Journal of Drug Delivery Science and Technology 87 (2023) 104803

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

journal homepage: www.elsevier.com/locate/jddst

Review article

Free radical based nano cancer therapy

Abduladheem Turki Jalil [a,*], Mohanad Ali Abdulhadi [b], Lubna R. Al-Ameer [c], Oday Faris Washeel [d], Sada Jasim Abdulameer [e], Muna S. Merza [f], Munther Abosaooda [g], Ayat Abdul Mahdi [h]

[a] College of Medicine, University of Thi-Qar, Al-Nasiriya, Iraq
[b] Department of Medical Laboratory Techniques, Al-maarif University College, Al-Anbar, Iraq
[c] College of Pharmacy, Al-Zahraa University for Women, Iraq
[d] National University of Science and Technology, Dhi Qar, Iraq
[e] Biology Department, College of Education for Pure Science, Wasit University, Kut, Wasit, Iraq
[f] Prosthetic Dental Techniques Department, Al-Mustaqbal University College, Babylon, 51001,Iraq
[g] College of Pharmacy, The Islamic University, 54001 Najaf, Iraq
[h] Medical Technical College, Al-Farahidi University, Baghdad, Iraq

ARTICLE INFO

Keywords:
Free radical
ROS
Cancer therapy
Chemodynamic
Photodynamic
Radiotherapy

ABSTRACT

Free radicals were formerly considered as a highly reactive, transient, and destructive entities. Free radicals are exceedingly unstable and highly reactive with other biological molecules, often having one or more unpaired electrons. Free radicals' open-shell electrical structure makes them ready for harnessing in biological applications. In particular, free radical regulation-based nanotherapeutics have become a novel therapy option for cancer. Recent developments on free radicals and their uses in cancer therapy are discussed in this review. Photodynamic treatment (PDT), sonodynamic therapy (SDT), radiation therapy (RT), chemodynamic therapy (CDT), and ferroptosis therapy are only some of the emerging approaches that rely on the creation of free radicals by nanoparticles (NPs) which discussed here. Finally, several challenges and promising future directions for free radical regulation-based nanotherapeutics in cancer therapy are highlighted.

1. Introduction

Cancer is a significant contributor to mortality rates worldwide, resulting in millions of deaths each year. The uncontrolled proliferation rate of cancer cells is a primary factor in this phenomenon, causing concern among healthcare professionals on a global scale. Nanotechnology has provided remarkable evidence of the fast expanding interest of researchers in finding solutions to the problems connected with traditional cancer treatment [1–4]. Nanoparticle (NPs)-mediated strategies hold greater potential for substantially enhancing the therapeutic efficacy in the treatment of cancer [5,6].

An unpaired valence electron is a characteristic feature of free radicals, which can be any type of atom, molecule, or ion [7–9]. With their unpaired electrons, free radicals are able to abstract them from other molecules, then increasing their reactivity. Free radicals are generally transient and react nonselectively with other molecules because of their high reactivity [10,11]. Light [12,13], heat [14], sonication [15], radiation [16], Fenton process [17], redox process [18], and electrolysis [19] are all common sources of free radicals.

In 1954, Commoner et al. used electron paramagnetic resonance spectroscopy to show that free radicals exist in living systems [20]. Aerobic organisms can only survive if there is oxygen present. The production of reactive oxygen species, often known as ROS, is a secondary byproduct of cellular metabolism [21]. The phrase "an imbalance between oxidants and antioxidants in favor of the oxidants" describes what is known as "oxidative stress." This imbalance causes a disturbance in redox signaling and control, which ultimately leads to molecular damage [22].

Free radicals are known to damage living organism. According to the well-known free-radical hypothesis of aging, free radicals are a major cause of aging [23]. Both endogenous and external pathways can generate free radicals. The majority of radicals are produced when mitochondrial electrons escape and react with oxygen to produce $O_2^{\bullet-}$. After that, H_2O_2 and $^{\bullet}OH$ can be generated by $O_2^{\bullet-}$. Reactive oxygen

* Corresponding author. College of Medicine, University of Thi-Qar, Al-Nasiriya, Iraq.
E-mail address: abedalazeem799@gmail.com (A. Turki Jalil).

https://doi.org/10.1016/j.jddst.2023.104803
Received 22 January 2023; Received in revised form 17 July 2023; Accepted 31 July 2023
Available online 4 August 2023

Formulation	Size	size	Trigger System	In vitro	tumor models	Ref.
mPEG-CUR@Au	–	73.8 ± 6.76	X-ray	4T1 mammary carcinoma cells	4T1 breast cancer	[42]
Match–AuNP–Tat	15.5 ± 1.9	37.7	ionizing radiation (IR) using a cesium-137 (137Cs)-irradiator	MDA-MB-435 cells		[43]
TiO_2(Gd) NPs	20	–	X-ray	MCF-7	MCF-7	[44]
dAuNP-TPP	23.31 ± 3.00	78.8 ± 1.36	X-ray	4T1	4T1	[45]
Mn-MOF	–	70	US irradiation	H22 and 4T1	H22 and 4T1	[46]
TiO_{1+x} NRs	1.8 ± 0.67 nm (width) × 28.68 ± 4.24 nm (length)	–	US	4T1	4T1	[47]
COF–TiO_2	380	–	US	4T1	4T1	[48]
SIWV-pSiNP (ICG)	184 ± 81	–	808 nm laser	U87MG and Huh7	U87MG	[49]
HMSNs-B-HA	170 ± 10	269 ± 3	808 nm laser	4T1 and 293T	–	[50]
CoSx QDs	5.8	–	CDT	A431 and 4T1	4T1	[51]
DOX@MDNs	200 ± 50	–	CDT	A549	–	[52]
Cu-Cys NPs	80	–	CDT	HeLa, MCF-7, and PC-3	MCF-7R	[53]
FCS MOFs	127.53 ± 24.47	–	ferroptosis	4T1	4T1	[54]
IONP–GA/PAA	13	70 ± 20	ferroptosis	HT1080	–	[55]

species include (ROS) $O_2^{\bullet-}$, H_2O_2, and $^{\bullet}OH$, however, only $O_2^{\bullet-}$ and $^{\bullet}OH$ are free radicals whereas H_2O_2 is not. Also, in/at peroxisomes, plasmatic, and nuclear membranes small amounts of endogenous radicals are generated. Ultraviolet irritation, pollution of the air and water, toxic chemicals, smoking, alcohol, drug abuse, and psychological stress are some outer stimuli that can generate exogenous radicals [24].

Not only, the unwanted free radicals can cause some biological problems such as aging, tissue damage, and various diseases, such as Parkinson, Alzheimer, diabetes mellitus and cardiovascular diseases, but also they can increase the risk of cancer [25]. In the meanwhile, free radicals are involved in several crucial biological processes. The balance between the production of free radicals and antioxidants is critical [26]. Free radicals, which play crucial roles in immune system, cellular signaling pathways, and mitochondrial respiratory chains, are kept at reasonable levels in healthy organisms [27,28]. Antioxidants include glutathione (GSH), superoxide dismutase (SOD), thioredoxin (TRX), and catalase (CAT) neutralize their adverse effects in the body [26].

Free radicals can be used in biological applications despite their health risks. This article provides a comprehensive overview of contemporary free radical uses in cancer therapy.

2. Free radicals and ROS

It should be noted that Free radicals and reactive oxygen species (ROS) are sometimes confused, but have distinct meanings. Although they frequently used interchangeably. If that is right in many instances, it is incorrect in certain instances. All atoms, molecules, and ions with unpaired valence electrons are considered free radicals, whether they are oxygen-related or not. While ROS are oxygen-containing chemically reactive species. ROS can also be non-radical species, such as singlet oxygen ($^1O_2$), in addition to the oxygen-related free radicals [8]. $O_2^{\bullet-}$, H_2O_2, and $OH^{\bullet}$ are the products of the oxygen reduction process. Interestingly, H_2O_2 is included in the ROS group, while it is not a free radical. Because H_2O_2 is chemically more active than O_2 [8]. Both free radicals and non-radical derivatives are included in the ROS group.

Researchers in the field of biomedicine did not separate free radicals from ROS since the majority of the free radicals found in biological environments are connected to oxygen [29]. In fact, ROS only cover a small part of what free radicals do, and because of their special physical and chemical characteristics, they have a lot of potential as cancer therapeutics.

3. Types of free radicals

In biological systems, oxidative breakdown of substrates is triggered by free radicals, which are a class of extremely active intermediates having one or more unpaired electrons [30]. Free radicals are very unstable, short-lived, and unselectively reactive towards surrounding molecules because of their high electrophilicity due to unpaired electrons.

Generally, there are three main type of free radicals [31]: i) Reactive oxygen species (ROS), ii) reactive nitrogen species (RNS), and iii) other radicals without O or N elements.

Because photosynthesis and aerobic respiration both use oxygen, oxygen radicals are the most prevalent free radicals in living systems. Singlet oxygen ($^1O_2$), superoxide ($O_2^{\bullet-}$), hydroxyl radical ($^{\bullet}OH$), and lipid peroxide (LPO) such as alkoxyl radical ($RO^{\bullet}$) and peroxyl radical ($ROO^{\bullet}$) are included in the ROS group. There are also non-radical ROS derivatives such as H_2O_2, HOCl, $^1O_2$, and ozone (O_3), however they are not a free radical [32].

Nitric oxide ($NO^{\bullet}$) and nitrogen dioxide ($NO_2^{\bullet}$) are included in the RNS group. Reactive chlorine/bromine species ($Cl^{\bullet}$, $Br^{\bullet}$), reactive sulfur species ($RS^{\bullet}$), alkyl/carbon-centered radicals ($R^{\bullet}/C^{\bullet}$), and other reactive atom-centered radicals are examples of atomic and ionic non O or N radicals [31]. Protein degradation and DNA altering DNA are caused by Carbon-centered radicals (C-radicals) [33].

4. Free radical based nano cancer therapy

The development of nanoagents for regulating free radicals as a potential therapy option for cancer has been substantial during the past few decades. Numerous special benefits result from the use of nanomaterials in free radical-regulating based treatment. In terms of their component materials, nanotherapeutics display a variety of intrinsically exciting biophysical and biochemical characteristics, such as a particular surface area, suitable nanoscaled size, and various aspect ratios. The blood half-life of nanomaterials is prolonged because they have the ideal size: large enough to avoid renal excretion (diameter of around 5–10 nm exceeds threshold size of kidney clearance by 40–50 kDa), yet tiny enough to infiltrate and concentrate in tumor [34]. Nanomaterials that are big tend to get stuck and build up in the spleen, liver, and lung capillaries [35]. On the one hand, nanotherapeutics can get beyond the shortcomings of classic small molecule medications' limited bioavailability and suboptimal targeting. In general, there are two ways for nanomaterials to get to the tumor: passive targeting and active targeting. Nanotherapeutics can be reach to tumor site by the passive targeting mechanism, also known as the enhanced permeability and retention (EPR) effect. In case of active targeting, nanomaterials can be engineered by targeting ligand to bind specifically to tumor cells, then can successfully transport payloads to tumor site [36].

However, large-scale clinical uses of animal-derived materials like monoclonal antibodies and cell treatments would be severely hampered by factors including their undesirable immunogenicity, high technical expense, and manufacturing complexity. Nanotherapeutics, on the other hand, have the promise for clinical applications since they not only reduce cost and production complexity but also increase biocompatibility of the payloads through surface modification.

Furthermore, to accomplish combination treatment, nanomaterials not only can transport numerous payloads at the same time, such as chemotherapeutic medicines, but also can be act as photosensitizers, sonosensitizers, and radio-sensitizers [37–39]. Combination cancer theraoy considerably boosting the final therapeutic efficacy. There are lots of reports that exploit nanotherapeutics for free radical based cancer therapy, which enables generate cascaded or highly efficient ROS/RNS [40].

When free radicals are produced in excess, they can disrupt tissue homeostasis and potentially kill off cells. As a result, cancer can be effectively treated with nanotherapeutics based on free radical production [14,41].

Here, we provide a comprehensive overview of the most up-to-date uses of free radicals in cancer therapy *via* Photodynamic treatment (PDT), sonodynamic therapy (SDT), radiation therapy (RT), chemodynamic therapy (CDT), and ferroptosis therapy approaches (Fig. 1.).

4.1. Radiation therapy (RT)

Because of its potential to effectively eradicate deep-seated tumors, X-ray-driven RT is still one of the most accessible conventional cancer treatment modalities paired with chemotherapy or surgery in the clinic.

Compton scattering, which produces high-energy electrons known as "secondary electrons," is the principal interaction of photons with cells that might alter biological structures in radiation treatment. According to the radiobiology literature, DNA is the most important radiation target in the cell. There are two possible routes through which radiation might interact with DNA: directly and indirectly. Damage to DNA molecule can be caused by direct ionization if enough radiation energy is deposited. In indirect mevhanism, radiation may damage DNA by first transferring its energy to nearby water molecules, which then produces free radicals, most notably hydroxyl radicals. Double-strand breaks (DSBs) and single-strand breaks (SSBs) are types of DNA damage caused by the removal of a hydrogen atom from deoxyribose by an activated hydroxyl radical. DNA DSBs are much less common than SSBs, but they cause far more genetic information to be lost and are thus among the most deadly lesions [56,57].

High-energy ionizing radiation (e.g. X-ray) may generate ROS including $^{1}O_2$ and $^{\bullet}OH$, which can subsequently attack neighboring tissues and macromolecules (particularly DNA) to cause cell damage, making RT a viable therapeutic modality without penetration depth constraint.

Even with progress, however, the fact that some malignancies are resistant to radiation is a major cause for concern since it might raise the risk of tumor recurrence after treatment. Because the tumor tissues absorb so little radiation energy, a high-energy dosage of the radiation beam is necessary, which may cause harm to nearby healthy tissues as well. To combat tumor radioresistance without causing unacceptable damage to surrounding normal tissue, many NPs have been produced and used in RT. Such NPs have a significant potential for therapeutic usage and are often constructed of high-atomic-number elements (high-Z NPs). Since high-Z NPs have a higher mass energy absorption coefficient than soft tissue, they are used as radiosensitizers to boost the dosage deposited in the target volume [58].

Photoelectric effect, Rayleigh scattering, Compton scattering, Auger electrons, and fluorescence photons are several physical processes which occurred when X-rays are used to irradiate materials. Among these processes, ROS may be produced to variable degrees using Auger electrons, Compton electrons, and electrons produced by the photoelectric effect.

A wide range of radiosensitizers have been used to increase the radiosensitization of cancer cells in order to increase ROS production and RT effectiveness [59]. Numerous studies have been conducted on high Z-NPs, such as gold (Au) [42,43], gadolinium (Gd) [44], Bismuth (Bi) [60], and hafnium (Hf) [61], as effective radiosensitizers for RT.

Recently, Zhao et al. prepared mitochondria-targeting and PSA-reactive gold nanoparticles (dAuNP-TPP) for induce significant ATP reduction and mitochondrial dysfunction, as well as radiosensitization under X-ray irradiation [45] (Fig. 2a and b). dAuNP-TPP are made by functionalization the surface of AuNPs with cationic triphenylphosphine (TPP) and a PSA-reactive group (1,3-cyclohexanedione, CHD). Intracellular ROS level within cancer cells show that Au NPs produce ROS. Also, the green fluorescence was brightest in the cells that were treated

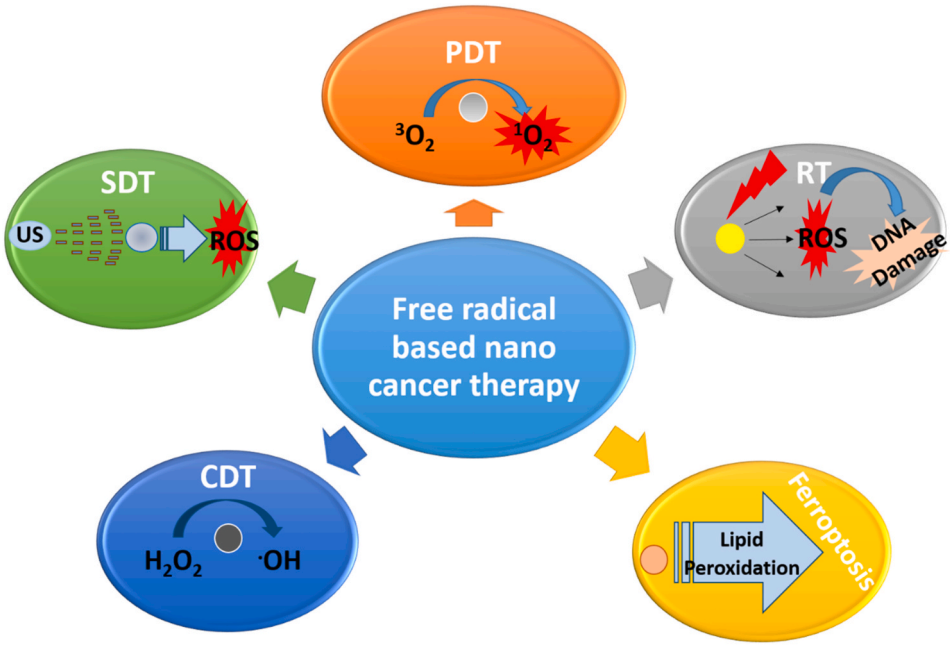

Fig. 1. Some possible approaches for exploiting free radicals in cancer therapy.

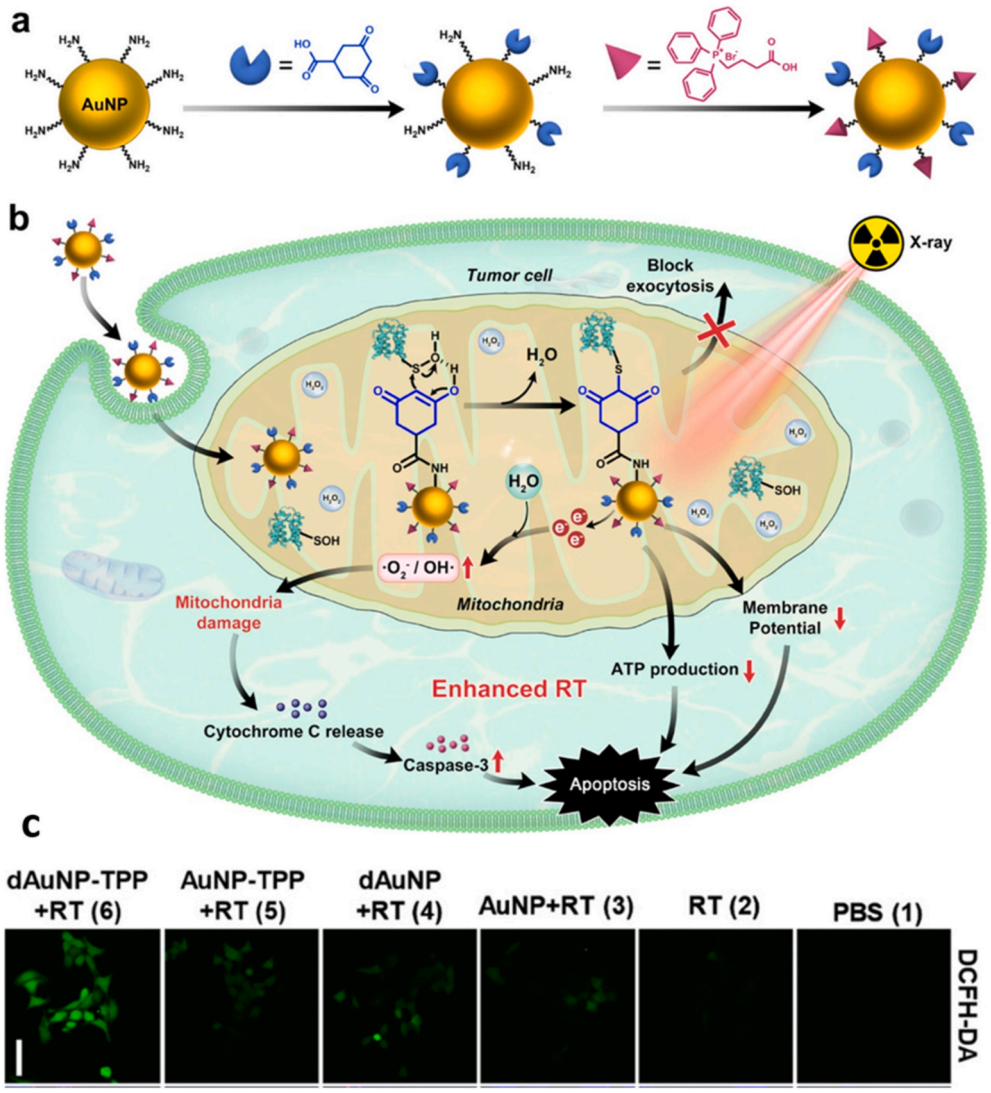

Fig. 2. a) Preparation of the dAuNP-TPP nanoprobe, b) Schematic illustration of ROS-induction by dAuNP-TPP in Mitochondria, and c) Fluorescence imaging of ROS in 4T1 cells. Adapted with permission [45]. Copyright 2022, ACS.

with dAuNP-TPP + RT, and was about 2.52 times stronger than in the control cells treated with AuNP-TPP + RT (Fig. 2c).

In another study, silica-coated iron oxide magnetic nanoparticles (SIONPs) ability in enhancement of radiation dose in MCF-7 cells was studied [62]. Cells treated with 5 and 10 μg/mL of IONPs exhibited dose enhancement factor DEF values of 1 and 1.09, whereas those treated with SIONPs at comparable concentrations had DEF values of 1.21 and 1.32. It was shown that PEGylated gold NPs are able to generate ROS near the surface of them after exposing to 6 Gy RT by 7-fold [63].

In order to specifically improve the efficacy of radiotherapy, folic acid (FA) conjugated Bi_2S_3–Au heterodimers (High Z-NPs), which have the potential to generate free radicals, are being studied by Abhari et al. [64] (Fig. 3a). As shown in Fig. 3b and c, their result not only approve the ROS generation inside 4T1 cells, but also show significant therapeutic efficacy of designed NPs.

In order to maximize the effect of $^{\bullet}OH$ production, Maksimchuk et al. irradiated UV-light-pretreated $(Gd,Y)VO_4:Eu^{3+}$ NPs with X-ray [65]. UV-treated $(Gd,Y)VO_4:Eu^{3+}$ NPs exposed to X-ray irradiation induces both hole release and H_2O_2 radiolysis.

It is critically important, but so far difficult, to create a radiosensitizer that reacts to both X-rays and the TME. Zhou et al. consider the use of bismuth heteropolytungstate (BiP_5W_{30}) nanoclusters as radiosensitizers for TME-manipulated radiotherapy improvement [66]. It is worth mention that Bi and W high-Z elements in the structure of NPs can increase radiation dose deposition in cancer cells. In addition, they are able to deplete GSH via redox reaction and catalyze the breakdown of H_2O_2 to $^{\bullet}OH$ to increase ROS formation following X-ray radiation because of their unusual electron structure and multi-electron feature. Furthermore, through enhancing electron-hole separation, reduced graphene oxide (rGO) paired with BiP_5W_{30} can further enhance radiocatalytic activity.

More recently, ZrRnMn-based metal–organic nanostructures (MON) radiosensitizer was harnessed to combining ROS generation and CO gas release [67]. In this well designed multifunctional X-ray reactor: i) Zr cluster entrap X-rays after absorbing them, then preventing energy and electron loss. ii) Ru (bpy)2 was later triggered to create ROS. iii) Converting X-ray energy into chemical energy enable bromipentacarbonylmanganese ([MnBr(CO)5], abbr: MnCO) to liberate CO gas. To amplify the RT effect from single X-rays, ZrRuMn-MONs@mem offers a potential power via combining ROS generation and CO gas release.

4.2. Sonodynamic therapy (SDT)

Ultrasonic waves have thermal and non-thermal effects. In specifically, the term "thermal effects" refers to a rise in temperature that occurs as a result of the absorption of ultrasonic waves by a tissue, which

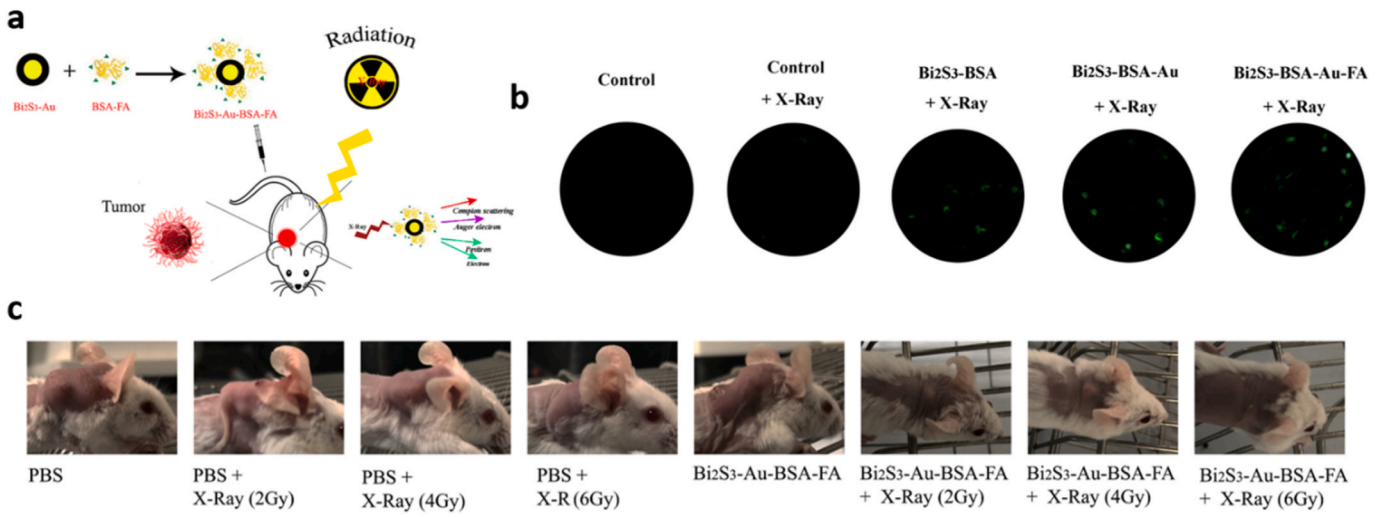

Fig. 3. a) Synthesis process and possible anticancer mechanism of Bi_2S_3–Au-BSA-FA hybrids, b) ROS generation within 4T1 cells, and c) Tumor photos of mice after treatment with different treatment plans. Adapted with permission [64]. Copyright 2020, ACS.

results in the tissue undergoing mechanical compression and decompression. The effects of friction cause some of this mechanical energy to be wasted, and it is turned into heat in the process. Because of this, changes can take place in the permeability of cell membranes in biological systems [68].

Microstreaming, radiation forces, and stable and inertial cavitation are some of the mechanisms that make up the non-thermal action of ultrasound, which is a complex and diverse set of phenomena [69]. These occurrences have the potential to cause a rise in temperature in addition to the induction of mechanical stresses, in particular those known as microjets and microstreams [70]. More specifically, during the process of non-inertial cavitation, also known as stable cavitation, the gas pockets that are present in the liquid oscillate around an equilibrium radius and can remain for several cycles of acoustic compression and decompression. Fluid streaming is produced as a result of these oscillations, and the medium is mixed as a result of the mechanical stresses [71]. The inertial cavitation process, on the other hand, is what happens when gas bubbles trapped in a fluid are exposed to ultrasound and undergo fast expansion and violent collapse. High pressures and temperatures (more than 800 atm) are created during such a collapse, releasing a significant amount of energy [71]. ROS can be produced as a result of inertial cavitation's ability to cause water thermal dissociation.

The development of SDT as an alternative method of treating cancer is quite new. It works by using low-power ultrasound and sonically activated sonosensitizer [72]. The greater tissue penetration depth of SDT over PDT is its primary benefit [73]. Ultrasound (US) is appealing as a possible external excitation in cancer treatment since it is a noninvasive mechanical wave with greater tissue penetrability with the depth over 10 cm below the skin and minimal injury to surrounding normal tissues [74]. In SDT, several compounds have been used, including porphyrins, some anticancer medications, and various type of NPs [75]. Additionally, microbubbles have been described in the literature as an adjuvant for sonosensitizers [76]. In SDT, US is used to activate sonosensitizers, which then generate free radicals, cavitation, gas bubbles, and hyperthermia, all of which can cause cell death [77]. As stated above, the production of ROS is triggered by the sonosensitizer when it is subjected to low-intensity ultrasound.

Organic tiny molecules (such as hematoporphyrin and rose bengal) and inorganic semiconductor NPs (e.g., TiO_2 and black phosphorus) are only two examples of the many sonosensitizers identified so far. In most cases, the excitation of sonosensitizers by US can result in the production of free radicals.

Porphyrin-based compounds or xanthene dyes were studied in the early research of SDT, because they were already in use for PDT. Ultrasound also induces comparable ROS-mediated cytotoxic effects with them [78]. To improve SDT and ferroptosis, Xu et al. fabricated a nanosensitizer composed of manganese porphyrin-based metal-organic frameworks (Mn-MOFs) [46]. This nanosensitizer can self-supply oxygen (O_2) while simultaneously decreasing GSH. In vitro results show that Mn-MOF able to act similar to catalase and decreased GSH. Inside cancer cells, Mn-MOF continued to catalyze tumor-overexpressed H_2O_2 to create O_2 in-situ to treat tumor hypoxia and reduce GSH and GPX4, which promoted the production of ROS and ferroptosis to accelerate the death of cancer cells during US radiation in hypoxic tumors. The majority of organic sonosensitizers suffer from limited water solubility, rapid metabolism, instability, and possible phototoxicity. Xie et al. synthesized water-soluble iridium (III)-porphyrin sonosensitizer (IrTMPPS) as sonosensitizers for improved SDT (Fig. 4a and b) [79]. Under US irradiation, IrTMPPS produced large amounts of singlet oxygen ($^1O_2$) and had unique US-activatable properties at depths more than 10 cm. Compared to other groups, green fluorescence from SOSG oxidation by $^1O_2$ was clearly visible in the IrTMPPS + US group, indicating that a substantial quantity of $^1O_2$ was unquestionably created (Fig. 4c).

NPs can improve the SDT efficacy, because of reducing the cavitation threshold through introducing cavitation bubble nucleation sites in a liquid [80]. Therefore, SDT nano-sonosensitizers have developed rapidly in recent years. TiO_2 NPs have attracted extensive attention as a nano-sonosensitizers, because of their excellent chemical stability and low phototoxicity. However, the quick electron-hole recombination of TiO_2 NPs results in poor ROS quantum yield and restricts their use in free radical-based SDT and subsequent clinical translation. Chen and colleagues created polyethylene glycol (PEG)-modified ultrafine titanium monoxide nanorods (PEG- TiO_{1+}x NRs) with dramatically increased sonosensitization and Fenton-like catalytic activity, to improve the formation of ROS (Fig. 5a) [47]. As can be seen in Fig. 5b the oxygen-poor structure of TiO_{1+x} NR, which acts as the charge trap to limit the recombination of US-triggered electron-hole pairs, the PEG-TiO_{1+x} NRs resulted in much more efficient US-induced generation of reactive oxygen species (ROS) compared to the conventional sonosensitizer, TiO_2 nanoparticles.

In another study, covalent organic framework–titanium oxide nanoparticles (COF–TiO_2 NPs) for enhanced SDT [48]. Because COF–TiO_2 nanoparticles have a narrower band gap than pure TiO_2 NPs a lot of ROS can be produced when exposed to US irradiation. Poly (ethylene glycol)–poly (propylene sulfide) (PEG–PPS) as a amphiphilic

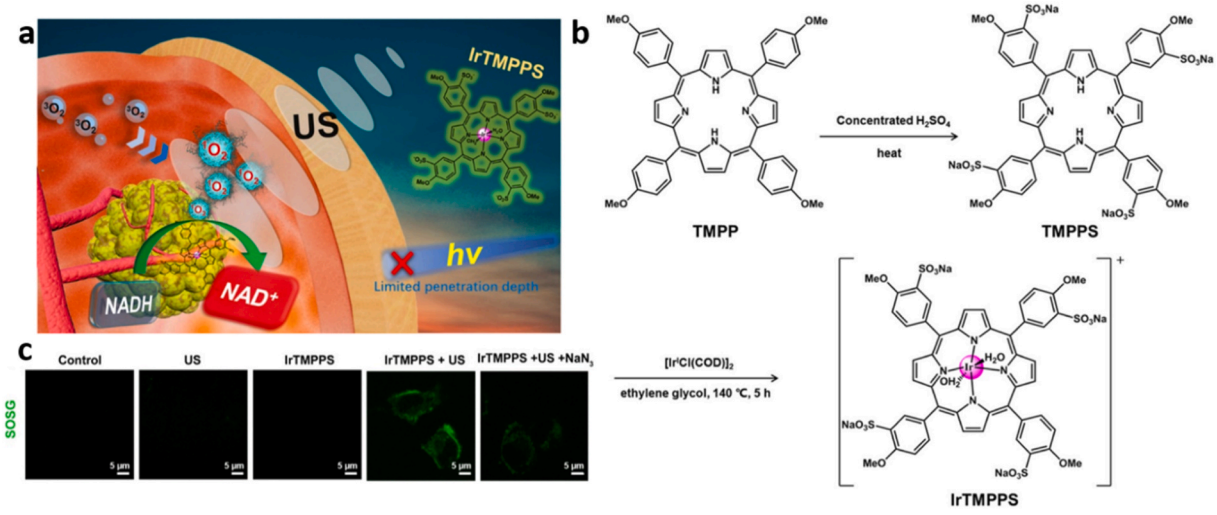

Fig. 4. a) Schematic illustration of anticancer activity of IrTMPPS under US, b) Synthesis process of IrTMPPS, and c) Intracellular ROS generation assay, confocal microscopy images of 4T1 cells treated with IrTMPPS and co-stained with SOSG. Adapted with permission [79]. Copyright 2021, ACS.

polymer used for preparation of micelle to encapsulation of Fe_3O_4 and hypocrellin (HC) for combination ferroptosis and SDT [81]. ROS was produced by HC under US irradiation, result is the breakdown of micelles. Then, the released Fe_3O_4 produces Fe^{2+}, which catalyzes the formation of $^{\bullet}OH$ from hydrogen peroxide. Schematic illustration of synthesis process and also possible combined ferroptosis and SDT was shown in Fig. 6.

4.3. Photodynamic therapy (PDT)

Current phototherapy-based approaches such as photothermal therapy (PTT) and PDT alone or in combination with conventional cancer treatments such as chemotherapy, surgery, immunotherapy, or radiotherapy may be promising for minimizing the risk of cancer progression or mortality [82]. PDT, is a type of therapeutic treatment that involves the use of a laser in conjunction with a photosensitizer (PS). When subjected to light, the PS transfers energy to the oxygens that are nearby, therefore producing ROS, which are responsible for the death of the target cancer cells [83]. In the aerobic conditions under the excitation of a specific wavelength light photoactivatable drugs (e.g. PS) can directly or indirectly produce cytotoxic ROS including $^{\bullet}OH$, $O_2^{\bullet-}$ and $^1O_2$.

NPs have been employed as potential tools for PDT due to their ability to increase the water solubility of the PS while also improving its delivery efficiency. On the other side, NPs can also act as PS, then improve targeting ability and PDT efficacy. While organic PSs are commonly employed as type-II PDT agents, various inorganic semiconductor nanomaterials have been investigated as type-I PSs. Although indocyanine green (ICG) is widely used as a PS agent in PDT, it has a number of limitations that limit its use. While several NPs-based strategies have been investigated as potential solutions to these problems, they still have drawbacks such immunogenicity and poor delivery to the tumor.

To address this problems Kang et al. developed SIWV peptide-functionalized and ICG-incorporated porous silicon NPs (pSiNPs) (Fig. 7) [49]. In addition to its nontoxicity and laser-triggered in situ ROS production, the SIWV-pSiNP(ICG) demonstrated remarkable targeting capacity to glioblastoma (GBM) cells. In comparison to nonlaser irradiated cells, the fluorescence of the ICG + laser-treated cells and the pSiNP(ICG) + laser-treated cells was 4.8 and 4.7 times greater, respectively. As compared to the control group, the laser-treated group had an intracellular ROS level 8.9 times higher for SIWV-pSiNP(ICG) and 1.9 times higher for ICG and pSiNP(ICG).

The pH-sensitive targeted drug delivery system based on hollow mesoporous silica NPs (HMSNs) used as nanocarriers for delivering doxorubicin hydrochloride (DOX) and indocyanine green (ICG) [50]. Huo et al. developed a near-infrared-driven PDT platform, known as UR-Cyan cells. It is based on photosynthetic cyanobacterial cells hybridized with PS rose bengal (RB)-loaded upconversion nanoparticles. By being photosynthetically active for oxygen production and photosensitive for the subsequent singlet oxygen generation by the photosensitizer, the formulated UR-Cyan cells allow for increased and sustained PDT efficacy against tumor cells/tissues when exposed to 980 nm laser and its upconversions to shorter wavelengths [84].

4.4. Chemodynamic therapy (CDT)

For in situ ROS formation and tumor therapy, CDT often relies on Fenton or Fenton-like reactions. CDT has attracted significant attention from researchers as a potential method for treating cancer-related diseases. This approach involves the use of on-site active chemical species to eliminate cancer cells, without the need for external stimuli sources [85]. Through the Fenton reaction driven by iron ions, CDT can trigger tumor cell death by converting intratumoral hydrogen peroxide (H_2O_2) into extremely deadly hydroxyl radicals ($^{\bullet}OH$). Toxic $^{\bullet}OH$ is a kind of harmful free radicals which may cause considerable protein inactivation, phospholipid membrane peroxidation, and DNA damage in tumor cells. Similarly, cancer treatment has made use of ROS formation *via* nanocatalytic reactions, such as those induced by other metal ions in Fenton-like reactions or other non-Fenton mechanism chemical processes [86]. CDT typically relies on the classical Fenton reaction ($Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + {}^{\bullet}OH + OH^-$) or Haber–Weiss reaction ($O_2^{\bullet-} + H_2O_2 \rightarrow {}^{\bullet}OH + OH^- + O_2$). Furthermore, the Fenton reaction is prone to being launched in the presence of TME, which contains an excess of hydrogen ions, lactic acid, and H_2O_2.

Along with the fast growth of nanotechnology, several Fenton nanocatalysts have been created for CDT in order to maximize its efficacy. Most developed CDT agents are inorganic nanomaterials containing transition metal ions (e.g., Fe, Co, Ni, Cu, and Mn).

Bu et al. developed a simple approach to manufacture amorphous iron nanoparticles (AFeNPs) with superior physicochemical attributes to those of its crystal equivalent, iron nanocrystals [87]. To specifically eliminate tumor cells, the as-prepared ionized AFeNPs released Fe^{2+} into the TME, which led to the disproportionation of H_2O_2, which in turn generated a significant number of radical $^{\bullet}OH$.

CDT seems promising, but to maximize its functional performance, either suitable metal-based nanomaterials or the right reaction

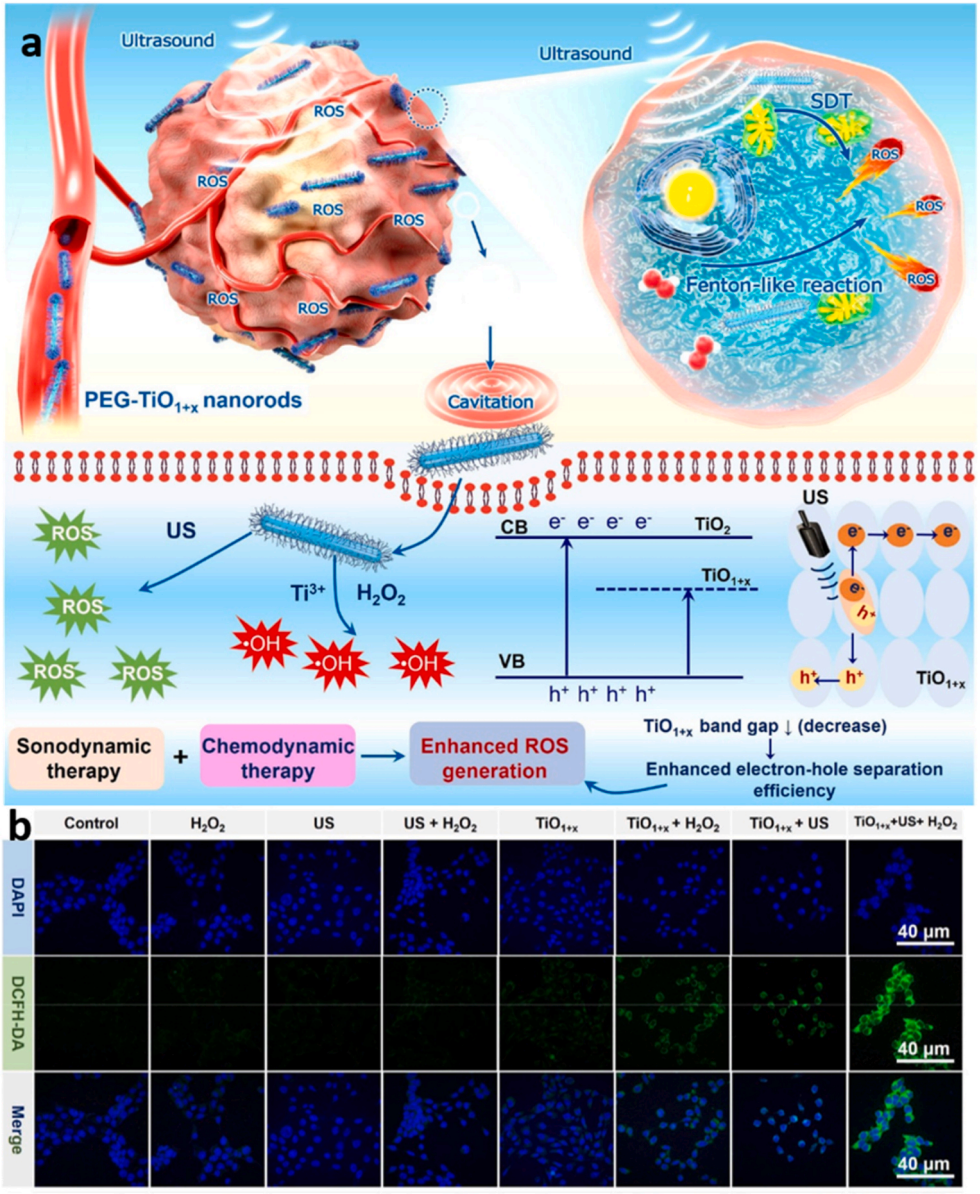

Fig. 5. a) Schematic illustration of ultrafine TiO_{1+x} NRs sonosensitizer for SDT/CDT of Cancer, b) Confocal images of DCFH-DA-stained 4T1 cells after different treatments. Adapted with permission [47]. Copyright 2020, ACS.

environment are needed (e.g., lowered pH, and GSH levels, or increased H_2O_2 quantities). Due of this, a lot of work is being put into creating possible CDT agents or altering TME to increase the effectiveness of CDT.

Chen et al., in order to enhancing the CDT effect designed β-lapachone (Lapa) loaded iron oxide nanocarriers (Fe_3O_4-HSA@Lapa) to amplify intracellular oxidative stress (Fig. 8a) [88]. In addition to boosting H_2O_2 production at tumor site *via* NAD(P)H: quinone oxidoreductase 1 (NQO1) catalysis, the released Lapa from intravenously administered Fe_3O_4-HSA@Lapa NPs was able to drastically lower GSH levels caused by the depletion of NADPH. Next, the iron ions introduced by Fe_3O_4 would set off a Fenton reaction under an acidic TME, converting the significantly elevated H_2O_2 within the cell into $^{\bullet}OH$, and therefore greatly improving the CDT's efficacy in NQO1-overexpressing malignancies. ROS generation assay (Fig. 8b and c) show that the Fe_3O_4-HSA NPs and Lapa cotreated group produced more ROS than the free Lapa treated group, providing further evidence that the NPs were responsible for the increase in ROS. Elevated Lapa accumulation in cells following endocytosis of Fe_3O_4-HSA@Lapa NPs significantly increased ROS levels compared to Fe_3O_4-HSA + Lapa treatment. In addition, because of improving cellular uptake of NPs *via* magnet (magnet--mediated cellular uptake), compared to Fe_3O_4-HSA@Lapa NPs without magnet treatment, Fe_3O_4-HSA@Lapa NPs with magnet treatment significantly increased ROS levels in A549 cells. Additionally, the NQO1 inhibitor dicoumarol (DIC) totally blocked ROS production generated by Lapa, revealing that ROS production was dependent on the NQO1 enzyme [88].

Other transition metals besides iron ions (Fe) include cobalt (Co) [51], copper (Cu) [89], silver (Ag) [90], manganese (Mn) [52], and nickel (Ni) [91] have Fenton-like capabilities for CDT.

For example, self-assembled copper–amino acid mercaptide nanoparticles (Cu-Cys NPs) was used for in situ glutathione-activated and H_2O_2-reinforced CDT (Fig. 9) [53]. Cu-Cys NPs might initially react with local GSH after being endocytosed into tumor cells, causing GSH depletion and reducing Cu^{2+} to Cu^{+}. The produced Cu^{+} would then undergo a Fenton-like reaction with nearby H_2O_2 to produce harmful $^{\bullet}OH$.

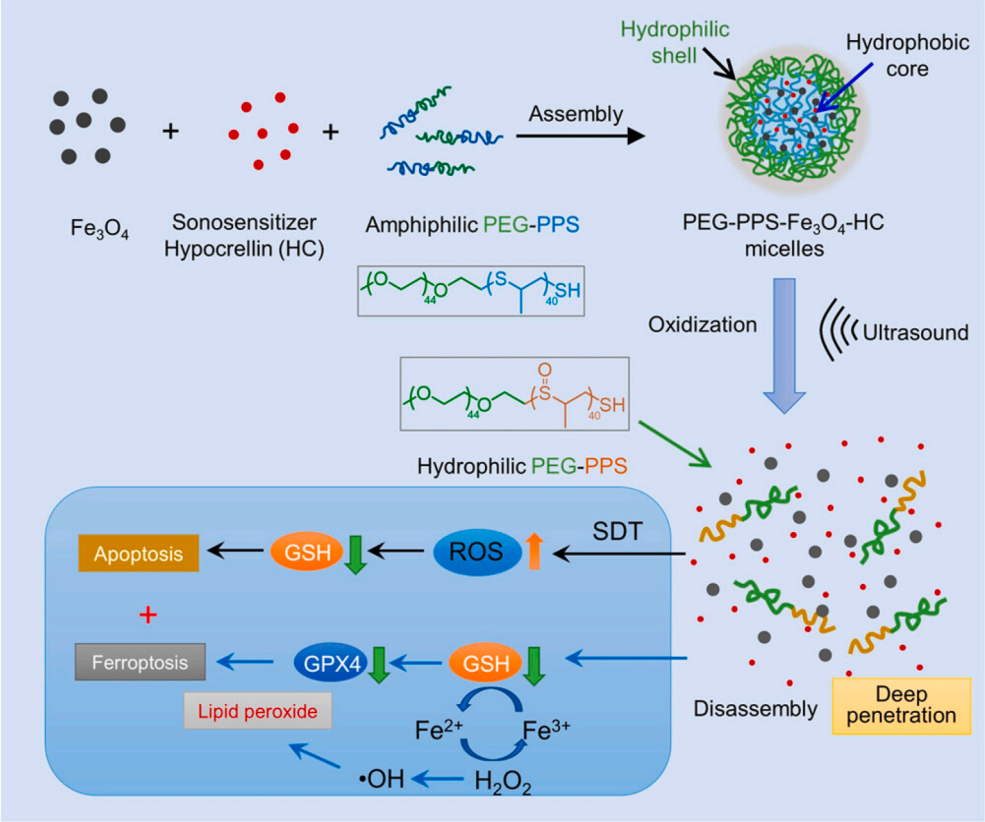

Fig. 6. Schematic illustration of synthesis process of HC and Fe3O4 co-encapsulated PEG–PPS and also possible combined ferroptosis and SDT. Adapted with permission [81]. Copyright 2022, ACS.

4.5. *Ferroptosis therapy*

Besides apoptosis, necrosis, and autophagy, ferroptosis is a recently identified mechanism of controlled cell death that is characterized by iron- and ROS-dependence as well as excessive polyunsaturated fatty acid peroxidation (PUFAs) [92,93]. Ferroptotic cells exhibit distinctive changed morphology, including intact cell membranes, dispersive chromatins, and remarkable mitochondrial modifications such as smaller, shrinkable mitochondria, diminished mitochondrial crista, and damaged mitochondrial outer membrane [94]. Ferroptosis differs from well-studied apoptosis, necrosis, and autophagy in biochemical and genetic characteristics as well as morphology. Ferroptosis is a type of controlled cell death that depends on iron and ROS. It is getting a lot of attention from researchers very quickly.

Inhabitation of the canonical ferroptosis induction of the molecular guardians is the first strategy to promote ferroptosis-induced cancer therapy, which can reduce lipid peroxidation. And another one the non-canonical ferroptosis induction, which involves increasing the labile iron pool (LIP) to improve ROS production [95]. On the basis of the aforementioned two methodologies, major efforts have so far fostered the logical design of ferroptosis-based nanotherapeutics for cancer therapy. i) Tumor cell lipid peroxidation caused by external manipulation of PUFAs and ii) tumor cells' ROS levels are elevated by inducing the Fenton reaction, leading to a greater loss of GSH, and decreasing production of glutathione peroxidase 4 (GPX4, a biomarker of ferroptosis that can destroy cellular lipid peroxides).

As a latter ferroptosis-facilitating strategy, which is linked to the ROS production mechanism, one of the most extensively used ways to induce ferroptosis is by raising the iron ion (Fe^{2+} or Fe^{3+}) concentration by utilizing iron-containing NPs within tumor cells to start Fenton reaction.

Liang et al. prepared a PEGylate metal-organic frameworks involving Fe & Cu ions with disulfide bonds (FCSP MOFs). FCSP MOFs can be degraded within tumor, result in GSH-depletion and GPX4 inactivation, as well as Fe ions releasing to produce ROS through Fenton reaction [54]. Since DOX may directly cause apoptosis and indirectly create H_2O_2 to accelerate Fenton reaction, it might be a better way to treat tumors more effectively by loading DOX.

Fernández-Acosta et al. synthesized iron oxide nanoparticles coated with gallic acid and polyacrylic acid (IONP–GA/PAA), which could induces ferroptosis in glioblastoma, neuroblastoma, and fibrosarcoma cells [55].

Under visible light irradiation, ferrous oxalate (FeC_2O_4) self-assembled nanorods coupled with a graphitic carbon nitride (g-C_3N_4) photo-Fenton catalyst may catalyze H_2O_2 to $^{\bullet}OH$ [96]. Ferroptosis occurs as a result of an increase in intracellular ROS and a reduction in GSH after exposure to visible light-irradiation of Fe/CN-180, which effectively react with hydrogen peroxide and forms hydroxyl radical.

5. Conclusions and future perspectives

PDT, SDT, RT, CDT, and ferroptosis therapy have used free radicals for cancer treatment. Free radicals have advantages over other substances used in cancer treatment, such as chemotherapeutic medicines, photothermal agents, and different nanostructures. Free radicals have a wide range and regulated reactivity, oxygen independence, molecular magnetic, NIR-I/NIR-II absorption/emission, etc. due to their unpaired valence electrons. These features give free radicals promising possibilities for addressing issues that conventional materials cannot address. But there are still some problems that make it hard to use free radicals in the biomedical field in a wide range of ways. The challenge with active radicals is how to further enhance their therapeutic precision while minimizing their adverse effects on healthy tissue. The behavior and fate of stable/stabilized radicals should be further investigated in animal models. The development of free radicals-mediated cancer theranostics

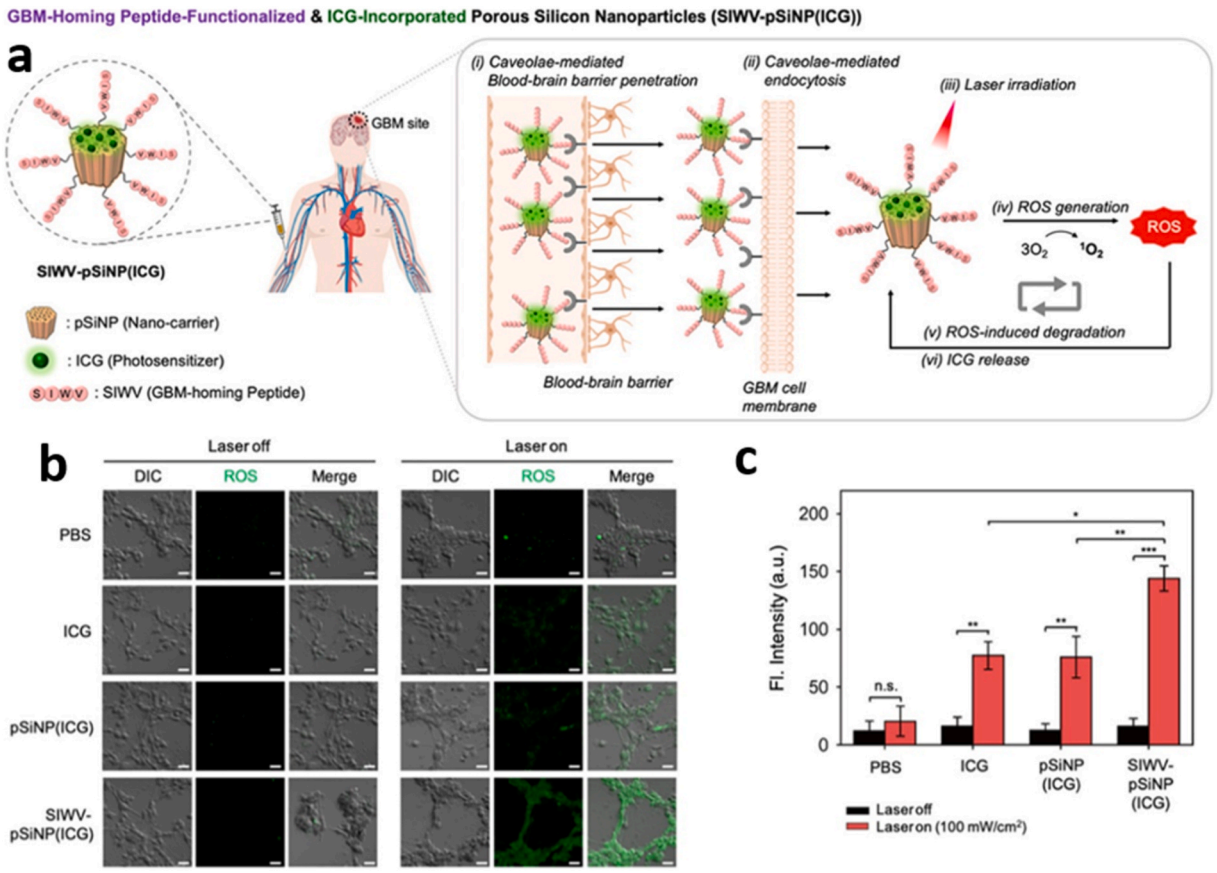

Fig. 7. a) Proposed mechanism of action of SIWV-pSiNP(ICG), and b and c) ROS generation assay: CLSM images of U87MG cells incubated. Adapted with permission [49]. Copyright 2022, ACS.

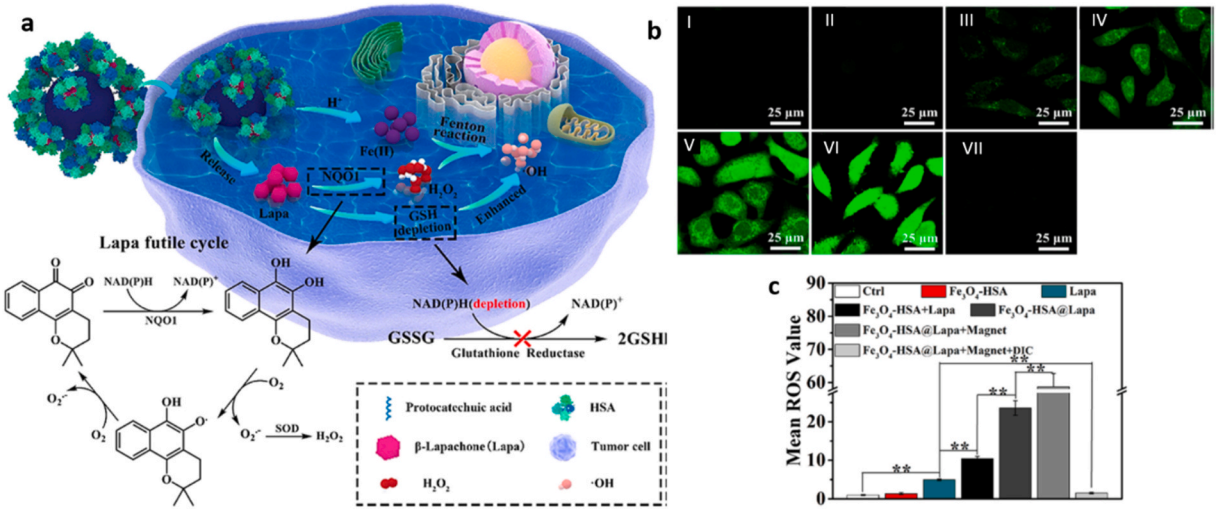

Fig. 8. a) Schematic illustration of possible anticancer mechanism of Fe_3O_4-HSA@Lapa NPs, b) Confocal microscopy images of DCF fluorescence in A549 cells exposed to Ctrl (I), Fe_3O_4-HSA NPs(II), Lapa (III), Fe3O4-HSA + Lapa (IV), Fe3O4-HSA@Lapa NPs (V), Fe3O4-HSA@Lapa NPs with magnet (VI), and Fe3O4-HSA@Lapa NPs with magnet + DIC (VII), followed by staining with DCFH-DA. DIC was used to inhibit activity of the NQO1 enzyme, c) DCF fluorescence intensity analysis from flow cytometry. Adapted with permission [88]. Copyright 2019, ACS.

is very important if we want to improve the effectiveness of cancer treatments. The following factors are worth considering for the future: I) Creating new free radicals with diverse reactivity and functionalities. II) Designing materials for improve tumor homing and avoiding the side effects. III) Further exploring the mechanism of action. IV) Using combination therapies to maximize their effectiveness.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

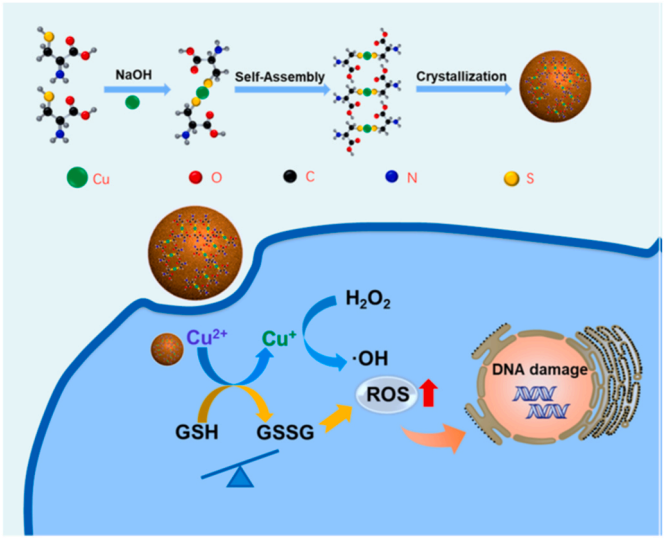

Fig. 9. Schematic illustration of the Cu-Cys NPs synthetic process and the possible Cu-Cys NPs Mediated CDT. Adapted with permission [53]. Copyright 2019, ACS.

Data availability

No data was used for the research described in the article.

Acknowledgments

This study was supported by the Al-Mustaqbal University College.

References

[1] R.K. Kankala, et al., Overcoming multidrug resistance through the synergistic effects of hierarchical pH-sensitive, ROS-generating nanoreactors, ACS Biomater. Sci. Eng. 3 (10) (2017) 2431–2442.
[2] H.R.A.K. Al-Hetty, et al., Nanomaterials for combination cancer photothermal therapy, Emergent Materials (2023) 1–14.
[3] M. Bazi Alahri, et al., Management of brain cancer and neurodegenerative disorders with polymer-based nanoparticles as a biocompatible platform, Molecules 28 (2) (2023) 841.
[4] M. Alahdal, H, et al., Trace elements-based Auroshell gold@ hematite nanostructure: green synthesis and their hyperthermia therapy, IET Nanobiotechnol. 17 (1) (2023) 22–31.
[5] R.K. Kankala, W.-Z. Lin, C.-H. Lee, Combating antibiotic resistance through the synergistic effects of mesoporous silica-based hierarchical nanocomposites, Nanomaterials 10 (3) (2020) 597.
[6] B. Jiang, et al., Potentiation of Curcumin-loaded zeolite Y nanoparticles/PCL-gelatin electrospun nanofibers for postsurgical glioblastoma treatment, J. Drug Deliv. Sci. Technol. 80 (2023), 104105.
[7] S. Liu, et al., Critical influences of metal compounds on the formation and stabilization of environmentally persistent free radicals, Chem. Eng. J. 427 (2022), 131666.
[8] V.I. Lushchak, Free radicals, reactive oxygen species, oxidative stress and its classification, Chem. Biol. Interact. 224 (2014) 164–175.
[9] A. Studer, D.P. Curran, Catalysis of radical reactions: a radical chemistry perspective, Angew. Chem. Int. Ed. 55 (1) (2016) 58–102.
[10] H.L. Runberg, et al., Stability of environmentally persistent free radicals (EPFR) in atmospheric particulate matter and combustion particles, Atmos. Environ. 240 (2020), 117809.
[11] M. Yan, et al., Radicals: reactive intermediates with translational potential, J. Am. Chem. Soc. 138 (39) (2016) 12692–12714.
[12] C.-Y. Huang, J. Li, C.-J. Li, A cross-dehydrogenative C (sp3)– H heteroarylation via photo-induced catalytic chlorine radical generation, Nat. Commun. 12 (1) (2021) 1–9.
[13] W. Wu, et al., Near infrared II laser controlled free radical releasing nanogenerator for synergistic nitric oxide and alkyl radical therapy of breast cancer, Nanoscale 13 (25) (2021) 11169–11187.
[14] G. Huang, et al., Magnetothermally triggered free-radical generation for deep-seated tumor treatment, Nano Lett. 21 (7) (2021) 2926–2931.
[15] Y. Wang, et al., Ultrasonic activation of inert poly (tetrafluoroethylene) enables piezocatalytic generation of reactive oxygen species, Nat. Commun. 12 (1) (2021) 1–8.
[16] M. Salehiabar, et al., Targeted CuFe2O4 hybrid nanoradiosensitizers for synchronous chemoradiotherapy, J. Contr. Release 353 (2023) 850–863.
[17] Y. Zhou, et al., Manipulating intratumoral fenton chemistry for enhanced chemodynamic and chemodynamic-synergized multimodal therapy, Adv. Mater. 33 (48) (2021), 2104223.
[18] J. Chen, et al., A redox-triggered C-centered free radicals nanogenerator for self-enhanced magnetic resonance imaging and chemodynamic therapy, Biomaterials 266 (2021), 120457.
[19] B. Tang, et al., A supramolecular radical dimer: high-efficiency NIR-II photothermal conversion and therapy, Angew. Chem. 131 (43) (2019) 15672–15677.
[20] B. Commoner, J. Townsend, G.E. Pake, Free radicals in biological materials, Nature 174 (4432) (1954) 689–691.
[21] B.L. Zaric, M.T. Macvanin, E.R. Isenovic, Free radicals: relationship to human diseases and potential therapeutic applications, Int. J. Biochem. Cell Biol. 154 (2023), 106346.
[22] H. Sies, C. Berndt, D.P. Jones, Oxidative stress, Annu. Rev. Biochem. 86 (2017) 715–748.
[23] K.B. Beckman, B.N. Ames, The Free Radical Theory of Aging Matures, Physiological reviews, 1998.
[24] M.J. McAllister, et al., Effects of psychological stress during exercise on markers of oxidative stress in young healthy, trained men, Physiol. Behav. 198 (2019) 90–95.
[25] H.J. Majima, S. Toyokuni, Mitochondria and Free Radical Studies on Health, Disease and Pollution, 2012, pp. 925–926. Taylor & Francis.
[26] M. Valko, et al., Free radicals and antioxidants in normal physiological functions and human disease, Int. J. Biochem. Cell Biol. 39 (1) (2007) 44–84.
[27] J.P. Fruehauf, F.L. Meyskens Jr., Reactive oxygen species: a breath of life or death? Clin. Cancer Res. 13 (3) (2007) 789–794.
[28] T. Finkel, Signal transduction by reactive oxygen species, JCB (J. Cell Biol.) 194 (1) (2011) 7–15.
[29] X.-Q. Wang, et al., Free radicals for cancer theranostics, Biomaterials 266 (2021), 120474.
[30] Z.-Q. Liu, Bridging free radical chemistry with drug discovery: a promising way for finding novel drugs efficiently, Eur. J. Med. Chem. 189 (2020), 112020.
[31] L. Zhu, et al., Free radical as a double-edged sword in disease: deriving strategic opportunities for nanotherapeutics, Coord. Chem. Rev. 475 (2023), 214875.
[32] K. Bedard, K.-H. Krause, The NOX family of ROS-generating NADPH oxidases: physiology and pathophysiology, Physiol. Rev. 87 (1) (2007) 245–313.
[33] C.L. Hawkins, M.J. Davies, Generation and propagation of radical reactions on proteins, Biochim. Biophys. Acta Bioenerg. 1504 (2–3) (2001) 196–219.
[34] O. Sedlacek, R. Hoogenboom, Drug delivery systems based on poly (2-oxazoline) s and poly (2-oxazine) s, Advanced Therapeutics 3 (1) (2020), 1900168.
[35] E. Blanco, H. Shen, M. Ferrari, Principles of nanoparticle design for overcoming biological barriers to drug delivery, Nat. Biotechnol. 33 (9) (2015) 941–951.
[36] M. Salehiabar, et al., Targeted CuFe2O4 hybrid nanoradiosensitizers for synchronous chemoradiotherapy, J. Contr. Release 353 (2023) 850–863.
[37] J. Cao, et al., Concise nanoplatform of phycocyanin nanoparticle loaded with docetaxel for synergetic chemo-sonodynamic antitumor therapy, ACS Appl. Bio Mater. 4 (9) (2021) 7176–7185.
[38] S. Zhang, et al., Photosensitizer-driven nanoassemblies of homodimeric prodrug for self-enhancing activation and synergistic chemo-photodynamic therapy, Theranostics 11 (12) (2021) 6019.
[39] H. Nosrati, et al., Improved synergic therapeutic effects of chemoradiation therapy with the aid of a co-drug-loaded nano-radiosensitizer under conventional-dose X-ray irradiation, Biomater. Sci. 8 (15) (2020) 4275–4286.
[40] Y. Qiao, et al., Stimuli-responsive nanotherapeutics for precision drug delivery and cancer therapy, Wiley Interdiscipl. Rev.: Nanomedicine Nanobiotechnol. 11 (1) (2019) e1527.
[41] D. Ding, et al., Mn3+-rich oxide/persistent luminescence nanoparticles achieve light-free generation of singlet oxygen and hydroxyl radicals for responsive imaging and tumor treatment, Theranostics 11 (15) (2021) 7439.
[42] H. Nosrati, et al., Prodrug polymeric nanoconjugates encapsulating gold nanoparticles for enhanced X-Ray radiation therapy in breast cancer, Adv. Healthc. Materials 11 (3) (2022), 2102321.
[43] B.M. Bavelaar, et al., Oligonucleotide-functionalized gold nanoparticles for synchronous telomerase inhibition, radiosensitization, and delivery of theranostic radionuclides, Mol. Pharm. 18 (10) (2021) 3820–3831.
[44] Y. Chen, et al., Enhancement of mitochondrial ROS accumulation and radiotherapeutic efficacy using a Gd-doped titania nanosensitizer, Theranostics 9 (1) (2019) 167.
[45] Y. Zhao, et al., Endogenous ROS-mediated covalent Immobilization of gold Nanoparticles in mitochondria: a “sharp sword” in tumor radiotherapy, ACS Chem. Biol. 17 (8) (2022) 2355–2365.
[46] Q. Xu, et al., Manganese porphyrin-based metal-organic framework for synergistic sonodynamic therapy and ferroptosis in hypoxic tumors, Theranostics 11 (4) (2021) 1937–1952.
[47] X. Wang, et al., Ultrafine titanium monoxide (TiO1+x) nanorods for enhanced sonodynamic therapy, J. Am. Chem. Soc. 142 (14) (2020) 6527–6537.
[48] L. Cai, et al., Covalent organic framework–titanium oxide nanocomposite for enhanced sonodynamic therapy, Bioconjugate Chem. 32 (4) (2021) 661–666.
[49] R.H. Kang, et al., Glioblastoma homing photodynamic therapy based on multifunctionalized porous silicon nanoparticles, ACS Appl. Nano Mater. 5 (4) (2022) 5387–5397.
[50] Y. Zhou, et al., Hyaluronic acid-functionalized hollow mesoporous silica nanoparticles as pH-sensitive nanocarriers for cancer chemo-photodynamic therapy, Langmuir 37 (8) (2021) 2619–2628.

[51] H. Zhu, et al., Sulfur defect-engineered biodegradable cobalt sulfide quantum dot-driven photothermal and chemodynamic anticancer therapy, ACS Appl. Mater. Interfaces 14 (22) (2022) 25183–25196.
[52] L. Lin, et al., Mn–DNA coordination of nanoparticles for efficient chemodynamic therapy, Chem. Commun. 57 (14) (2021) 1734–1737.
[53] B. Ma, et al., Self-assembled copper–amino acid Nanoparticles for in situ glutathione "AND" H2O2 sequentially triggered chemodynamic therapy, J. Am. Chem. Soc. 141 (2) (2019) 849–857.
[54] Y. Liang, et al., Tumor microenvironments self-activated nanoscale metal-organic frameworks for ferroptosis based cancer chemodynamic/photothermal/chemo therapy, Acta Pharm. Sin. B 11 (10) (2021) 3231–3243.
[55] R. Fernández-Acosta, et al., Novel iron oxide nanoparticles induce ferroptosis in a panel of cancer cell lines, Molecules 27 (13) (2022) 3970.
[56] P.J. Tofilon, K. Camphausen, Increasing the Therapeutic Ratio of Radiotherapy, 2017. Springer.
[57] Y. Liu, et al., Metal-based nanoenhancers for future radiotherapy: radiosensitizing and synergistic effects on tumor cells, Theranostics 8 (7) (2018) 1824.
[58] K.T. Butterworth, et al., Physical basis and biological mechanisms of gold nanoparticle radiosensitization, Nanoscale 4 (16) (2012) 4830–4838.
[59] I. Kiran, et al., Emerging nanomaterials as radio-sensitizer in radiotherapy, in: Harnessing Materials for X-Ray Based Cancer Therapy and Imaging, Springer, 2022, pp. 59–75.
[60] S. Wen, et al., Tailoring bismuth-based nanoparticles for enhanced radiosensitivity in cancer therapy, Nanoscale 14 (23) (2022) 8245–8254.
[61] E.S. Shiryaeva, et al., Hafnium oxide as a nanoradiosensitizer under x-ray irradiation of aqueous organic systems: a model study using the spin-trapping technique and Monte Carlo simulations, J. Phys. Chem. C 123 (45) (2019) 27375–27384.
[62] M.M. Fathy, et al., Dose-enhancement of MCF 7 cell line radiotherapy using silica-iron oxide nanocomposite, Biochem. Biophys. Res. Commun. 632 (2022) 100–106.
[63] J. Choi, et al., A gold nanoparticle system for the enhancement of radiotherapy and simultaneous monitoring of reactive-oxygen-species formation, Nanotechnology 29 (50) (2018), 504001.
[64] F. Abhari, et al., Folic acid modified bismuth sulfide and gold heterodimers for enhancing radiosensitization of mice tumors to X-ray radiation, ACS Sustain. Chem. Eng. 8 (13) (2020) 5260–5269.
[65] P.O. Maksimchuk, et al., UV-Light-Activated (Gd,Y)VO4:Eu3+ nanoparticles for radiotherapy enhancement, J. Phys. Chem. C 126 (22) (2022) 9371–9377.
[66] R. Zhou, et al., Tumor microenvironment-manipulated radiocatalytic sensitizer based on bismuth heteropolytungstate for radiotherapy enhancement, Biomaterials 189 (2019) 11–22.
[67] Q. Dai, et al., Ruthenium-based metal–organic nanoradiosensitizers enhance radiotherapy by combining ROS generation and CO gas release, Angew. Chem. Int. Ed. (2022), e202211674.
[68] F. Sabir, et al., DNA based and stimuli-responsive smart nanocarrier for diagnosis and treatment of cancer: applications and challenges, Cancers 13 (14) (2021) 3396.
[69] T.J. Dubinsky, et al., High-intensity focused ultrasound: current potential and oncologic applications, Am. J. Roentgenol.-New Series- 190 (1) (2008) 191.
[70] Y.-F. Zhou, High intensity focused ultrasound in clinical tumor ablation, World J. Clin. Oncol. 2 (1) (2011) 8.
[71] I. Rosenthal, J.Z. Sostaric, P. Riesz, Sonodynamic therapy—a review of the synergistic effects of drugs and ultrasound, Ultrason. Sonochem. 11 (6) (2004) 349–363.
[72] H. Chen, et al., Recent progress in development of new sonosensitizers for sonodynamic cancer therapy, Drug Discov. Today 19 (4) (2014) 502–509.
[73] H. Yang, et al., Deep and precise lighting-up/combat diseases through sonodynamic agents integrating molecular imaging and therapy modalities, Coord. Chem. Rev. 453 (2022), 214333.
[74] S. Sonmezoglu, et al., Monitoring deep-tissue oxygenation with a millimeter-scale ultrasonic implant, Nat. Biotechnol. 39 (7) (2021) 855–864.
[75] R. Canaparo, et al., The promising interplay between sonodynamic therapy and nanomedicine, Adv. Drug Deliv. Rev. (2022), 114495.
[76] L. Sun, et al., Ultrasound microbubbles mediated sonosensitizer and antibody Co-delivery for highly efficient synergistic therapy on HER2-positive gastric cancer, ACS Appl. Mater. Interfaces 14 (1) (2021) 452–463.
[77] T. Xu, et al., Recent advances in nanomaterials for sonodynamic therapy, Nano Res. 13 (11) (2020) 2898–2908.
[78] A.P. McHale, et al., Sonodynamic Therapy: Concept, Mechanism and Application to Cancer Treatment, 2016, pp. 429–450. Therapeutic Ultrasound.
[79] J. Xie, et al., Water-soluble iridic–porphyrin complex for non-invasive sonodynamic and sono-oxidation therapy of deep tumors, ACS Appl. Mater. Interfaces 13 (24) (2021) 27934–27944.
[80] J.C. Matos, et al., Biomimetic amorphous Titania nanoparticles as ultrasound responding agents to improve cavitation and ROS production for Sonodynamic therapy, Appl. Sci. 10 (23) (2020) 8479.
[81] S. Shen, et al., Nanoscale micelles loaded with Fe3O4 nanoparticles for deep-tissue penetration and ferroptosis/sonodynamic tumor therapy, ACS Appl. Nano Mater. 5 (12) (2022) 17664–17672.
[82] R.R. Allison, et al., A clinical review of PDT for cutaneous malignancies, Photodiagnosis Photodyn. Ther. 3 (4) (2006) 214–226.
[83] J.P. Celli, et al., Imaging and photodynamic therapy: mechanisms, monitoring, and optimization, Chem. Rev. 110 (5) (2010) 2795–2838.
[84] M. Huo, et al., Upconversion nanoparticles hybridized cyanobacterial cells for near-infrared mediated photosynthesis and enhanced photodynamic therapy, Adv. Funct. Mater. 31 (16) (2021), 2010196.
[85] C.-G. Liu, et al., Rerouting engineered metal-dependent shapes of mesoporous silica nanocontainers to biodegradable Janus-type (sphero-ellipsoid) nanoreactors for chemodynamic therapy, Chem. Eng. J. 370 (2019) 1188–1199.
[86] Y. Cheng, et al., Non-fenton-type hydroxyl radical generation and photothermal effect by mitochondria-targeted WSSe/MnO2 nanocomposite loaded with isoniazid for synergistic anticancer treatment, Adv. Funct. Mater. 29 (45) (2019), 1903850.
[87] C. Zhang, et al., Synthesis of iron nanometallic glasses and their application in cancer therapy by a localized Fenton reaction, Angew. Chem. 128 (6) (2016) 2141–2146.
[88] Q. Chen, et al., Tumor-specific expansion of oxidative stress by glutathione depletion and use of a fenton nanoagent for enhanced chemodynamic therapy, ACS Appl. Mater. Interfaces 11 (34) (2019) 30551–30565.
[89] Y. Yu, et al., A Core–Shell Liquid Metal-Cu Nanoparticle with Glutathione Consumption via an in Situ Replacement Strategy for Tumor Combination Treatment of Chemodynamic, Microwave Dynamic and Microwave Thermal Therapy, Biomaterials Sci. (2022).
[90] K. Zhou, et al., Hybrid Ag nanoparticles/polyoxometalate-polydopamine nano-flowers loaded chitosan/gelatin hydrogel scaffolds with synergistic photothermal/chemodynamic/Ag+ anti-bacterial action for accelerated wound healing, Int. J. Biol. Macromol. 221 (2022) 135–148.
[91] Y. Qian, et al., NIR-II responsive PEGylated nickel nanoclusters for photothermal enhanced chemodynamic synergistic oncotherapy, Theranostics 12 (8) (2022) 3690.
[92] Z. Shen, et al., Emerging strategies of cancer therapy based on ferroptosis, Adv. Mater. 30 (12) (2018), 1704007.
[93] C. Bae, et al., Induction of ferroptosis using functionalized iron-based nanoparticles for anti-cancer therapy, Materials Today Bio 17 (2022), 100457.
[94] Y. Xie, et al., Ferroptosis: process and function, Cell Death Differ. 23 (3) (2016) 369–379.
[95] B. Hassannia, et al., Nano-targeted induction of dual ferroptotic mechanisms eradicates high-risk neuroblastoma, J. Clin. Investig. 128 (8) (2018) 3341–3355.
[96] M.M.A. Jassim, B.J. Hamad, M.H. Hussein, Review on breast cancer in Iraq women, Univ. Thi-Qar J. Sci. 9 (1) (2022) 92–94. https://doi.org/10.32792/utq/utjsci.v9i1.887.