellin B (HB), hypocrellin C (HC), and hypocrellin D (HD)"-are significant PSs belonging to the perylenequinone class. These substances are taken from the stromata of *Hypocrella bambusae* and *Shiraia bambusicola*.[15,16] The fungal enzyme l-lysine α-oxidase shows notable cytotoxic and anti-proliferative effects against several forms of cancer, including prostate, ovarian, breast, and myeloid leukemia.[17] For the past two decades, hypocrellins and their derivatives have attracted a lot of interest because they can selectively build up in cancerous cells and its exceptional light-induced antiviral capabilities against viruses and cancers.[18] Because of the challenges associated with their chemical synthesis, the primary source of hypocrellin for medical applications is the fruiting bodies.[19] Research has shown that the hydrophobic nature of hypocrellins, which results in low water solubility, presents challenges in formulating pharmaceutical preparations. Various strategies, including structural alterations as well as complexation with metal ions, have been explored to address this solubility issue. However, the resulting water-soluble derivatives from these methods demonstrate significantly decreased photodynamic activity in vitro, most likely because of lower cellular absorption.[20] Alternatively, carriers like surfactants, liposomes, ceramic nanoparticles (NPs), butter oil, and amylase have all been utilized for delivering hypocrellins.[21] The development of novel techniques is intended to improve the stability, safety, and efficacy of hypocrellin delivery systems.

In addressing challenges within the field of biological sciences, a carefully integrated applied science fusion has been employed to advance the development of enhanced medical treatments, nanomedicines, as well as therapeutic technologies.[22] Thus, a shift towards integrating multiple therapeutic approaches can significantly improve cancer therapies. Nanomedicine is a fast-growing field driven by nanotechnology, improves cancer treatment by targeting cancers at the molecular level.[23] A single NP in nanomedicine can incorporate multiple treatment methods, leading to a combined or synergistic therapeutic effect.[24] Due to increasing a fascination with nanomedicine, various versatile nano-compositions such as liposomes, micelles, NPs, and nano-emulsions has been demonstrated considerable potential for delivering advanced anti-cancer drugs.[25] The administration of therapeutic compounds for cancer treatment can be greatly streamlined by using these NPs to address problems with inadequate solubility in water, unfavorable side effects that may commonly observed during medication delivery as well as increasing blood flow duration to enhance cancer accumulating.[26] In this review, we emphasized the hypocrellin-based PDT nanoconjugates leverage nanotechnology for targeted cancer therapy, generating reactive oxygen species upon light exposure, offering improved solubility, tumor penetration, and reduced toxicity, promising for further clinical investigation.

Photodynamic Therapy

A revolutionary treatment called PDT produces single oxygen that is fatal to cancer cells by transferring photoelectrons into the surrounding oxygen molecules using laser energy at a certain wavelength.[27] As a result, it is a therapy technique that works effectively for epidermoid carcinomas, with the advantages of excellent spatiotemporal selectivity and low invasiveness.[28] PDT, in addition to immediately killing cancer cells, causes an inflammatory reaction known as immunogenic cell death, which promotes the generation of tumor-associated antigens from cancer cell fragments.[29] However, the tumor microenvironment (TME) has an immunosuppressive effect, which contributes to the poor immune response under PDT.[30] Furthermore, the TME's condensed tumor extracellular matrix restricts or impedes the efficient passage of oxygen and therapeutic chemicals, reducing the effectiveness of PDT.[31] As a result, when combined with other types of treatment, PDT has a limited therapeutic effect on distal and metastatic malignancies.[32]

Mechanism of Action

The Food and Drug Administration (FDA) approved PDT over forty years ago[9] PDT involves non-toxic components that, when oxygen is present, interact to yield therapeutic effects. Singlet oxygen ($^1O_2$) is produced by a photochemical process in a PS that is triggered by light with a particular wavelength. Cell death is brought about by this singlet oxygen by the sensitizer.[33,34]

Mechanism of Photodynamic Therapy

Photodynamic therapy utilizes light-activated PSs to produce deadly ROS, including Singlet oxygen ($^1O_2$), superoxide radicals ($\cdot O^2-$), and hydroxyl radicals ($\cdot OH$). It mostly uses type I and type II mechanisms to function (Figure 1). Light is first absorbed by PSs in their ground state (S_0), which then changes into an excited singlet state (S_1 or $^1PS^*$). Subsequently, they create a triplet state (T_1 or $^3PS^*$) by intersystem crossing (ISC).[35] In the type II mechanism, the effectiveness of PDT relies heavily on the presence of oxygen (O_2), as the triplet state PS ($^3PS^*$) transmits energy straight to surrounding oxygen molecules, leading to the production of highly reactive $^1O_2$.[34,36] In the type I mechanism, $^3PS^*$ typically engages in electron transfer with cellular substrates in a biological setting, generating harmful free radicals independently of oxygen. These resulting ROS can inflict irreversible and sustained harm on cancer cells, ultimately triggering cell death through apoptosis and/or necrosis, eliciting an immune response, and causing microvascular damage.[37]

Light Source

In cancer treatment using PDT, three crucial elements are necessary in tumor tissues: a suitable light source, sufficient PSs, and O_2.[38] Of these components, selecting the appropriate light source holds significant importance as it must uniformly reach the intended region to guarantee healing efficacy. Most PSs employed in PDT exhibit peak absorption within the visible spectrum (400–700 nm).[39] Until now, four types of laser light sources have been investigated by PDT research: diode, solid-state, metal-vapor, and argon-pumped lasers. Furthermore, PDT research have investigated three sources of non-laser light: daylight, light emitting diodes (LEDs), and lamp light.[35] Numerous light sources, such as a red-light argon dye laser, solid-state laser, red-light LED lamp emitting at 635 nm, red-light lamp with a wavelength range of 570–670 nm, green light at 520 nm, blue light-emitting diode at 420 nm, and natural daylight, have found therapeutic applications.[39] These light sources only penetrate a depth of 1 to 6 mm because of two main reasons: first, different biological tissues have endogenous chromophores that can absorb visible light, like haemoglobin and cytochromes; and second, biological tissues have heterogeneous structures that cause light to diffuse, scatter, and become disoriented, which significantly affects the photodynamic effect.[40]

Photosensitizers

Photosensitizers are essential to PDT's efficacy. The best PSs for PDT are ideally versatile, amphiphilic substances that work well in biological environments. These PSs ought to have a long triplet lifespan, high molar absorption of light with

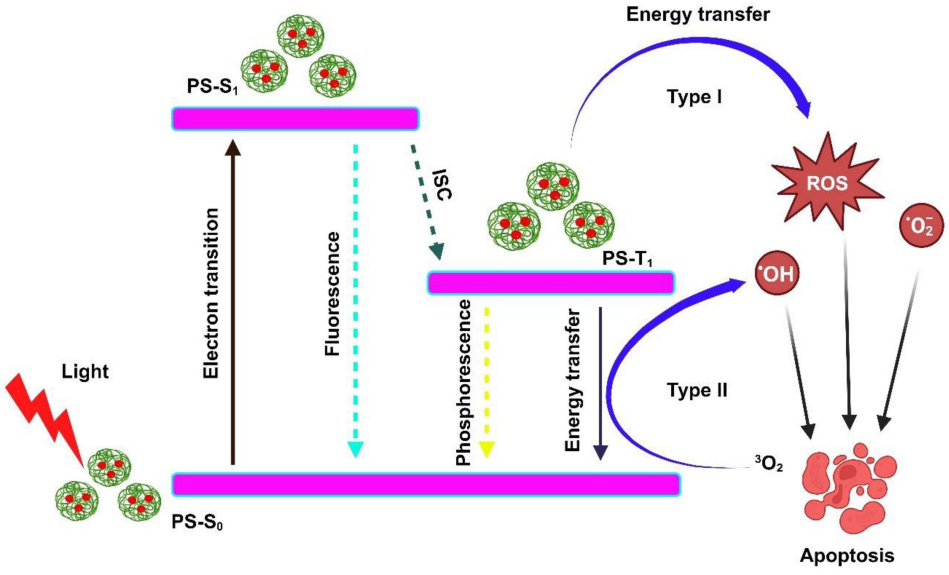

Figure 1 Mechanism of photodynamic therapy. PSs in S_0 can absorb light to change into S_1. The ISC allows the S_1 to become a T_1. ROS can be produced to cause apoptosis via direct energy transfer from T_1 to $^3O_2$ or electron transfer between T_1 and cellular substrates.
Notes: Created in BioRender. Chandran, R. (2024) BioRender.com/v43i631.

extended wavelengths, and an exceptional quantum yield for $^1O_2$. They should also be non-toxic when exposed to no light.[41] In PDT research, numerous PSs have undergone assessment both in vivo and in vitro; however, only a limited selection has shown optimal characteristics. Consequently, recent research has concentrated on developing and assessing the effectiveness of new PSs.[34] During PDT, harmless PSs are administered systemically, capable of accumulating within cells and inducing cytotoxicity. Multiple studies have indicated the utilization of various substances as PSs in PDT.[42]

Mechanisms of Cell Death in PDT

Although PDT can control a variety of cellular communication processes, its main objective is usually to cause cell death. Numerous routes by which mammalian cells die have been made clear by recent discoveries, including those that are brought on by PDT. The process and severity of cell death can be affected by the concentration, physicochemical characteristics, and intracellular position of the PS, as well as by oxygen concentrations, the right wavelength and intensity of light, and cell-specific characteristics.[43,44]

PDT-Mediated Autophagy in Cancer Cells

The PDT impact can result in either if a cell deaths apoptotically or not, contingent on the level of light exposure and NPs-PS administered.[45] When exposed to light, the NPs-PS localized in the lysosome degrades and eventually kills the cell. PDT produces enough ROS to cause apoptosis; in the absence of ROS, autophagy is triggered to ensure cell viability. Elevated B cell lymphoma-2 (Bcl-2) protein levels protect cells from phototoxicity caused by PDT.[46] In some circumstances, PDT-induced autophagy precedes apoptosis. Type I and III phosphoinositide 3-kinase proteins control the sequestration of cytoplasmic material.[47] After PDT, anti-apoptotic Bcl-2 protein was expressed more frequently in resistant mouse cells, which resulted in non-apoptotic cell death.[48] However, other research indicates that the Bcl-2 protein prefers to bind with Beclin-1, which inhibits the autophagic response that causes PDT resistance.[49] Damage to cells caused by PDT causes some cellular components to break down and recycle, which starts the pro-survival process of autophagy (Figure 2).[50] Upon activation within the mitochondria, the PS generates ROS, reducing adenosine triphosphate

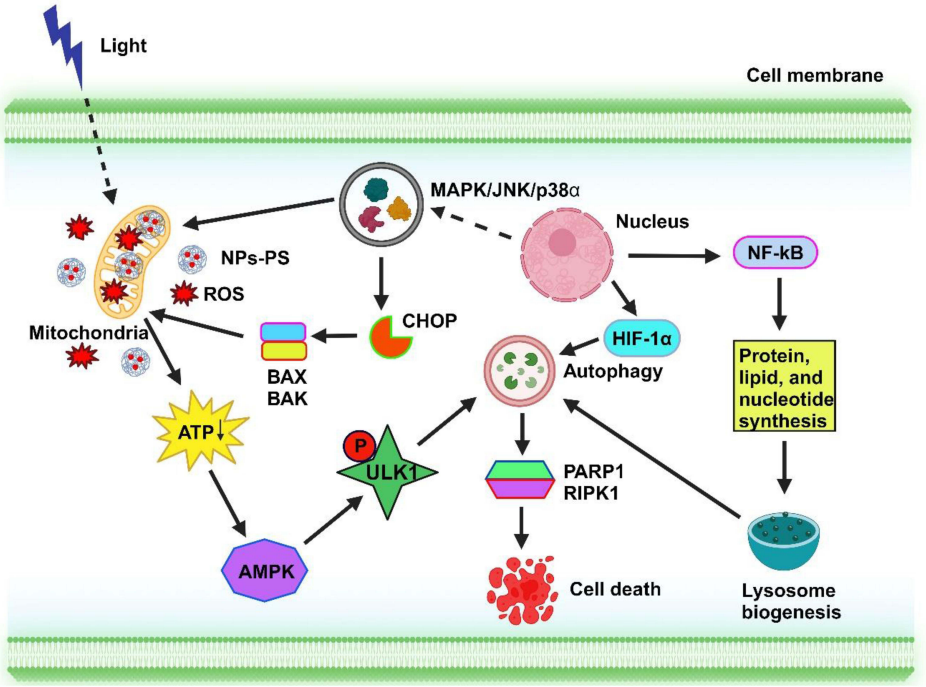

Figure 2 Response of autophagy to photodynamic treatment. When NPs-PS is activated in the mitochondria, ATP synthesis is reduced, and ROS generation is increased. Autophagy is triggered by the activation of ULK1 by energy sensing AMPK. To start lysosome biogenesis and autophagy, PDT can also activate the autophagy machinery NFκB, which is involved in protein, lipid, and nucleotide synthesis. Through MAPK, CHOP, and HIF-1α, mitochondrial photo-oxidation can transcriptionally control autophagy.

Notes: Created in BioRender. Chandran, R. (2024) BioRender.com/h14r744.

(ATP) production. AMP-activated protein kinase (AMPK) detects this ATP decrease, activating autophagy via autophagy-initiating kinase 1 to reprogram metabolism. Additionally, cytoplasmic photodamage in PDT increases the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB) and autophagy via HIF-1α/VIMP1 and mitogen-activated protein kinase (MAPK)1/3 pathways.[51,52] Autophagy activating kinase 1 (ULK1) is activated by the energy-sensing AMPK to initiate autophagy. By encouraging the synthesis of proteins, lipids, and nucleotides to start lysosome formation and autophagy, PDT can also activate the autophagy machinery through NFkB. Furthermore, autophagy can be transcriptionally regulated by photooxidation of mitochondria through the actions of MAPK, C/EBP homologous protein (CHOP), and hypoxia-inducible factor 1-alpha (HIF-1α).[53] Moreover, circumstances such as a lack of nutrients and oxidative stress brought on by ROS produced during PDT can support the activation of autophagy.[53]

PDT-Mediated Apoptosis in Cancer Cells

After PDT-induced organelle disintegration, apoptosis pathways are initiated through various techniques.[34] When the PS is in mitochondria, apoptotic cell death occurs with direct damage, leading to Bcl-2 degradation and cytochrome c (Cyt c) release.[54] When PDT induces apoptosis in mammalian cells, caspases mediate both the extrinsic pathway, regulated by tumor necrosis factor receptors (TNF-R) death domains protein, and the intrinsic pathway, which the Bcl-2 protein family controls.[55] The extrinsic apoptotic pathway is initiated by apoptotic genes such as death receptor 5 (DR5), Fas, and tumor protein (p53), which are linked to PMP22.[6] The Golgi-mediated trafficking of Fas receptors may be facilitated by p53 overexpression, which could lead to an increase in Fas surface expression. This enables p53 to cause cells to undergo Fas-mediated apoptosis before experiencing transcription-dependent effects.[56] T cells generate FasL and interact with Fas to initiate activation.[57] Like how tumor necrosis factor-α (TNF-α) related apoptosis-inducing ligand (TRAIL), or TNF-α related apoptosis-inducing ligand, activates the caspase-8 pathway to cause apoptosis and activate DR5.[58] The intrinsic pathway activates proapoptotic members of the Bcl-2 family, such as Bcl-2-associated X protein (Bax), p53 upregulated modulator of apoptosis (Puma), and proteins possessing Bcl-2 homology-3 (BH3) (Noxa).[59] Bcl-2 family activation and the domain-only death agonist protein (BID) and BH3 proteins aid in the development of mitochondrial pores, which permits Cyt c release. After being dormant in the cytoplasm, BID is triggered by TNF-R and cleaved by caspase-8, which in turn causes Bax activation and the creation of apoptosomes in the mitochondria. The connection between intrinsic and extrinsic pathways is made by BID.[2] By encouraging Cyt c and apoptotic protease-activating factor 1 (Apaf-1) to be released from mitochondria and assemble with procaspase-9 to activate caspase-9, p53 is associated with the activation of apoptosomes.[60] While caspase-9 observes alterations in the mitochondria, the signaling by death receptors is detected by caspase-8. They trigger the stimulation of caspase −3, −6, and −7, which are effector caspases, which cleave vital cellular targets that maintain homeostasis (Figure 3).[6]

Hypocrellins as PSs

In the 1980s, a research group began studying hypocrellins, which are natural PSs derived from a parasitic fungus called *Hypocrella bambusae sacc*. found in China. These hypocrellins consist mainly of two components: HA and HB, 95% of them.[61] However, under alkaline conditions, HA can transform into HB through dehydration. Understanding the mMolecular processes was the study's main objective underlying the photodynamic effects of HA and HB as well as their chemical structures, photophysics, and photochemistry were studied by He et al, 2000.[62] Prof. Petrich from the University of Iowa in the USA researched the antiviral effects and toxicity of hypocrellins, comparing them with hypericin.[63,64] Additionally, other scientists and research groups contributed significantly to understanding various aspects of hypocrellins, including their excited state properties, structural alterations, photosensitization mechanisms, quantum-chemical analysis, and the damage they cause to biomolecules like lipids and DNA during photodynamic processes.[65–69]

Enhanced Ability of PSs to Generate ROS

Beyond enhancing the stability and targeting capabilities of PSs, additional progress in improving the efficiency of ROS generation remains necessary.[70] The photodynamic impact of PSs based on type II is measured by the quantum yield of $^1O_2$ production. Increasing the ISC rate constant by adding heavy atoms or 2,2,6,6-tetramethyl-piperidinyloxy (TEMPO), lowering the energy gap (ΔE_{ST}) between S_1 and T_1 or including groups that give electrons or take them away from the

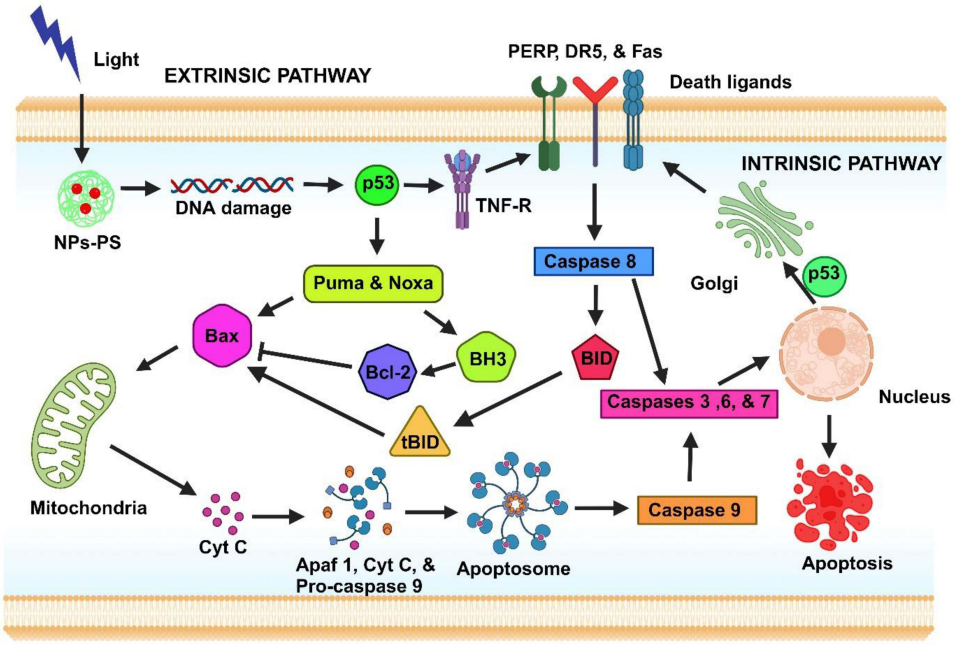

Figure 3 Apoptosis reaction to photodynamic therapy: Apoptotic pathways involve intrinsic (Bcl-2 family activation leading to mitochondrial permeability and cytochrome c release) and extrinsic (TNF-R superfamily activation by FasL and TRAIL) pathways that converge on caspase activation (caspase-9 via apoptosome and caspase-8 via death domain activation) to cause cell death.
Notes: Created in BioRender. Chandran, R. (2024) BioRender.com/u70h553.

conjugated structure are some ways to boost the generation of ROS in PSs.[71] For instance, Zhou and associates a Pt(II)-based supramolecular coordination complex with a Ru(II) polypyridyl complex to form the metallic heterometallic cycle Ru-Pt in metallic heterometallic cycle Ru-Pt in near-infrared (NIR)-triggered PDT. Pt's heavy atom effect is responsible for the extraordinary $^1O_2$ generation quantum yield seen in this Ru-Pt combination. Studies conducted in vivo confirmed that Ru-Pt can effectively suppress tumor growth when exposed to modest light doses.[72] TEMPO can enhance the ISC rate not only through the heavy atom effect but also through a radical-triplet pair mechanism. When TEMPO was added to Cy7 dyes, the resultant dye combination showed a higher quantum yield of $^1O_2$ production than Cy7.[73] It is possible to enhance the energy transfer from ^{3}PS* to O_2 and raise the ISC rate with a small ΔE_{ST}, indicating that lowering the ΔE_{ST} of PS can effectively increase the quantum yield of $^1O_2$. Phenyl-substituted DPP (PDPP) and thienyl-substituted DPP (TDPP), two DPP derivatives, were successfully synthesized by Shi et al.[74] Groups that donate and withdraw electrons have an impact on complicated energy levels and improve the ISC process. For example, compared to a Ru(II) PS without coumarin (Ru2), a Ru(II) PS modified with coumarin (Ru2) exhibits a reduced capacity for oxidation and a greater coefficient of extinction, which results in increased ROS production effectiveness.[75] A variety of push-pull AIEgens with enhanced $^1O_2$ production capacity are produced by combining diphenylamine with various carbazolyl ring electron-withdrawing groups.[76] Size, shape, heteroatom doping, and surface state tuning can all be used to improve semiconductor nanomaterials' ability to generate ROS efficiently.[39]

Accumulation of Nano-Conjugated Hypocrellin in Cancer Cells

Hypocrellin is a natural pigment derived from fungi of the genus *Hypocrella* that has shown significant promise in PDT due to its capacity to produce ROS upon exposure to light, leading to select in cancer cells.[77] The specificity of hypocrellin for cancer cells is enhanced by selective uptake, targeted delivery, TME, and cellular uptake processes, all of which contribute to PDT efficacy. However, difficulties like poor solubility, quick elimination, and nonspecific distribution in vivo have hindered its clinical translation.[78] To get around these restrictions scientists have developed nano-conjugated hypocrellin formulations using nanotechnology.[22] These nanostructures, usually made up of biocompatible substances like lipids, polymers, or inorganic NPs, serve as carriers to encapsulate and deliver hypocrellin to tumor sites

with enhanced specificity and efficacy.[79] Selective accumulation in cancer cells by nano-conjugated hypocrellin relies on several key mechanisms.

Enhanced Permeability and Retention Effect

Nano-conjugated hypocrellin formulations harness the enhanced permeability and retention (EPR) effect is a phenomenon that exploited in cancer therapy (Figure 4). The EPR effect arises from the unusual tumor vasculature, defined by fenestrations and discontinuous endothelial lining, coupled with poor lymphatic drainage. These structural anomalies facilitate the preferential accumulation of NPs within the tumor microenvironment.[80] When encapsulated within nanocarriers, hypocrellin can exploit this passive targeting mechanism, allowing for its selective delivery to cancerous tissues while minimizing exposure to healthy cells.[81] As NPs extravasate through leaky blood vessels and accumulate in the tumor interstitium, they remain retained due to impaired lymphatic drainage, thereby enhancing drug concentration specifically at the tumor site.[82] This targeted approach not only improves therapeutic efficacy by maximizing drug availability within tumors but also reduces systemic toxicity associated with conventional chemotherapy.[83] By capitalizing on the EPR effect, nano-conjugated hypocrellin formulations offer a viable approach that reduces harmful effects on healthy tissues while improving the selectivity and efficacy of cancer treatment.[2]

Active Targeting

In addition to benefiting from passive accumulation, nano-conjugated hypocrellin adapted to specifically target cancer cells through surface engineering. By integrating specific focusing on ligands like small compounds, peptides, and antibodies onto the surface of the NPs, a high level of precision can be achieved.[84] To be able to precisely target and recognize overexpressed the surface of cancer cells has receptors and enable accurate targeting and absorption of the NPs into the malignant cells, these ligands have been carefully selected.[85] By increasing the selectivity of medication delivery to malignant tissues, this active targeting strategy maximizes therapeutic efficacy while decreasing off-target effects on healthy cells.[86] Furthermore, the use of targeting ligands can improve the pharmacokinetics of the nano-conjugated hypocrellin by increasing its circulation time and reducing its clearance from the bloodstream.[87] Through active targeting, nano-conjugated hypocrellin holds great promise as an extremely productive and precise therapeutic

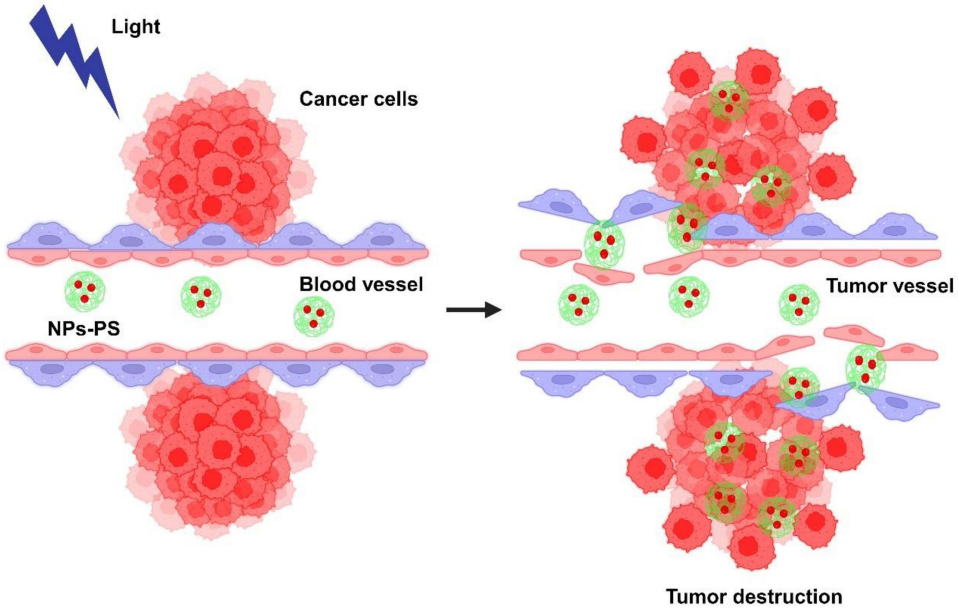

Figure 4 Enhanced permeability retention through NPs-PS mediated PDT. For efficient PDT therapy, NPs-PS can be employed as a photosensitizing carrier. The NPs-PS integrin interaction and PS irradiation increase the permeability of tumor vasculature and the number of NPs that accumulate in tumor tissues.
Notes: Created in BioRender. Chandran, R. (2024) BioRender.com/l56m638.

representative of cancer treatment, offering the possibility of enhanced therapeutic results and decreased toxicity in the system compared to conventional chemotherapy approaches.[88,89]

Controlled Release

Nano-conjugated hypocrellin formulations present a strategic avenue for precise drug delivery, particularly in cancer treatment. By leveraging the distinctive characteristics of NPs, these formulations can be customized to enable controlled release of hypocrellin specifically at tumor sites, ensuring prolonged exposure and optimized therapeutic effects.[90] The incorporation of stimuli-responsive nanocarriers further refines this precision, facilitating dynamic adjustment of drug release caused by environmental factors such as pH, temperature, or light.[91] This adaptable nature not only allows for precise timing and location of drug delivery but also mitigates unintended effects, thus reducing overall systemic toxicity.[92,93] Additionally, the nanocarriers can preferentially release hypocrellin, enhancing its accumulation within tumors via nanoparticle-based passive targeting, active targeting, and combination of chemotherapy and PDT.[88] This targeted delivery approach shows promise as a tactic to improve the safety and effectiveness of cancer therapy, providing a sophisticated solution to the challenges associated with conventional chemotherapy and ultimately improving patient outcomes.[94]

Multimodal Imaging and Therapy

Nano-conjugated hypocrellin extends beyond PDT, serving as a versatile platform for integrating various techniques in cancer treatment. Using contrast agents or fluorescent dyes as imaging agents within the nanostructures, these formulations not only deliver therapeutic agents to targeted areas but also enable simultaneous visualization of tumor localization and real-time monitoring of treatment response.[95] This multidimensional approach enables personalized assessment of treatment efficacy, empowering clinicians to monitor tumor responses over time. Moreover, by delivering immediate feedback on treatment outcomes, this integration supports the implementation of tailored treatment strategies that closely match each patient's unique needs.[96] Ultimately, this holistic approach holds significant potential for improving therapeutic outcomes in cancer care by offering adaptable and precise management strategies.[97]

PDT Systems Mediated by Nanoparticles

In addition to light-delivery techniques, third-generation photosensitizing agents—an means attempt of improving treatment efficacy—involves delivering PS in the form of NPs, either with or without active targeting.[98] PDT-NPs are intended to improve kinetics and dispersion properties, ease multimodal therapy, and/or address biocompatibility issues related to free PS. These factors become particularly important when working with more recent organic or inorganic PS constructions since they necessitate striking a compromise between efficacy and biocompatibility.[99] Third-generation PDT mostly uses nanoparticle systems, while there are advantages to using traditional molecular PSs in conjunction with antibodies, folate moieties, or other small compounds.[100] Lipid nanoparticles (LNPs) and their derivatives are frequently used in NPs-based PDT. Lipid-based structures are referred to as LNPs. These structures include solid LNPs, liposomes, and micelles. Due to their proven stability, biocompatibility, favorable distribution characteristics, controlled drug release kinetics, potential for active targeting using aptamers, ability to deliver other anti-cancer medications concurrently, and capacity to make drugs that are inherently toxic safe for human use, these LNPs are PSs.[101]

Polymeric NPs, specifically poly-lactic-co-glycolic acid (PLGA), are another widely used nanocarrier platform for PSs in addition to LNPs. While PLGA is not as sophisticated as LNPs in this aspect, it's been widely used to administer chemotherapy drugs in preclinical and clinical settings.[100] In comparison to LNPs, PLGA has some advantages in the PS delivery process. It is particularly good in encasing extremely hydrophobic medications, such as those made from phthalocyanates, hypocrellins, and porphyrins.[102] Because of its more stiffness, less permeability, and thicker walls, PLGA also shows a tendency to be more stable and to release drugs at slower rates than LNPs.[103] This property of PLGA is helpful for PDT even if it could make it more difficult to achieve a gradual release with chemotherapy drugs. It permits a prolonged duration of PS stability in tissue prior to mild activity at the location of illness. These characteristics have been beneficial to PLGA perform well in several preclinical PDT studies. For example, compared to the PS alone, experiments employing in ovarian cancer cells, hypericin-loaded PLGA has demonstrated enhanced photoactivity and therapeutic efficiency.[104] Preclinical research has been done on several other constructions that combine PSs with NPs in

addition to the widely used LNP and polymeric NPs platform. These comprise inorganic systems like fullerenes, dendrimers, nanosilica, and gold nanoclusters.[103,105–107] Although these alternative architectures exhibit certain advantageous qualities, none of them have yet managed to attain the perfect equilibrium of toxicological profile, biodistribution, biocompatibility, and clinical application information found with LNPs and polymeric NPs. There is still more research being done on the use of NPs in PDT; one particularly intriguing potential is light-independent activation, which may be accomplished by ionizing radiation.[108]

Benefits of PDT Utilizing Hypocrellin

Previous studies suggest that hypocrellin's dependence on UV or blue light activation is a disadvantage when using it for clinical PDT. Because of its restricted dissolution in water and a lipophilic structure in molecules, hypocrellin aggregates inside blood plasma.[109,110] After intravenous injection, this aggregation may cause significant circulatory system obstructions. Chemical changes to increase hypocrellin's solubility in aqueous solvents and changes to the excitation wavelength toward the red or NIR spectrum are required to enable the use of hypocrellin in PDT for deeper tissue treatment.[111] As PSs, hypocrellins have certain interesting characteristics, such as their rapid excretion from the body and their light-triggered antiviral and anticancer effects. These qualities make hypocrellins attractive options for phototherapy (PT)-acquired cancer, maybe including skin cancer treatment.[112] When exposed to light, hypocrellins efficiently create singlet oxygen. In addition to producing ROS, cell phototoxicity is partially attributed to hypocrellin radicals. Mitochondria and microsomal enzymes can be harmed by anions of semiquinone radicals generated from HA and HB. Lipid peroxidation of the membranes results from this, which can cause necrosis or apoptosis. Even in hypoxic environments, hypocrellin-based PDT can make human tumor cells more sensitive to radiation and chemotherapy.[113] The small wavelength at which hypocrellins absorb light (less than 600 nm) is a major drawback for PT.[114] Hypocrellins have been shown to bond with lipids, and some research has suggested that There may be a concentration of hypocrellin and its derivatives in the cell membranes, mitochondria, and lysosomal compartments.[115] Apoptosis or necrosis brought on by lipid membrane peroxidation can both cause cells to die.[116] In cancer PT, hypocrellins-light-exposed proteins having antiviral and anticancer properties-have been effectively employed to treat skin and breast cancer.[117,118] Natural PSs for PDT have two key benefits: they selectively act against cancer cells and have little systemic cytotoxicity to normal cells.[109] The advantages of PDT make it a promising adjunct to conventional treatments, as well as a means of treating and diagnosing neoplastic alterations.[115]

Hypocellins Functioning as PDT Agents

There have only been a few studies done up to this point. Table 1 summarizes important hypocrellin-PDT research and shows the results of PDT and PSs in both in vitro and in vivo situations. The study demonstrated that HA and HB are effective PDT agents because to their unique configuration in lab settings, especially in cancer cells.[119] The results of the study showed that HB's photodynamic action significantly inhibited cell growth and resulted in damaging the structure and function of the mitochondria in cells associated with ovarian cancer when exposed to LED light. The significance of mitochondrial damage as a critical component of HB's PDT for ovarian cancer is therefore highlighted.[120] The potential of HA as a PS to target A549 cells in vitro was investigated in a different investigation. One of the first steps towards cellular death has been identified as HA-induced oxidative damage, which interferes with the protective NF-κB signaling pathway. Due to this disturbance, there was a mitochondrial Cyt c release, changes in the potential of the mitochondrial membrane, activation of caspases, and ultimately apoptosis.[121] The study discovered that while transcutaneous PT with ethanolaminated HB had no effect on the skin, it permanently eliminated EMT6/Ed tumors on the flanks of Balb/c mice.[112] According to the research, nitric oxide has cytoprotective properties. Therefore, using pharmacological agents that modify nitric oxide or nitric oxide synthase in HepG2 cells should improve the effectiveness of HB in PDT.[122] Another study found that HB-LED PDT causes A431 cells to undergo apoptosis through a route mediated by mitochondria, providing a strong foundation for the creation of cutting-edge therapy strategies to address cutaneous squamous cell carcinoma.[123] PDT with HB caused collagen destruction, as demonstrated by a study and other findings. This provides strong reasons to investigate the therapeutic potential of HB-LED PDT for diseases like keloids or additional fibrotic skin conditions.[124]

Table 1 Hypocrellin-PDT Research in Both in vitro and in vivo Studies

Photosensitizer	Wavelength (nm)	Experimental Model	Observation	Reference
Hypocrellin A (HA) and Hypocrellin B (HB)	Unknown	CNE2, TW0-1, CCL-220.1, and SD cells	HA and HB are effective PDT agents because to their unique configuration in lab settings, especially in cancer cells	[119]
HB	470	HO-8910 cells	After receiving PDT, HB's mitochondria displayed significant damage, including enlarged mitochondria with almost nonexistent cristae and a markedly reduced mitochondrial membrane potential.	[120]
HA	470	A549 cells	Following PDT, the effects of HA-mediated cytotoxicity and apoptosis in human lung adenocarcinoma A549 cells were assessed.	[121]
HB	630	BALB/C mice	BALB/C mice's EMT6/Ed tumors forming in their flanks are permanently abated by transcutaneous phototherapy with HBEA-R1, with little adverse effects.	[112]
HB	463	HepG2 cells	HepG2 cells containing Nω-monomethyl-L-arginine (L-NMMA), an inhibitor of nitric oxide synthase (NOS), and 2-(4-carboxyphenyl)-4, 5, 5-tetramethylimidazoline-1-oxyl-3-oxide (cPTIO), a scavenger of nitric oxide (NO) increased caspase-3, −9 activation and apoptosis mediated by HB/light, while dramatically reducing NO production as measured by DAF fluorescence.	[122]
HB	300–700	A431 cells	In these A431 cells, HB-LED PDT increased nuclear fragmentation and suppressed proliferative activity. HB-LED PDT caused A431 cells to undergo apoptosis, produce more reactive oxygen species, and reduce mitochondrial activity.	[123]
HB	Unknown	KFB cells	KFB cell viability was significantly reduced, and apoptosis was triggered by HB-LED PDT therapy. In KFB cells, HB-LED PDT treatment significantly increased BAX overexpression and decreased BCL-2 downregulation, which raised intracellular free Ca2+ and activated caspase-3.	[124]
HB	630	A549 cells, BALB/C mice	In vitro experiments revealed that HB–P-NPs were more phototoxic than HB-NPs. The anticancer activity of free HB, HB-NPs, and HB-P-NPs improved in that order in the animal trial.	[88]
HB	543	HeLa cells	Lipid-HB-AuNCs compound allows for one-time injection of irradiation for antitumor treatment and two-photon photothermal/photodynamic cancer therapy in vitro.	[125]
HB	470	MDA-MB-231 cells	The photodynamic action of HB exposed to LEDs has the potential to cause apoptosis and substantially destroy breast cancer cells. This shows that LED-activated HB is a viable treatment option for breast cancer.	[118]
HB	470	HO-8910 cells	The new LED source's blue light could effectively activate HB, and when HB is activated by blue light, it can seriously harm ovarian cancer HO-8910 cells.	[14]
HA, HB, and Hypocrellin Y (HY)	580–620	CNE2, TW0-1, CCL-220.1, and SD cells	The caspase proteases that HA, HB, and HY generated tumor cell killing also show that HB is a more potent and potential PS for the treatment of mucosal cancer cells.	[126]
HB	560	MCF-7 cells	Experiments conducted in vitro have shown that HB doped NPs are efficient in PDT-killing tumor cells.	[127]
HB	470	HeLa, SMMC-7721, SGC-7901, and A549 cells	Tumor cells have been shown to actively absorb HB-GO through in vitro experiments, and radiation treatment significantly damages these impregnated cells.	[111]
Hypocrellin SL052	665	SCCVII cells	The formulation of SL052 in PLGA-NPs maximizes the benefits of nanotechnology, making this PS extremely effective for cancer PDT and increasing the likelihood that it will be used in clinical settings.	[128]
HB	470	HO-8910 cells	When it comes to two-photon PDT on solid tumors and mucosal cancer, HB may be a highly promising agent.	[129]
2-butylamino-2-demethoxy-hypocrellin A (2-BA-2-DMHA)	600–700	MGC803 cells	2-BA-2-DMHA exhibits significant red spectral absorption, very low dark cytotoxicity, and outstanding photo potentiation properties; phototoxicity primarily results in death in MGC803 cells.	[130]
HA and HB	580–620	CNE2, TW0-1, and NPC cells	In CNE2 and TW0-1 cells, larger quantities of HA and HB were shown to raise the levels of Fas and FasL, which in turn exacerbated the phototoxic effects of PDT.	[131]
HB	470	MGH cells	The PDT action mediated by HB targets the tumor vasculature, hence leading to tumor mortality, and is suggestive of a mostly vascular-driven response during brief drug-light intervals in MGH cells.	[132]

Furthermore, studies showed that after PDT, those receiving HB-P-NPs had improved treatment outcomes against lung cancer. As a result, PDT in addition with chemotherapy, which used hyaluronic acid-ceramide NPs for targeted administration, increased PDT's effectiveness in treating lung cancer in vivo in mice.[88] According to a different study, cancer cells internalize HB-loaded gold nanocages, and the photothermal effect significantly increases the photodynamic anticancer treatment when the cells are subjected to two photons of light.[125] Another study suggested that when exposed to light from diodes that emit light, the photodynamic impact of HB successfully eliminated breast cancer cells and caused apoptotic cell death. This suggests that LED-activated HB is a promising treatment for breast cancer.[118] Another finding showed that HB was effectively

triggered by blue light from LED sources, which led to the death of HO-8910 cells. This implies that using blue light to activate HB may be a therapeutic strategy that is promising in the fight against ovarian cancer.[120] According to a different study, HA, HB, and HY-induced tumor cell demise is mediated by caspase proteases. Furthermore, it was discovered that HB is a more effective and promising PS for mucosal cancer cell targeting.[126] The in vitro study demonstrated that HB-doped NPs efficiently kill tumor cells by PDT, providing a unique way to target the acidic interstitial fluid seen in many tumor forms.[127] It has been demonstrated in lab experiments that HB-graphene oxide is actively incorporated into the cytoplasm of tumor cells, causing substantial harm to these invaded tumor cells upon radiation exposure.[111] According to the study, adding hypocrellin PS (SL052) to PLGA-NPs optimizes the advantages of nanotechnology and increases PS's effectiveness for cancer PDT, which raises the possibility that it will be used in clinical settings.[128] Another finding revealed that in an in vitro investigation, PDT with HB dramatically increased the induction of both apoptosis and prevented the adhesion and cancer cell migration.[129] An antisense bcl-2 RNA retrovirus vector was used in another investigation to investigate the effects of photosensitization by 2-butylamino-2-demethoxy-hypocrellin A (2-BA-2-DMHA) on the human gastric adenocarcinoma MGC803 cell line.[130] In a different study, HA and HB were used to induce increased levels of Fas and FasL in CNE2 and TW0-1 cells, which higher concentrations were associated with an increase in PDT's phototoxic effects.[131] The study confirms that in the human bladder tumor (MGH cell line) model, the PDT effect mediated by HB is suggestive of a predominantly vascular-mediated response during short drug-light intervals. This implies that PDT targets the tumor vasculature, hence contributing to tumor death.[132]

Clinical Implication of Hypocrellin

An adverse consequence of PDT therapy that is clinically notable for patients is phototoxicity of the skin. Following an intravenous injection, patients using clinically authorized PDT medications, such as verteporfin and porfimer sodium, are needed to refrain from light exposure for a few days or even weeks.[133] However, several clinical studies have demonstrated that PDT is an effective treatment for people with neovascular age-related macular degeneration (AMD) who have subfoveal and juxtafoveal lesions, which are diagnostic of choroidal neovascularization (CNV).[134] As of right now, verteporfin is the only PS that is authorized for the therapeutic treatment of AMD neovascularization.[135] When verteporfin is delivered clinically, a red laser is used to absorb light at a wavelength of 686 nm for a maximum of 83 seconds. Although deeper tissue penetration is made possible by activation by light in the red area of the spectrum, this process also carries a higher risk of damaging healthy tissues.[136] Furthermore, the skin phototoxicity and pharmacokinetics of liposomal hypocrellin B (LHB) in vivo and in a CNV-modeling rat was studied to analyse the safety and efficacy of PDT. The findings provide valuable preclinical information for the treatment of AMD with LHB.[133]

Future Perspectives

This review discussed the prospective uses of nano-conjugated hypocrellin-based PDT in cancer treatment, emphasizing its targeted delivery, enhanced therapeutic efficacy, and ongoing attempts to optimize clinical translation. A rising number of researchers are interested in using targeted delivery systems and nanotechnology to improve tumor accumulation and decrease off-target effects while also increasing the specificity and efficacy of formulations based on hypocrellin. It is still important to comprehend the complex processes behind hypocrellin-mediated PDT, including how the tumor microenvironment, immune response, and therapy effects interact. Conducting well planned clinical studies to assess safety, efficacy, and long-term outcomes in cancer patients is also necessary to translate preclinical discoveries into clinical practice. All things considered, hypocrellin PDT research has enormous potential to transform cancer treatment by providing efficient, focused, and less intrusive treatment choices.

Conclusion

In conclusion, using the special photosensitizing abilities of hypocrellins to cause tumor-specific cytotoxicity, hypocrellin-based PDT is a potentially effective cancer treatment strategy. Preclinical research has made great strides, but before hypocrellin PDT is extensively used in clinical practice, several obstacles must be resolved. Future research efforts should prioritize addressing formulation difficulties, clarifying therapy mechanisms, investigating combination tactics, carrying out thorough preclinical validation, and progressing clinical translation. Hypocrellin PDT has the capacity to revolutionize cancer treatment by addressing these issues and utilizing interdisciplinary cooperation. This would allow

patients to receive individualized, minimally invasive, and effective treatment alternatives that improve their quality of life and outcomes. Future research must investigate the effectiveness of hypocrellins against different types of cancer cells using preclinical experimental animal models, in vitro models, and human trials. Developing nano formulations (Hypocrellin-Herceptin-Gold nanoparticle conjugates) to induce PDT apoptosis in human breast cancer cells in vitro will be the future focus of our study.

Acknowledgments

The University of Johannesburg and the Laser Research Centre are acknowledged by the authors for their contributions to this review study. The authors also thank the South African Research Chairs Initiative of the National Research Foundation and the Department of Science and Innovation (SARChI/NRF-DSI, Grant No. 98337) for their financial support. Every figure was created with BioRender.com.

Disclosure

There are no disclosed conflicts of interest by the authors of this study.

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