REVIEW PAPER

Application of Manganese oxide (MnO) nanoparticles in multimodal molecular imaging and cancer therapy: A review

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ABSTRACT

Contrast agents (CAs) play a critical role in high-resolution magnetic resonance imaging (MRI) applications to enhance the low intrinsic sensitivity of MRI. Manganese oxide nanoparticles (MnO) have gotten developing consideration as substitute spin–lattice (T1) MRI CAs as a result of the Gd-based CAs which are related with renal fibrosis as well as the inherent dark imaging characteristics of superparamagnetic iron oxide NPs. In this review, previous developments in the usage of MnO nanoparticles as MRI CAs for cancer theranostic applications such as developments in toxicological properties, distribution and tumor microenvironment (TME)-responsive biomaterials were reviewed. A literature search was accomplished to discover distributed research that elaborates the use of MnO in multimodal imaging and therapy. In the current study, the electronic search including PubMed/Medline, Embase, ProQuest, Scopus, Cochrane and Google Scholar was performed dependent on Mesh key words. CAs can significantly improve the imaging contrast among the lesions and normal tissues. In this study we generally concentrate on typical advancements of MnO nanoparticles about properties, bimodal or multimodal imaging, and therapy. Numerous researches have demonstrated MnO-based nanostructure produce considerable biocompatibility with the lack of cytotoxicity. Therefore, remarkable features improved photothermal therapy, chemotherapy and Chemodynamic therapy.

Keywords: *Magnetic resonance imaging; MnO nanoparticles; Multimodal imaging; Nanomaterial*

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INTRODUCTION

Molecular imaging innovation has emerged as a new area for non-invasive tumor analysis and prognosis monitoring because of its high exactness and dependability for describe biological processes, function of bioactive molecules and image some action at the cellular and subcellular level as well as disease monitoring [1]. Among several various molecular diagnostic modalities, MRI as a strong noninvasive clinical diagnostic method with great-resolution anatomical, three-dimensional scanning and functional images of organs could be highly suitable in the molecular imaging mission and monitoring of disease in biological organisms [2].

The MRI signal creates from observing nuclear spins relaxation, specifically, water hydrogen, that, which are plentiful in living system [3]. The primary inconvenience of MRI strategy is its generally relatively low sensitivity which could due to low intrinsic contrast among typical and abnormal tissues. To address this inadequacy, contrast agents (CAs) are needed to upgrade the difference in this strategy through changing the relaxation times of nearby protons [4, 5].

Contrast agents in MRI could be partitioned into two classes, T_1 and T_2 CAs. The first is a T_1-weighted magnetic resonance CAs, which T_1 and T_2 shortening effect by generally a similar amount, creating an increase image signal. The other classification is T_2 CAs, which generally quenching T_2 of the specific tissues and decreases the signal intensity (SI) in T_2 weighted images and result a darker image [6]. Paramagnetic Gd (III) and Mn (II) based CAs with insignificant magnetic anisotropy

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are instances of T_1 CAs, while ferromagnetic and superparamagnetic iron oxide-based CAs by great magnetic anisotropy are samples of T_2 CAs. Superparamagnetic iron oxide nanoparticles (SPIOs) are the greatest favorite candidates for conventional imaging as MRI CAs. Notwithstanding their great sensitivity in T_2 weighted MR images and capability of nanometer dimensions, there are various restrictions related with the utilization of SPIOs agent, for example 'blooming effects' and problem in recognizing hypointense physiological situations and bleeding as well [7]. The common of clinically accessible contrast agents are gadolinium based media (Gd^{3+}) like Magnevist (Gd-DTPA), a FDA approved CAs which generate bright signal intensity on T_1 weighted images. Nevertheless, their molecular constructions restrict their utilization because of their fast renal discharge. In addition, recent investigation has discovered the toxic effect to Gd (III) particularly in patients with kidney disorders. Hence, several researchers have discovered nanometer T_1 CAs that own positive contrast attributes close to Gd(III) complexes, which beat the restrictions of ionic structures by rising circulation time and bestowing extra performance on their surface [8, 9].

In this regard, manganese oxide nanoparticles (NPs) (MONs, for example, MnO, MnO2, Mn3O4, and MnOx) based contrast agents have been investigated as promising nanoparticle in MRI. Mn^{2+} particles have illustrated a T_1 contrast effect identical to that of Gd^{3+}, enhancing the signal intensity (SI) of T_1-weighted images [10].

Besides, manganese oxide nanoparticles and MON-based nanostructure have been broadly functionalized as a drug delivery mechanism to enhance the efficacy of chemotherapeutic drug in cancer treatment. Photothermal therapy (PTT) is a noninvasive method using nanoagents that transform electromagnetic radiation into energy for cell erosion. Regarding PTT, MnO based nanoprobes have been utilized in the PTT of tumors [11]. To the best of our knowledge, few reviews have been written on the usage of MnO NPs in cancer imaging, Therefore, in this review study, the ability of MnO NPs in theranostic procedures, as well as photothermal therapy, chemotherapy and chemodynamic theraphy were investigated.

Search strategy and selection criteria

The literature review was conducted and reported according to the standards set out in PRISMA (Preferred Reporting Items for Systematic Reviews and Meta Analyses) checklist.

Inclusion and exclusion criteria

Articles were included in current review based on the following inclusion criteria: (i) the original, quantitative, review papers, thesis, conference papers, meetings and ongoing papers in English language were included; (ii) the study involved only experimental procedures, not simulation (such as Monte Carlo methods, Geant 4); (iii) studies which investigated the efficiency of Manganese Oxide (MnO) Nanoparticles in Multimodal Molecular Imaging and therapy.

Search strategy, design and study selection

A literature search was performed to find published studies that involved application of Manganese Oxide (MnO) Nanoparticles in Multimodal Molecular Imaging and therapy. An organized search of PubMed/Medline, Embase, ProQuest, Scopus, Cochrane and Google Scholar was performed based on Mesh key words and suitable synonyms. Two researchers (TM and JPE) independently and separately performed literature search. Our search strategy in each database were done by the following terms: ((Manganese Oxide (MnO) [Title/Abstract]) AND ((“Manganese Oxide (MnO) applications”[Mesh]) OR Manganese Oxide in therapeutic application[Title/Abstract])) AND ((Toxicity [Title/Abstract]) OR “ Multimodal Imaging”[Mesh]) OR ((Photothermal therapy (PTT), Chemotherapy [Title/Abstract]) OR “ Relaxivity, Chemodynamic therapy (CDT)”[Mesh]). Database search had no limitation in time, and our last update on search was in May 2020. To have a comprehensive search and to find possible relevant articles, manual search was conducted on the reference list of articles. The search was limited to articles published in English.

Application of Manganese oxide (MnO) nanoparticle as MRI CAs

Thanks to small volume, simple surface manipulating as well as low cytotoxicity, MnO nanomaterial are acceptable T_1 contrast agents. Notwithstanding, MnO nanomaterials might be trapped by the reticuloendothelial (RES) cells and therefore this process will happen in the liver and spleen, which cause Mn (II) induced toxicological properties [12]. MnO nanoagents are usually manufactured through thermal

disintegration of metal forerunners in organic media. Ligands like serum albumin, polyethylene glycol (PEG), phospholipid and dimercaptosuccinic acid have been utilized as substitute oleoic acid and change Manganese oxide nanoagents into water-soluble particles. Polyethylene glycol (PEG) chelating can possibly simultaneously develop the biocompatibility and colloidal stability of NPs in physiological medium and can likewise be formed particular polypeptides and different aptamers so as to enormously increase the targeting capabilities of the system [13]. Huang et al coated MnO NPs with dopamine-terminated mPEG connected with succinic anhydride (mPEG-SA-DA). They confirmed that this method could obtain enough water-solubility and greater longitudinal relaxivity (r_1) equal to 16.14 $mM^{-1}s^{-1}$ when the chelating density of mPEG-SA-DA spreads in 6.51 mmol m^{-2} approximately. So as to upgrade tracing ability, mPEG&cRGD-g-PAsp@MnO nanomaterials (longitudinal relaxivity (r_1=10.2 $mM^{-1}s^{-1}$), transverse relaxivity (r_2=62.3 $mM^{-1}s^{-1}$, 3 Tesla) have been acquired through conjugates Manganese oxide nanomaterials and poly aspartic acid (PAsp)-based join polymer by conjugating with cRGD to produce the CA [13]. PEG-MnO nanomaterials by a hydrodynamic diameter around 15.08±2.67 nm as-prepared via Li et al. demonstrated a great longitudinal relaxivity values of 12.942 $mM^{-1}s^{-1}$ and a short r_2/r_1 fraction of 4.66 at 3.0 Tesla, which was 3 times higher than conventional utilized gadolinium chelate (Fig 1). Moreover, the AS1411 aptamer presented through covalent coupling allow the PEG-MnO nanoprobe's to obviously image renal carcinoma tumor cells [15]. Hollow mesoporous silica nanoparticles (HMSNs), through a huge cavity inside each original MSN, have recently been developed to significantly enhance potential for tumor imaging and drug loading capacity [16]. Silica has been perceived as a decent candidate for a covering particle since it is generally biologically compatible and resistance to get biodegrading [17]. Particularly, mesoporous silica structure is an amazing candidate because of its solidness in fluid arrangement and great labeling capability [18]. Besides, mesoporous silica permits simple accessibility for water molecules to the magnetic core, which fundamentally advances the water hydrogen relaxation behavior [19].

Taeho Kim et al. reported a different plan of Manganese oxide NPs that have a ' hollow ' Manganese oxide center framework and a covering comprising of mesoporous silica (HMnO@$mSiO_2$). The great surface area-to-volume proportion donated the water molecules to penetrate complete the pores considers the system as an impressive T_1 MR CAs. This was exhibited after marking of multipotent mesenchymal stem cells (MSCs) with HMnO@$mSiO_2$ Nanomaterials [20]. At that point, hollow MnO nanoparticles with a ~25 nm thick permeable silica layer have been planned as great stability cell targeting imaging nanoprobes [21]. Contrasted and the last mentioned, the r_1 of these nanoparticles showed up somewhat expanded (r_1= 0.99 mM^{-1} s^{-1} at 11.7 Tesla), permitting the following of mesenchymal stem cells (MSCs). Nevertheless, the longitudinal relaxivity (r_1) of these suspensions was as yet four (4) to ten (10) times lower than that detected for normal conventional CAs, like gadolinium-DTPA and gadolinium-DOTA [21]. In certainty, covering MnO nanoparticles by a layer of silica impressively influences ideal water exchange among the lattice and the surface paramagnetic ions, which is an important factor ensuring the exhibition of "positive" MR CAs [22]. Despite the fact that Mn^{2+} particles are paramagnetic, Manganese oxide nanoagent in the range 5–10 nm could represent an antiferromagnetic conduct [23]. Furthermore, attractive nanoparticles have been exhibited to link with mesoporous structure, noble metallic chemical elements, carbon-based particles, and

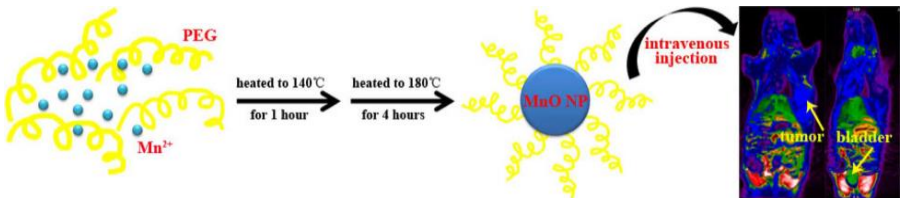

Fig 1. Schematic design of the one-pot preparation of hydrophilic PEG-MnO nanomaterials for MRI of nephritic carcinoma [15]

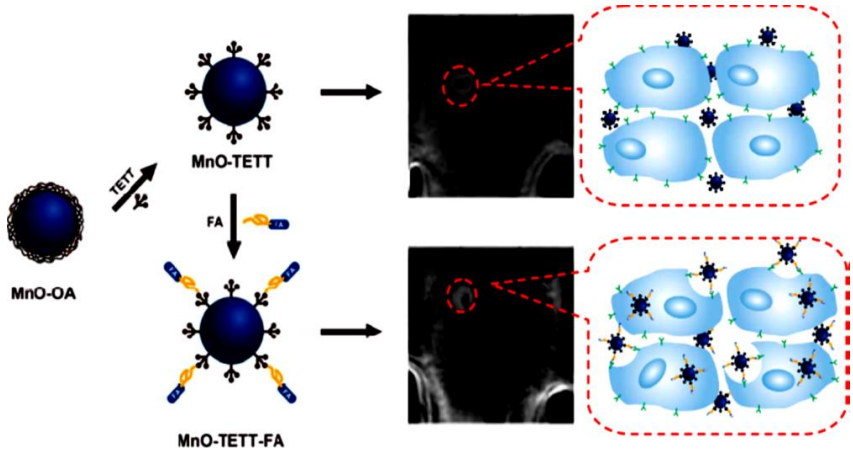

Fig 2. Folic Acid-Conjugated Manganese oxide NPs as a T1 CAs for MRI of Tiny Brain Gliomas [8]

fluorophores to work all the more productively. Li and coworkers chelated MnO NPs with carboxymethyl dextran (CMDex- MnO NPs) (r_1=0.44 $mM^{-1}s^{-1}$, r_2=3.45 $mM^{-1}s^{-1}$, 3.0 Tesla) [24]. Chen et al enhanced the water dissolvability of Manganese oxide nanoparticles using transesterified oleic acid with N-(trimethoxysilylpropyl) ethylene diamine triacetic acid (TETT) silane (Fig 2) [8]. Hu and coworkers chelated biocompatible polyvinylpyrrolidone (PVP) on MnO nanomaterials utilizing layer-by-layer electrostatic gathering. Specifically, MnO@PVP nanoagents can go across the blood–brain barrier (BBB) in addition progressively metabolize to different locales through blood stream. This is demonstrated as an intravascular contrast agent (r_1=1.937 $mM^{-1}s^{-1}$, r_2=27.879 $mM^{-1}s^{-1}$, 3.0 Tesla) and an extensive utilization in essential neuroscience study [25]. Hsu and colleagues prepared MnO NPs with silica-F127 ($PEO_{106}PPO_{70}PEO_{106}$) so as to make them profoundly hydrophilic. Moreover, under similar situations, the permeable silica-PEO nanochelating layer can improve the differentiation of T_1-weighted (r_1=1.17 $mM^{-1}s^{-1}$, r_2=30.73 $mM^{-1}s^{-1}$, 7.0 Tesla) when contrasted with PEG-phospholipids, thick silica framework, and mesoporous silica framework [26]. Moreover, the morphology of manganese oxides NPs can influence its relaxation attributes. Octagonal Manganese oxide NPs have a bigger surface zone than spherical NPs of a similar scale, bringing about noteworthy improvement of low-temperature ferromagnetic conduct [27]. Table 1 accentuate a few models based on MnO NPs as MRI contrast agants.

Use of manganese oxide nanoparticle in Multimodal Imaging

Primary and metastatic tumors represent a genuine danger to human healthiness. Improving exact determination of cancer cells stays a challenging difficult issue. Multimodal imaging has gotten to be an investigation hotspot and a part for prospect advancement due to its capability to assimilate different imaging methods. [28, 29]. T_1-weighted images can be providing detailed anatomic information; however, T_2-weighted images are additional sensible for pathological analysis. Both T_1 and T_2 imaging integration is capable to pointedly increase MRI effectiveness. Antibody immobilization permits both T_1 and T_2 imaging combination can altogether improve MRI productivity. The interval between T_1 nanoparticles

Table 1. List of the most utilized MnO-Based NP in Magnetic Resonance Imaging

Diagnostic agent	Surface coating	Applications	Target	Year	Refs
MnO	TETT	T_1-MRI	folic acid	2014	[8]
MnO	PVP	T_1-MRI	-	2013	[24]
MnO	mPEG	T_1-MRI	cRGD	2015	[13]
MnO	CMDex	T_1-MRI	-	2015	[23]
MnO	PEG	T_1-MRI	AS141	2018	[14]
MnO	PEO	T_1-MRI	-	2014	[25]

and T_2 nanoparticles should be more than 20 nm to prevent the signal quenching. Multimodal imaging is inquired to integrating numerous diverse imaging modalities in a single system, including ultrasound (US), CT, MRI, Fluorescence (FL), SPECT imaging (Fig 3)[28, 30]. These days, various strategies for integrating MnO (T_1 contrast agent) and Fe_3O_4 (T_2 contrast agent) so as to improve T_1-T_2 double modal contrast agents (DMCAs) have been broadly considered [31]. For instance, Peng E et al. MnO (denoted as T_1-nanoparticles) magnetic nanoparticles and hydrophobic Mn-doped Fe_3O_4 (denoted as T_2-nanoparticles) were simultaneously decorated onto a grapheme oxide (GO) sheets as DMCAs [32]. They designed Fe_3O_4@MnO/$mSiO_2$–CD133 nanoparticles by placed Manganese oxide into the core-shell mesopores of Fe_3O_4@$mSiO_2$ [29]. They discovered that after the MnO clusters has been placed in the nano effect region of Fe_3O_4 NPs, local induced MR field strength of DMCAs can be tuning by modifying the size of Fe_3O_4 NPs to diminish the MRI serious destruction to target tissue. To confirm this assumption, they conjugated a CD133 antibody to the surface of Fe_3O_4@MnO/$mSiO_2$ for imaging of living ependymal brain cells. Results indicated a higher T_1–T_2 bi-modal contrast agent's don not impact by local destruction under external magnetic field produced from magnetic resonance imaging. Because of the dependability and usefulness of both MR and optical imaging dual-modal imaging in cancer cells discovery and theraphy, optical/MR bi-modal nanotracer which depend on MnO-based nanomaterial that considered. Zheng et al. designed an MRI and near-infrared fluorescence (NIRF) bi-modal imaging NPs (MnO-PEG-Cy5.5 NPs) were utilized as an MRI CAs and possible drug carrier for myocardial infarction region approximation and focusing on the infarcted myocardium for the crucial for positive therapeutic outcomes [33]. Also, Chen et al prepared the (MnO-PEG-Cy5.5 NPs) nanoprobe, which can upgrade the T_1-weighted imaging of glioma tumor [34]. Several techniques which don't utilize fluorescent color have been presented. Lai and colleagues understood that MnO nanoparticles which has been prepared via direct thermal decomposition method shows fluorescence excitation properties across its whole visible spectrum [35]. In this study, to confirm its Dual-modal imaging presentation, C6 glioma cells

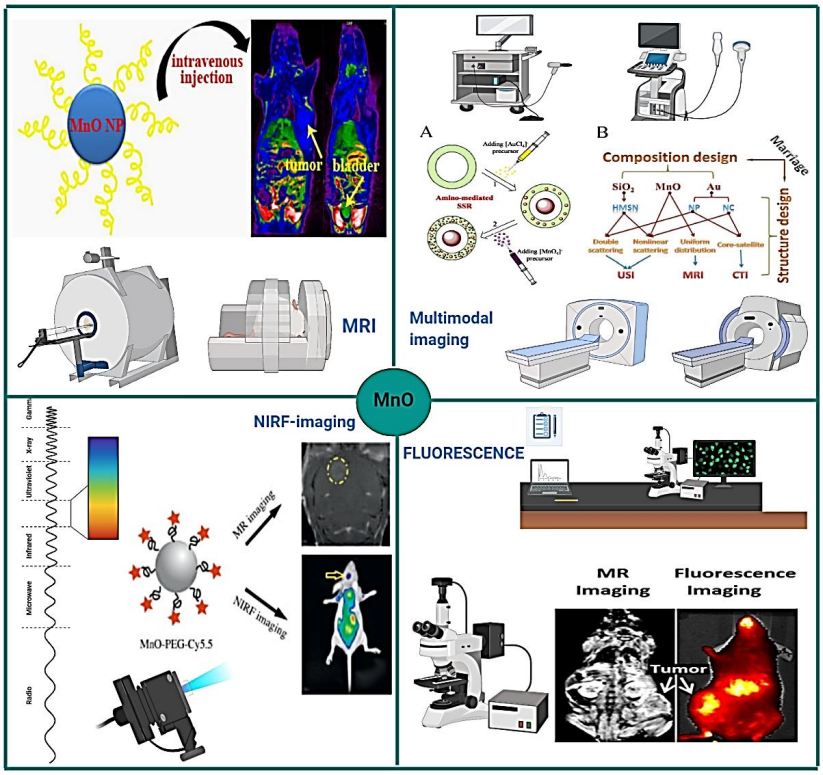

Fig 3. Schematic of MnO-based nanoplatforms for diagnostic applications

were diagnosed pursuant surface engineering of TETT silane, and it was understood that cells displayed green and blue color fluorescence at 405 nm and 458 nm, respectively. Moreover, the r_1 relaxivity at 7Tesla scanner was 4.68 $mM^{-1}s^{-1}$. Multifunctional nanoprobes reinforce synchronous multi-source imaging modalities, which comes about in more exact data. Zhang and colleagues planned an exceptionally performance MR/US/CT multi-modal nanoprobes (Au@HMSN/Au&MnO) [36]. Large gold NPs have been emerged in hollow cavity of HMSN NPs (HMSNs), whereas minor-sized gold nanocrystals and MnO NPs are equitably dispersed within the mesoporous shell. Liu et al detailed an acidic tumor microenvironment TME-responsive CT/MRI/PA multi-mode tumor imaging contrast agent, specifically MnO nanocomposites enveloped in permeable Au nanoclusters [37]. Photoacoustic imaging has high-resolution, as a developing noninvasive imaging, and exact measurement in the diagnosis of tumor [38]. Computed tomography (CT) imaging technique has the features of whole-body imaging (WBI) and without tissue permeation depth restriction [39]. MRI is the powerful select for soft tissue diagnosis. Subsequently, Integrating CT/MR/ PA three-modal imaging on a nanostructure permits more exact tumor detection. This porous gold nano particle layer can impede the discharge of Mn (II) ions to improvement of longitudinal relaxation time (T_1) signal and enhanced Photoacoustic imaging depth. Taking after the intratumora administration of MnO@Au nanocomposites into HepG2 cell-transplanted tumor in rats, the Photoacoustic (PA) signal intensity has been fundamentally improved. Table 2 accentuate a few models based on MnO NPs as Multimodal imaging contrast agants.

Therapeutic applications of MnO

MnO-based nanoparticles not only have been applied in different diagnostic system, moreover have been used as remarkable therapeutic agents, and in this way are broadly utilized in RT, PDT, CDT, gene treatment, chemotherapy, and different combination treatment.

Photothermal therapy (PTT)

In recent decades, photothermal therapy (PTT) has acquired a lot of consideration because of its great efficiency in cancer cells therapy [40]. PTT relies upon convert light energy into hyperthermia, resulting in the thermal ablation of adjacent cancer cells. Photothermal agents (PAs) which can absorb light energy, which causes excitation and resulting non-radiative relaxation [41]. Regarding PTT, MnO-coated nanotubes of carbon (i.e. MWNTs–MnO-PEG) were utilized for the PTT of tumor metastasis. In arrange to study by Wang. S et al. the therapeutic impact of the dual-modality tracer in combination with A549 cells, it was discovered that beneath the NIR light of 3 w/cm^2, approximately no cells stayed alive and normal cells have not been meaningfully decreased. Mice bearing Lymph nodes (LNs) metastasis models of A549 cells was utilized for dual-modality guided photothermal therapy (Fig 5). The temperature expanded fast from 25.28°C to 55.64°C in 5 min beneath NIR light, while the nearby normal tissues did not increment significantly [42]. In the study by Xiang and colleagues, MnO was loaded with carbonaceous nanospheres (MnO@CNSs) to acquire with MRI and photothermal therapy efficiency (Fig 4) [11]. To improve the phototherapy impact, Zhou et al, combined a mitochondrial-targeted multifunctional dye-anchored (IR808@ MnO NP), as a targeting agent of tumor. In response to low NIR laser irradiation, IR808 convert O_2 to exceedingly toxic singlet oxygen $^1O_2$ and produces high warm as well. The MCF-7 cell tumor-bearing nude mice incubated with IR808@ MnO nanomaterials were totally suppressed by

Table 2. List of the most available MnO-Based NP in Multimodal imaging

Diagnostic agent	Surface coating	Applications	Target	Year	Refs
MnO	PEG-Cy5.5	MRI- NIRF/T_1-weighted	_	2015	[33]
MnO@Au	DMSA	T_1-weighted -MR/PA/CT Imaging	-	2013	[36]
Au@HMSN/Au&MnO	mesoporous	US/MR/CT	_	2015	[35]
Fe_3O_4/MnO	silica shell	T_1–T_2 dual modal	CD133	2017	[28]
MnO	TETT	T_1-MRI/Fluorescence	-	2018	[34]

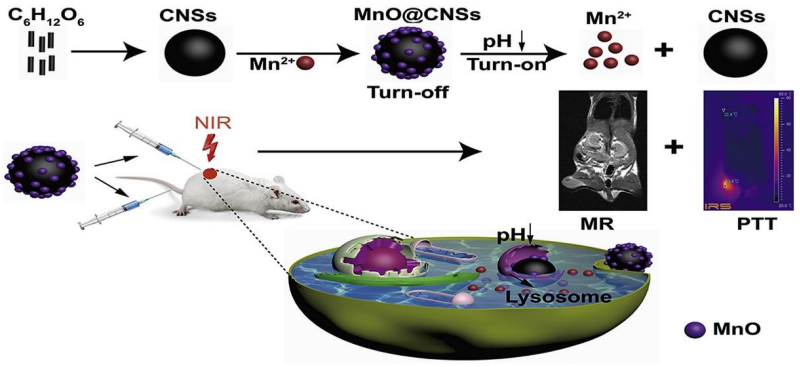

Fig 4. Schematic representation of Biocompatible and pH-sensitive Manganese oxide-loaded carbonaceous nanospheres (MnO@CNSs) [11]

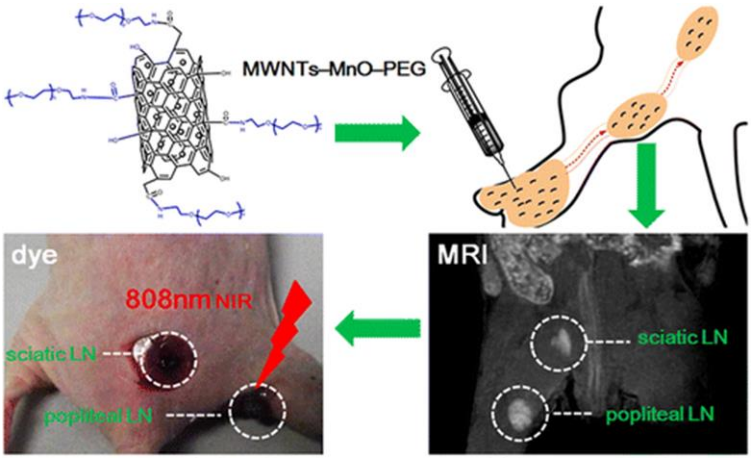

Fig 5. Schematic representation of the bifunctional application (dye and T1-weighted MRI) guided photothermal therapy of metastatic Lymph nodes (LNs) by MWNTs-MnO-PEG nanocomposites [42]

808 nm NIR light exposure [43].

Chemotherapy

At the present time, chemotherapy is quite possibly the greatest clinically dominant treatments. Chemo combination therapy, utilizing at least two or further drugs together pursuant to nanotechnology, can keep up the physicochemical attributes of the chemotherapeutic agents, which inhibited tumor growth potently [44]. Manganese Oxide nanoparticles and MON-based nanostructure were comprehensively functionalized for drug transportation in order to improved chemotherapy efficacy on account of their novel attributes. The loading of therapeutic drugs or on the other hand blend of a few clinical treatments to accomplish real-time analysis and treatment of cancerous cells has been widely examined. MnO has got numerous favorable conditions for cancer therapy. MnO-based nanostructure generally applied in RT, PDT, CDT, gene treatment, chemotherapy, and diverse combination treatment. Hydrophilic MnO nanocrystals which have been produced by microwave-assisted strategies could persuade genuine autophagy and produce p53-activationin autonomous. This autophagy phenomenon benefits MnO nanocrystals to have synergistic effect in combination with doxorubicin in arrange to create more considerable on tumors cells (Fig 6) [45]. In the study by Lu Y et al. the 2-carboxyethyl-triphenylphosphonium [COOH- (CH2)2-PPh3$^+$] gave their system mitochondrial targeting property [46]. This MnO@SiO2-PPh3+ NPs is exceedingly particular for mitochondria. It makes

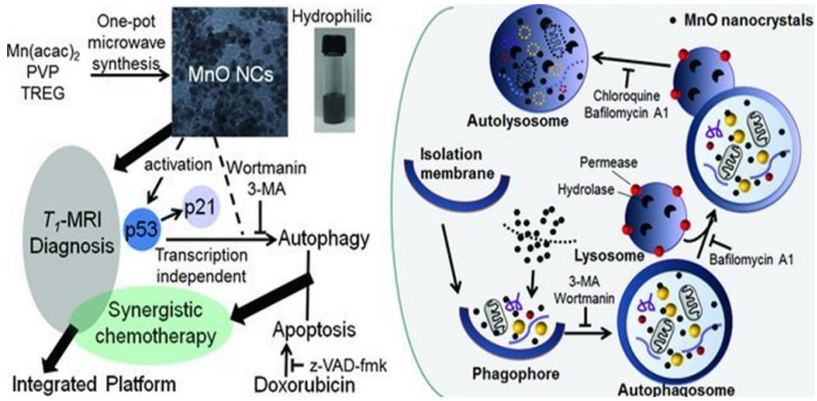

Fig 6. Schematic illustration of the Platform of the Manganese oxide nanocrystals (NCs) for the combination of MRI and genuine autophagy induction for chemotherapy [45]

significant cytotoxicity in 4h incubation and induce the severe apoptosis to tumors cells. Howell and et al. designed multifunctional lipid-micellar nanoparticles (MLMNs) by using MnO NPs in order to combined chemotherapy. *In vitro* results established that M-LMNs-loaded doxorubicin or plasmid DNA was completely consumed by HEK293 cells [47]. *In vivo* drop intranasal administration of lipid-micellar nanoparticles illustrated lungs accumulation. Abbasi and associates encapsulated the docetaxel (DTX) drug and MnO NPs in a conjugation of fluorophore with the amphiphilic polymer. The longitudinal relaxivity of the system estimated r_1=2.4 $mM^{-1}s^{-1}$ which was 2.7 fold more than that of free MnO nanoparticles. Nevertheless, fluorescence imaging (FI) had an optimistic prolonged efficient and allowed high delivery efficiency and sustain DTX release profile, reducing essential drug dose for inhibition of cell growth by 3 to 4.4 times [48].

Chemodynamic therapy (CDT)

CDT, a developing therapeutic procedure, is characterized through converting intracellular H2O2 by uses fenton-like reactions to create cytotoxic (°OH) in order to kill tumor cells through destructive biomolecules (Fig 7) [49]. Choi and associates found that after 48h incubation of manganese oxide with lung adenocarcinoma cells line, upper and dose-dependent increment in oxidative stress situations were demonstrated. Nevertheless, the system cytotoxic effect of MnO NPs was not obvious [50]. Besides, Cai et al similarly affirmed that MnO nanoparticles have

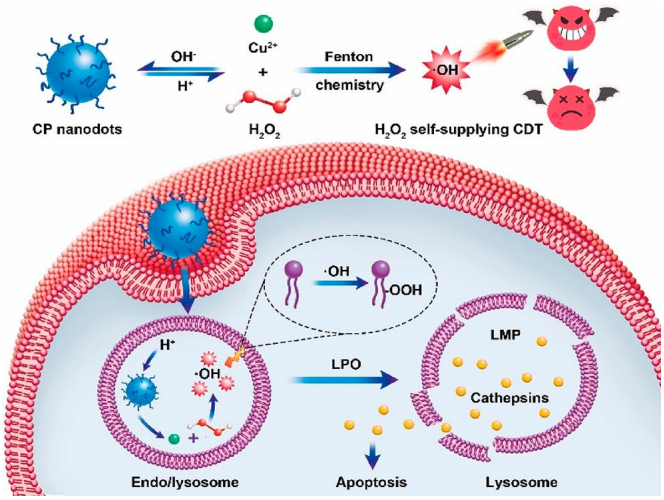

Fig 7. Formation of copper peroxide (CP) Nanodots for H_2O_2 Self-Supplying Chemodynamic Therapy [49]

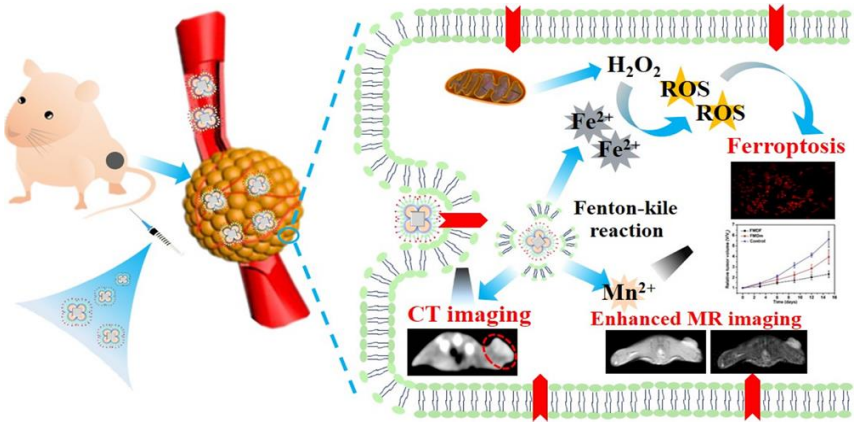

Fig 8. Schematic illustration of the acidity-triggered dual-ions release for enhanced MR imaging-guided ferroptosis chemodynamic therapy of FMDF NPs by rapidly releasing active Fe^{2+} to catalyze intracellular H_2O_2 into ROS [51]

the ability of generating free radical (°OH, °O2−) so as to enhance CDT [28].

Also, Baochan Yang et al. prepared a high efficiency nanotheranostic Structure (FePt@MnO)@DSPE-PEG5000-FA (FMDF NPs) for MRI guided ferroptosis chemodynamic therapy (FCDT) of tumor (Fig 8). Mn^{2+} released from MnO domains because of acidic intracellular microenvironment and extra organize through Glutathione (GSH) to improve the longitudinal-transverse relaxivity (T_1). the FMDF nanoparticles exhibited a period-depended dual Fe^{2+} release at pH = 5.8 with a release rate of up to 23% Mn^{2+} and maximum 51% inside 15 h while barely any release at pH= 7.4, that demonstrated that FMDF nanoparticles have a potential for tracing improved MRI-guided ferroptosis CDT [51].

Relaxivity improvement of manganese oxide nanoparticles

It is obvious that magnetic resonance imaging (MRI) technique is progressively function of beneficial field for more noteworthy signal to-noise ratio (SNR) and greater spatial resolution or shorten acquisition time. However, the relaxivity of MRI CAs ordinarily diminishes in powerful magnetic field [52]. Transverse and longitudinal relaxation rates ($1/T_2$ and $1/T_1$) are estimated from the slope of MRI signal intensity against TE or TR, and plotted against Manganese concentration rates to compute r_2 and r_1 (the "relaxivities"). High r_1 rates and r_2/r_1 rates between 1-2 are important to exhibit the capability of "positive" contrast agents for sub-atomic MRI [53].

In many research, very low molar relaxivities MnO NPs have been observed, generally in the range 0.2–0.5 mM−1 s^{-1}, At least 1 times larger than free Mn(II) particles at the similar Manganese concentration [54].

To be used as an efficient T_1 MRI CAs, manganese oxides nanomaterials should contain the divalent Mn (II) particles, which are described through the attendance of 5 unpaired electrons in their d^3 shell [55]. This makes a significant magnetic moment and produces magnetic relaxation due to the cores of the systems. MnO nanoagents have potential to be considered as T_1-weighted MR CAs [56]. For instance, Shin et al. arranged manganese oxide nanoagents with a relaxivity of 1.42 mM^{-1} s^{-1} and exhibited their MRI CAs productivity in a mouse brain upon local injected by MnO nanoparticles [57]. Kim et al. announced that the longitudinal r_1 value of HMnO@$mSiO_2$-labeled Mesenchymal stem cell (MSC) diminishes as of 1.72 mM^{-1} s^{-1} at 1.5 Tesla to 0.99 mM^{-1} s^{-1} at 11.7 Tesla [58]. This could be credited to the induced magnetization of paramagnetic complexes in powerful magnetic fields, which benefits the conquered of transverse relaxation time effects and diminished effectiveness of MnO to optimizing longitudinal relaxation time (r_1) of water. Subsequently, it features the needed to create MnO-based CAs with high relaxation. For a basic explanation of the phenomenon, the longitudinal relaxation time (T_1) CAs could be imagined to have various solvation spheres [59]. Since the main strategies of relaxivity emerges from the dipole–dipole (DD) linking among hydrogen of water and the paramagnetic particle,

the inner-sphere waters can adjust more powerful dipole–dipole connections and would be extra sensitive to r_1 relaxivity [52, 60]. Consequently, so as to increment the spin-lattice relaxation of MnO-based CAs, current mechanism is generally focused towards growing the accessibility of the waters molecules to the magnetic core. On account of core–shell MnO-based composite NPs, this can be accomplished by getting higher surface-to-volume proportion of MnO NPs, just as morphological engineering of the layer coated to improve its water penetrability. Moreover, r_1 relaxivity more effective when the tumbling process of T_1 CAs closest to Larmor frequency of the proton [61]. However, for nanotracer mechanism which depend on the discharge of Mn^{2+} particles for T_1 contrast improvement, all things considered, the minor aqueous phase have a great tumbling process [62]. So, the rotational correlation time should be adjusted so that it matches closest the Larmor frequency of the proton, along these lines accomplishing a higher spin-lattice relaxation.

Toxicity

In order to be used as biomarkers, it is critical and fundamental to examined toxicological characteristics of nanoparticles. One of the main concern of clinical utilizing Mn-based CAs is their cytotoxicity [63]. The toxicological characteristics of Mn-based nanoparticles is basically because of high affinity of Mn^{2+} for Ca^{2+} ion channels due to the similar ionic radius and may be accumulated in undesirable tissues and cause cardiac greater contractility [64].

This effect has restricted the application of free manganese Mn(II) as paramagnetic substances for *in vivo* detection [54]. Moreover, manganese complexes are moderately instable *in vivo* and be inclined to separate in physiological media. Also, manganese particles can be dislodged through other metal cations, like Zn^{2+}, Ca^{2+}, or Mg^{2+}. Consequently, more concerns be around the potential long-term cytotoxicity related with the use of free manganese contrast agents [65]. The cytotoxicity of MnO NPs could be prompted by numerous strategies containing the production of receptive oxygen species (ROS) and an over the top gathering of manganese particles by reason of NP depreciation. MnO nanomaterials have indeed been utilized for labeling and mapping transplanted stem cells [66]. Nevertheless, toxicological studies give constrained data on the long-term affect. At the conclusion of the investigation, numerous nanomaterials are still within the procedure of disintegrating endosomes and lysosomes creates an enclosed environment in an acidic pH. Systematic studies are required to way better get it the itemized particle metabolic rate and their durable impacts to a living organs, particularly from a neurotoxic disease. To overcome these cytotoxicity concerns, different procedures have been planned to improve the behaviors of Mn+2-chelates, which usually include the design of new chelating ligands.

Na and coworkers designed polyethyleneglycol (PEG) –phospholipid micelles (DSPE–mPEG) to conjugated with MnO nanoparticles. The possible cytotoxicity of these PEG–phospholipid chelated MnO NPs was consequently evaluated with eight dissimilar human cell lines. It has been detected that the IC50 rate reached as of 0.36 mM of Mn by NCI-H460 cells to 4.73 mM in MRC-5 cells. ICP-AES recommended no considerable manganese-particle leaking from the MnO NPs when retained for seven days at room temperature whereas the *in vivo* biocompatibility was confirmed by an nonappearance of fluctuations in behavior or signs of weight loss in mice that were bolus-administration by the polyethyleneglycol (PEG)–phospholipid chelated MnO nanoparticles [67]. Schladt et al. manufactured greatly soluble MnO NPs through functionalization by a dopamine-PEG-protoporphyrin IX (DA-PEG-PP) hydrophilic ligand. Cytotoxicity analyze of the DA–PEG–PP functionalized MnO NPs showed insignificant level of toxicity as a great cell viability of over 90% was detected after incubation period at a concentration of 25–100 mgml-1 [68].

CONCLUSION

Contrast agents can significantly improve the imaging contrast among the lesions and normal tissues. Although gadolinium (Gd) homologue have been conventionally utilized for this purpose, the toxicological properties of Gd ions has motivated the scientists to design and develop the innovative CAs with low cytotoxicity, great sensitivity, effectiveness, and capability to be used in molecular and cellular imaging based on other paramagnetic metal ion. Manganese-based NPs are a comparative new class of CAs. The advancement of MnO as spin−lattice (T_1) MRI CAs is a growing field of study with expanded prospects for bioimaging function. In this review

we generally concentrate on typical advancements of MnO NPs about properties, bimodal or multimodal imaging, and therapy viewpoint. Nonetheless, despite the momentous advances, here are some complications in advance to additional clinical translation of MnO NPs .In spite of numerous researches which have demonstrated MnO-based nanostructure produce considerable biocompatibility with the lack of cytotoxicity, many other issues should be measured before better understanding of disease, for example dispersal, metabolism, possible immunoreactions, etc. In addition, the outline of numerous useful constituents for example particles, polymers, or biological molecular, makes it firmer. Manipulating an ultimate design by merging the multiple therapeutic method into one structure that lets MnO-mediated nanostructures to attain balanced combination of each constituent is still a challenge. In other words, there is a time-consuming way to attain clinical utilization. Though, we rely on that MnO-related nanostructure hold massive potential in biomedical arena. Hold enormous promise in biomedical field.

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