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REVIEW ARTICLE

Metal-Based Nanomaterials Incorporate with Ultrasound as Acceptable Approach towards Cancer Therapy

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ABSTRACT

Among current biological researches, there have a plenty of works related to cancer therapy issues by using functional or pure-phased composites in non-invasive strategies. Especially in fabricating anticancer candidates, functional composites are divided into different sorts with different characteristics. Additionally, nanotechnology provides various approaches in utilizing composites' functionality for cancer diagnostics and therapeutics. Compared with previous Photodynamic Therapy (PDT), Photo-Thermal Therapy (PTT), chemotherapy and radiotherapy, ultrasound is used to activate sonosensitizer to produce cytotoxic Reactive Oxygen Species (ROS) toward target cancer cells. In recent years, the form of Sonodynamic Therapy (SDT) has been making much effort to develop highly efficient metal based Nanomaterials (NMs) as sonosensitizers, which can efficiently generate ROS and has the advantage of deeper tissue penetration. However, the traditional sonosensitizers, such as porphyrins, hypericin, and curcumin suffer from complex synthesis, poor water solubility, and low tumor targeting efficacy. For contrasting this limitation, the metal based inorganic NMs show biocompatibility, controllable physicochemical properties, and ease of achieving multifunctional properties, which greatly expanded their application in SDT. In this review, we systematically summarize the metal based inorganic NMs as carrier of molecular sonosensitizers, and produce ROS under ultrasound. Moreover, the prospects of advanced metal based materials application are also discussed.

INTRODUCTION

Currently, some of contents in ultrasound induced application toward cancer therapy have been well understood in current researches. Although in different applications by using candidate such as nonmetallic composites [1], organic polymers [2,3], and metal based functional materials [4], it has shown these corresponded materials had utilization in Sonodynamic Therapy (SDT) completely. As demonstrated in nanotechnology, it had been used to develop and change current situation as one traditional concept in curing cancer therapy effectively. By using different functional NMs in SDT treatments, it conveyed the relationship of cancer therapy mechanism and the main manufactures in demonstrating effect while producing cytotoxic Reactive Oxygen Species (ROS) [5,6]. Compared to the traditional organic sonosensitizers, inorganic NMs had the advantages of high stability, good hydrophilicity, excellent circulation ability, and high tumor targeting ability (Figure 1). As demonstrated in SDT applications, it seemed metal based functional materials were highly efficient during curing different cancer cell-lines. However, there still were great challenges in metal-based NMs incorporated with ultrasound as acceptable approach toward cancer therapy. As being well

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Figure 1 Schematic illustration of metal-based nanomaterials incorporated with ultrasound as acceptable approach toward cancer therapy.

considered as one non-invasive approach in cancer therapy, it eliminated the negative influences while utilizing radiotherapy and chemotherapy technologies. It just utilized the physical mechanisms of sound waves and ultrasound energy transferring while integrating with target tissue or cancer cells.

The foundation about ultrasound treatment in organic compounds was mainly referred to ROS response, it firstly reported about this suggestion and considered as SDT influences, was treated as one effective approach toward cancer therapy. As one contrast in light induction, this was utilized in Photodynamic Therapy (PDT). The ultrasound effect showed better penetrability in biological tissues [7,8]. However, the ROS production mechanism in ultrasound treatment had not been well indicated. Conventionally, there had been three different kinds of approaches to produce ROS, the sonosensitizer played key role of being activated by an appropriate intensity of ultrasound, and then reacted with O_2 to produce ROS. In other words, the liquid medium formed cavitation of micro-bubbles under ultrasound treatment, which additionally activate the sonosensitizer to generate ROS as much as possible. Here, the ROS could induce a series of biological events including polymers fragmentation, cytoskeletal shrinkage, and chromatin condensation, leading to cell death. So, the ROS production mechanism in SDT should be well documented, such as PDT and PTT utilization and mechanism illustration. Especially to integrate SDT with metal based functional materials, it should have several reliable mechanisms such as sonoluminescence, pyrolysis, ROS production by the collapse of cavitation bubbles, and ROS independent cytotoxicity. By undergoing ultrasound treatment, the physical ultrasound interacted with target tissues in the aqueous atmosphere, it caused a phenomenon known as "cavitation". It involved the nucleation, growth, and impulsive collapse of gas bubbles under appropriate ultrasound conditions [9,10]. Basically, this phenomenon can be classified into two types, stable and

inertial cavitation. Oscillation of stable cavitation bubbles resulted in the streaming of surrounding media. In contrast, inertial cavitation involved the growth of gas-bubbles to resonance size and then to maximum size before collapsing savagely. As illustrated in initial stage, this phenomenon of ultrasound induced could be used in synthesis of NMs by using different metal elements for fabrication functional materials completely, such as metal oxides, alloyed metallic composition, heterogeneous functional structure, and organic molecular modifications. It was utilized in further works as one efficient candidate well used in biological or medical curing. Similarly, ultrasound function not only can be used in material constructions, but also utilized in bio-application as in clinical treatment due to its physical and chemical effects. So, the combination of above two sides about inorganic metal materials and ultrasound effect could offer one new-approach to overcome original challenge in biological or physical fields as shown in figure 2. Especially in cancer therapy, the inorganic NMs could be treated as one fundamental activator toward cancer cell and enhanced to produce ROS for reducing cancer cell growth. Finally, the introduction of merged nanotechnology might provide a new way of delivering sonosensitizers and showed unique advantages in the field of cancer therapy. Compared to organic compounds, metal based functional NMs had the following advantages: 1) the controllable size distribution and outer morphology, 2) excellent chemical and physiological stability, and 3) high tumor targeting efficacy. In this review, we summarized the recently progress in metal-based NMs incorporated with ultrasound or sonosensitizers as acceptable approach toward cancer therapy, the similar SDT applications were also summarized further.

Gold Nanoparticles (NPs) and other typical triggered with ultrasound treatment in further applications

The adjusted optical properties of gold Nanoparticles

Figure 2 Basic principle and three typical conversion pathways for metal materials' valorization in SDT enhancement and related application in cancer therapy.

(NPs) have great potential in sensing and photo-acoustic imaging [11,12]. It had intriguing potential as one of cancer carrier candidates, possesses unique energy absorption (optical), size and stability (physical), and reacted with thiols (chemical) characteristics, which offered them various functional platform for further investigations [13,14]. Preparation of gold NPs by using PEG molecule modified as coating outer, and the folic acid was used as a target moiety toward fabrication (Figures 3A-3C). It has been reported that cellular uptake of the gold NPs was mainly through the receptor-mediated clathrin-dependent endocytosis pathway. It also conveyed that small diameter of nanocarriers could lead to fast uptake and high concentration of gold NPs inside the cells with relative to larger carriers. It found that gold NPs could interact with heparin binding glyco-proteins, which concluded the vascular permeability and basic growth factors that mediate angiogenesis. The Surface Plasmonic

Resonance (SPR) was selective in using of optical physical properties while the gold materials induced electron transfer between agent-A and agent B. As demonstrated under ultrasound influenced, gold plays an important role and the morphology determines the SPR (Figures 3D-3F) which comes from electronic relaxation [15,16]. Although gold NPs themselves can be used as therapeutic agents to destroy tumor cells, they had also been used in the field. Specially, the presence of ultrasound, by combining gold NPs with ultrasound (1 and 3 MHz, 2 W/cm²) and an intense pulse of light was found to significantly improve the therapeutic effect in colon tumors [17]. There were reporting conducted *in vivo*, it was found that ultrasound (1.1 MHz, 2 W/cm²) applied to gold NPs conjugated to the sonosensitizer PpIX (Au-PpIX) resulted in greater inhibition of the Colon Cancer (CT26) than when using PpIX alone. This was attributed to gold NPs acting as nucleation agents, leading to more

Figure 3 (A) TEM image of gold nanoparticles covered with citrate corona. (B) Activation of folic acid carboxyl group by NHS and dicyclohexylcarbodiimide in anhydrous DMSO and conjugation of NHS-ester activated folate to NH₂-PEG 3.5kDa-SH in anhydrous DMSO in presence of TEA. NHS: N-hydroxysuccinimide. (C) TEM image of FA-PEG-GNP. (D) Schematic illustration of the spectral dispersion of the thermal lens phenomenon in nanocomposite mediums. (E) Calculated spectral dispersion of the thermal contribution to the nonlinear refraction (red) and absorption (violet) coefficients of the virtual thin Au/ SiO₂ film. (F) The ultrafast electronic relaxation and coherent vibrational oscillation of strongly interacting gold nanoparticle aggregates measured by femtosecond laser spectroscopy. (G) TEM image of gold used in this experiment. (H) Phase-contrast and fluorescence images of trypan blue stained BEAS-2B and A549 co-cultures with and without ultrasound exposure. (I) Recorded fluorescence emission spectrum from the TA solution containing GNPs in the field of 1 MHz ultrasound waves at intensities of 0.5, 1, and 2 W/cm² in continuous mode, excitation wavelength = 310 nm, and emission and excitation band width = 5 nm. These are reprinted with permission from Brazzali [14-17].

collapsing cavities in addition to improving uptake of the Au-PpIX by the tumor cells [18].

Additionally, due to the presence of gold NPs in the liquid medium, it applied nucleation sites for producing bubbles in ultrasound treatment because of its surface roughness. It resulted in decrease in the ultrasonic pressure threshold needed for cavitation to occur, hence enhancing the cavitation processes while adding to cultured media, the initial discovery that gold NPs enhanced inertial cavitation [19]. As incubating of this fabrication with two cancer cell lines (KB and HCT-116), followed by exposure to ultrasound (8×10^{-6} and 8×10^{-5} J.cm⁻² for 5 min at 1.866 MHz) significantly reduced cancer cells growth and proliferation together with the significant generation of ROS species. Another report as showed in Kosheleva, et al. [20] work, the lung cancer cells (A549) showed higher sensitivity to the treatment with gold NPs combined with 4 MHz high intensity focused ultrasound, than treatment with the gold NPs only (Figures 3G-3I).

Pure-phased titanium dioxide as effective candidate in ultrasound type therapy

The development in this area about pure phased inorganic materials as candidate in ultrasound were well focused on the metal based materials and composites, which was modified and the surface could be linked strongly through adjusting the solution atmosphere (pH and solvent components). Some of the phase in different conditions, it gave the corresponded phenomenon while the candidate was integrated with target tissues. In order to do the determination about full systems in cancer therapy, the efficiency of SDT candidates, it influenced the cancer cell completely in cell applications, during the mechanism process, such as the sensitive functional material during in electron transfer process, Titanium Dioxide (TiO₂) NMs as sonosensitizers in generating ROS under ultraviolet light irradiation [21,22]. It conveyed the demonstration about TiO₂ materials that can explore the ROS under ultrasound and provided a new sonosensitizer for SDT application. Therefore, it was necessary to fabricate one effective candidate by using TiO₂ as hard template. There were some requirements as follows: the resulted candidate should overcome its low hydrophilic stability in materials' integration, because pure TiO₂ has poor water dispersion and low ROS efficacy [23]. To overcome these issues, TiO₂ were modified with some macromolecular polymer materials (e.g., proteins, dextran, and polyion complexes), which can improve the biocompatibility and water solubility [24]. For example, You, et al. synthesized Carboxymethyl Dextran (CMD)-modified TiO₂ had superior *in vivo* stability and excellent inhibitory effect on subcutaneous tumors under ultrasound irradiation. Similarly, it had proved that grafted TiO₂ with polyallylamine to form one coreshell structure, this composite micelle which can improve the

dispersion stability of hard-template under physiological conditions. In addition, it was one of useful approach of making heterogeneous structure by using TiO₂ integrated with fluorescent materials. This fluorescent labeling results conveyed that the cellular uptake rate of TiO₂ was very fast. TiO₂ itself could generate ROS by using ultrasound treatment. There was another one example such as the green fluorescence produced by the reaction between oxygen pieces, it was sensitive toward green and could be observed in the cytoplasm, but almost no fluorescence signal was observed in ultrasound-blank areas.

Due to the obtained correspondence, it had reported one approach such as protein modified TiO₂ which had much higher accumulation efficiency in bicompatibility test while compared with unmodified metal candidate. Also, it showed optimized SDT effect about TiO₂ by controlling the ultrasound dose in further investigation [25,26]. It was found that the pre-S1/S2 protein modified metal candidate combined with dual ultrasound treatment caused the amount of damage to biological tests. The avidin modified TiO₂ could effectively target MCF-7 cells, and its phagocytosis rate could reach to 80%, while the phagocytosis rate of normal cells was only 30%. With longtime treatment by using ultrasound, the survival rate of tumor cells was significantly reduced (Figure 4). Similarly, due to the higher surface area of structural characterizations, it could load some of drugs or chemicals toward the combination of therapeutic effects. The surface of MTN was modified with ROS responsive chemical bonds and assembled with β -cyclodextrin (β -CD), which further broken the ROS response chemical bond and released DTX. MTN@DTX-CD composite had an excellent tumor inhibition efficacy in MCF-7 tumor-bearing mice model due to the combination of SDT and chemotherapy. However, the rapid electron-hole recombination of TiO₂ resulted in a low ROS generation yield, which limits its SDT efficacy. Much effort had been devoted to improve the ROS generation ability of TiO₂.

In recent progress, Ag₂S QDs were treated as one good fluorescence imaging agent *in vivo* and also had ideal PTT and PDT therapeutic effects under laser irradiation, indicating that they could be an excellent multifunctional NMs for tumor therapy [27,28]. To date, application of Ag₂S QDs as a sonosensitizer had not been investigated. In this study, it successfully constructed biomimetic candidate by wrapping Pluronic F-127-modified Ag₂S QDs toward enzyme-augmented SDT. These particles were employed *in vivo* for fluorescence image-guided non-invasive treatment of tumors, in which, Ag₂S was used as a sonosensitizer to generate ROS under ultrasonic stimulation immediately. Encapsulation of the QDs in RBC membranes, it not only prolonged the circulation time of the probe but also catalyzed endogenous hydrogen peroxide by the catalase in RBCs to ameliorate tumor hypoxia. Besides, ultrasound effect could also promote tumor blood flow, relieved the

Figure 4 (A) Schematic image of TiO₂ NP-entrapped polyion complex micelles for SDT. The figure is reprinted with permission from; B: Titanium dioxide (TiO₂) activation method that uses ultrasound irradiation (US/ TiO₂) instead of ultraviolet irradiation. These are reprinted with permission from Harada [21,25].

hypoxic condition, and enhanced the SDT effect of the probe. This novel nanoplatform provided an elegant approach for improving tumor hypoxia for the treatment of deep-seated tumors (Figure 5).

Gold based heterogeneous structure as effective candidate in cancer therapy under ultrasound treatment

Toward the treatment effect, there is much effort being done in order to devote to improve the ROS generation ability of metal candidate. As used Au based heterogeneous structure, this structure could maximize the efficient production of ROS. As mentioned in previous works, it had successfully synthesized Au@TiO₂ with the adjustable shell as an anti-cancer therapeutic agent. Under the ultrasound irradiation, the heterogeneous structure provided a charge transfer channel at the metal-semiconductor interface [29,30]. Au crystalline had electron traps that could effectively inhibit the recombination of pairs of electrons (e⁻) and holes (h⁺) that were generated by TiO₂ under ultrasound treatment. Thus, the ROS production of Au@TiO₂ was enhanced. It was worth noting that Au had a strong absorbance at 1064 nm, and the photothermal conversion efficiency was 42.05%. According to *in vitro* experiments, the cell viability was decreased to 20.3% after the combination of PTT and SDT [31,32]. By changing the size of gold NPs, it illustrated that the SDT effect of TiO₂ co-loaded with small and large sized

gold was stronger than that of smaller gold NPs modified TiO₂ surface. It could be attributed to the density of gold NPs being too low to prevent (e⁻) and (h⁺) recombination, while gold NPs with large size in heterogeneous structure, it resulted plasma-induced electron pump effect only in the visible light region (beyond 500 nm). The surface of gold NPs were modified by TiO₂ and showed higher ROS generation efficiency and better tumor suppression rate than those pure gold NPs or TiO₂, respectively.

Recently, the prepared PEG modified ultrafine Ti nanorods, which had greatly improved sonosensitization and Fenton-like catalytic activity [33]. In this system, the oxygen deficient structure in TiO_{1+x} Nanorods (NRs) could be used as the charge trap to inhibit the recombination of (e⁻) and (h⁺) pairs, resulted a higher ROS generation yield. The PEG-TiO_{1+x} NRs also exhibit horseradish peroxidase activity, which could catalyze endogenous hydrogen peroxide to generate hydroxyl radicals, thereby achieved chemo-dynamic therapy. The PEG-TiO_{1+x} NRs could be effectively passively retained in tumor after intravenous injection. Furthermore, no significant long-term toxicity was observed in the mouse model experiments. It used polymers or high mass molecular weight soft materials as outer shell in order to increase its biocompatibility in cancer therapy.

Figure 5 (A) Schematic illustration of the synthesis route of (QD@P)Rs, (B) tumor fluorescence imaging, and combined therapy. (B) A general strategy for monitoring the behaviors of PNCs *in vivo* by encapsulating a Ag₂S quantum dot (QD) with fluorescence in the second near-infrared window (NIR-II, 1000–1700 nm) inside the PNC, using simian virus 40 (SV40) PNC (PNCsV40) as a model. These are reprinted with permission from Li [27,28].

In addition to the oxygen-deficient structure, it increased the possibility that emphasizes the significance of metal coordination by porphyrins in SDT. As mentioned in previous discussion, three kinds of metal 4-methylphenylporphyrin (TTP) complexes (MnTTP, ZnTTP, and TiOTTP) had been proved to yield large amounts of ROS under ultrasound irradiation and demonstrated superb abilities of ultrasound activation with tissue depths. MnTTP complex illustrated optimal ROS activation, owing to the smallest energy gap between the highest occupied molecular orbital and the

lowest unoccupied molecular orbital based on the density functional theory [34]. Metal Organic Framework (MOF)-derived mesoporous carbon nanostructure containing porphyrin-like metalcenters were also an exceptional sonosensitizer with high ROS productivity and superior stability [35]. Different from MnTTP, the superior sonosensitization effect of PMCS might be related to its energy gap. These discoveries would help intensify the comprehension of the sonochemistry mechanism of metal-porphyrin complexes in SDT augmentation.

Metal based magnetic nanocomposites in ultrasound therapy

Currently, the combination of magnetic materials with other functional materials had been well investigated and used in cancer diagnosis and related treatment [36]. Especially to magnetic template as one coherent part, its inherent characteristics played important roles while making integrated structure, such as nickel, iron, and cobalt elements, which could be used in synthesis dual-metal based composites and functional material? In recent studies, a nickel ferrite/carbon nanocomposite ($\text{NiFe}_2\text{O}_4/\text{C}$) which combined multiple diagnostic and therapeutic functions, i.e., MRI, magnetic drug delivery, hyperthermia, and SDT was synthesized [37]. Under ultrasound treatment (1.0 W/cm^2), $\text{NiFe}_2\text{O}_4/\text{C}$ could produce a large amount of ROS due to the catalytic metal compositions (Ni, Fe). In addition, the excellent biocompatibility further expanded the application field of $\text{NiFe}_2\text{O}_4/\text{C}$ in cancer treatment [38].

Similarly, there was ultra-small MnWO_x -PEG that can serve as a novel sonosensitizer for multi-modal imaging-guided SDT application [39]. Due to its higher hydrophilicity in water mediums, its surface functionality should be well understood in water soluble or buffer solution dispersion (Figure 6). Among the synthetic processes, $\text{W}(\text{CO})_6$ precursor, $\text{Mn}(\text{acac})_3$ powder and other auxiliary agents reacted at 260°C for 30 min under the protection of nitrogen. The amphiphilic polymer was used to synthesize MnWO_x and improved their water suspension stability in further measurement. The unique oxygen defect structure of MnWO_x -PEG provided electron capture sites which can prevent the recombination of (e^-) and (h^+), resulting a high ROS generation efficiency [40,41]. Moreover, MnWO_x -PEG prevent Glutathione (GSH) from clearing ROS, and further enhance the effect of SDT treatment. The presence of Mn and W in this Nano platform provided two diagnostic methods (magnetic resonance and computed tomography) that can be used to track the accumulation of materials in tumors applications [42].

Among distinctive sorts of metal oxide NMs, manganese-based oxides including manganese dioxide had been synthesized through appropriate approach [43] and had considerable importance in several technologies. It had medical applications such as energy storage, imaging, theranostics, hyperthermia, drug/ gene delivery, biosensing, ultrasound-promoted tumor chemotherapy and SDT. This kind of manganese-based nanostructures had tunable morphology and structures, inherent magnetic resonance and biodegradable character with excellent biosecurity. It had ability to degrade hydrogen peroxide in the cancer micro-environment to relieve hypoxia. During this, the oxygen generation as well as the ability of GSH depletion, could enhance chemodynamic, PDT, SDT and starvation therapies which might provide favorable application in T_1 -MR imaging [44].

Furthermore, Superparamagnetic Iron Oxide (Fe_3O_4) or its oxidized formed maghemite ($\gamma\text{-Fe}_2\text{O}_3$) with diameters ranging between 1 and 100 nm. As illustrated in previous studies, the consisted iron oxide cores could be targeted to a specific location via externally applied magnets. A magnet was placed externally over the targeted area producing a strong magnetic field that attracted the Fe_3O_4 to the desired location. It was promising as one kind of carriers capable of delivering drugs to the body ascribed to being biodegradable and simple to synthesize [45]. The different types of functional groups included carboxyl groups ($-\text{COOH}$) and carbodiimides ($\text{N}=\text{C}=\text{N}$), that could be grafted on the particle surface. Chemotherapeutic drugs could then be conjugated to these functional groups. However, because drugs were only loaded on their surface, magnetic particles had been found to release their drug load soon after injection into the bloodstream (burst effect). The anti-neoplastic agents then failed to reach their therapeutic levels at the desired site [46]. In order to reduce their premature drug release, biocompatible polymers were usually used to coat the metal cores. There had various polymers such as PEG molecules, polylactico-glycolic acid, polyethylene-co-vinylacetate, and polyvinylpyrrolidone, which had been used as coating materials in aqueous solutions also [47].

Through the surface modification, these coatings protected magnetic core and allowed drug binding by forming covalent bonds, adsorption or entrapment on particle surface. For example, coating Fe_3O_4 with the cross-linked polymer, poly (ethylene glycol)-co-fumarate, caused a significant reduction in premature released (21%) compared to the non-coated magnetic particles [48]. For the purpose of increasing its targeting abilities, and improving the surfaces ability of the magnetic particles, they could be crafted with targeting molecules such as folic acid, RGD, proteins, transferrin, and hyaluronic acid, and so on [49]. Several *in vitro* studies had shown no, or low, cytotoxic effects of Fe_3O_4 on cell cultures. However, others *in vivo* studies showed controversial toxicity patterns of particle itself; from negative to positive toxicity in several preclinical animal models in form of surface molecule exchanged or charged transfers. Generally, the toxicity of Fe_3O_4 depends on their size, dose, surface coating, and species.

It investigated the effect of exposing Fe_3O_4 particles to ultrasound (1 MHz and intensity of 2 W/cm^2) on the viability of cancer cells [50]. The study showed that the level of ROS in the cells was enhanced by following ultrasound treatment. It reported that high concentrations of Fe_3O_4 (above 100 mg/mL) behave as sonosensitizers generating ROS (synergic effect). Coating Fe_3O_4 with sonosensitizers, e.g., titanium dioxide (TiO_2), was a promising technique for enhancing ultrasound-assisted stimulation by inducing the formation of ROS, including hydrogen peroxide and super-oxides. There also had one report by Shen, et al. [51] investigating the cytotoxicity while DOX loaded titanium dioxide-encapsulated Fe_3O_4 ($\text{Fe}_3\text{O}_4\text{-TiO}_2$) coupled with ultrasound

Figure 6 (A) Transmission electron microscopy image Fe₃O₄. (B) Effect of Fe₃O₄ NPs on the viability of two types of cancer cells (HepG2 and 549) and two types of normal cells (rat hepatocytes and IMR-90). (C) FE-SEM image of Fe₃O₄@C core-shell nanoparticles. (D) The proposed mechanism of ROS generation by MnWO_x-PEG under ultrasound irradiation. (E) Microscopy images of H&E- and TUNEL-stained tumor slices. (F) Illustration of the fabrication of FeWO_x-PEG-RGD NPs for (T2/T1-weighted) MR/ CT dual-modal imaging-guided PTT/PDT/CDT synergistic therapy. These are reprinted with permission from Ahamed [36,37,39,42].

(1 MHz, 1 W/cm²). This study reported that the magnetic based heterogeneous structure produced ROS following the exposure to ultrasound. Incubation of cancer cells with Fe₃O₄-TiO₂-DOX followed by sonication showed higher toxicities compared to the treatment with free DOX or Fe₃O₄-TiO₂-DOX alone.

CONCLUSION AND OUTLOOK

In this review, we had concluded the summary of metal based materials as functional candidates in cancer therapy. Especially in constructing the functional materials, the metal elements were mixed together and the metal diffusion in alloyed process. Such incorporation of metal materials, conveyed the new conception about biological applications

and the further investigation in cancer therapies, offered one possibility for medical clinical works and new drug delivery systematic fabrications. For example, in spite of the charming future of the research field, the developed metal based materials and its system for the SDT applications was very limited at present. Over past 20 years, there were plenty of SDT materials candidate that have been developed, one of which is photo-sensitive candidate which is highly desired, which would be the further direction to advance the functional materials and ultrasound integration. In addition, the loading of sound sensient for achieving was highly efficient, selective, and steady ultrasound transfer conversion. The sound sensient played multifunctional roles in whole systems: 1) boosted the combination and bond-efficiency of metal materials and ultrasound corresponded

molecules, which enhanced the final functions, 2) preventing the dual steps construction of compositional combination (metal materials and ultrasound) and 3) expanded the promotion in activation of the inducing processes. Till now, great progresses were achieved in the design and synthesis of metal-based NMs incorporated with ultrasonic applications. Thus, the tailoring of active functional materials would greatly contribute to achieving high-efficiency ultrasound conversion system.

Furthermore, compared with existed metal materials, how to utilize the metal alloys was the most common difficulty, which would expand the range of metal elements' fabrications, and also enhance function toward cancer therapy once modified by functional group completely. Among cancer therapy, the medium condition was the special requirement for metal materials; its acquirement should be in the form of an inert candidate without any changes in its properties exhibitions. Moreover, the ultrasound treatment generally induced non-selective agent in cancer treatment, especially to metal platform, the chemical stability was easily influenced and appeared damages in whole constructions. Finally, to implement the ultrasound corresponded with SDT cure from laboratory study to "practical" applications, the construction of fixed ultrasound sensitizer must be taken into account. Particularly, the photosensitizer/sonosensitizer fixed the whole system as one flexible substrate should be a preferred option. This would not only prevent sedimentation and promotes candidates recycling, but also alleviated the cost of reduced mass transfer between the target cancer issues and reactant. In the long run, only through the collective optimization of the metal based photosensitizer or sonosensitizer, reaction media and reactor, the practical application of cancer therapy valorization can be reliable.

AUTHOR CONTRIBUTIONS

X. H., and S.C., contributed equally in this review paper. X. M. conceived the idea, X. H, S. C, collected data, prepared and revised the manuscript. All authors have read and agreed to the published version of the manuscript.

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