J Herbmed Pharmacol. 2026; 15(2): 175-188.

http://www.herbmedpharmacol.com doi: 10.34172/jhp.2026.53576

Journal of Herbmed Pharmacology

# Chrysin and its nanoformulations in cancer therapy: A systematic review of their radiosensitizing, phototherapy-enhancing potentials

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**ARTICLE INFO**

***Article Type:***
Review

***Article History:***
Received: 8 Dec. 2025
Revised: 4 Feb. 2026
Accepted: 13 Feb. 2026
epublished: 1 Apr. 2026

***Keywords:***
Flavonoids
Neoplasms
Nanoparticles
Radiotherapy
Radiation-sensitizing agents
Photochemotherapy
Phototherapy

**ABSTRACT**

**Introduction:** Chrysin (CHY) is a naturally occurring flavonoid known for its anti-inflammatory and antioxidant properties. This systematic review aims to evaluate the photosensitizing and radiosensitizing effects of CHY and its nanoparticle (NP) formulations, and their potential to enhance therapeutic efficacy while reducing treatment-related adverse effects.

**Methods:** This systematic review included 14 *in vivo* and *in vitro* studies published before October 21, 2025, that met specific inclusion and exclusion criteria. After screening, 14 studies met the inclusion criteria. Then information from each study was extracted and recorded. Subsequently, a risk-of-bias assessment was conducted for experimental studies, followed by a final analysis of the results.

**Results:** CHY and its NPs, when combined with radiotherapy (RT) and phototherapy (PT), generate singlet oxygen ($^1O_2$) and various reactive oxygen species (ROS), causing photooxidative damage, DNA injury, cell-cycle arrest often at the G1 phase, and apoptotic cell death. Beyond direct cytotoxicity, CHY participates in key regulatory signaling pathways, including the modulation of apoptotic pathways, thereby enhancing apoptotic responses while increasing the production of inflammatory mediators. Under RT conditions, CHY and its nanoformulations boost γ-irradiation-induced tumor suppression by shifting the redox balance toward oxidative stress, increasing caspase-3 activity, and downregulating survival markers. Conversely, CHY shows notable protective effects in normal cells by reducing oxidative stress, neuroinflammation, and DNA damage through restoring antioxidant defenses, lowering lipid peroxidation, and maintaining neuronal integrity.

**Conclusion:** Overall, CHY and its NPs suggest potential dual roles based on preclinical evidence as photo- and radiosensitizers while also providing protective effects against therapy-induced adverse outcomes.

*Implication for health policy/practice/research/medical education:*
This review shows that chrysin and its nanoparticle forms offer two main benefits: they enhance the effectiveness of radiotherapy and phototherapy against cancer cells and help protect healthy tissues. These features could help improve treatment strategies by improving success rates and lowering side effects. For policymakers, the results suggest it is worth investing more in research on nanoflavonoids, especially to review how natural radiosensitizers and photosensitizers are regulated and used these phytochemicals as radioprotective agents. Clinicians may be able to use these targeted compounds to improve cancer treatment protocols, once their safety and dosing are confirmed. For researchers, the findings highlight the need for consistent study designs, deeper investigation into how these compounds work, and early clinical trials to better understand their effects and safety in the body.

*Please cite this paper as:* Saedi Marghmaleki M, Karimian M, Raeisi E. Chrysin and its nanoformulations in cancer therapy: A systematic review of their radiosensitizing, phototherapy-enhancing potentials. J Herbmed Pharmacol. 2026;15(2):175-188. doi: 10.34172/jhp.2026.53576.

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## Introduction

In recent years, cancers have increased significantly due to environmental pollutants and changing lifestyle patterns such as obesity, reduced physical activity, infections, alcohol drinking, and smoking (1,2). Cancers reduce various aspects of quality of life and impose high costs (direct and indirect costs) on the patient, caregivers, and the healthcare system (3-5). Recent advancements in cancer therapeutics are critical to progress in cancer treatment. While conventional approaches and standard treatment strategies have achieved notable success in particular cancer types, challenges such as tumor cell drug resistance, cancer recurrence, and metastasis continue to impede long-term outcomes (6). Therefore, innovative technologies are urgently required to improve future cancer therapies. Radiotherapy (RT) induces DNA damage, ultimately leading to cancerous cell death. While this process disproportionately affects cancer cells compared to normal cells, the increasing number of patients undergoing chemotherapy has resulted in a high incidence of RT-associated side effects encountered by healthcare providers (7). Despite advances in cancer treatment, some patients still experience RT failure or require further intervention. RT side effects are acute, late, or chronic, affecting both rapidly dividing and mature tissues. Acute effects typically emerge within weeks, while chronic complications may develop months or years later, often affecting organs such as the kidneys, liver, and heart (8,9).

On the other hand, particular, precise on-site delivery of photothermal agents and photosensitizers is a key area that demands focused research to drive meaningful advancements (6). Phototherapy (PT) is a promising cancer treatment due to its minimal side effects and ability to target tumors precisely while sparing healthy tissue. The primary forms of photodynamic therapy (PDT), photothermal therapy (PTT), and photoimmunotherapy (PIT) destroy cancer cells through distinct mechanisms (10). Nevertheless, challenges, including low reactive oxygen species (ROS) production, poor tumor targeting, inefficient heat generation, and the challenging tumor environment, limit clinical success. Recent research has focused on overcoming these barriers, with nano-PTs, nanocarrier systems, and natural products showing potential to enhance PT penetration and delivery (10). In this regard, PDT is a complex process that induces tumor cell apoptosis, stimulates anti-tumor immune responses, degrades tumor vasculature, and generates ROS and inflammatory reactions within the treated lesion (11). Therefore, protecting healthy cells from these changes and strengthening these mechanisms are among the most essential strategies for the effective treatment of these lesions via precise light irradiation (12). An increasing number of naturally derived substances exhibiting photosensitizing activity are now being identified and investigated. Due to their naturally lower toxicity to healthy tissues and fewer adverse effects, these natural photosensitizers are receiving considerable attention as potential alternatives for PTs, prompting substantial research into their therapeutic value (13-15).

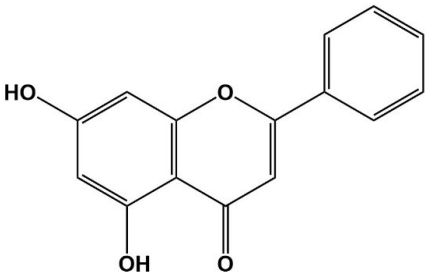


**Figure 1.** Chemical structure of chrysin.

Various natural strategies, such as the use of antioxidants and phytochemicals, have been employed to mitigate the toxicity of ionizing radiation during RT and enhance its therapeutic efficacy (13,16-18). Chrysin (CHY) is a plant flavonoid that is naturally found in passionflower (*Passiflora* spp.), honey, and propolis (19). It has attracted interest owing to its demonstrated antioxidant, anti-inflammatory, anticancer, and neuroprotective activities (19,20). CHY, or 5,7-dihydroxyflavone, has the formula $C_{15}H_{10}O_4$ and possesses a molecular weight of 254.24 g/mol (Figure 1).

Despite the promising therapeutic effects of CHY, its clinical application is limited by poor bioavailability, low water solubility, and rapid metabolism in the gastrointestinal tract and liver. To overcome these limitations, researchers have explored advanced delivery methods, including nanoparticle (NP) systems, to improve CHY's absorption and efficacy (19).

The selective activity of many nanomaterial-based therapeutic systems in cancer treatment has developed based on redox-dependent dual behavior. NPs can maintain a relative antioxidant behavior under physiological conditions while switching to pro-oxidant behavior (ROS generation and inhibition of antioxidant agents) or exhibiting drug-releasing activity within the microenvironment of a tumor cell. This redox-triggered transformation enhances tumor selectivity by enhancing preferential NP activation, drug release, or catalytic ROS amplification specifically in cancer cells. This dual function potentially improves tumor selectivity and efficacy (21,22).

Previous studies have focused on the general pharmacological or anticancer properties of CHY or flavonoids, and chemosensitizing effects (19,23-25). This review provides an overview of the new role of CHY as a photosensitizer and radiosensitizer in cancer therapy. We also discuss new developments in CHY-based nanocarrier systems that enhance bioavailability and treatment accuracy, providing a focused view not found in previous reviews of CHY or flavonoids. Given the importance of cancer and the lack of a comprehensive review of the

photosensitizer and radiosensitizer effects of CHY and its NPs, this study was designed and conducted. In the present study, we also investigate the protective effects of CHY against the adverse effects of these therapeutic methods.

## Materials and Methods

### Reporting guidelines and literature search strategy

We conducted a thorough electronic literature search on October 21, 2025, in accordance with the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews and meta-analyses. To identify studies relevant to our research, we searched major databases, including PubMed/MEDLINE, Scopus, Web of Science, and Embase. Our search included both Medical Subject Headings (MeSH) and commonly used keywords from previous studies (Supplementary file 1, Table S1), including:

((“Chrysin” OR “5,7-dihydroxyflavone”) AND (“radiotherapy” OR “radiation” OR “γ-rays” OR “Gamma rays” OR “X-rays” OR “ionizing radiation” OR “radioprotective” OR “radio-protective” OR “radioprotection” OR “irradiation” OR “radio-enhancement” OR “radiosensitize” OR “radiotherapy sensitizers” OR “radiation sensitizers” OR “radiosensitivity” OR “radiosensitizer” OR “radiosensitizing” OR “radiation sensitivity” OR “radiosensitization” OR “phototherapy” OR “photochemotherapy” OR “light therapy” OR “photodynamic therapy” OR “photothermal therapy” OR “low-level light therapy” OR “photoimmunotherapy” OR “photosensitizing” OR “photosensitizer” OR “near-infrared radiation” OR “laser therapy” OR “sono-photodynamic therapy”)).

We first conducted a comprehensive search using the specified keywords, then reviewed the discussion sections of the included articles and similar reviews to ensure that no studies were missed. The search strategy was refined iteratively until all publications eligible for inclusion in the review had been completely screened. To eliminate duplicate records, all publications were imported into EndNote version 21.0.1 (July 25, 2023, Thomson Reuters), where duplicates were systematically identified and removed.

### Eligibility criteria

Our research encompassed all experimental and clinical studies (if any) focusing on the radiosensitizer and photosensitizer properties of CHY. We also reviewed CHY’s radioprotective properties (against ionizing radiation). The PICO (population, intervention, comparison, and outcome) framework helped guide focused data collection, improve search strategies, and clearly define the research questions (26) (Table 1).

During the screening phase, review articles (any reviews), letters to the editor, and case reports were excluded from further consideration. Additionally, publications without original data, publications available only in abstract form (such as conference posters), preprint studies, unpublished study protocols, and articles published in languages other than English were excluded. The full text of each selected article was thoroughly assessed to determine eligibility. Reasons for exclusion were systematically documented, and all studies were evaluated independently.

### Risk of bias assessment

Two method risk-of-bias assessment instruments were thoughtfully applied, tailored to the methodological frameworks of the individual studies. For research involving animal models, the SYRCLE Risk of Bias (RoB) tool, explicitly designed for preclinical investigations, was used. This instrument systematically appraises biases across multiple domains. Each domain was judiciously classified as “yes” (representing low risk), “no” (indicating high risk), or “unclear” should the available data prove insufficient for a conclusive determination (27). To evaluate the quality of *in vitro* studies, the QUIN (Quality Assessment Tool for In Vitro Studies) was meticulously used. Parameters were scored as follows: a value of 2 was ascribed to adequately reported items, 1 to those insufficiently described, and 0 to parameters that remained unreported (28,29).

The Robvis visualization package was utilized to render a visual representation of the risk of bias evaluation. In addition, a Traffic Light Plot was used to elucidate the distribution of risk of bias across all evaluative domains for each respective experimental study (30).

**Table 1.** Detailed description of the PICO (population, intervention, comparison, and outcome) components, determined according to the objectives of our study

| Components | | Study aims |
|---|---|---|
| P | Population/Patient/ Problem | Patients, animal models with cancer, or cancerous cell lines were subjected to various forms of RT (including γ-rays, X-rays, protons, electrons, and neutron beams) and PT methods (PDT, PTT, and LLLT). |
| I | Intervention | The application of CHY and its NPs in combination with or without chemotherapy methods. |
| C | Comparison / Control | Patients, animal models, or cancer cell lines that received a placebo, standard therapeutic intervention, or no treatment served as the control group. |
| O | Outcome | Mechanisms associated with photo, RT enhancing effect, and radio or photo-protective effects in cancer treatment. |

### Study screening and full-text evaluation

Two investigators carefully reviewed the titles and abstracts of each record, following a clear set of inclusion and exclusion criteria. If a study appeared to meet the inclusion criteria, it was entered into our form, and the full text of the article was read. Each investigator then reviewed the full articles separately to decide whether to include them, using the same process. When the reviewers disagreed, they discussed it with a third reviewer. If two members agreed on the matter, that agreement was considered.

### Data collection and extraction

The studies utilized a standardized form to collect the required information, such as lead author, year, reference, study design, experimental model including population, animals, cells, irradiation/PT type, dosage, CHY and its NPs treatment details including dosage and duration, principal radio/photo sensitizer mechanisms, protection mechanisms, and safety.

### Narrative data synthesis

The synthesis of the evidence entailed developing a narrative integration of the findings derived from the studies incorporated into the review and subsequent analytical procedures. The primary focus was to investigate the impact of CHY and CHY-loaded NPs on cancerous cells and to explore the possible mechanisms underlying their action.

## Results

### Search results

Figure 2 presents the PRISMA flow diagram, detailing the systematic search strategy employed in this review. The initial electronic screening yielded 827 records based on titles and abstracts. Of these, 152 publications were excluded based on duplication. An additional 651 records were excluded from the EndNote database owing to discrepancies between the titles or abstracts and the stated research objectives. Exclusions were subsequently applied to five studies deemed incongruent with the overarching research objectives (31-35). Additionally, four studies were excluded because, despite examining natural sources of CHY (like propolis), the investigated materials contained extraneous constituents that could introduce confounding effects and compromise the specificity of the findings attributed to CHY (36-39).

A total of 6 articles examined the photosensitizer effects of CHY (40-45). Moreover, 8 articles also examined the radioprotective and radiosensitizing effects of this

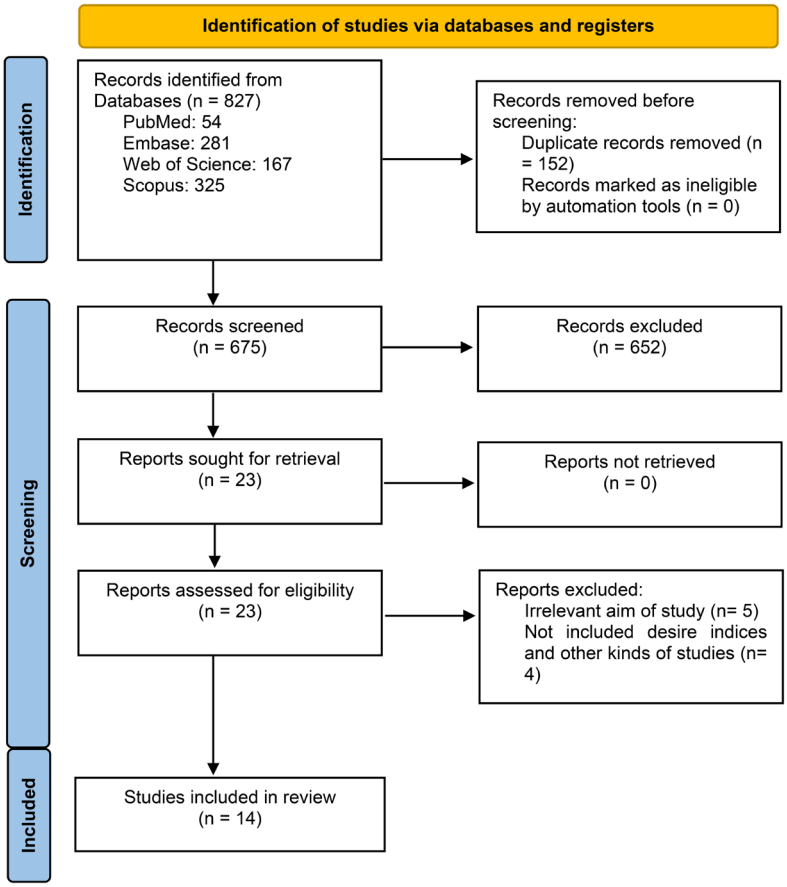


**Figure 2.** Flowchart illustrating the study screening process for the systematic review.

phytochemical (7,46-52). A total of 14 articles were included in the analysis.

### Description of the included studies

Most studies investigating the photosensitizing and protective effects of CHY were conducted in cell lines, with few studies conducted in animals. CHY revealed two crucial roles in cancer treatment in combination with RT. First, it acts as a photosensitizer, helping induce apoptosis (programmed cell death) in tumor cells when combined with light during therapies such as photodynamic or photothermal treatment. Second, it works as a protective agent for healthy tissues, safeguarding them from oxidative damage and inflammation through its antioxidant and anti-inflammatory effects (Table 2).

Unlike the studies listed in Table 2, most studies on RT were conducted in vivo. CHY acts as a selective modulator of cellular responses to ionizing radiation. It protects normal tissues mainly through its antioxidant and anti-inflammatory properties. Conversely, CHY increases tumor cell radiosensitivity by promoting apoptotic pathways, inhibiting proliferative signaling, and is associated with anti-tumor immune responses (Table 3).

43% of all assessments and indicating insufficient methodological reporting across several key areas. Low-risk ratings accounted for 33% of the evaluations, indicating that approximately one-third of the criteria met acceptable methodological standards. High-risk judgments made up approximately 23% and were mainly linked to blinding procedures, underscoring ongoing vulnerability to performance and detection biases. The overall methodological quality varied widely among the studies, with total scores ranging from 2 to 5, indicating a generally moderate level of rigor. These findings highlight that poor reporting, especially regarding blinding, allocation, and randomization methods, was a primary factor contributing to the increased risk of bias observed in the *in vivo* studies analyzed (Figure 3).

A risk of bias assessment of the 12 *in vitro* studies evaluated with the QUIN tool revealed a pattern of moderate methodological quality, with total scores ranging from 9 to 14 (37.5%-58.3%). Most of these articles were classified as having a medium risk of bias, indicating that although some methodological criteria were adequately met, key aspects lacked sufficient detail. Overall, the evidence suggests that, despite well-designed study objectives and methodological plans, persistent gaps in reporting randomization, blinding, and sampling strategies were significant contributors to the observed risk of bias (Table 4).

## Discussion

In this study, we investigated the photosensitizing and radiosensitizing effects of CHY and its NP forms to determine whether they can protect cells from these treatments. The results of this review revealed that CHY and its NPs, along with enhanced RT and PT, increased various ROS, improved apoptotic responses, downregulated survival markers, and increased inflammatory mediators in experimental cells and animals. Conversely, CHY indicated notable protective effects in normal cells, alleviating oxidative stress,

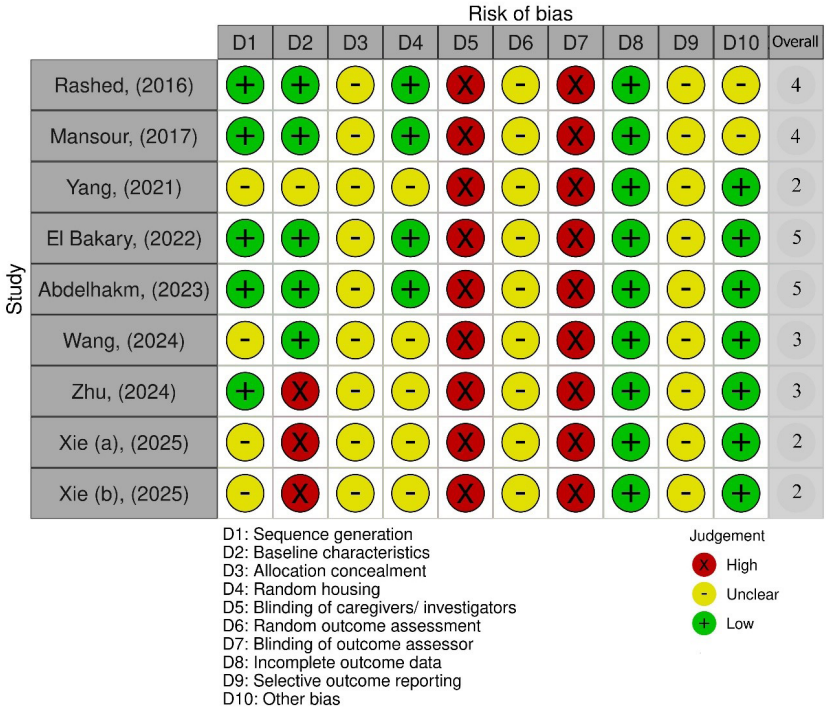


**Figure 3.** Results of risk of bias assessment using SYRCLE RoB.

**Table 2.** Characteristics and principal mechanisms of CHY's photosensitizer effects across the included studies

| Lead author, year (Ref) | Study design | Experimental model (Population/ Animals/Cells) | PT type and dosage | Treatment parameters of CHY (Dosage and duration) | Principal therapeutic mechanisms |
|---|---|---|---|---|---|
| Liu, 2020 (7) | *In vitro* | MGC-803 (gastric carcinoma) and HeLa (cervical carcinoma) | PDT using a 12 W LED purple lamp, emission 380–460 nm, 20 cm distance, irradiation for 10 min, intensity ≈ 50 mW·cm$^{-2}$ | Porphyrin-CHY derivative (compound 4a) administered at 0, 20, 40, and 60 μM; incubation for 24-48 h. | Porphyrin-CHY hybrids act as strong photosensitizers, promoting the production of $^1O_2$ and other ROS. This process causes photooxidative injury, leading to cell cycle arrest and apoptosis, likely via G1-phase arrest. |
| Yang, 2021 (46) | *In vivo* and *in vitro* | *In vitro*: SCC9, CAL27, BGC823, and HCC-LM3.<br>*In vivo*: Female nude mice subcutaneously inoculated with SCC9 cells | PTT using NIR (808 nm) laser irradiation twice on days 8 and 15 with fluorescent lamps. | *In vitro*: Cells treated with 40 μM CHY for 48 h.<br>*In vivo*: CHY was administered to tumor-bearing nude mice via intragastric gavage at 20 mg·kg$^{-1}$ per day. | Revealed anti-tumor and pro-apoptotic effects in TSCC via let-7a-3p-p53-BAX/BCL-2 signaling and photothermal enhancement under NIR irradiation, providing synergistic photothermal tumor ablation without systemic toxicity. |
| Zhang, 2023 (47) | *In vitro* | Human cervical cancer HeLa cells and human lung cancer A549 cells | UV-light PDT using a 12 W UV lamp, irradiation distance 20 cm, exposure time 10 min | 32, 16, 8, 4, 2, 1, 0.5, 0.25 μmol/L of porphyrin-CHY derivatives were used for 4 hours before light exposure and 48 hours afterward. | Improved the generation of ROS, inducing DNA damage, and triggering photo-induced apoptosis, primarily via efficient $^1O_2$ production and strong DNA binding affinity. |
| Dutta, 2024 (48) | *In vitro* | HeLa, A549, HPL1D cell lines | Visible light irradiation PDT (400-700 nm) at a dose of 10 J/cm$^2$ | CHY-cobalt (III) complexes (Co5 and Co6) were administered at 20 μM for approximately 25-30 min of continuous irradiation. | It generated $^1O_2$ and other ROS, inducing oxidative stress-mediated apoptosis in cancer cells through a type-II PDT pathway. |
| Wang, 2024 (49) | *In vivo* and *in vitro* | *In vitro*: Human retinal pigment epithelial cells (ARPE-19)<br>*In vivo*: C57BL/6J mice | Laser used for CNV induction: 810 nm, 110 mW, 100 ms, 50 μm. | 25 mg/kg of CHY was applied daily for one week after PT | CHY reduced DNA double-strand breaks and telomere erosion in retinal pigment epithelial cells, suppressing oxidative stress-induced inflammation and cellular senescence. It also downregulated IL-17/STAT3 and NF-κB (p65) signaling pathways, leading to decreased VEGF and IL-6 expression and ultimately inhibiting CNV and retinal inflammation. |
| Zhu, 2024 (50) | *In vivo* and *in vitro* | *In vitro*: MDA-MB-231 breast cancer cells<br>*In vivo*: C57BL/6 mice bearing MDA231 tumors | PTT using 808 nm laser applied 0.70-1.4 W·cm$^{-2}$ for 200 s (*in vitro*) or 5 min (*in vivo*) | CHY@mPDA administered in two forms:<br>*In vitro,* 100 μM for 12 h.<br>*In vivo*: 2 mg·kg$^{-1}$ via tail vein injection daily | Laser-induced heat promoted CHY release under acidic conditions. Key genes (ESR1, BRCA1, CTNNB1, BAX). *In vivo*, Chrysin@mPDA with PTT suppressed tumor growth, reduced estrogen receptor-positive cells, and elevated CD4$^+$ and CD8$^+$ T cell infiltration. |
| Xie (a), 2025 (51) | *In vivo* and *in vitro* | *In vitro*: B16 melanoma cells and 4T1 breast cancer cells<br>*In vivo*: Female Balb/c mice | PDT with 680 nm LED laser, 0.05 W/cm$^2$, irradiation for 5–10 min | Ce6-TEGDM-CHY conjugate was applied with a CHY 0.5 μM/L concentration and incubated for 24 h before irradiation | Under irradiation, it induced apoptosis in cells via ROS overproduction (including $^1O_2$, $\cdot O_2^-$, $H_2O_2$, and ·OH). It also revealed tumor-selective accumulation through EPR and LDL receptor–mediated targeting, enhancing PDT efficacy. |
| Xie (b), 2025 (52) | *In vivo* and *in vitro* | *In vitro*: B16 melanoma cells and 4T1 breast cancer cells<br>*In vivo*: Female Balb/c mice | PDT with 680 nm LED laser, 0.05 W/cm$^2$, irradiation for 5–10 min | CHY conjugated with PPA at 0.5-20 μM/L, exposure durations: irradiation 5 min + post-incubation 4 h | Enhanced $^1O_2$ and ROS generation (including $\cdot O_2^-$, $H_2O_2$, and ·OH) induced apoptosis in cells, reduced tumor growth via photoactivated oxidative stress. It also improved water dispersibility and inhibited porphyrin aggregation. |

CHY: Chrysin; PT: Phototherapy; PDT: Photodynamic therapy; ROS: Reactive oxygen species; NPs: Nanoparticles; PTT: Photothermal therapy; NIR: Near-infrared; UV: Ultraviolet; CNV: Choroidal neovascularization; VEGF: Vascular endothelial growth factor; NF-κB: Nuclear factor kappa B; IL-17: Interleukin-17; STAT3: Signal transducer and activator of transcription 3; Chrysin@mPDA: Chrysin loaded on mesoporous polydopamine; ESR1: Estrogen receptor 1; BRCA1: Breast cancer gene 1; CTNNB1: Catenin beta 1; BAX: BCL2-associated X apoptosis regulator; TEGDM: Triethylene glycol monomethyl ether; EPR: Enhanced permeability and retention; LDL: Low-density lipoprotein.

**Table 3.** Characteristics and central mechanisms of radiosensitizers and their radioprotective effects

| Lead author, year (Reference) | Study design | Experimental Model (Population/ Animals/Cells) | Irradiation type and dosage | Treatment parameters of CHY (Dosage and duration) | Principal therapeutic mechanisms |
|---|---|---|---|---|---|
| Rashed, 2016 (40) | *In vivo* | Adult male albino rats | γ-radiation applied 5 Gy/day, 5 days/week for 4 weeks, and the dose rate was 0.61 Gy/min | CHY 100 mg/kg/day administered by gavage for 4 weeks. | ↑ Brain GSH, decreased MDA, and BDNF levels<br>↓ TNF-α, GABA levels<br>So, mitigated oxidative stress, neuroinflammation, and neurotoxicity. |
| Mansour, 2017 (41) | *In vivo* | Male Wistar rats | γ-irradiation irradiated a single dose of 5 Gy, dose rate 0.456 Gy/min | 50 mg/kg of CHY applied daily for 21 days. | ↓ MDA levels<br>⊥ Caspase-3 activity<br>↑ BDNF and neurotransmitter levels (SER, epinephrine, norepinephrine), and protection of neural tissue integrity.<br>So, mitigated γ-radiation-induced neurotoxicity through antioxidant and neuroprotective mechanisms. |
| El Bakary, 2022 (42) | *In vivo* | Adult female Swiss albino mice, bearing Ehrlich Ascites Carcinoma (EAC) solid tumor | γ-irradiation using Gamma Cell-40 ($^{137}$Cs) irradiator and total dose 1 Gy divided into two fractions (0.5 Gy each) at 0.403 Gy/min | CHY was administered intraperitoneally at 20 mg/kg for 21 consecutive days. | ↓ IFN-γ levels, TNF-α, free radicals, and NO levels<br>↑ Caspase-3 activity in tumor tissues<br>Combined CHY and γ-irradiation produced synergistic anti-tumor effects by modulating redox balance and promoting apoptosis in EAC-bearing mice. |
| Abdelhakm, 2023 (43) | *In vivo* and *in vitro* | *In vivo*: Swiss albino female mice<br>*In vitro*: Human breast cancer cell line MCF-7 | Whole-body γ-irradiation using a $^{137}$Cs biological irradiator. Single low dose of 0.5 Gy at 0.653 rad/sec after tumor inoculation. | CuNPs were synthesized using CHY at 0.667 mg/kg. Additionally, CHY was used in an in vitro study at concentrations of 0.5-1000 µg/ml for three hours. | CuNPs with RT lead to:<br>⊥ Ehrlich solid tumor growth, NF-κB, p38 MAPK, and Cyclin D1<br>↓ GSH, CAT, ALT, Cr, and $Ca^{2+}$<br>↑ MDA, caspase-3 expression and activity, and necrosis and apoptosis in tumor tissues. |
| Jafari, 2023 (44) | *In vitro* | Human triple-negative breast cancer cell line (MDA-MB-231) | 4 Gy photon 6 MV with a dose rate of 300 cGy/min | CHY concentrations tested ranged from 30 to 70 µM, and the exposure duration was 48 hours. | CHY in combination with RT showed:<br>↓ HIF-1α, Bcl-2, Cyclin D1, p-STAT3<br>↑ Cytotoxicity, apoptotic cell rate by Bax and p53 levels. |
| Jafari, 2024 (45) | *In vitro* | B16-F10 murine melanoma cell line and bone marrow-derived dendritic cells (BMDCs) | 4 Gy photon 6 MV with a dose rate of 300 cGy/min | 25-125 µM and 60 µM of CHY were pre-treated for two hours before irradiation, followed by 48 hours of incubation. | ↓ B16-F10 cell viability and increasing apoptosis, p-STAT3/STAT3, and PD-L1<br>↑ ATP, CRT, HSP70, HMGB1, and IL-12 production in DCs, thereby promoting the activation of a Th1. |

↑: Increase; ↓: Reduce; ⊥: Inhibit.

CHY: Chrysin; GY: Gray; GSH: Glutathione; MDA: Malondialdehyde; TNFα: Tumor necrosis factor alpha; BDNF: Brain-derived neurotrophic factor; RT: Radiation therapy; GABA: Gamma-aminobutyric acid; SER: Serotonin; EPI: Epinephrine; NE: Norepinephrine; NO: Nitric oxide; CuNPs: Copper nanoparticles; CAT: Catalase; ALT: Alanine aminotransferase; $Ca^{2+}$: Calcium; Cr: Creatinine; HIF-1α: Hypoxia-inducible factor 1 alpha; STAT3: Signal transducer and activator of transcription 3; IL: Interleukin; DCs: Dendritic cells; Th1: T helper 1 cells; ATP: Adenosine triphosphate; CRT: Calreticulin; HSP70: Heat shock protein 70; HMGB1: High-mobility group box 1.

**Table 4.** Results of risk of bias assessment using QUIN tool

| Studies (year) | 1. Clearly stated aims/ objectives | 2. Explanation of sample size calculation | 3. Explanation of sampling technique | 4. Details of comparison group | 5. Explanation of methodology | 6. Operator details | 7. Randomization | 8. Method of measurement of outcome | 9. Outcome assessor details | 10. Blinding | 11. Statistical analysis | 12. Presentation of results | Overall score (n/%) | Risk of bias |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Liu, 2020 (7) | 2 | 0 | 0 | 2 | 2 | 0 | 0 | 2 | 0 | 0 | 0 | 1 | 9 (37.5%) | High |
| Yang, 2021 (46) | 2 | 0 | 0 | 2 | 2 | 0 | 0 | 2 | 0 | 0 | 2 | 2 | 12 (50 %) | Medium |
| Zhang, 2023 (47) | 2 | 0 | 0 | 2 | 2 | 0 | 0 | 2 | 0 | 0 | 2 | 2 | 12 (50 %) | Medium |
| Abdelhakm, 2023 (43) | 2 | 0 | 0 | 2 | 2 | 0 | 0 | 2 | 0 | 0 | 2 | 2 | 12 (50 %) | Medium |
| Jafari, 2023 (44) | 2 | 1 | 1 | 2 | 2 | 0 | 0 | 2 | 0 | 0 | 2 | 2 | 14 (58 %) | Medium |
| Wang, 2024 (49) | 2 | 0 | 0 | 2 | 2 | 0 | 0 | 2 | 0 | 0 | 2 | 2 | 12 (50 %) | Medium |
| Zhu, 2024 (50) | 2 | 0 | 0 | 2 | 2 | 0 | 1 | 2 | 0 | 0 | 2 | 2 | 14 (58.3%) | Medium |
| Dutta, 2024 (48) | 2 | 0 | 0 | 1 | 2 | 0 | 0 | 2 | 0 | 0 | 0 | 2 | 9 (37.5%) | High |
| Jafari, 2024 (45) | 2 | 1 | 1 | 2 | 2 | 0 | 0 | 2 | 0 | 0 | 2 | 2 | 14 (58 %) | Medium |
| Xie (a), 2025 (51) | 2 | 0 | 0 | 2 | 2 | 0 | 0 | 2 | 0 | 0 | 2 | 2 | 12 (50 %) | Medium |
| Xie (b), 2025 (52) | 2 | 0 | 0 | 2 | 2 | 0 | 0 | 2 | 0 | 0 | 2 | 2 | 12 (50 %) | Medium |

Adequately specified=2; Inadequately specified=1; Not specified=0.
Final score: >70% = Low risk of bias; 50 to 70% = Medium risk of bias; <50% = High risk of Bias based on the formula of QUIN tool: Final score = Total score * (100) / (2 * number of criteria applicable).

neuroinflammation, and DNA damage by restoring antioxidant defenses, reducing lipid peroxidation, and maintaining cell integrity. In this regard, a study indicated that CHY could inhibit the androgen receptor, playing a major role in prostate cancer growth and metastasis. In lung cancer cells, it triggers caspase-dependent apoptosis pathways and reduces the production of certain proteins, which in turn lowers tumor spread in animal studies. For colon cancer, CHY also leads to cell death, stops cells in the G2/M phase, and lowers levels of cyclin B1 and cyclin-dependent kinase 2, helping to slow cell growth. It also limits tumor growth and spreads by preventing new angiogenesis. Still, using CHY in clinical settings is challenging because it does not dissolve well, is difficult to access, and has low bioavailability, despite affecting several cancer-related pathways (23). Moreover, Sood et al reported in their study that CHY has anticancer properties and exhibits a synergistic effect on cancer treatments, such as RT and chemotherapy. They also demonstrated that CHY induces apoptosis in cancer cells by causing DNA damage, inhibiting angiogenesis, arresting the cell cycle, and slowing down their progression and metastasis (24). In line with our study, another article also reported that nanomedicine can help address challenges and improve CHY solubility and delivery. Moreover, CHY exhibits anticancer properties, affecting various signaling pathways associated with cancer. CHY acts in multiple ways, including triggering cell death, regulating the cell cycle, influencing the immune system, and inhibiting angiogenesis in various neoplasms (25). CHY revealed broad anticancer molecular activity through activating caspase-mediated apoptosis, often through improvement of TRAIL signaling and inhibition of the PI3K/Akt pathway. Across multiple cancer cell types, CHY induces apoptosis via ROS generation in cells, mitochondrial and membrane dysfunction, cytochrome c release, and cell cycle arrest, particularly at the G2/M phase. It modulates critical key signaling pathways, including MAPK, NF-κB, mTOR, and PI3K/Akt, suppresses inflammation, inhibits angiogenesis and metastasis, and alters epigenetic and metabolic regulators, such as TET1 and hexokinase-2. Additionally, CHY enhances the efficacy of current therapeutic methods and enhances autophagy in resistant colorectal cancer cells, highlighting its potential as a multifunctional anticancer agent (19). These properties are reviewed below in detail:

## Photosensitizing and radiosensitizing properties

CHY, as a naturally occurring flavonoid, has emerged as a candidate radiosensitizer and photosensitizer due to its capacity to modulate key cellular pathways involved in oxidative stress, DNA damage response, and apoptosis in tumor cells. It also prevents their side effects, which we will discuss below.

### *Photodynamic and photothermal enhancement*

PDT is a noninvasive, targeted treatment modality for skin cancers that uses a photosensitizing agent, a

specific wavelength of light, and oxygen to generate ROS that induce cytotoxicity and neoplastic cell death (53). PDT works by administering a photosensitizer, either topically on the skin or intravenously, which accumulates in tumor tissue during a specified waiting period. After this, the area is exposed to light of a specific wavelength, commonly red (at least 600 nm) or blue (400-450 nm) (12,53). The photosensitizer does not act on its own; when exposed to light, it transfers energy to oxygen in the tissue. This creates ROS like $^1O_2$, superoxide ($O_2^-\bullet$), hydrogen peroxide ($H_2O_2$), and hydroxyl radical (HO•). These ROS initiate a chain of biochemical reactions that damage and destroy the target cancerous tissue (12,54). Additionally, PTT is a minimally invasive delivery route that uses photothermal agents to turn absorbed NIR light into heat (55). This heat causes hyperthermia, which destroys cancerous or diseased tissues while leaving healthy cells unharmed. The process works by depositing photothermal materials, such as gold NPs, carbon-based nanomaterials, or conjugated polymers, at the target area (56-58). When NIR light is applied, it penetrates tissue and rapidly raises its temperature, breaking down proteins and DNA, cell cycle arrest, disrupting endoplasmic reticulum (ER) stress, disrupting mitochondrial membrane permeability, and eventually leading to cell death via the apoptotic pathway (upregulation of caspase-9 and caspase-3) or necrosis (10,59). PTT has been widely studied for treating solid tumors in cancer and is also being explored for antibacterial therapy, managing vascular lesions, and combining with chemotherapy, RT, or immunotherapy. Its main advantages are precise control, low overall toxicity, and compatibility with imaging-guided treatments (10).

Various studies have shown that CHY, in combination with PT, increases singlet oxygen ($^1O_2$)-mediated oxidative injury resulting from photodamage, compromises the membrane's protective capacity against subsequent visible light-induced damage and ROS generation, which induces DNA damage (7,47). Dutta et al in their study reported that, *in vitro* exposure of HeLa, A549, and HPL1D cells to visible-light PDT (400-700 nm; 10 J/cm$^2$) in the presence of 20 μM CHY-cobalt(III) complexes (Co5 and Co6) for 25–30 min generated $^1O_2$ and additional ROS, thereby eliciting oxidative-stress-driven apoptosis through a type-II photodynamic pathway (48). Xie demonstrated that treating B16 melanoma and 4T1 breast cancer cells, as well as female Balb/c mice *in vivo*, with Ce6-TEGDM-CHY (0.5 μM/L, 24-hour incubation) followed by 680-nm PDT (0.05 W/cm$^2$, 5 to 10 minutes) induced apoptosis through excessive ROS, including $^1O_2$, $\cdot O_2^-$, $H_2O_2$, and ·OH (51). In a similar study, CHY-PPA conjugates administered at 0.5–20 μM/L, followed by 5-minute irradiation and 4-hour post-incubation, further enhanced photoinduced oxidative stress by increasing $^1O_2$ and $\cdot O_2^-$, $H_2O_2$, and ·OH, suppressed tumor growth, and improved physicochemical performance (52).

Targeting tumor cells at specific stages of the cell cycle may significantly enhance the therapeutic efficacy of PT. For instance, targeting treatment to cells in the S phase, when DNA synthesis is active, and the G(0)/G(1) cell cycle could increase photosensitizer uptake and ROS production, thereby promoting more effective cell death signaling (60,61). Additionally, since many photosensitizers and nano-photosensitizers exhibit radiosensitizing properties, their combination with PDT and RT regimens may provide a practical approach for inhibiting tumor proliferation through coordinated cell-cycle arrest (61). An included study revealed that PDT administered on MGC-803 gastric carcinoma and HeLa cervical carcinoma cells applying a 12 W LED purple lamp (380-460 nm, 20 cm distance, 10 minutes irradiation, ≈ 50 mW·cm$^{-2}$) with the porphyrin-CHY derivative 4a applied at 0, 20, 40, and 60 μM after 24-48 hours of incubation generated substantial $^1O_2$, inducing photooxidative damage that culminated in G1-phase cell-cycle arrest (in a concentration-dependent manner) and apoptosis (7).

On the other hand, ROS accumulation and CHY-enhanced photothermal effects contribute to tumor ablation and strengthen apoptotic signaling pathways within the tumor microenvironment through various pathways, including the p53-BAX/BCL-2 axis, without systemic toxicity (7,46-48,51,52).

In an inflammatory context, heat-triggered CHY release from nanoplatforms under 808 nm irradiation modulates the expression of ESR1, BRCA1, CTNNB1, and BAX. It promotes T-cell ($CD4^+/CD8^+$) infiltration, thereby enhancing tumor suppression and ultimately apoptosis in MDA-MB-231 breast cancer cells (50). Moreover, Wang et al. conducted a study using ARPE-19 human retinal pigment epithelial cells and C57BL/6J mice in which choroidal neovascularization (CNV) was induced by an 810-nm argon laser photocoagulation protocol (110 mW, 100 ms, 50 μm). Their results demonstrated that the intervention downregulated the IL-17/STAT3 and NF-κB (p65) signaling pathways, leading to decreased expression of vascular endothelial growth factor (VEGF) and IL-6 and ultimately suppressing choroidal neovascularization and retinal inflammation (49).

### *Radiosensitizing mechanisms*

RT uses precise targeted high-energy X-rays, gamma radiation from radioactive sources, or subatomic particles (such as electrons) to induce cytotoxic DNA damage in cancer cells. It remains a key treatment option for various types of cancer (62). As previously noted, the primary therapeutic mechanisms of radiation therapy stem from differences in DNA damage response pathways between cancerous and normal cells. Ionizing radiation induces DSBs, leading to mitotic catastrophe, so radiosensitivity primarily depends on a cell's ability to proliferate (63). Moreover, ionizing radiation eliminates heavily damaged cells by inducing irreversible G1/S cell-cycle arrest, a phenomenon particularly pronounced in apoptosis-

resistant human diploid fibroblasts (64). Activation of the p53-p21 pathway suppresses S-phase (DNA synthesis phase) entry and can promote apoptosis. However, this effect may be attenuated by oncogenes, including C-MYC (avian myelocytomatosis viral oncogene homolog). In p53-deficient cells, the lack of G1 arrest allows proliferation despite significant genomic damage, thereby contributing to radiation-induced genetic instability (64,65).

In a study, CHY-derived copper NPs (CuNPs) enhanced the effects of low-dose γ-irradiation in Swiss albino mice bearing Ehrlich tumors and in MCF-7 breast cancer cells. Combined treatment reduced GSH, catalase (CAT), alanine aminotransferase (ALT), creatinine (Cr), and $Ca^{2}$ levels while increasing MDA levels, indicating intensified oxidative stress. This redox imbalance was accompanied by marked elevation of caspase-3 expression and activity, leading to enhanced apoptosis and necrosis in tumor tissues. Overall, CHY-mediated CuNPs also inhibited cell proliferation via the p38 MAPK/NF-κB signaling axis and Cyclin D1, and significantly potentiated radiation-induced cytotoxicity (43). CHY has demonstrated antioxidant, immune-stimulating, and anti-apoptotic properties. In a study, adult female Swiss albino mice with Ehrlich Ascites Carcinoma solid tumors received γ-irradiation at a total dose of 1 Gy, administered in two fractions using a $^{137}Cs$ Gamma Cell-40 irradiator, in combination with intraperitoneal CHY treatment at 20 mg/kg for 21 days. This combined treatment reduced levels of Interferon gamma (IFN-γ), tumor necrosis factor alpha (TNF-α), free radicals, and nitric oxide (NO), while increasing caspase-3 activity in tumor tissues. The observed decreases in inflammatory and oxidative markers, along with enhanced apoptotic signaling, indicate that CHY synergizes with γ-irradiation to improve anti-tumor efficacy (42). Another study investigated the effects of 4 Gy photon irradiation, delivered with 6 MV beams at a dose rate of 300 cGy/min, on B16-F10 murine melanoma cells and bone marrow-derived dendritic cells (BMDCs). Melanoma cells were pre-treated with CHY at concentrations of 25-125 μM, with 60 μM as the primary dose, followed by a 48-hour incubation post-irradiation. The combined treatment reduced B16-F10 cell viability and increased apoptotic responses, as indicated by elevated p-STAT3/STAT3 and PD-L1 expression. In BMDCs, the intervention increased the release of ATP, calreticulin (CRT), HSP70, HMGB1, and IL-12, thereby promoting a Th1-oriented immune response (45).

## Protective mechanisms of CHY against treatment toxicity

Protective mechanisms are essential for reducing damage to normal tissues during RT and PT. These effects, unlike those involved in the destruction of cancer tumors, are based on preventing damage to healthy cells through the same mechanisms. Toxicities were evaluated in parallel with antitumor efficacy to assess the translational safety profile among included studies. With respect to neurotoxicity, CHY at 50-100 mg/kg in rats demonstrated protective rather than deleterious effects on neural tissues, as evidenced by reduced malondialdehyde (MDA) levels in experimental models, modulation of gamma-aminobutyric acid (GABA) concentrations, restoration of brain glutathione (GSH) and brain-derived neurotrophic factor (BDNF), normalized neurotransmitter levels (serotonin, epinephrine, and norepinephrine), preserved neural tissue integrity, and suppression of pro-inflammatory mediators such as TNF-α and IFN-γ. These results demonstrated the effective mitigation of oxidative stress and neuroinflammation following neuronal damage caused by RT (40,41). The study on retina and choroidal-damaged retinal pigment epithelium revealed that CHY at 25 mg/kg, applied daily for one week after PT, attenuated DNA double-strand breaks (DSBs), telomere erosion, oxidative stress-driven inflammation, and cellular senescence in retinal pigment epithelial cells, concomitant with downregulation of IL-17/STAT3 and NF-κB signaling and inhibition of pathological neovascularization (49). In terms of immune regulation, the combined effect indicates that CHY (60 μM of CHY) with 4 Gy RT, not only induces tumor-selective apoptosis via ROS but also improves antitumor immunity by modulating dendritic cell function, IL-12 production, and Th1 polarization. This represents an indirect protective effect, as it supports immune surveillance and tumor control without causing systemic immune dysregulation (45).

Antioxidants appear to mitigate several RT-induced toxicities. Polyphenols, functioning as antioxidant agents, have been proposed to expand the therapeutic window of RT. These compounds may increase tumor radiosensitivity while simultaneously protecting normal tissues from treatment-related injury. Such protective effects might be attributed to their ability to reduce radiation-induced DNA damage and to provide immunomodulatory, antioxidant, and anti-inflammatory actions that enhance cellular resilience during irradiation (66). Polyphenolic compounds have demonstrated benefits across multiple mucosal and cutaneous endpoints, enteritis, dermatitis, pelvic injuries, and biochemical changes during RT (67-69).

## Types and advantages of CHY-NPs

In recent years, NPs have been utilized in various fields, including medicine, food, and cosmetics. They can improve drug delivery, increase bioavailability, and enhance the effectiveness of other treatments (70-72). Various NP-based methods have been developed for cancer therapy, including solid lipid NPs (SLNs), magnetic NPs, nanoemulsions, inorganic NPs, dendrimers, metal NPs, liposomes, extracellular vesicles, and carbon quantum dots (73). CHY is among the most naturally occurring compounds investigated due to its potent anti-cancer properties across different stages of tumor development (19). Despite its promising biological activities, CHY's

**Table 5.** Characteristics and outcomes of Chrysin (CHY)-nanoformulations used in the included studies

| Lead author, year (Reference) | Nanoformulation | Classification | Outcomes |
|---|---|---|---|
| Abdelhakm, 2023 (43) | CHY-CuNPs (Copper NPs) | Metal-complex nanostructures | The bioavailability of CHY is enhanced, enabling the application of copper and low-dose gamma radiation in cancer therapy by applying newly synthesized CuNPs as radiosensitizers. |
| Dutta, 2024 (48) | CHY-Co(III) nanocomplexes | Metal-complex nanostructures | CHY NPs may be used to improve the biocompatibility and phototherapeutic efficacy of metal complexes containing bioessential transition-metal ions, such as Co(III), while reducing metal-induced toxicity. |
| Xie (a), 2025 (51) | Ce6-TEGDM-CHY nano-conjugate | Hybrid organic nano-photosensitizer | Improves solubility, stability, tumor accumulation, cellular uptake, and photodynamic efficiency while enabling multifunctional therapy. |
| Xie (b), 2025 (52) | CHY-PPA nano-photosensitizer | Organic self-assembled NPs | Improved tumor-targeting ability, decreased the dark toxicity of the photosensitizer, and enhanced PDT treatment. |
| Zhu, 2024 (50) | CHY-loaded mesoporous polydopamine NPs (CHY@mPDA) | Polymer-based nanocarrier/drug-delivery NP | The NPs showed a strong ability to encapsulate CHY and maintained considerable stability. Photothermal evaluation demonstrated that they could generate heat upon laser irradiation, which significantly increased CHY release under acidic conditions. |

NP: Nanoparticle; PPA: Pyropheophorbide-a; CuNPs: Copper nanoparticles; TEGDM: Tetraethylene glycol dimethacrylate; PDT: Photodynamic therapy.

low water solubility and bioavailability limit its clinical use (25). Using CHY-NPs can enhance bioavailability, water solubility, tumor-targeted delivery, stability, control drug release profiles, improved permeability, and CHY tissue accumulation (43,51). Additionally, combining nanoradio and photosensitizers with chemotherapy or immunotherapy to enable targeted or localized activation has the potential to enhance delivery and treatment outcomes while reducing side effects (74,75). The CHY-nanoformulations used in this study, along with their results, are presented in Table 5.

Drug delivery and release in CHY-based phototherapeutic systems are governed by advanced, stimuli-responsive mechanisms designed to enhance both targeting accuracy and bioavailability. Collectively, these integrated mechanisms maximize drug loading, prolong circulation time, and optimize photoactivation, ultimately advancing the therapeutic efficacy of CHY-porphyrin platforms in both photodynamic and photothermal cancer treatments.

## Limitations

The lack of clinical trial data is one of the most critical limitations of this study, as it affects the determination of the effective dose and possible adverse effects. The smaller number of studies on the RT enhancement and radioprotective effects of CHY is also a factor that can negatively affect the reliability of the results; consequently, if there were more of these studies, more reliable results could be obtained. Moreover, a moderate to high risk of bias range limits confidence in mechanistic conclusions from experimental studies. In animal studies, high-risk ratings are commonly associated with inadequate blinding methods and widespread unclear reporting of allocation and randomization, which increase the potential risk of bias in observed effects. *In vitro* studies also showed medium risk, with gaps in reporting key methodological details. These limitations suggest that observed outcomes may not reliably reflect true mechanistic processes, warranting cautious interpretation. Additionally, this review was not registered in PROSPERO.

## Conclusion

The results of experimental studies showed that CHY and its NPs effectively enhanced the efficacy of RT and PT while reducing adverse effects associated with these treatments, due to their antioxidant, anti-inflammatory, and anti-apoptotic properties. Moreover, CHY-NPs promote tumor eradication, reveal biocompatible properties, improve CHY's dispersion capacity, solubility, stability, and tumor-selective accumulation. However, applying these findings in clinical settings and therapeutic areas requires further clinical studies using different doses to facilitate their use in cancer treatment. Comprehensive toxicological and pharmacokinetic assessments are necessary to establish the protective effects of CHY in normal tissues.

## Acknowledgements

Grammarly (Grammarly Inc., USA), an AI-assisted language-editing tool, was used exclusively to enhance the English-language editing process by improving grammar, spelling, and clarity of this paper.

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## Conflict of interest

The authors declared no conflict of interest, financial or otherwise.

## Ethical considerations

Ethical issues (including plagiarism, and double publication) have been completely observed by the authors.

## Funding/Support

Nil.

## Supplementary files

Supplementary file 1 contains Table S1.

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