



Smart Responsive Nanoformulation for Targeted Delivery of Active Compounds From Traditional Chinese Medicine

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Traditional Chinese medicine (TCM) has been used to treat disorders in China for ~1,000 years. Growing evidence has shown that the active ingredients from TCM have antibacterial, antiproliferative, antioxidant, and apoptosis-inducing features. However, poor solubility and low bioavailability limit clinical application of active compounds from TCM. “Nanoformulations” (NFs) are novel and advanced drug-delivery systems. They show promise for improving the solubility and bioavailability of drugs. In particular, “smart responsive NFs” can respond to the special external and internal stimuli in targeted sites to release loaded drugs, which enables them to control the release of drug within target tissues. Recent studies have demonstrated that smart responsive NFs can achieve targeted release of active compounds from TCM at disease sites to increase their concentrations in diseased tissues and reduce the number of adverse effects. Here, we review “internal stimulus-responsive NFs” (based on pH and redox status) and “external stimulus-responsive NFs” (based on light and magnetic fields) and focus on their application for active compounds from TCM against tumors and infectious diseases, to further boost the development of TCM in modern medicine.

Keywords: smart responsive nanoformulation, traditional Chinese medicine, targeted drug delivery, tumor, infectious disease

INTRODUCTION

Traditional Chinese medicine (TCM) as an important approach to treat disorders has been used widely in China for ~1,000 years. Accumulating evidence has shown that TCM exhibits excellent effects on tumors (Luo et al., 2019), bacteria (Kim et al., 2008; Moloney, 2016; Wang Z. et al., 2018b), and viruses (Li et al., 2018a; Yao et al., 2018; Yang et al., 2020) because of their active compounds. Some active compounds, such as artemisinin, curcumin, and epigallocatechin gallate, emodin, and celastrol, show prominent efficacy against tumors (Wang et al., 2014; Shanmugam et al., 2017). Flavonoids, polyphenols, alkaloids, and terpenoids are considered to be efficacious against antibiotic-resistant bacteria (Zhao et al., 2019b). Also, TCM shows multitarget features against viruses in direct or indirect ways (Ai et al., 2018; Li et al., 2018a).

However, the poor solubility and low bioavailability of the active compounds from TCM limit their clinical application. To address these shortcomings, novel drug-delivery nanoformulations

(NFs) are being employed to increase solubility, improve the efficiency of targeted delivery, and reduce the number of adverse effects. Recently, liposomes, nanoparticles, vesicles, mesoporous silica nanoparticles, and micelles as potential drug-delivery NFs have shown great promise in TCM (Ma et al., 2019).

“Smart responsive NFs” are new types of targeted NFs that deliver drugs specifically to target tissues or organs *via* an “intelligent response” in target sites. Usually, smart responsive NFs are classified into “internal stimuli-responsive NFs” and “external stimuli-responsive NFs” according to different stimuli conditions as shown in **Figure 1**. Internal stimuli-responsive NFs are mainly from the microenvironment of the targeted site and include pH, enzymes, redox status, and receptors. External stimuli-responsive NFs are mainly from magnets, heat, light, or ultrasound.

Here, we reviewed internal stimulus-responsive NFs and external stimulus-responsive NFs. We focused on the application of active compounds from TCM against tumors and infectious diseases, to further boost the development of TCM concepts in modern medicine.

INTERNAL STIMULUS-RESPONSIVE NFs

pH-Responsive NFs for Delivery of Active Compounds From TCM

The metabolism of tumor cells involves aerobic glycolysis to obtain energy for overgrowth and proliferation (Ganapathy-Kanniappan and Geschwind, 2013). Aerobic glycolysis is based on the conversion of glucose to pyruvate, which results in fermentation and lactate production (Shi et al., 2018), and the resulting acidosis is a ubiquitous characteristic of cancer (Tang et al., 2018). It has been demonstrated that the tumor tissues’ acidic environment is about pH 6.5 (Som et al., 2016), whereas the pH of normal tissue is 7.4 (Liu et al.,

2014). The microenvironment of tissues infected by bacteria is also acidic (Tao et al., 2019a). As shown in **Table 1**, based on the characteristics of an acidic microenvironment, pH-responsive NFs have been developed for targeted delivery of active compounds from TCM.

Delivery of Artemisinin and Dihydroartemisinin

Artemisinin and dihydroartemisinin are active agents from the Chinese herb *Artemisia annua*. They are used as antimalarial drugs in China (Tu, 2016). They are also potential anticancer agents when interacting with iron ions to produce reactive oxygen species (ROS), which can kill malignant cancer cells (Efferth, 2017). Chen et al. developed Fe₃O₄ nanoparticles as a pH-sensitive NF, for treating cervical cancer (Chen et al., 2014). In this NF, artemisinin was stored in the outer mesoporous shells. Fe²⁺ was liberated from the core of the Fe₃O₄ nanosphere in acidic organelles and cleaved the endoperoxide bridges of artemisinin to generate free radicals to kill HeLa cells. Artemisinin-hollow mesoporous silica-Fe₃O₄ nanoparticles have also been used to treat breast cancer *via* pH-responsive Fe₃O₄ nanoparticles (Bhaw-Luximon and Jhurry, 2017). Sustained release of artemisinin occurred in the lysosomal compartment (pH 3.8–5.0), and Fe₃O₄ was metabolized to free Fe²⁺ to generate many free radicals through reaction with the released artemisinin. In addition, an Fe₃O₄@MnSiO₃-folate nanosphere was developed for the treatment of lung cancer (Chen et al., 2015). Folate was introduced to increase the enhanced permeability and retention (EPR) effect. Meanwhile, Mn²⁺ was released from the silicate shells and interacted with artemisinin in an acidic tumor environment and organelles of A549 cells.

Liu et al. (2015) prepared dihydroartemisinin–graphene oxide–transferrin nanoparticles. The Fe (III) conjugated on transferrin was released in lysosomes and was reduced to Fe

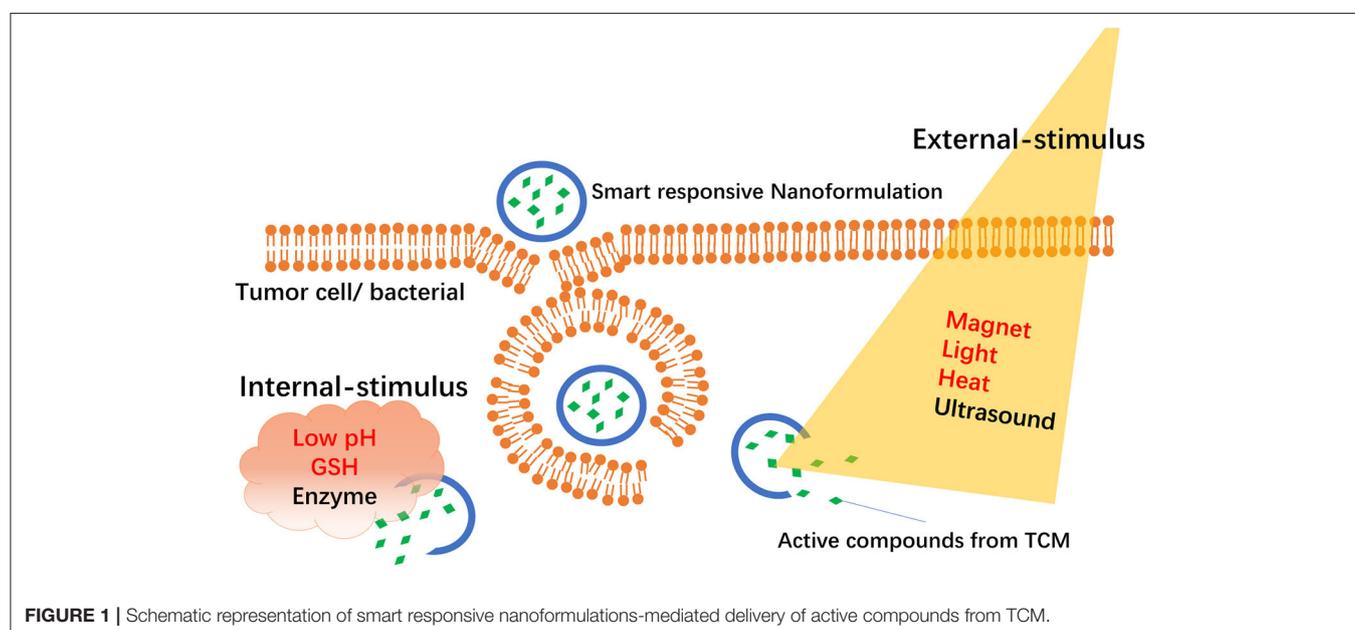


TABLE 1 | pH-responsive nanoformulations in active compounds from TCM.

| Active compounds | Response agent | Application | Cell line/animal | References |
|--------------------|----------------------------------------------------------|------------------------------------------------------------|-------------------------------------------------------------------------------|-------------------------------|
| Artemisinin | Fe ₃ O ₄ nanocrystal | Cervical cancer | HeLa | Chen et al., 2014 |
| | Fe ₃ O ₄ @MnSiO ₃ | Lung cancer | A549 Nude mice | Chen et al., 2015 |
| | Fe ₃ O ₄ nanoparticles | Breast cancer | ZR75-30 | Bhaw-Luximon and Jhurry, 2017 |
| Arsenic trioxide | Polyamidoamine | Glioma | C6 | Lu et al., 2018 |
| Dihydroartemisinin | Fe (III) | Breast cancer | EMT6 EMT6 tumor-bearing nude mice | Liu et al., 2015 |
| Baicalein | Hydrazone bond | Lung cancer | A549/DTX cell A549/DTX tumor-bearing nude mice | Li et al., 2017 |
| Berberine | Chitosan | <i>H. pylori</i> infection | | Lin et al., 2015 |
| | Amine bond | Cervical cancer | HeLa | Pandey et al., 2013 |
| Cinnamaldehyde | Acetal | Anticancer | DU145 SW620 RAW264.7 HEK 293 BALB/c nude mice | Yoo et al., 2018 |
| | Acetal | <i>E. coli</i> infection <i>P. aeruginosa</i> infection | <i>E. coli</i> Drug-resistant <i>P. aeruginosa</i> DRPA-001 ICR mice | Park et al., 2016 |
| | Acetal | Colon cancer | HCT116 BALB/cA nu/nu mice | Zhao et al., 2019a |
| Curcumin | PAE | Breast cancer | MCF-7 BALB/c nude mice | Yu et al., 2015 |
| | Amine bond | Liver cancer | HepG2 | Luan et al., 2017 |
| | ZnO nanoparticle | Gastric cancer | AGS | Dhivya et al., 2018 |
| | PAE | Hepatocellular carcinoma | SMMC 7721 HUVEC BALB/c nude mice | Zhang et al., 2017 |
| | PAE | Anticancer | MCF-7 HepG2 | Cai et al., 2016 |
| | <i>cis</i> -Aconitic anhydride linker | Anticancer | A2780 SMMC 7721 | Fang et al., 2016 |
| | Poly(isoprene- <i>b</i> -acrylic acid) deblock copolymer | Acute myelocyte leukemia | HL-60 HL-60/Dox HL-60/CDDP | Jelezova et al., 2015 |
| | Carboxylic groups of AGA | Colorectal cancer | HCT-116 | Madhusudana Rao et al., 2015 |
| | Menthone 1,2-glycerol ketal | Anticancer | SCC-7 tumor-bearing BALB/c mice | Chen et al., 2016a |
| | Hydrazone bond | Breast cancer | MCF-7 BALB/c nude mice | Cui et al., 2017 |
| Hydrazone bond | Breast cancer | MCF-7 Nude mice | Liu et al., 2019 | |
| Calcium phosphate | Anticancer | MGC-803 A549 | Wu et al., 2020 | |
| Eucalyptus oil | PLGA | Skin cancer | HaCaT | Sahu et al., 2017 |

(Continued)

TABLE 1 | Continued

| Active compounds | Response agent | Application | Cell line/animal | References |
|------------------------------------------------------------|---------------------------------|----------------------------------|----------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| Glycyrrhetic acid | Chitosan | Liver cancer | QGY-7703 BALB/c nude mice Wistar rats | Tian et al., 2010 |
| Glycyrrhetic acid | Hydrazone bond | Liver cancer | HepG2 HUVEC | Yan et al., 2018 |
| Physcion | ZIF-8 | Antibacteria | <i>Pseudomonas putida</i> <i>Escherichia coli</i> Engineered <i>Escherichia coli</i> <i>Staphylococcus aureus</i> | Soomro et al., 2019 |
| Myricetin Quercetin Fisetin Luteolin Quercetin | Coordination bond | Antibacteria | — | Bertleff-Zieschang et al., 2017 |
| | PAA | Anticancer | — | Sedghi et al., 2013 |
| | PLGA | Skin cancer | HaCaT A431 | Gupta et al., 2016 |
| | <i>N</i> -acetyl-L-histidine | Anticancer | NIH/3T3 Red blood cell | Wu et al., 2016 |
| | Boronic ester bond | Anticancer | MCF-7 A549 HepG2 IRC mice | Xing et al., 2017 |
| | Polydopamine | Multidrug-resistant colon cancer | HCT-8 HCT-8/TAX | Shao et al., 2019 |
| | Amide bond and ionic bond | Multidrug-resistant | MCF-7 MCF-7/DOX | Liu et al., 2017 |
| | Chitosan | Anticancer | MCF-7 | de Oliveira Pedro et al., 2018 |
| Triptolide | Ionizable imidazole side chains | Hepatocellular carcinoma | Bel-7404 HCCLM3 Old athymic mice | Ling et al., 2014 |
| | Tertiary amine group | Pancreatic cancer | PANC-1 MIA PaCa-2 BALB/C nude mice | Kong et al., 2019 |
| | Silk | Pancreatic cancer | MIA PaCa-2 PANC-1 | Ding et al., 2017 |
| Ursolic acid | Chitosan | Anticancer | HeLa CD-1 female mice | Wang M. et al., 2017 |

(II) by ferric reductase. Fe (II) reacted with dihydroartemisinin on graphene oxide to yield ROS and oxygen/carbon-centered radicals, which then induced the death of EMT6 cells.

Delivery of Baicalein

Baicalein is a flavonoid from *Scutellaria baicalensis* Georgi. which has antioxidant, antiviral, antibacterial, anti-inflammatory, and antiallergic properties (Bie et al., 2017). Baicalein can inhibit the cell cycle; scavenge oxygen radicals; attenuate the activity of mitogen-activated protein kinase, protein kinase B, or mammalian target of rapamycin signaling pathways; and induce apoptosis by activating caspase-9/-3 (Liu et al., 2016). Recently, baicalein was delivered by a pH-responsive cleaved hydrazone bond in transferrin decorated docetaxel baicalein co-loaded solid lipid nanoparticles (Li et al., 2017). A modification based on polyethylene glycol (PEG) provided this system a long

circulation in the body. Also, transferrin could guide delivery of nanoparticles into tumor cells by transferrin receptors. At an acidic condition, the hydrazone bond ruptured, resulting in shedding of the PEG layer from nanoparticles and the targeted release of baicalein.

Delivery of Cinnamaldehyde

Cinnamon is used not only as a spice, but also in TCM. Cinnamaldehyde is an active compound in cinnamon that can induce the apoptosis of tumor cells (Sadeghi et al., 2019). Yoo et al. (2018) used acetal linkages to couple cinnamaldehyde and maltodextrin to fabricate a cinnamaldehyde-maltodextrin nanoparticle. The acetal linkage dissociated in the acidic environment, and cinnamaldehyde and maltodextrin could return to their native states. Zhao et al. (2019a) also used acetal linkages to couple cinnamaldehyde

and dextran in 10-hydroxy camptothecin-cinnamaldehyde nanoparticles. The acetal linkage of cinnamaldehyde was hydrolyzed from dextran at an acidic pH, which broke the nanoparticles into water-soluble fragments, and resulted in rapid dissociation. Ferrocene-loaded poly[(3-phenylprop-2-ene-1,1-diyl)bis(oxy)bis(ethane-2,1-diyl)diacrylate]-co-4,4'-(trimethylene dipiperidine)-copoly(ethylene glycol) micelles have been designed to release ferrocene and cinnamaldehyde rapidly at the site of bacterial infections (which are characterized by a low pH) (Park et al., 2016). Cinnamaldehyde induced the generation of hydrogen peroxide (H_2O_2) and iron in ferrocene and then converted H_2O_2 into highly toxic hydroxyl radicals.

Delivery of Curcumin

Curcumin is a polyphenol extracted from the herb turmeric. It has gained attention worldwide because of its antioxidant, anti-inflammatory, antimicrobial, and antiviral activities (Giordano, 2019). NF development can circumvent the poor bioavailability of curcumin to improve treatment outcome (Adiwidjaja and McLachlan, 2017).

Poly(β -amino ester) (PAE) is a typical pH-responsive biodegradable polymer. PAE has outstanding characteristics, such as positive charges, readily degradable linkages, high biodegradability, and high biocompatibility (Cordeiro et al., 2019). Yu et al. developed poly(ethylene glycol)-poly(lactide)-PAE micelles to deliver curcumin to the breast cancer cell line MCF-7. PAE is insoluble at pH 7.4 and maintains a large micelle structure with a hydrophobic PLA/PAE core (Yu and Zhang, 2014). However, PAE is soluble at pH 6.8 (thanks to protonation of tertiary amino groups) and shrinks the micelle structure to a hydrophobic PLA core. D- α -Tocopheryl PEG 1000-block-PAE (TPGSPA) nanoparticles used in treatment of hepatocellular carcinoma have a similar mechanism of action (Zhang et al., 2017). The tertiary diamine moieties of the PAE core are protonated at low pH so that the hydrophobic curcumin is released from the hydrophilic core-shell structure. In curcumin-pluronic P123-PAE (Cai et al., 2016), P123 is constituted by poly(ethylene oxide)-poly(phenylene oxide)-poly(ethylene oxide) (PEO-PPO-PEO). The PPO/PAE core offers a local hydrophobic microenvironment for curcumin loading, and the hydrophilic PEO shell maintains a large micelle structure at pH 7.4. PAE is protonated and dissolves at weakly acidic pH, making the nanocarrier shrink to be a small micelle structure and release curcumin.

pH-sensitive linkages have also been used for curcumin delivery. At pH 4.5, chains of β -acrylic acid undergo transition to the protonated state. This action lowers their solubility abruptly and isolates them from the aqueous phase and results in rearrangements of the bilayer membrane and curcumin leakage. Fang et al. (2016) coupled a poloxamer (F68) and curcumin by a *cis*-aconitic anhydride linker. In acidic environments, the pH-sensitive *cis*-aconitic anhydride linker of F68-*cis*-curcumin conjugates were cleaved to release curcumin. Chen et al. (2016a) reported a menthone 1,2-glycerol ketal (MGK), which was used in Cur-hyaluronan-histidine-MGK. The ketal moieties of MGK could be degraded in a tumor microenvironment. Also, the imidazole group of histidine, which linked oligomeric hyaluronic

acid (oHA) and MGK, could destroy lysosomal membranes to prevent the drug being degraded in cells. Luan et al. found that an acidic condition (pH < 6.5) could cause breakage of internal linkages in aliphatic amines grafted konjac glucomannan (KGM-g-AH) between a primary amine of octylamine and an aldehyde group and release curcumin. The responsive agent in KGM-g-AH8 micelles was KGM (Luan et al., 2017). Similarly, pH-sensitive hydrazone bonds have been used to deliver curcumin. Polymer oHA-hydrazone bond-folic acid biotin nanomicelles consisting of folic acid, biotin, and cluster of differentiation (CD)44 receptors can mediate the targeting of tumor tissue and cancer stem cells, from which the icariin and curcumin are released into the tumor microenvironment, depending on the pH-sensitive hydrazone bond (Liu et al., 2019).

Eucalyptus from *Eucalyptus robusta* Smith has been developed as a transdermal delivery vehicle for curcumin (Liu and Chang, 2011). Sahu et al. reported a 5-fluorouracil double-walled nanogel (FDWNL) to load eucalyptus with pH-sensitive chitosan. The hydrophilic pendant groups of chitosan (-OH and -NHCOCH₃) and strong ionic attraction between the ionized nanogel and hydrated counter ions caused rapid swelling of the FDWNL to release curcumin at acidic pH (Sahu et al., 2017).

Among metal nanoparticles, ZnO nanoparticles are pH-sensitive nanoplatforms used for curcumin delivery. The nontoxic ZnO nanoparticles are stable at pH ~7, but dissolve and open up the polymer linkages of polymethyl methacrylate-acrylic acid ZnO nanoparticles to release curcumin together with toxic Zn²⁺ at a low pH (~5.4) (Dhivya et al., 2018). Curcumin was also connected to one side of the disulfide-condensed menthone 1,2 glycerol ketal as a redox response prodrug material. The other side of menthone 1,2 glycerol ketal was connected to hyaluronic acid with an ester bond that made pH/redox response. The pH-responsive calcium phosphate shell made this NF broken at pH 5.5 to release curcumin to kill cancer (Chen et al., 2017). Wu et al. also used calcium phosphate as a pH-responsive shell to wrap the curcumin-adsorbed sodium caseinate micelles to improve the stability of curcumin. In the study, Wu et al. found that the calcium phosphate shell covering the sodium caseinate micelles was broken in the acidic stroma outside the tumor cells (Wu et al., 2020).

Delivery of Glycyrrhetic Acid

Glycyrrhetic acid (GA) is extracted from licorice and is modified for targeting of liver cells (Zhu et al., 2019, 2020; Li et al., 2020). In doxorubicin-loaded chitosan/poly(ethylene glycol)-GA nanoparticles, GA increases the affinity for liver cancer cells (Tian et al., 2010). Moreover, protonation of the amino groups of chitosan at an acidic condition and the acid-soluble doxorubicin hydrochloride cause the swelling of nanoparticles and release doxorubicin. In GA-modified chitosan-polyethyleneimine-4-hydrazinobenzoic acid-doxorubicin nanoparticles, GA improves the liver-targeting ability, and the hydrazone bond between doxorubicin and GA-CS-PEI-HBA is broken to release the "payload" in the intracellular environment (pH 4.5–6.5) of tumor cells (Yan et al., 2018).

Delivery of Triptolide and Celastrol

Triptolide and celastrol are contained in *Tripterygium wilfordii*. Triptolide has excellent inhibitory effects in the treatment of pancreatic cancer (Kim et al., 2018). Kong et al. (2019) enhanced the efficacy of triptolide by developing triptolide prodrug-loaded ultra-pH-sensitive micelles (T-UPSMs). After internalization by the endocytic organelles of cancer cells, the pH reached the apparent acid dissociation constant of T-UPSMs due to lysosomal acidification. The tertiary amine groups of T-UPSMs absorbed protons and induced micelle dissociation to elicit immediate drug release as a pH buffer in endosomes/lysosomes. Ding et al. (2017) found that triptolide or celastrol was weakly adsorbed or bonded to silk fibroin nanoparticles. At a low pH, silk loses its overall acidic surface properties and negative net charge, and the balance of the negative charge is shielded at an acidic pH, which destroys aggregates. Ling et al. (2014) developed nanoformulated triptolide nanoparticles for treatment of hepatocellular carcinoma. Internally packed imidazole was employed for pH-sensitive ionization and dispersion. During endosomal maturation, the decrease in pH could lead to the collapse of nanoparticles and triptolide release.

Delivery of Ursolic Acid

Ursolic acid (UA) is present in *Prunella vulgaris L.* but is also abundant in most fruits and vegetables (Yin et al., 2016). UA use has been reported in treatment of cancer (Jaman, 2018; Manayi et al., 2018; Mlala et al., 2019) and some infections (Tohmé et al., 2019). UA has been encapsulated in nanoparticles or liposomes and found to inhibit progression of cervical cancer (Wang M. et al., 2017; Wang S. et al., 2017). Jiang et al. (2017) prepared UA-loaded mesoporous silica nanoparticles and folic acid conjugated chitosan (UA@M-CS-FA) nanoparticles in which the acid-labile amide bond between CS-FA and mesoporous silica nanoparticles was broken in acidic conditions. This action made the chitosan chains swell and opened the mesopores of UA@M-CS-FA nanoparticles, resulting in UA release.

Delivery of Berberine

Berberine is isolated from *Coptis chinensis* and has antibacterial effects. Berberine was shown to markedly increase the survival rate of mice challenged with the bacterial endotoxin lipopolysaccharide (2 EU/mL) (Chu et al., 2014). Chitosan and heparin are ionized and form polyelectrolyte complexes *via* electrostatic interactions at pH 1.2–6.0 to protect berberine from destruction by gastric acids. At pH 7.0, chitosan is deprotonated, and berberine-loaded fucose-conjugated nanoparticles are broken apart to release berberine (Lin et al., 2015). Moreover, berberine as a hydrophobic part was linked to chitosan oligosaccharides with a dithiodipropionic acid linker, and 3,4-dihydroxyphenylpropionic acid as a hydrophilic part was also linked to another end of the chitosan oligosaccharides to form a polymer monomer. The positively charged 3,4-dihydroxyphenylpropionic acid attracted the negatively charged hyaluronic acid to form an oHA-3-carboxyphenylboronic acid shell and encapsulate curcumin. In the acidic microenvironment of tumor, the exposed hyaluronic acid specifically binds to the CD44 receptor, and the micelles are endocytosed by the

cells and undergo charge reversal. The high concentration of glutathione (GSH) in tumor cells hydrolyzes the disulfide bonds of dithiodipropionic acid; the micelles collapse and release berberine and curcumin (Fang et al., 2019b).

Delivery of Physcion

Usually, zeolitic imidazolate framework-8 (ZIF-8) is fabricated using zinc ions and 2-methylimidazolate. ZIF-8 has high porosity, good structural regularity and tunability, adjustable surface functionality, and intrinsic pH-induced biodegradability (Gao et al., 2019b). Soomro et al. (2019) developed physcion@ZIF-8 to deliver the physcion present in rhubarb. In acidic conditions, the coordination linkage between zinc and imidazolate was broken, whereas the imidazolate was protonated, resulting in physcion release from ZIF-8.

Delivery of Quercetin

Quercetin from *Hypericum ascyron L.* has been reported to be beneficial for cardiovascular disease (Patel et al., 2018). In recent years, the nanotechnology transformation of quercetin has revealed that quercetin has considerable effects against tumors (Vinayak, 2019). Bertleff-Zieschang et al. reported quercetin/Fe (III) nanoparticles as potential antibacterial NFs. In that work, formation of a quercetin/Fe (III) network was pH-dependent based on coordination between a flavonoid ligand and Fe (III). At an acidic pH, quercetin/Fe (III) capsules were disassembled readily (Bertleff-Zieschang et al., 2017). Furthermore, amphiphilic pH-responsive 8-arm- and 12-arm-dendritic polyacrylic acid block copolymers were synthesized for quercetin loading. *In vitro* release experiments showed that both of these new materials achieved complete release faster at pH 5.0 than at pH 7.4. But the 12-arm dendritic polyacrylic acid polymer blocks copolymer release quercetin faster than the 8-arm-one (Sedghi et al., 2013). In a self-assembled micelle of *N*-acetyl-histidine-phosphocholine-chitosan conjugate, histidine was a pH-responsive molecule because of its imidazole group. At pH ≤ 6.0 , the micelles swelled and ruptured to release the encapsulated quercetin due to the protonation of the imidazole group (Wu et al., 2016).

Redox-Responsive NFs

GSH depletion promotes cancer cell death through processes such as apoptosis, necroptosis, autophagy, and ferroptosis (Lv et al., 2019). GSH deficiency, or a decrease in the ratio of GSH and glutathione disulfide (GSSG), leads to an increased susceptibility to oxidative stress implicated in the progression of cancer cells (Traverso et al., 2013). The GSH:GSSG ratio, as the major pool of thiol groups, is a key factor in the antioxidative capacity of cells. GSH is an ideal and omnipresent internal stimulus for rapid degradation of disulfide linkages (Zhang et al., 2018b). As shown in **Table 2**, there are many applications of disulfide bonds in redox-responsive delivery of TCM agents.

Wang B. et al. (2019) designed quercetin–dithiodipropionic acid–oHA–mannose–ferulic acid “nano-dandelions” for synchronous delivery of curcumin and baicalein. This was achieved by using the nano-dandelions as reduction-sensitive amphiphilic carriers. The coated oHA targeted CD44 receptors

TABLE 2 | Redox-responsive nanoformulations in active compounds from TCM.

| Active compounds | Response agent | Application | Cell line/animal | References |
|---------------------------------------------------------------|-----------------------------------------------|---------------------|------------------------------------------------|----------------------|
| Eucalyptus oil | Disulfide bond in 3,30-dithiodipropionic acid | Lung cancer | A549 RAW264.7 A549 bearing mice | Wang B. et al., 2019 |
| Baicalin Curcumin Quercetin Ferulic acid Curcumin | Dithiodipropionic acid–Cur | Anticancer | HepG2 A549 tumor-bearing mice | Wang K. et al., 2018 |
| Curcumin | Cystamine | Glioma | G422 | Tian et al., 2018 |
| | Disulfide bond | Anticancer | MDA-MB-231 | Dong et al., 2018 |
| | Disulfide bond | Anticancer | HepG2 BALB/c mice | Zhang et al., 2019 |
| Glycyrrhetic acid | PLGA | Lung cancer | Beas2B A549 NCI-H226 | Zhang et al., 2020b |
| Homoharringtonine | PLGA | Lung cancer | Beas2B A549 NCI-H226 BALB/c-nude mice | Zhang et al., 2020 |
| Oridonin | Oxalate ester bond | Colon carcinoma | CT26 | Ou et al., 2019 |
| Quercetin | Disulfide bond | Multidrug-resistant | 4T1 L-02 BALB/C mice | Chen et al., 2018 |

and could facilitate uptake of nano-dandelions in tumor locations. Mannose-targeting CD206 receptors could be engulfed readily by tumor-associated macrophages. The S-S linkage in 3,30-dithiodipropionic acid connecting the hydrophobic and hydrophilic parts could be broken by the high concentration of GSH within tumor cells, which facilitated release of curcumin and baicalein.

Wang K. et al. (2018) developed distearoyl phosphatidyl ethanolamine derivatized PEG-modified nano-echinus materials. Dithiodipropionic acid–curcumin (S-S-Cur) was chemically conjugated onto the side chain of the conjugated GA-oHA (GA-HA) to generate an amphiphilic polymeric prodrug of curcumin (GA-HA-S-S-Cur). HA targeted CD44 receptors on the surface of tumor cells, and the breaking of disulfide bonds by a high concentration of GSH in a tumor environment led to disassembly of nano-echinus materials, and then released curcumin. Tian et al. (2018) developed HA-S-S-CUR micelles for glioma treatment, in which the disulfide bond of cystamine linked HA (hydrophilic group) and curcumin (hydrophobic group). Reductive cleavage of the disulfide bond by GSH in glioma cells caused instability of the hydrophobic core, resulting in micelle degradation and curcumin release.

In alendronate-oHA-S-S-curcumin micelles (Dong et al., 2018), a disulfide bond combines hydrophobic curcumin with hydrophilic oHA and alendronate to form micelles in water. These micelles fracture under a reducing environment to release curcumin. Cleavage of the disulfide bonds of PEGylated prodrug nanomicelles (Zhang et al., 2019) can transfer these nanomicelles into hydrophilic curcumin-mercapto. This action accelerates

hydrolysis of the adjoining ester bond and releases curcumin from PEGylated prodrug nanomicelles.

Recently, synthetically designed polymers containing disulfide bonds have been used to deliver TCM-active compounds. Homoharringtonine (HHT)-loaded poly(lactic-co-glycolic acid)-SS-PEG (Zhang et al., 2020a) is an epidermal growth factor receptor (EGFR) aptamer-modified PLGA targeted to the EGFR (which shows high expression in lung cancer cells). The drug is delivered into the cytoplasm *via* receptor-mediated endocytosis. The disulfide bonds of PLGA are broken by GSH in lung cancer cells.

Additionally, ester bonds have also been used in the development of redox-responsive NFs. In the podophyllotoxin (POD) delivery, PODPEG nanoparticles (Ou et al., 2019) are formed by PEG and POD with oxalate ester bond bridges. The latter are cleaved in the presence of H₂O₂ to release the drug.

EXTERNAL STIMULUS-RESPONSIVE NFs

External stimuli-responsive NFs for delivery of active compounds from TCM are mainly including magnetic, light, and thermal response as shown in Table 3.

Magnetic-Responsive NFs for Delivery of Active Compounds From TCM

Magnetic-responsive NFs can be used to monitor tumors *in vivo* by noninvasive magnetic resonance imaging (MRI) (Kang et al., 2017). In this way, they can deliver chemotherapy drugs, small-molecule agents, photosensitizers, and small interfering

TABLE 3 | External stimulus-responsive nanoformulations in active compounds from TCM.

| Response method | Active compounds | Response agent | Application | Cell line/animal | References |
|-----------------|--------------------|---------------------------------------------------------------------|---------------------------------------|-----------------------------------------------------------------------------|------------------------------|
| Magnetic | Artemisinin | Magnetic iron oxide | Breast cancer | BALB/c mice | Gharib et al., 2015 |
| | Dihydroartemisinin | Fe ₃ O ₄ nanoparticle | Head and neck squamous cell carcinoma | A549 HeLa HeLa tumor-bearing nude mice | Li et al., 2019a |
| | | Fe ₃ O ₄ nanoparticle | Myeloid leukemia | K562 HL-60 SHI-1 NB4 BALB/c male mice | Chen et al., 2016b |
| | Quercetin | γ-Fe ₂ O ₃ | Glioma | C6 | Cruz Dos Santos et al., 2019 |
| | Stevioside | Fe ₃ O ₄ | Lung cancer | A549 | Gupta and Sharma, 2019 |
| Thermal | Curcumin | Poly(<i>N</i> -isopropylacrylamide) | Anticancer | L929 KB MCF-7 PC3 | Rejinold et al., 2011 |
| | Honokiol | (PEG-PCL-PEG, PECE) hydrogel | Malignant pleural effusion | LL2 Red blood cell C57B/6 mice | Fang et al., 2009 |
| Light | Artesunate | Covalent bond between carboxylic groups and amino groups of nGO-PEG | Liver cancer | HepG2 4T1 tumor-bearing mice | Pang et al., 2017 |
| | Aloe emodin | Aloe emodin | Gastric cancer | SGC-7901 | Li et al., 2016 |
| | Hypericin | Hypericin | Glioma | U87-MG | Huntosova et al., 2012 |
| | | Hypericin | Colon carcinoma Antibacterial | Caco-2 HT-29 <i>E. faecalis</i> <i>E. coli</i> <i>S. aureus</i> | Montanha et al., 2017 |
| | Hypericin | Hypericin | Ovarian cancer | A2780N A2780N tumor-bearing nude mouse | Han et al., 2020 |
| Quercetin | Gold nanocages | Multidrug-resistant breast cancer | MCF-7/ADR | Zhang et al., 2018c | |
| Tetrandrine | Fe-GA | Anticancer | 4T1 U87MG | Wang K. et al., 2019 | |

RNA molecules (Zhu et al., 2017). Iron oxide nanoparticles are essential in magnetic-responsive NFs (Vangijzegem et al., 2019).

Gharib et al. created artemisinin- and transferrin-loaded magnetic nanoliposomes coated with iron oxide. The external magnet achieved high concentrations of artemisinin and transferrin in tumors to enhance the antitumor effect of artemisinin in BALB/c mice (Gharib et al., 2015). HHT- Fe₃O₄ magnetic nanoparticles were designed to deliver the HHT to tumor sites. HHT inhibited the synthesis of the short-lived protein Mcl-1 by targeting the A-site cleft of eukaryotic ribosomes (Chen et al., 2016b).

Dihydroartemisinin-MLP nanoliposomes were created using Fe₃O₄ nanoparticles. The negative charge of

dihydroartemisinin-MLPs nanoliposomes under the action of a magnetic field delivered dihydroartemisinin with nonspecific binding to plasma proteins (Li et al., 2019a). Tetrandrine-Fe₃O₄-PLGA nanoparticles were used to direct tetrandrine to specific sites upon manipulation by an external magnetic field to increase the tetrandrine concentration. Tetrandrine is derived from *Stephania tetrandra* and is an active compound of a TCM called “Fangji” (Wang K. et al., 2019).

In the design of magnetic-responsive nanoliposomes to deliver quercetin, quercetin was not only loaded as an antitumor flavonoid drug and also has strong antioxidant properties to prevent the nanomagnetic liposomes from being oxidized. However, the incorporation of quercetin might weaken the magnetic properties of the nanoliposomes, and it was necessary

to precisely control the ratio of quercetin to ensure that the superparamagnetism of the magnetic liposomes was maintained (Cruz Dos Santos et al., 2019).

Light-Responsive NFs for Delivery of Active Compounds From TCM

NFs can be activated by light (visible, ultraviolet, infrared) for using in photodynamic imaging, photodynamic therapy (PDT) or photothermal therapy (PTT) (Rkein, 2014; Chen and Zhao, 2018). Light-responsive agents (“photosensitizers”) play an important part in such light-responsive NFs (Reeßing and Szymanski, 2017).

Traditional photosensitizers and TCM agents can be co-encapsulated, or a TCM agent can be encapsulated in light-responsive inorganic/organic nanoparticles. Moreover, some active compounds of TCM can be used as photosensitizers to carry out PDT or PTT after light activation.

An artesunate-modified PEGylated nanographene oxide (nGO-PEG-ARS) (Pang et al., 2017) delivered artesunate to liver cancer with the light-responsive agent. The light responsive agent was a covalent bond between carboxylic groups and amino groups of nGO-PEG. Near-infrared irradiation triggered the artesunate loaded on nGO-PEG to produce nitric oxide and peroxynitrite groups to achieve a synergistic chemophotothermal anticancer effect.

In Fe-gallic acid-PEG coordination polymer-based nanoparticles, ultrasmall (5 nm) Fe-gallic acid nanoparticles were formed by mixing FeCl₃ solution and gallic acid solution (Jin et al., 2017). Surface modification of PEG increased its passive accumulation in tumor cells. Also, the temperature was increased by 20°C after laser irradiation for 5 min (808-nm laser at 0.8 W cm²).

In the treatment of gastric cancer, Li et al. (2016) used aloe emodin to fabricate aloe emodin nanoliposomes for transfection of the r-caspase-3 gene and PDT. Moreover, hypericin is an excellent photosensitizer in hypericin-low-density lipoprotein-dextran complexes for glioma treatment. In these complexes, dextran is modified on the surface of low-density lipoprotein particles, which reduces the interaction of low-density lipoprotein with other serum constituents to prevent hypericin redistribution to other free lipoproteins (Huntosova et al., 2012).

Also, single-walled carbon nanohorn-hypericin has been shown to improve the water solubility, photostability, and therapeutic effects of hypericin and to protect it from light degradation. Single-walled carbon nanohorn-hypericin can simultaneously generate sufficient ROS and hyperthermia upon light irradiation at 590 and 808 nm (Gao et al., 2019a).

Thermal-Responsive NFs for Delivery of Active Compounds From TCM

In thermal-responsive chitosan-g-poly(*N*-isopropylacrylamide) co-polymeric nanoparticles, the polymer-polymer interaction of poly(*N*-isopropylacrylamide) is greater than the polymer-curcumin interaction, whereas the hydrogen bond is weakened

at a lower critical solution temperature, so curcumin molecules can escape from the entrapped polymer matrices (Rejinold et al., 2011). Honokiol hydrogel (Fang et al., 2009) loads honokiol as a free-flowing sol at room temperature or below the critical gelation temperature. Honokiol can become a gel at body temperature and remain *in situ* for a long time to reduce the burst release of honokiol.

MULTIPLE-RESPONSIVE NFs FOR DELIVERY OF ACTIVE COMPOUNDS FROM TCM

Multiple-responsive NFs usually have two or more different responsive functions and modes. The combination of multiple responsive modes can overcome the shortcomings of a single responsive mode to achieve targeted delivery of drugs. The main multiple-responsive NFs are shown in **Table 4**.

Dual Internal-Responsive NFs

For targeted delivery of cinnamaldehyde, quinone methide-cinnamaldehyde (Noh et al., 2015) was prepared as a dual-responsive NF combining a redox response and pH response. The H₂O₂-sensitive boronate linkage and acid-sensitive acetal linkage were oxidized rapidly to release quinone methide to abrogate GSH. Also, the acetal linkage degraded in acidic tumor environments to release ROS-generating cinnamaldehyde, which killed DU145 and SW620 cells efficiently *in vitro* and *in vivo*. The same type of response mode was used in tumor-specific enhanced oxidative stress polymer conjugate (Ma et al., 2020) delivery of cinnamaldehyde on CT26 and 4T1 cells. The acidic condition accelerated hydrolysis of acetal linkages in phenylboronic acid containing cinnamaldehyde derivatives, and H₂O₂ facilitated detachment of boric acid groups and intramolecular rearrangement to produce quinone methide and further accelerated the hydrolysis of acetal linkages and cinnamaldehyde release.

Celastrol was delivered to desmoplastic melanoma cells by aminoethylanisamide-polymer-disulfide bond nanoparticles (Liu et al., 2018). In an acidic tumor microenvironment, tertiary amines of mitoxantrone and celastrol copolymer were protonated and reversed the zeta potential from a negative charge to a positive charge, thereby attracting negatively charged cell membranes. Also, the disulfide bond was broken in the presence of GSH, resulting in an increased particle size.

Disulfide bonds and β-thiopropionate linkages endowed a redox response and pH response of T7-peptide-S-S-nanoparticles (Li et al., 2019b) for POD delivery. Disulfide bonds were disassociated by a high concentration of GSH, and the β-thiopropionate linkage was broken by an acidic environment, and then POD was released rapidly. Massaro et al. replaced the keto group of curcumin with a pH-responsive imine group and used a carbon chain with a disulfide bond to connect the silicon on halloysite nanotubes to prepare a pH/redox responsive curcumin prodrug. In the different pH and 10 mM GSH

TABLE 4 | Multistimulus-responsive nanoformulations in active compounds from TCM.

| Response method | Active compounds | Response agent | Application | Cell line/animal | Reference |
|----------------------|------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|-------------------------------------------------------------------|------------------------|
| pH and redox | Berberine | pH: vitamin B ₆ redox: dithiodipropionic acid | Anticancer | HepG2 HepG2 tumor-bearing nude mice | Fang et al., 2019a |
| | Berberine and curcumin | pH: borate ester bond redox: dithiodipropionic acid | Anticancer | PANC-1 PANC-1 tumor-bearing nude mice | Fang et al., 2019b |
| | Celastrol | pH: tertiary amines Redox: disulfide bond | Desmoplastic melanoma (DM) | BPD6 NIH 3T3 DM tumor-bearing mice | Liu et al., 2018 |
| | Cinnamaldehyde | Acetal and quinone methide | Colon cancer Breast cancer | CT26 4T1 CT26 tumor-bearing mice | Ma et al., 2020 |
| | | | Prostate cancer Colon cancer | DU145 SW620 NIH3T3 BALB/c nude mice | Noh et al., 2015 |
| | Curcumin | Redox: dithiodipropionic acid pH: hydrazone pH: imine bond Redox: disulfide bond | Multidrug-resistant | MCF-7/ADR | Wang Y. et al., 2018 |
| | | | Anticancer | Hep3B HA22T/VGH | Massaro et al., 2016 |
| | | | Anticancer | MCF-7 A549 MDA-MB-231 BALB/c mice | Chen et al., 2017 |
| Podophyllotoxin | Redox: disulfide bond pH: disulfide bond and b-thiopropionate | Breast cancer | MCF-7 MCF-7/ADR A549 A549/PTX MCF-7/ADR tumor-bearing nude mice | Li et al., 2019b | |
| Magnetic and pH | Artemisinin | Magnetic: Fe ₃ O ₄ @C pH: MIL-100(Fe) | Anticancer | HeLa A549 BALB/c nude mice | Li et al., 2019a |
| | Berberine | Magnetic: Fe ₃ O ₄ head pH: carboxylate functional group modified on the surface and pore of silica rod | Hepatocellular carcinoma | HepG2 HL-7702 | Wang M. et al., 2017 |
| | Berberine and doxorubicin | Magnetic: Janus M-MSNs pH: Janus M-MSNs | Hepatocellular carcinoma | H22 HepG2 NIH-3T3 HL-7702 H22 tumor-bearing ICR mice | Zhang et al., 2019 |
| | Quercetin | Magnetic: Fe ₃ O ₄ @SiO ₂ (FITC) pH: imine and acetal | Multidrug-resistant | A549 A549/DOX | Daglioglu, 2017 |
| Magnetic and thermal | Stevioside | Fe ₃ O ₄ | Glioma | C6 | Gupta and Sharma, 2019 |
| Thermal and pH | Cinnamaldehyde | Thermal: glycine and Pluronicpolymer pH: Fe ₃ O ₄ nanoparticles | Breast cancer | MCF7 MDAMB231 | Wani et al., 2014 |
| | Berberine and evodiamine | Thermo: <i>N</i> -isopropylacrylamide pH: methacrylic acid | Anticancer | HepG-2 HCT-8 HeLa HUVEC EMT-6 tumor-bearing nude mice | Feng et al., 2019 |

(Continued)

TABLE 4 | Continued

| Response method | Active compounds | Response agent | Application | Cell line/animal | Reference |
|---------------------------------------|------------------|-----------------------------------------------------------------------------------------------------------------------------|----------------|-----------------------------------------------------|---------------------|
| Light and redox | Curcumin | Zinc phthalocyanine and curcumin | Melanoma tumor | B16F10 mouse | Zhang et al., 2020b |
| Magnetic and light and thermal and pH | Artemisinin | Magnetic and photothermal: PB MOF Magnetic and PH: MIL-100(Fe) MOF | Anticancer | HeLa BALB/c nude mice | Li et al., 2019a |
| Magnetic and light and thermal | Gallic acid | Magnetic and thermal: SPIONs Light: ICG | Anticancer | MCF7 HT-29 4T1 tumor-bearing mice | Jin et al., 2017 |
| Light and thermal and pH | Quercetin | pH: poly(ethylene glycol) _{5k} -poly(β -aminoesters) _{10k} Light and thermal: Ag ₂ S | Anticancer | HepG-2 HL-7702 HepG-2 tumor-bearing nude mice | Zhong et al., 2020 |

environment, it showed a good release behavior of curcumin (Massaro et al., 2016).

External/Internal-Responsive NFs

Multiple-responsive NFs with both external and internal responses are conducive to targeted release of TCM agents at lesion sites. As stated above, often magnetically responsive delivery is combined with other responsive modes for higher efficiency of drug delivery.

A multiple-responsive NF called Prussian blue-iron carboxylate dual-metal organic frameworks [PB@MIL-100(Fe)dual-MOFs] can deliver artemisinin to HeLa cells through integrated magnetic, light and pH responses (Wang et al., 2016b). The inner Prussian blue MOFs and outer MIL-100(Fe) MOFs serve as MRI contrast agents. Under the illumination of an 808-nm near-infrared laser, the inner Prussian blue MOF induces hyperthermia by converting light energy to heat. The MIL-100(Fe) MOF can collapse in acidic environments to release artemisinin.

Dihydroartemisinin was delivered using a strategy combining a magnetic response and pH response. Fe₃O₄@C@MIL-100(Fe) nanoparticles were designed by Wang and colleagues (Wang et al., 2016a). Fe₃O₄@C nanoparticles were magnetic targeting, and carbon dots were two-photon fluorescence imaging agents. MIL-100(Fe) MOFs degraded and released dihydroartemisinin and Fe (III) ions in acidic conditions. When the pH within an endosome decreased, Fe³⁺ reduced to Fe²⁺ by ferric reductase and other reductive molecules within cells.

Magnetic field-induced endocytosis and pH-responsive drug release of berberine-loaded Fe₃O₄-mSiO₂ nanoparticles were exhibited in hepatocellular-carcinoma treatment because the pH-responsive carboxylate functional group was modified on the surface and pores of silica rods and the magnetic-responsive Fe₃O₄ head (Wang Z. et al., 2017). In stevioside (STE)-MNP, STE reduced the size of Fe₃O₄ nanoparticles to control magnetic properties and aligned rapidly with the external magnetic field (Gupta and Sharma, 2019). The carbohydrate nature of STE enhanced the interaction between STE-MNP and C6 cells. STE-MNP aggregated as cluster-like formations in the glioma site to enhance hyperthermia.

The magnetic-responsive agents, superparamagnetic iron oxide nanoparticles (SPIONs), and a light-responsive agent, indocyanine green (ICG), were combined in SPIONs-GA-ICG (Ghorbani et al., 2018). The SPIONs produced hyperthermia; gallic acid was oxidized and bonded to ICG by free-radical production, and gallic acid also acted as a biological coating for ICG-loaded SPIONs.

A thermal- and pH-responsive NF was used as a cinnamaldehyde-delivery platform with glycine and a pluronic polymer. Cinnamaldehyde tagged Fe₃O₄ nanoparticles capped with glycine and pluronic polymer nanoparticles increased the temperature to 41.6°C within 1 min after radiofrequency pulses of 20 MHz (Wani et al., 2014). Also, the ionic interaction between the free aldehyde group of cinnamaldehyde and the liberated protons under acidic conditions delivered cinnamaldehyde rapidly from the nanoparticles.

SUMMARY

Most of the active compounds extracted from TCM are small molecules. They have unfavorable pharmacokinetics and suboptimal biodistribution (e.g., prominent accumulation in multiple healthy organs) (Golombek et al., 2018). Through nanotechnology modification, drug molecules have a better EPR effect to increase the accumulation of drugs at lesion sites (Maeda, 2017). Thus, several types of nanodelivery system have been employed to improve the clinical outcome of the active compounds in TCM formulations: nanoparticles, liposomes, micelles, nanocapsules, and nanoemulsions (Ma et al., 2019).

Stimuli-responsive NFs can release drugs under internal and external stimuli. We reviewed the applications of stimuli-responsive NFs used commonly in the delivery of active compounds from TCM.

Four types of pH-responsive agents can be classified. The first type is inorganic material. Iron-containing nanoparticles play a key part in the pH-responsive delivery of artemisinin. The endoperoxide linkages (R-O-O-R') in artemisinin can be cleaved with intracellular Fe²⁺ to generate toxic radicals to kill cancer cells and treat malaria (Asano and Iwahashi, 2017; Ding

et al., 2018). Fe_3O_4 dissociates rapidly at low pH in lysosomes and transforms to Fe^{2+} (Bhaw-Luximon and Jhurry, 2017). Simultaneously, Fe_3O_4 is also a magnetic agent that can induce a magnetic response. In $\text{Fe}_3\text{O}_4@ \text{MnSiO}_3$ -FA nanospheres, Mn^{2+} has the same function as Fe^{2+} (Chen et al., 2015). ZIF-8 is a well-known pH-sensitive imidazole derivative (Chen et al., 2018; Gao et al., 2019b) composed of Zn^{2+} coordinated by four imidazolate rings (Mateo et al., 2019). ZnO nanoparticles are also degraded readily to Zn^{2+} (Hahn and Ahmad, 2012). ZnO is stable at pH ~ 7 , but dissolves rapidly at pH < 6 (Dhivya et al., 2018). The second type of pH-responsive material is a natural product with pH instability. Chitosan is a commonly used drug-delivery agent with special amphiphilic characteristics that enables “packaging” of a poorly soluble drug in water phases (Younes, 2015). Its pH-responsive function is attributed mainly to protonation of amino groups in acidic conditions, which make chitosan hydrogels swell rapidly and release the loaded drug. The third type of pH-responsive materials is artificial polymers such as PAE, PAGA, and PLGA. The fourth (and most common) types of pH-responsive material used in the delivery of active compounds from TCM are amine bonds and hydrazone bonds. They are linked ingeniously with the active agent from the TCM and the matrix of NFs until they encounter an acidic microenvironment. This strategy protects the drug from leaking prematurely in the circulation and promotes the targeted release of the drug at the lesion site.

Redox-responsive NFs of active compounds from TCM are dependent mainly on modification of disulfide bonds. Metabolic imbalances in tumor cells produce high levels of GSH, which can cleave disulfide bonds to release the loaded agent in target cells. In addition, pathogen infection induces an inflammatory reaction to increase H_2O_2 levels in infected tissues, which are prone to redox reactions.

In light-responsive NFs, besides the many chemical photosensitizers, several naturally active ingredients of TCM are used as photosensitizers in PDT, including curcumin (Tao et al., 2019b), hypericin (Lin et al., 2016; Li et al., 2018b; Zhang et al., 2018a), and aloe emodin. These active compounds from TCM have been shown to be useful in PDT or PTT in multiple studies.

Some active substances from TCM have been used for nanotargeted delivery. In doxorubicin-loaded CTS/PEG-GA

nanoparticles (Tian et al., 2010), GA can target GA receptors on liver cancer cells. Also, GA receptors have been shown to be useful as liver-cancer targets in GA NFs (Sun et al., 2017). Similarly, in quercetin/Fe (III) (Bertleff-Zieschang et al., 2017) delivery, quercetin (as a phenolic compound) can form a complex organic-inorganic network with iron and gallic acid, and STE contributes to regulation of iron ions to form an “ideal” size of magnetic nanoparticles. Some active compounds from TCM contain both water-soluble sugar groups and water-insoluble aglycones, which form biocompatible NFs readily by self-assembly. Also, most active compounds from TCM have multiple active binding sites in biological tissues.

In stimuli-responsive NFs, internal stimulus-responsive NFs have great advantages in specifically releasing active compounds from TCM to the target site, subsequently increasing their therapeutic efficacy and decreasing the side effects. However, it is very difficult to artificially control the amounts and time of drug release from internal stimulus-responsive NFs. External stimulus-responsive NFs have advantageous properties in artificial control of drug release because they could respond to external light and magnetic energy. Therefore, we could regulate light and magnetic energy to control the release amounts and time of drugs from these NFs.

The information provided above indicates that smart responsive NFs hold great promise in targeted delivery of active compounds from TCM. However, the confirmed evidences are mainly from *in vitro* and *in vivo* experimental studies. Few clinical trials are investigated on smart responsive NFs as the targeted carriers for delivering active compounds from TCM. The main challenges are the complexity of smart responsive NFs such as tedious preparation, complicated characterization, biosafety of nanoparticle materials, and uncertainty of the *in vivo* fate of NFs. Thus, further exploring and addressing the above problem should be urgent tasks for translating smart responsive NFs as targeted delivery carriers of active compounds from TCM to clinical application.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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