FABAD J. Pharm. Sci., 51, 3, 1513-1536, 2026
Doi: 10.55262/fabadeczacilik.1925104
REVIEW ARTICLE

A Current Alternative to Conventional Cancer Treatment Strategies: Photothermal Therapy

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SUMMARY

Photothermal therapy is a minimally invasive treatment modality that uses light-absorbing agents to convert light into heat, thereby targeting tumor tissues. Near-infrared light, typically in the 700-2000 nm range, is employed to generate localized hyperthermia. Photothermal agents, including gold and copper sulfide nanoparticles, carbon nanotubes, graphene-based materials, and organic dyes, induce tumor cell death by increasing the temperature within the tumor microenvironment. Treatment efficacy depends on factors such as irradiation time, fluence rate, laser wavelength, and the biocompatibility of the materials used. Biodegradable organic structures have recently attracted considerable attention because of their improved safety and clearance profiles. When combined with nanoscale drug delivery systems, these materials can enhance tumor accumulation and tissue penetration. Furthermore, combining photothermal therapy with chemotherapy, photodynamic therapy, or immunotherapy produces synergistic effects, resulting in improved therapeutic outcomes.

Keywords: *Photothermal therapy, cancer, photothermal agents, nanoscale structures, combination therapy*

Konvansiyonel Kanser Tedavi Stratejilerine Güncel Bir Alternatif: Fototermal Terapi

ÖZ

Fototermal terapi, ışık emici ajanlar aracılığıyla ışığın ısıya dönüştürülmesini sağlayarak tümör dokularını hedefleyen minimal invaziv bir tedavi yöntemidir. Bu yaklaşımda genellikle 700-2000 nm aralığındaki yakın kızılötesi ışık kullanılarak lokalize hipertermi oluşturulur. Altın ve bakır sülfür nanopartikülleri, karbon nanotüpler, grafen bazlı materyaller ve organik boyalar gibi fototermal ajanlar, tümör mikroçevresindeki sıcaklığı artırarak tümör hücre ölümünü indükler. Tedavi etkinliği; ışınlama süresi, akıcılık oranı, lazer dalga boyu ve kullanılan malzemelerin biyouyumluluğu gibi faktörlere bağlıdır. Biyobozunur organik yapılar, gelişmiş güvenlik ve vücuttan uzaklaştırılma özellikleri nedeniyle son yıllarda önemli ölçüde ilgi görmektedir. Bu yapılar nano boyutlu ilaç taşıyıcı sistemlerle birleştirildiğinde, tümörde birikimi ve doku penetrasyonunu artırabilmektedir. Ayrıca fototermal terapinin kemoterapi, fotodinamik terapi veya immünoterapi ile kombinasyonu sinerjik etkiler oluşturarak tedavi etkinliğini artırmaktadır.

Anahtar Kelimeler: *Fototermal tedavi, kanser, fototermal ajanlar, nano ölçekli yapılar, kombinasyon tedavisi*

Recieved: 07.04.2026
Revised: 17.09.2026
Accepted: 24.09.2026

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INTRODUCTION

Cancer metastasis is a serious problem in society and contributes to increased mortality rates. Cancer metastasis is a complex, multi-step process that leads to great diversity. This process results in the spread of cancer cells from the primary tumor tissue to surrounding non-cancerous cells and/or the systemic circulation.

Currently, treatments such as surgery, radiotherapy, and chemotherapy are used to improve and prevent tumor cell metastasis. However, all these treatments are sometimes associated with undesirable limitations.

Surgical removal of macroscopic tumor tissue is an effective treatment strategy but has certain limitations. The entry of cancer cells into the systemic circulation or their invasion of surrounding healthy tissues can complicate the treatment process and negatively affect the prognosis of the disease. Furthermore, failure to detect microscopic lesions during surgical intervention can lead to incomplete removal of tumor tissue, significantly increasing the risk of recurrence.

The difficulty with radiotherapy is its low selectivity and limited effect. On the other hand, chemotherapy is an invasive technique and is associated with systemic side effects. Therefore, there is a need worldwide for fast, precise, effective, and reliable cancer treatments with lower risk rates that will help increase survival rates each year (Zhang et al., 2018; Zou et al., 2016).

Photothermal therapy (PTT) is a light-mediated, non-invasive technique that uses light-absorbing materials to convert light energy into heat energy, thereby damaging tumor cells. This therapy is optimized using near-infrared (NIR) absorbing agents such as gold, copper sulfide, copper selenide, carbon nanotubes (CNTs), nanographene, and indocyanine green (ICG) to provide effective heat production in the tumor area (Deng, Shao, & Zhao, 2021).

In PTT, it is important to heat the tumor tissue to an optimized temperature and minimize damage to the normal tissues surrounding the tumor tissue. Typically, the tumor tissue is heated to a temperature of 45 °C or higher to cause inflammation, necrosis, and ultimately thermal damage (Yarmolenko et al., 2011).

Biocompatibility with biological tissue and the biopersistence of NIR absorbers have critical importance in cancer treatment. While most inorganic materials used as photothermal agents exhibit the ability to remain in the body for longer periods, organic conductive materials have gained significant attention in recent years due to their biodegradability. For example, materials such as porphyrin and polypyrrole dissolve more rapidly in biological systems, making them promising options for cancer treatment. However, the selection of laser wavelength for photothermal absorbers is also an important parameter, as appropriate wavelengths enable deep tissue penetration and significantly enhance treatment efficacy.

The integration of these organic materials with nano drug delivery systems allows them to localize more effectively to tumors and penetrate deeply into the target tissue. This synergistic effect enables more efficient tumor ablation with the right laser light exposure. Despite the challenges and critical parameters mentioned above, PTT stands out as a potentially effective non-invasive approach for tumor ablation (Han & Choi, 2021; Yarmolenko et al., 2011).

MOLECULAR MECHANISMS OF PHOTOTHERMAL THERAPY

PTT is a treatment method that uses light irradiation to induce cell death by controllably increasing cellular temperature. This treatment triggers cell death through apoptosis or necrosis by exploiting the sensitivity of cells to heat. Figure 1. represents the mechanism of action for nanoscale structures developed for PTT.

To generate photothermal heat in tumor tissues, photothermal agents that absorb light energy at spe-

cific wavelengths are used. When these agents transition from their ground state to an excited state, they release heat into the surrounding tissues as they return to their ground state. The vibrational relaxation of the excited state produces heat energy through an increase in kinetic energy in photothermal agents.

It was previously accepted that PTT could damage not only tumor tissues but also normal tissues due to non-specific localized heat production, increasing the risk of treatment. However, thanks to advances in technology, photothermal agents have now been made more specific by targeting tumor tissues and increasing the local heating effect (Deljavan Ghodrati, Amasya Çelikten, & Şengel-Türk, 2025).

PTT can also modulate the tumor microenvironment; for example, it enhances vascular permeability and blood flow of tumor tissues. This effect leads to deeper tissue absorption of photothermal agents, causing effective cellular necrosis in the targeted areas.

PTT, when combined with other treatment methods such as chemotherapy, radiotherapy, photodynamic therapy (PDT), immunotherapy, and surgery, enables more effective therapeutic outcomes (Han & Choi, 2021). It is important to fully understand the cell death mechanism observed after photothermal treatment, because pro-inflammatory cytokines and growth factors released during the necrotic cell death mechanism can increase the metastatic potential of remaining cancer cells, thereby reducing the effectiveness of treatment (Ali, Ali, Rankin, & El-Sayed, 2016). Therefore, the type of cell death mechanism can have a profound effect on the fate of cells remaining in the tumor region. It has been established that temperature is a decisive factor in whether tissue undergoes cell death via necrosis or apoptosis.

Apoptosis is a regulated form of programmed cell death that can be induced by PTT under appropriate treatment conditions. However, many cancer cells acquire resistance to apoptotic signaling, which may reduce the therapeutic efficacy of apoptosis-dependent treatments. In addition, the relatively weak immunogenicity of apoptosis may limit the induction of robust antitumor immune responses (Poon, Lucas, Rossi, & Ravichandran, 2014).

On the other hand, necrosis is an immunogenic process but is uncontrolled, and this can lead to protumorigenic inflammation that contributes to cancer development by suppressing anti-tumor defense mechanisms (Greten & Grivennikov, 2019).

In general, the threshold temperature range for tissue damage has been determined to be between 42- 47 °C (Kumar, Kumar, Rhim, Kim, & Nam, 2014). It has been reported that above 45 °C, the molecular events of inflammation begin, leading to necrosis and cell death. Under optimized photothermal conditions, it is possible to control unnecessary heating of normal cells and prevent necrosis.

In addition to apoptosis and necrosis, necroptosis, initiated by receptor-interacting protein kinase-1 and -3 and characterized by necrosis-like morphological changes, has emerged as an alternative cell death mechanism. During the necrotic process, the release of damage-associated molecular patterns upon tumor cell death triggers the production of immunostimulatory cytokines (Greten & Grivennikov, 2019; Zhao et al., 2020a). Furthermore, increased plasma membrane permeability causes cellular contents to leak into the external environment, rendering necrosis a highly immunogenic and pro-inflammatory process. Morphologically, necrosis is distinguished by organelle swelling and increased plasma membrane permeability (Zhang, Chen, Gueydan, & Han, 2017).

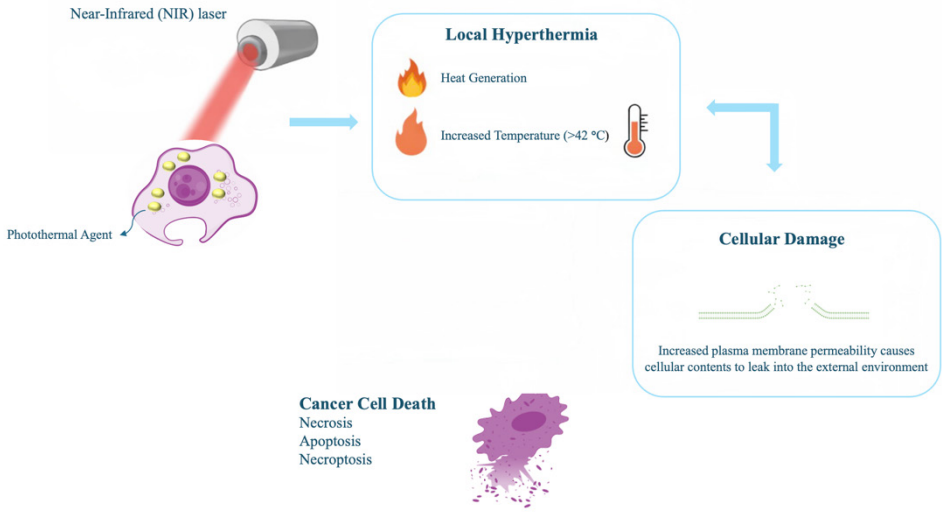

Figure 1. Mechanism of action for nanoscale structures developed for PTT

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FACTORS AFFECTING THE ANTI-TUMOR EFFICACY OF PHOTOTHERMAL THERAPY

Temperature

PTT eliminates tumor cells through various mechanisms, such as DNA damage and protein denaturation, depending on the temperature.

Mild hyperthermia (approximately 42 °C) primarily induces apoptosis, whereas increasing temperatures promote a gradual shift toward necrotic cell death (Iba et al., 2025). At temperatures above approximately 46 °C, rapid protein denaturation and irreversible membrane damage result in predominantly necrotic cell death (Mantso et al., 2018). However, the dominant cell death mechanism also depends on factors such as exposure time, cell type, and treatment conditions (Han & Choi, 2021; Iba et al., 2025; Tu et al., 2025).

Cancer cells are more sensitive to heat than normal cells due to irregular and insufficient blood flow and are therefore more prone to hyperthermia-induced cell death. However, the biggest disadvantage of hyperthermia in tumor ablation is the non-homogeneous distribution of heat within the tissue. This problem can be overcome by PTT, which uses photothermal molecules to localize the hyperthermia effect.

One of the challenges faced by PTT is thermotolerance. Thermotolerance is a homeostatic response that develops as a result of the upregulation of heat shock proteins (HSPs) via heat shock transcription factor 1 (HSF1). This response allows the cell to gain resistance to heat and adapt to high-temperature stress. Cancer cells exhibit a stronger heat shock response compared to normal cells and are more prone to thermotolerance. Increased HSPs and proteasome activity enable cells to survive under high temperatures. Furthermore, the anti-apoptotic properties of these proteins may limit the effectiveness of hyperthermia treatment by increasing the chances of cell survival at low temperatures (~39-41 °C) or during short-term exposure to high temperatures (Ahmed, Zaidi, Mati-Ur-Rehman, Rehman, & Kondo, 2020).

Photothermal agents

The non-homogeneous distribution of heat within tumor tissues may cause undesired thermal damage to surrounding healthy tissues. Therefore, PTT employs photothermal agents that efficiently absorb NIR light and convert it into heat. However, selective tumor

ablation is achieved not only through localized heat generation but also through the preferential accumulation of photothermal agents within tumor tissues. This selective accumulation can be accomplished through passive targeting based on the enhanced permeability and retention (EPR) effect, active targeting by surface functionalization with ligands such as antibodies, peptides, aptamers, folic acid, or hyaluronic acid that recognize overexpressed receptors on cancer cells, and stimulus-responsive strategies that exploit tumor-specific characteristics such as acidic pH, enzyme activity, or redox conditions. These targeting approaches enhance tumor specificity while minimizing thermal damage to healthy tissues. The molecular design of photothermal agents is therefore critical for maximizing therapeutic efficacy. Ideally, these agents should exhibit strong NIR absorption, high photothermal conversion efficiency (PCE), good biodegradability, and excellent photostability (Cheng, Wang, Feng, Yang, & Liu, 2014).

Photothermal agents are broadly classified into organic and inorganic materials. Organic photothermal agents generally exhibit favorable biocompatibility and biodegradability and can be readily functionalized with targeting ligands to improve tumor-specific accumulation. Inorganic photothermal agents often possess superior PCE and can likewise be functionalized for targeted delivery. However, the limited biodegradability and potential long-term toxicity associated with some inorganic nanomaterials remain important challenges for their clinical translation (Jung et al., 2018).

Wavelength of laser light

In PTT applications, the effectiveness of photothermal agents depends on the light's ability to penetrate tissues. Light penetration into tissue occurs through a light-absorbing molecule, and when light of a specific laser wavelength reaches the tissue surface, part of it is reflected back, while the remainder penetrates the tissue. While part of the penetrating light scatters within the tissue, another portion is absorbed by molecules. However, not all of the incoming light energy is converted into thermal energy by molecules; only part of the light is absorbed and converted into heat. This process defines the interaction of light within the tissue (Lagos, Buzzá, Bagnato, & Romero, 2021).

The wavelength of the laser used in PTT aims to allow light to penetrate deeply and achieve maximum absorption. Since wavelength is inversely proportional to energy, shorter wavelengths provide high-energy light that can penetrate deeper into tissues. However, in practice, this may not always be the case. Light in the NIR region is preferred for effective penetration into tissues and typically uses wavelengths between 700-2000 nm. NIR light allows photothermal agents to absorb light more efficiently because it is less absorbed by biological components (Fernandes, Rodrigues, Moreira, & Correia, 2020). Within the NIR region, two biological windows have been defined: NIR-I (700-900 nm) and NIR-II (1000-1700 nm). NIR-II has deeper penetration into tissues compared to NIR-I and is more effective for tumor cell ablation. NIR-II is divided into two sub- windows: NIR-IIa (1300-1400 nm) and NIR-IIb (1500-1700 nm). NIR-IIa is preferred because it prevents light from being absorbed by water molecules, which allows for deeper penetration (Guo et al., 2020b).

Fluence rate

Fluence rate is one of the key parameters that should be optimized before PTT. However, factors such as tumor heterogeneity, size, and the intratumoral distribution of photothermal agents make it difficult to determine the optimal irradiation conditions in advance. Therefore, irradiation parameters should be carefully optimized to achieve sufficient heat generation for effective tumor ablation while minimizing thermal damage to surrounding healthy tissues. Excessively high fluence rates may cause temperatures to exceed 60 °C, leading to predominantly necrotic cell death and increasing the risk of damage to normal tissues (Nomura et al., 2020).

Irradiation duration

In PTT, irradiation time is a critical parameter that directly affects the effectiveness of the treatment and must be carefully analyzed and optimized based on many factors. These factors include the frequency of the irradiated laser beam and the temperature to be achieved. Each of these factors is important for strategically determining the irradiation time (Lyu, Li, & Pu, 2019). In general, it has been observed that the irradiation time of the laser beam should not exceed 10 minutes (Le et al., 2011; Liu et al., 2023; Santhosh et al., 2024).

An increase in irradiation time indirectly exposes cancer cells to prolonged heat exposure, placing them in hyperthermic conditions and potentially triggering the development of thermotolerance. Non- responsive cancer cells may cause insufficient apoptosis by producing HSPs, which can lead to tumor recurrence. Therefore, shorter irradiation times should be used, and different strategies should be applied to maximize the effect of photothermal agents (Hu, Cheng, & Zhang, 2018).

NEW GENERATION NANOSCALE STRUCTURES DEVELOPED FOR PHOTOTHERMAL THERAPY

Nano-scale structures developed in recent years have significantly expanded their applications in cancer treatment due to their unique structural and functional properties. For example, gold nanoparticles (Au NPs) can achieve effective photothermal conversion via the surface plasmon resonance (SPR) mechanism. Additionally, nanoparticles are known to increase tumor tissue penetration by activating the EPR effect or by directly causing endothelial leakage.

The size, shape, and surface properties of nanoscale structures have a decisive effect on biocompatibility, biodegradability, and photothermal performance. Therefore, research on photothermal agents is focused primarily on the design and development of new nanostructures. By utilizing the optical absorption properties of NIR light, the effectiveness of PTT can be enhanced through various nanostructures such as CNTs, gold nanorods, and graphene oxide (GO) sheets.

In general, noble metal-based nanoscale structures have led to significant advances in the field of PTT. However, in recent years, many new-generation nanostructures have been developed for use in this field, and their application potential has steadily increased (Setyawati, Tay, Bay, & Leong, 2017; Tay, Setyawati, & Leong, 2017). Figure 2. presents the classification of nanoscale structures used in PTT and, Table 1. represents a summary of nanostructures used in PTT, including their advantages, limitations, and therapeutic outcomes.

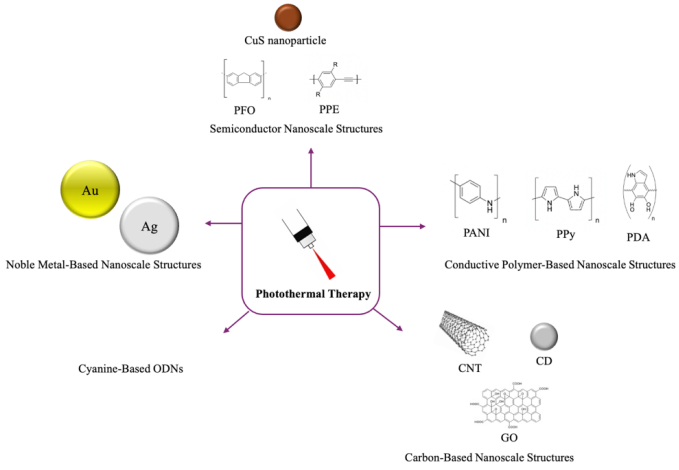

Figure 2. Classification of nanoscale structures used in PTT

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Table 1. Summary of nanostructures used in PTT, including their advantages, limitations, and therapeutic outcomes

Nanostructure Class	Advantages	Disadvantages	Outcomes
Noble Metal-Based	Tunable NIR absorption via SPR; high photostability (Cui et al., 2023)	Poor biodegradability; long-term retention and cytotoxicity (Han & Choi, 2021)	Gold nanomaterials were the first studied for cancer PTT and remain prominent in preclinical and clinical trials (Khafaji, Zamani, Golizadeh, & Bavi, 2019)
Carbon-Based	High stability and flexibility; versatile for combination therapies (Duan et al., 2023)	Limited tissue penetration; poorly understood long-term biological fate (Chen, Zhou, Wang, Hu, & Guo, 2022)	CNTs loaded with doxorubicin (DOX) successfully combined PTT and chemotherapy for targeted breast cancer treatment (Duan et al., 2023)
Semiconductor	High thermal conversion efficiency; versatile for bio-imaging (Khafaji et al., 2019)	Potential toxicity from long-term retention; requires extensive toxicological evaluation (Doughty et al., 2019)	Effective in chemo-photothermal combination therapy, showing synergistic therapeutic efficacy with minimal side effects in preclinical studies (Khafaji et al., 2019)
Conductive Polymer	Good biocompatibility and degradability; facile surface modification (Li et al., 2019)	Lower PCE and stability than inorganic agents (Han et al., 2025)	Polymer-based nanomaterials improve drug delivery, targeting, and therapy efficiency in combination treatments (Han et al., 2025)
Cyanine Dyes-Based	Strong NIR absorption; biocompatible and clinically approved (Doughty et al., 2019)	Poor photothermal stability; complicated synthesis (Han & Choi, 2021)	Useful as photothermal absorbers to enhance heat generation in target tissues with reduced damage to surrounding healthy tissue (Doughty et al., 2019)
Phthalocyanine Dyes-Based	Effective for combined PTT and PDT (Wang et al., 2024)	Poor aqueous solubility; pronounced aggregation tendency and limited tumor specificity (Lee et al., 2024)	Applied in PTT to generate reactive oxygen species (ROS) and heat, inducing apoptosis and immunogenic cell death in tumors (Hou et al., 2020)

Noble metal-based nanoscale structures

Early studies in the field of PTT focused on nanoscale structures based on noble metals such as gold (Au), silver (Ag), platinum (Pt), and palladium (Pd). These structures provide high light-to-heat conversion efficiency by effectively absorbing light. When noble metal nanoparticles absorb light energy, they excite their electrons, then convert this energy into heat, revealing their photothermal effects.

In this context, Au NPs, in particular, stand out due to their SPR properties, enabling strong light absorption in the NIR region, low toxicity, stable photothermal performance, and well- defined surface chemistry properties (Chang & Murphy, 2018).

First used in 2003 for PTT, Au-based nanoparticles have significantly accelerated research in this field.

Over time, Au NPs with different morphologies have been developed. These include hollow spherical structures, core/shell configurations, nanorods, nanocages, and nanoclusters. Au nanorods, in particular, are remarkable because the SPR absorption wavelength can be shifted to the NIR region by adjusting their length-to-width ratio and because they offer high PCE.

Modification of nanoparticle surfaces with polyethylene glycol (PEG) and tumor-targeting ligands (e.g., lactoferrin) extends circulation times and increases tumor-specific accumulation. These approaches have significantly improved the biological performance of nanoparticles for targeted PTT (Lee et al., 2018; Yang et al., 2020).

In recent years, studies on Au NPs with different geometries have also created new opportunities

in the field of PTT. For example, flower-shaped Au NPs, when combined with GO to form composites, have demonstrated higher light-to-heat conversion efficiency compared to pure Au-based systems (Liu, Zhai, Zhou, Yang, & Zhang, 2019). Similarly, star-shaped Au NPs and glycol polymer-based hybrid systems have been developed; these structures offer high colloidal stability and superior photothermal performance (Zheng et al., 2020).

Au-based nanoscale structures have significant potential not only in cancer treatment but also in various medical applications such as drug delivery systems and imaging agents. However, some limiting factors, such as limited biodegradability and reduced photostability over time, still need to be addressed. Therefore, the development of new-generation noble metal-based nanostructures with high photostability and biocompatible structures is one of the main points of research in this field (Yang et al., 2019a).

Carbon-based nanoscale structures

The limitations of noble metal-based photothermal agents have led researchers to develop alternative inorganic materials; in this context, carbon-based structures such as CNTs, graphene, GO, carbon dots (CDs), nanodiamonds, and activated carbon have come to the forefront.

CNTs, in particular, have attracted attention for their impressive light-to-heat conversion capabilities in medical applications and have also been evaluated in drug delivery systems and imaging (Wang et al., 2018). However, there are many parameters affecting the biological safety of CNTs, such as size, dose, and surface chemistry. Therefore, surface modifications have become a critical strategy, particularly to reduce toxicity. PEG coating applications are widely used to both enhance biocompatibility and prolong circulation time (Liao et al., 2019).

The effective use of CNTs in clinical applications requires careful optimization of synthesis methods and the development of tumor targeting capabilities. In this regard, Lu et al. (2019) produced single-walled carbon nanotubes (SWNTs) with high water solubility, biological stability, and low toxicity. The obtained SWNTs were functionalized with CY7 dye and conjugated with specific antibodies capable of targeting tumors for use in imaging-guided PTT in pancreatic tumors. Transmission electron microscopy (TEM) analyses showed that structural integrity was maintained throughout the synthesis process; furthermore, ultrasonic dispersion ensured a homogeneous distribution of the nanotubes in solution (Lu et al., 2019).

Graphene is a nanomaterial formed by the arrangement of sp^2 hybridized carbon atoms in a two-dimensional plane; it has found wide application in various biomedical applications due to its properties such as a large surface area, high mechanical flexibility, and superior thermal conductivity. However, graphene's high hydrophobicity significantly limits its potential use in medical applications. Developed to overcome this problem, GO has gained both solubility and surface functionalization capabilities thanks to the hydroxyl, epoxy, and carboxyl groups on its surface, making it more suitable for biomedical applications compared to graphene (Su et al., 2018).

GO stands out as an important photothermal agent in PTT applications due to its ability to efficiently convert laser light into heat energy (Di Santo et al., 2019). Liang et al. developed a folic acid-functionalized GO nanocomposite (NCGO-FA) as a dual-responsive drug delivery platform with enhanced tumor-targeting capability. The nanoplatform enabled high drug loading, efficient photothermal conversion, and controlled drug release in response to both acidic tumor conditions and photothermal heating. When loaded with DOX, it demonstrated significantly enhanced antitumor efficacy through synergistic photothermal-chemotherapy compared with either treatment alone, highlighting the potential of multifunctional GO-based nanoplatforms for targeted cancer therapy (Liang et al., 2019). Chang et al. developed a multifunctional GO-based nanoplatform by depositing $BaHoF_5$ nanoparticles onto PEGylated GO and

loading the heat shock protein 90 inhibitor NVP-AUY922. The nanoplatform provided dual-modal magnetic resonance/computed tomography imaging and improved the effectiveness of PTT by increasing the sensitivity of tumor cells to heat, allowing efficient tumor treatment under low-power laser irradiation. This approach demonstrates the potential of multifunctional GO-based nanoplatforms for safer and more effective PTT (Chang et al., 2019).

CDs are notable for their ease of synthesis, high water solubility, strong photostability, and easily modifiable surfaces. Furthermore, their ability to simultaneously generate ROS and heat under laser irradiation allows them to be used as effective agents in both photothermal and PDT applications (Guo et al., 2020a). Zhao et al. developed lysosome-targeted CDs as a multifunctional phototheranostic platform capable of simultaneously generating ROS and heat under 635 nm laser irradiation. The CDs exhibited high PCE together with fluorescence and photoacoustic imaging capabilities, enabling synergistic PDT and PTT. Their selective accumulation in lysosomes further enhanced therapeutic efficacy, highlighting the potential of CDs as multifunctional agents for cancer diagnosis and treatment (Zhao et al., 2020b).

In general, carbon-based nanoscale structures offer great potential for PTT applications due to their high drug loading capacities and biomedical imaging capabilities. However, the low dispersion ability of these materials in aqueous environments is a significant limiting factor for their transition to clinical applications. Methods such as PEG coating or surface modification with functional polymers are used to overcome this problem; these strategies also increase the NIR light absorption capacity of nanoscale structures. To achieve more successful results in clinical applications, advanced modification techniques aimed at improving the surface properties of carbon-based nanoscale structures are needed (Liu, Chen, Li, & Huang, 2019).

Semiconductor nanoscale structures

In addition to carbon-based nanoscale structures, certain semiconductor materials also offer significant potential in PTT applications. Specifically, copper chalcogenide compounds ($Cu_{2-x}E$; E = S, Se, Te) enhance their light-to-heat conversion capacity by forming natural holes in their structures during crystallization (Jiang et al., 2018). These holes enhance the localized SPR mechanism, enabling more efficient conversion of NIR light into heat energy. Thus, the applied laser energy contributes directly to local heat production, allowing for the targeting of tumor cells (Li et al., 2018).

In initial studies, CuS nanoparticles were evaluated for photothermal ablation of tumor cells under 808 nm laser irradiation (Li, Lu, Huang, Li, & Chen, 2010). Subsequently, different structures such as Cu_9S_5 nanocrystals, CuS superstructures, and CuS@nanogel-DOX nanocomposites were developed. More recently, CuS-Au heterostructures were prepared without a reducing agent and exhibited a PCE of 36.5% with high NIR absorption at a wavelength of 1064 nm (Z. Wang et al., 2019).

CuS nanoparticles also catalyze hydrogen peroxide (H_2O_2) in the tumor microenvironment via Fenton-like reactions, producing toxic hydroxyl radicals and thus represent promising agents for chemodynamic therapy (Lin et al., 2019). Y. Wang et al. (2019) developed hollow Cu_9S_8 nanoparticles with an increased surface area to enhance the number of catalytic active sites and improve Fenton-like reactions. The nanoplatform combined photoacoustic imaging with PTT and chemodynamic therapy, where photothermal heating further promoted hydroxyl radical generation, resulting in enhanced antitumor efficacy. This strategy highlights the potential of hollow Cu_9S_8 nanostructures as multifunctional platforms for synergistic cancer therapy (Y. Wang, An, Lin, Tian, & Yang, 2019).

CuS nanoparticles have also been integrated into combined treatment approaches by combining them with different nanoscale carrier systems (An et al., 2018). For example, Zhang et al. designed a smart nanocomposite that provides oxygen production and PTT in the tumor microenvironment by coating the CuS core with mesoporous silica ($mSiO_2$) and MnO_2 layers (Zhang et al., 2020). Similarly, Sun et al. developed a targeted PTT-PDT combination by coating CuS nanoparticles with ICG molecules using hyaluronic acid (Sun et al., 2020).

In addition, semiconducting polymers are also prominent for photothermal treatment applications. These polymers can convert light energy into heat energy with high efficiency thanks to the π-π conjugation structures in their main chains, and with these properties, they offer advantages such as high photothermal stability, biocompatible surface modification, and integration into drug delivery systems.

Polymers such as polyfluorene (PFO) and poly(phenylene acetylene) (PPE) are among the developed nanoscale systems due to their strong NIR absorption and high photothermal conversion efficiencies.

Semiconducting polymer nanoparticles can be prepared by precipitation, microemulsion, or self- assembly methods. However, due to limitations such as size control and purity in these methods, strategies such as surface modification with amphiphilic molecules or phospholipid encapsulation have been developed (Zeglio, Rutz, Winkler, Malliaras, & Herland, 2019).

In general, semiconductor-based nanoscale structures stand out as strong candidates for photothermal treatment applications in pharmaceutical technology due to their high photothermal stability, biocompatibility, and targetability (Chen et al., 2019b). However, the limited photothermal efficiency of copper-based nanoscale systems at a wavelength of 808 nm limits their potential for clinical applications; alternatively, the use of 980 nm laser light, which is absorbed by water molecules, can cause unwanted damage to healthy tissues. Therefore, the development of more effective and reliable semiconductor nanoscale structures remains a priority research topic in the field of pharmaceutical technology (Li et al., 2010).

Conductive polymer-based nanoscale structures

Conductive polymers (CPs) such as polyaniline (PANI), polypyrrole (PPy), and polythiophene have gained significant importance in various biomedical applications, including controlled drug delivery, biosensors, and neural prostheses. These polymers represent the new generation of modern organic nanoscale structures.

The optical absorption properties of CPs have also made them promising candidates for PTT applications. Compared to metal-based nanoscale structures, CPs offer advantages in terms of lower cost, biocompatibility, and biodegradability. However, the PTT mechanism of CPs differs from that of inorganic structures. Heat energy is released as a result of bipolaron formation and their decay following specific light excitation. Furthermore, the optical absorption peak of nano-CPs (516 nm) can be shifted by doping. During doping, changes in the band structure create new energy levels and shifts in excitation energy levels. These changes are used to increase the conductivity of polymers (Zhou et al., 2013).

PANI offers advantages such as high conductivity under acidic conditions, distinct redox properties, easy synthesis, and high doping capacity due to its π-conjugated structure. It has attracted widespread interest in nanomedical applications such as cell stimulation, drug delivery systems, and tissue engineering (Wang, Wu, Cheng, & Zhang, 2014). However, the tendency for interparticle aggregation limits its use. PANI demonstrates stability in PTT applications as a pH-responsive organic polymer. A pH-dependent transformation occurs between the EB and ES forms; in a strongly acidic environment, the absorption band shifts to the NIR region (~1100 nm). However, this

transformation is limited to the tumor microenvironment at pH 5.4-7.0 (Korupalli et al., 2016).

To overcome this issue, acidic groups were added to PANI to enhance its doping properties; however, this method was not found suitable for biological applications. Au NP-coated PANI systems (Au@PANI) provided strong NIR absorption in the pH 6.5-8.0 range, but the non-biodegradability of Au NPs carries a long-term toxicity risk (Jiang, Shao, & Wang, 2014).

Tian et al. (2019) developed a bovine serum albumin-PANI nanoplatform that responds to the mildly acidic tumor microenvironment (pH < 7), overcoming the protonation limitation of conventional PANI. The pH-triggered transition enhanced both photoacoustic imaging and PTT, enabling more effective tumor-targeted treatment. This strategy demonstrates the potential of pH-responsive PANI-based nanoplatforms for imaging-guided cancer therapy (Tian et al., 2019). Similarly, Wang et al. developed poly(vinylpyrrolidone) (PVP) coated PANI nanoparticles to improve their dispersion, biocompatibility, and photothermal performance. The PVP coating significantly reduced cytotoxicity while maintaining efficient photothermal conversion under NIR irradiation, resulting in effective tumor cell ablation *in vitro* and complete tumor elimination *in vivo* after a single treatment. These findings demonstrate the potential of PVP-coated PANI nanoparticles as safe and effective photothermal agents for cancer therapy (Wang, Vivek, Wu, Wang, & Wang, 2018).

PPy attracts attention as a low-cost photothermal agent due to its high biocompatibility, photostability, and effective photothermal conversion performance. While Au NPs exhibit a strong SPR effect in the visible region, this effect cannot reach the NIR region under natural conditions. However, photothermal efficiency in the NIR region has been increased with PPy-coated Au NPs (Lin et al., 2014).

Polydopamine (PDA) offers absorption capacity in the ultraviolet-visible-NIR range and high biocompatibility. It shows no toxicity even at high doses and biodegrades in the body. A PCE of 38.2% was achieved with PDA nanoparticles, and NIR absorption was increased with surface modifications (Li et al., 2020).

In general, conductive polymer-based nanoscale structures offer the advantages of low cost, easy production, and high optical stability; however, more work is needed in terms of biodegradability and metabolism.

Cyanine-based organic dye nanoparticles

Cyanine-based organic dye nanoparticles (CB ODNs) are among the most extensively investigated organic photothermal agents owing to their excellent NIR absorption, favorable biocompatibility, and high PCE. In addition to their optical properties, cyanine dyes can be readily incorporated into nanocarriers or functionalized with targeting ligands to improve their stability, tumor accumulation, and therapeutic efficacy. Furthermore, their biodegradability reduces the risk of long-term toxicity, making them promising candidates for PTT (Wu et al., 2019).

Cyanine dyes are commonly classified into several subclasses according to their chemical structures, including heptamethine cyanines, hemicyanines, and cryptocyanines. Among these, heptamethine cyanines, particularly ICG, are the most extensively investigated for PTT applications. In general, all these CB ODNs exhibit fluorescent properties due to their significant absorption of NIR light and can convert part of the light into heat. However, there are some disadvantages to the direct use of these dyes; they are rapidly eliminated from the body and have low cellular uptake. Heptamethine cyanines are the most extensively investigated subclass of cyanine dyes for PTT because of their strong absorption in the NIR region and high PCE. Among them, ICG, an FDA-approved imaging dye, is the most widely studied representative and has attracted considerable interest for photothermal applications (Lyu et al., 2018). However, the clinical use of ICG is limited by its poor aqueous stability, rapid clearance from the body, and low tumor

accumulation. To overcome these limitations, ICG is frequently encapsulated into nanocarriers such as liposomes, PEGylated systems, or functionalized with antibodies and other targeting ligands to improve its stability, circulation time, and tumor-specific delivery. Typical power densities used for ICG-mediated PTT range from 1.0 to 1.25 W/cm^2 (Jung et al., 2018). Other heptamethine cyanine derivatives generally exhibit higher photothermal conversion efficiencies than ICG but often suffer from lower water solubility and reduced photostability, limiting their direct biomedical applications. These derivatives typically exhibit maximum absorption around 808 nm, with reported power densities ranging from 0.5 to 1.5 W/cm^2 (Feng, Chen, Ma, Liu, & Yin, 2020).

Phthalocyanine-based organic dye nanoparticles

Phthalocyanine-based organic dye nanoparticles (PTC ODNs) have attracted considerable attention as photothermal agents because of their strong absorption in the NIR region and high PCE. However, the inherent hydrophobicity of phthalocyanines limits their aqueous solubility and biological applications. To overcome these limitations, phthalocyanines are commonly incorporated into nanocarriers or chemically modified to improve their water solubility, biocompatibility, and tumor accumulation. Depending on their chemical structure and surface modifications, phthalocyanine derivatives exhibit maximum absorption wavelengths around 671, 770, 785, and 808 nm. Reported power densities for phthalocyanine-mediated PTT generally range from 1.3 to 6.4 W/cm^2 with irradiation times of 3-12 min (Jung et al., 2018).

DEVELOPMENT OF SYNERGISTIC TREATMENT THROUGH THE INTEGRATION OF PHOTOTHERMAL THERAPY AND OTHER TECHNOLOGIES

Photothermal-photodynamic therapy combination

PTT and PDT are methods that use light for therapeutic purposes, and the fundamental mechanism in both therapies relies on the accumulation of nanoparticles in the tumor microenvironment. Irradiating cancer cells with light leads to the destruction of tumor cells. PDT follows a different mechanism in destroying tumor cells; ROS is produced by the photosensitizer agent, and this ROS damages tumor cells, leading to cell death.

Two types of combination strategies have been developed by merging these two methods. In the first method, two different NIR wavelengths are used to activate the photothermal agent and photosensitizer separately. In the other method, both agents are activated simultaneously using the same wavelength. Both combination strategies have shown similar effects in destroying malignant cells (Yang et al., 2019b).

Photothermal-chemotherapy combination

The combination of PTT and chemotherapy is a very powerful strategy for tumor shrinkage. PTT enhances the intratumoral delivery of chemotherapeutic agents through several mechanisms. Localized hyperthermia increases tumor vascular permeability, improves blood perfusion, enhances cellular membrane permeability, and can trigger the controlled release of drugs from thermosensitive nanocarriers, thereby promoting greater drug accumulation within the tumor (Li et al., 2019; Yang et al., 2023). Although chemotherapy remains a cornerstone of cancer treatment, therapeutic efficacy is often limited by drug resistance, incomplete eradication of tumor cells, and tumor recurrence. Combining chemotherapy with PTT can help overcome these limitations by improving drug delivery, sensitizing tumor cells to chemotherapeutic agents, eliminating residual cancer cells, and ultimately reducing the risk of tumor recurrence (Li, Xiao, Yin, & Hu, 2026; Overchuk, Weersink, Wilson, & Zheng, 2023; Shang, Yi, Xiang, & Zhou, 2025). Au NPs are used as drug carriers in different structures such as hollow nanospheres, nanocages, and nanorods in combination with DOX (Shao et al., 2020). Au nanorods coated with DNA molecules provide binding sites for DOX. Copper sulfide nanoparticles coated with folic acid and PEG are used for DOX re-

lease after hyperthermia. Similarly, copper selenide nanoparticles loaded with DOX have also been investigated for combination therapy (Poulose et al., 2016).

Furthermore, hollow polymer-silica nanostructures have been developed as systems that can combine PTT and chemotherapy by encapsulating drugs such as paclitaxel. These structures have been found to be effective in eliminating malignant tumors in experimental animals and have also been reported to reduce the side effects of drugs (Zhao et al., 2017).

CNTs, organic dyes, and conjugated organic polymers have also been combined with DOX to design systems that create a synergistic effect. Most of these nanoparticle systems have been used in combination with DOX, which blocks the topoisomerase enzyme that repairs DNA after DNA damage, thereby promoting cell death. Additionally, other chemotherapeutic agents such as paclitaxel and methotrexate also cause tumor cell death (Lee, Kim, & Kim, 2016).

Photothermal-immunotherapy combination

The combination of PTT and immunotherapy can create a powerful and synergistic effect in tumor treatment. Proteins released from cells exposed to PTT are easily recognized by immune system cells. Furthermore, tumor-specific antigens released from necrotic cells are recognized by antigen- presenting cells, triggering the production of MHC-I molecules. These molecules cause cytotoxic T cells to activate, and these cells then travel to the tumor site and destroy tumor cells. Consequently, it can be stated that photothermal hyperthermia transforms nonimmunogenic tumors into immunogenic tumors, thereby assisting the immune system in eradicating these malignant cells (Dong et al., 2019).

Immunotherapy, on the other hand, aims to enhance the immune system's ability to recognize and eliminate tumor cells by reversing tumor-induced immunosuppression and promoting T-cell activation. However, its therapeutic efficacy is often limited by the poor immunogenicity of tumors, insufficient infiltration of cytotoxic T cells, and immune checkpoint-mediated immune suppression within the tumor microenvironment. By inducing immunogenic cell death and releasing tumor-associated antigens, PTT converts immunologically "cold" tumors into "hot" tumors, thereby improving antigen presentation and immune cell recruitment (ChenLiu, Gu, Wang, Wu, & Tang, 2025). Consequently, PTT enhances the responsiveness of tumors to immunotherapy, while immunotherapy amplifies and sustains the antitumor immune response initiated by PTT, resulting in a more robust and durable therapeutic effect (Chen et al., 2019a).

Therefore, the combination of PTT and immunotherapy not only achieves effective local tumor ablation but also enhances systemic antitumor immunity, eliminates residual tumor cells, and promotes long-term immune memory, thereby reducing the risk of tumor recurrence and metastasis (Kong & Chen, 2022). Consequently, this synergistic strategy has attracted considerable attention, and numerous preclinical studies have investigated various nanoparticle platforms in combination with different immunomodulatory agents.

For example, Chen et al. demonstrated the effectiveness of combining ICG with glycosylated chitosan for photothermal and immunotherapy combination (Chen et al., 2002). Similarly, combinations of ICG with the immune system regulator imiquimod, CNTs with the immune checkpoint inhibitor α-CTLA4, and Prussian blue dye with α-CTLA4 have also been investigated. Chen et al. (1997; 2002) also achieved significant results by using ICG organic dye in combination with α-CTLA4 (Chen, Adams, Carubelli, & Nordquist, 1997; Chen et al., 2002).

Wang et al. have used chitosan-coated copper sulfide nanoparticles for both photothermal and immunotherapeutic purposes (Wang et al., 2014). On the other hand, Bear et al. (2013) have made a significant innovation by combining Au nanoshells with adoptive T cell transfer. In this study, instead of suppressor Treg cells, which increase after PTT application, ther-

apeutic T cells were transferred, thereby ensuring the effectiveness of the immune system against secondary tumors (Bear et al., 2013).

In conclusion, the combined application of PTT and immunotherapy offers a highly effective approach not only in eliminating the existing tumor but also in developing the body's immune memory against the tumor.

PROGRESS TOWARD CLINICAL IMPLEMENTATION OF PHOTOTHERMAL THERAPY

PTT has advanced toward clinical translation, although most nanomaterial-mediated approaches remain experimental. Current clinical PTT largely relies on laser devices that induce thermal ablation by exciting endogenous tissue chromophores, thereby avoiding regulatory complexities associated with novel agents. For example, endobronchial tumors can be treated using endoscopic Nd:YAG laser photocoagulation, which selectively damages tumor vasculature and causes thermal tumor destruction (Hansen & Sundset, 2006). MRI-guided laser ablation has also proven safe and effective for solid tumors such as liver and prostate cancers. Nd:YAG laser therapy in patients with colorectal liver metastases (<5 cm in diameter) and hepatocellular carcinoma (<3 cm in diameter) demonstrated low recurrence (~2%) and high ablation efficacy (~81%), with minimal complications (<1%) in large patient cohorts (Arienti et al., 2008; Vogl et al., 1995; Vogl, Straub, Eichler, Söllner, & Mack, 2004). In the late 2000s, the FDA approved MRI-guided stereotactic laser ablation systems for high-grade glioma, including Visualase Thermal Therapy® and NeuroBlate®.

Among clinically used photothermal agents, ICG, an FDA-approved intravenous contrast dye, has attracted significant attention due to its NIR absorption, favorable biocompatibility, and efficient photothermal conversion capability (Han & Choi, 2021). A 2011 pilot study in patients with advanced metastatic breast cancer evaluated laser immunotherapy combining intratumoral ICG and glycated chitosan followed by 805 nm laser irradiation (1 W/cm^2). In 10 treated patients, the therapy achieved an objective response rate of 62.5% and a clinical benefit rate of 75%, with no major adverse effects beyond localized thermal injury (Li et al., 2011).

Nanomaterial enhanced PTT aims to improve selectivity and reduce required laser power, but clinical evidence remains limited. The most advanced system is Aurolase®, developed by Nanospectra Biosciences, which uses PEG-coated Au nanoshells (AuroShell®) that accumulate in tumors via the EPR effect and convert NIR light into localized heat (Kumari, Sharma, & Sahi, 2021). Several ClinicalTrials.gov studies have evaluated this platform. In lung tumors (NCT01679470), intravenously administered AuroShell® followed by bronchoscopic NIR irradiation produced thermal ablation of primary and metastatic lesions (U.S. National Library of Medicine, 2016). In head and neck cancers (NCT00848042), patients received intravenous nanoshells and 808 nm laser exposure, although adverse effects were reported in refractory or recurrent cases (U.S. National Library of Medicine, 2017). More favorable outcomes were observed in prostate cancer trials (NCT02680535), where MRI/ultrasound-guided focal laser ablation achieved successful treatment in 94% of patients with minimal damage to surrounding tissue and no significant deterioration in urinary or sexual function scores (U.S. National Library of Medicine, 2021a). An ongoing extension study (NCT04240639) continues to evaluate MRI/US-guided focal ablation in prostate tumors (U.S. National Library of Medicine, 2021b).

CONCLUSION

PTT has emerged as a promising minimally invasive strategy for cancer treatment because of its ability to achieve precise localized tumor ablation. Recent advances in nanotechnology have enabled the development of photothermal agents with improved PCE, biodegradability, biocompatibility, and tumor targeting capability, thereby enhancing therapeutic efficacy. Moreover, combining PTT with conventional treat-

ment modalities, including chemotherapy, immunotherapy, PDT, and radiotherapy, has demonstrated significant synergistic effects and improved therapeutic outcomes. Although considerable progress has been achieved, further optimization of photothermal agents and treatment protocols is essential to facilitate the successful clinical translation of PTT.

FUTURE PERSPECTIVES

Despite significant progress, several challenges remain before PTT can be routinely translated into clinical practice. Future studies should focus on improving the long-term safety, biodegradability, biodistribution, clearance, haemotoxicity, and immunotoxicity of photothermal agents, while also enhancing tumor-specific targeting and establishing standardized laser irradiation protocols. In addition, the development of multifunctional and stimuli-responsive nanomaterials, together with the application of NIR-II lasers, is expected to improve tissue penetration and enhance the therapeutic efficacy of tumors located in deeper tissues (Chauhan et al., 2025).

Artificial intelligence (AI) and machine learning (ML) are expected to further accelerate the clinical translation of PTT by enabling the rational design of photothermal agents through the prediction of physicochemical properties and biological interactions, thereby improving biocompatibility and tumor targeting capability (Fekrazad, Hamblin, & Fekrazad, 2025). Furthermore, ML can optimize laser parameters, including wavelength, power density, and exposure time, while deep learning-based thermal and infrared imaging enables real-time temperature monitoring and more accurate tumor delineation for personalized treatment planning (Agboklu, Adrah, Agbenyo, & Nyavor, 2024). In addition, AI-assisted prediction of photothermal agent clearance and patient-specific therapeutic responses may help reduce systemic toxicity and improve treatment precision. Preclinical studies have already demonstrated that AI-guided PTT can improve therapeutic accuracy while limiting damage to healthy tissues (Singh, Gupta, Gupta, Singh, & Akhtar, 2024).

Overall, continued advances in nanotechnology, laser engineering, artificial intelligence, and multimodal therapeutic strategies are expected to overcome current limitations and accelerate the clinical translation of PTT, establishing it as a safer, more precise, and more effective treatment modality for cancer (Chauhan et al., 2025).

ACKNOWLEDGEMENTS

This review is based on the information obtained within the scope of the Scientific and Technological

Research Council of Turkey (TÜBİTAK) funded 1001 project No 123S716. We gratefully acknowledge TÜBİTAK for their support.

AUTHOR CONTRIBUTION STATEMENT

ADG: Conceptualization, Data curation, Investigation, Writing-original draft, Writing-review & editing. GA: Conceptualization, Data curation, Investigation, Supervision, Writing-original draft, Writing-review & editing. CTST: Conceptualization, Data curation, Investigation, Supervision, Writing-original draft, Writing-review & editing.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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