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Review

Challenges and strategies in progress of drug delivery system for traditional Chinese medicine *Salviae Miltiorrhizae Radix* et *Rhizoma* (Danshen)

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ABSTRACT

Traditional Chinese medicines (TCMs), with a history of thousands of years, are widely used clinically with effective treatment. However, the drug delivery systems (DDSs) for TCMs remains major challenges due to the characteristics of multi-components including alkaloids, flavones, anthraquinones, glycosides, proteins, volatile oils and other types. Therefore, the novel preparations and technology of modern pharmaceutics is introduced to improve TCM therapeutic effects due to instability and low bioavailability of active ingredients. *Salviae Miltiorrhizae Radix* et *Rhizoma*, the radix and rhizomes of *Salvia miltiorrhiza* Bunge (Danshen in Chinese), is a well known Chinese herbal medicine for protecting the cardiovascular system, with active ingredients mainly including lipophilic tanshinones and hydrophilic salvianolic acids. In this review, this drug is taken as an example to present challenges and strategies in progress of DDSs for TCMs. This review would also summary the characteristics of active ingredients in it including physicochemical properties and pharmacological effects. The purpose of this review is to provide inspirations and ideas for the DDSs designed from TCMs by summarizing the advances on DDSs for both single- and multi-component from Danshen.

Contents

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1. Introduction

Traditional Chinese medicines (TCM) comprise medicinal products from plants, animals and minerals. TCMs exert strong therapeutic actions based on multi-components and multi-targets and have been used in China for thousands of years to prevent and treat kinds of diseases. Active constituents in TCMs include alkaloids, flavones, anthraquinones, glycosides, proteins, volatile oils and other types (Li, Feng, Hong, Lin, & Shen, 2018). Different physicochemical properties contribute to pharmacodynamics differences of active constituents in TCMs. In order to improve bioavailability and efficacy of TCMs, drug delivery systems (DDSs) such as sustained/controlled release, or targeted platform based on nanotechnology are introduced and combined with TCMs. However, the design, preparation and evaluation of DDSs for TCMs are more suitable for single constituent (Xu et al., 2015). More attention should be paid on multi-constituents in TCMs preparations.

Salviae Miltiorrhizae Radix et *Rhizoma* (originated from *Salvia miltiorrhiza* Bunge, Labiatae family), also known as Danshen in Chinese, has been widely used in clinics for treatment of cardiovascular diseases such as coronary heart disease (CHD), angina pectoris, myocardial infarction and atherosclerosis (Li, Xu, & Liu, 2018). Danshen is also applied in anti-cancer therapy or used as the supplementary treatment for tumor diseases (Chen et al., 2018; Kim et al., 2019). In addition, it shows promising therapeutic effects on inflammatory diseases (Luo et al., 2019), Alzheimer' disease (AD) and other central nervous system diseases (Maione et al., 2018), fibrotic diseases (Liua et al., 2019), etc. Up to now, more than 30 hydrophobic ingredients with diterpene chinone structures were successfully identified, such as tanshinones I–VI (Tans I–VI), cryptotanshinone (CPT), dihydrotanshinone I (DHT I) and isotanshinones. More than 50 hydrophilic ingredients with phenolic acid structure, for instance of salvianolic acids A–K (Sals A–K), danshensu (DSS, also known as salvianic acid A, SAA), protocatechuic aldehyde (PD) and rosmarinic acid (RA) were also detected in Danshen (Li et al., 2018; Wang, Morris-Natschke, & Lee, 2007; Pang et al., 2016). No matter single components or water/ethanol extracts from Danshen exhibited pharmacological effects, thus utilizing potential agents for clinical treatment from TCMs is quite necessary.

Formulations of Danshen like decoctions, injections, tablets and capsules have displayed excellent clinical effects. Compound Danshen Dripping Pill composed of Danshen, *Notoginseng Radix* et *Rhizoma* (Sanqi in Chinese) and Borneolum (Bingpian in Chinese) (Luo, Song, Yang, Xu, & Chen, 2015), is the first Chinese patent drug completed Phase III clinical trial in the United States (https://www.clinicaltrials.gov/ct2/show/NCT03270787). However, pharmacokinetic studies on active constituents from Danshen suggested that oral administration of major components (DSS and Tan IIA) were absorbed rapidly (Zhang et al., 2004), which showed extremely low bioavailability (Zhou, Zuo, & Chow, 2013). Bioavailability and biological effects of Danshen are affected by intestinal and liver First Pass Effect, fast distribution metabolism in body, short duration of action (Lai, Liu, Li, & Cai, 2011). Researchers have devoted themselves to exploring novel DDSs for TCMs, such as liposomes, emulsions, micelles, nanoparticles and others (Fig. 1). In this review, we discuss about the active ingredients including their pharmacological effects and summarize the DDSs for single- and multi-components from Danshen. The challenges and strategies in progress of DDS for Danshen are further reviewed, and it may provide inspirations for researchers to design the DDSs of TCMs in the future.

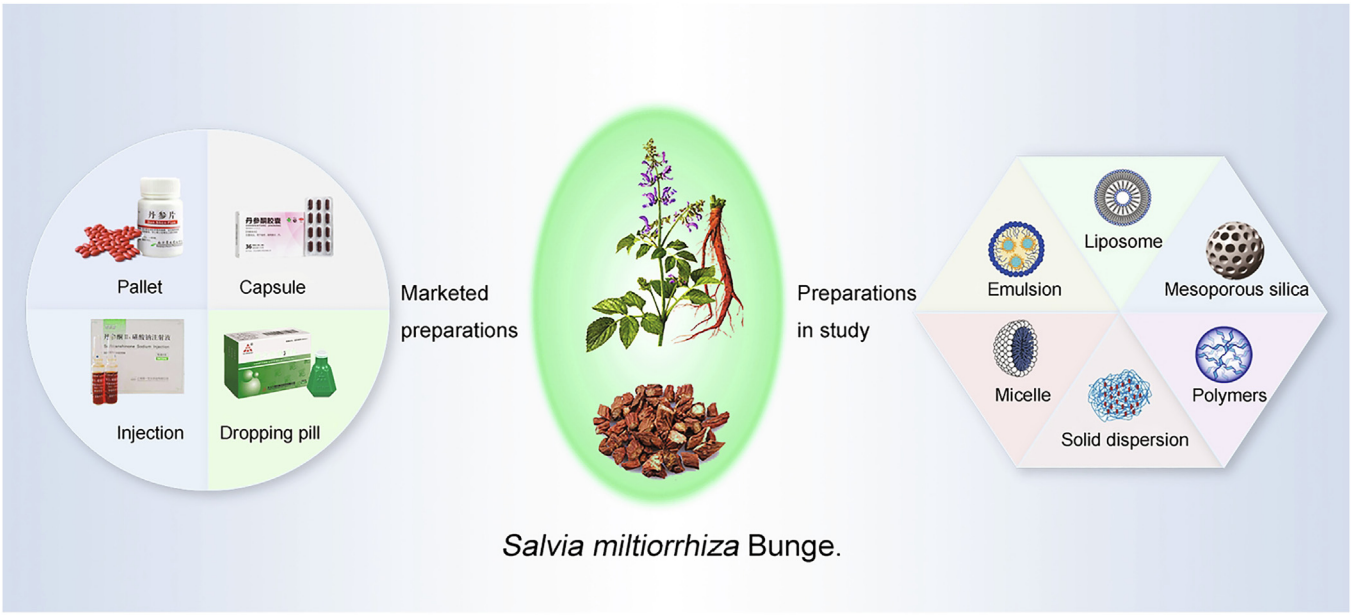
2. Active ingredients in Danshen

The active ingredients in Danshen are mainly classified into two types, hydrophilic and hydrophobic components. Hydrophilic components are mainly phenolic acids, and hydrophobic compounds are mainly tanshinones (TANs). Lipophilic constituents Tan I, Tan IIA, tanshinone IIB, CPT, DHT I, etc. as well as hydrophilic constituents DSS, Sals A and B, PD, etc. contribute to the protective effects on cardiovascular system of Danshen (Li et al., 2018). In addition to cardiovascular protective effects, Danshen also exhibited other pharmacological effects, such as antioxidative, neuroprotective, antifibrotic, anti-inflammatory and antineoplastic activities (Ren, Fu, Nile, Zhang, & Kai, 2019).

2.1. Protective effects for cardiovascular system

Both hydrophilic and hydrophobic ingredients from Danshen exhibited cardiovascular protective effects. Preparations made from Danshen like Compound Danshen Dripping Pills, Fufang Danshen Tablets, Danhong Injection, etc. are widely used in clinic to treat CHD, angina pectoris and myocardial infarction. The cardioprotective effect and pharmacological mechanisms of single component and total aqueous/ethanol extracts have been reported. DSS, Sal B, RA, DHT I, CPT and Tan IIA could protect against cardiovascular diseases through various mechanisms.

Elevated plasma total homocysteine (Hcy) level in cardiovascular diseases was significantly lowered via increasing transsulphuration pathway and regulation of Hcy metabolism when treated with DSS (Cao et al., 2009; Gao, Siu, Chan, & Lai, 2017).



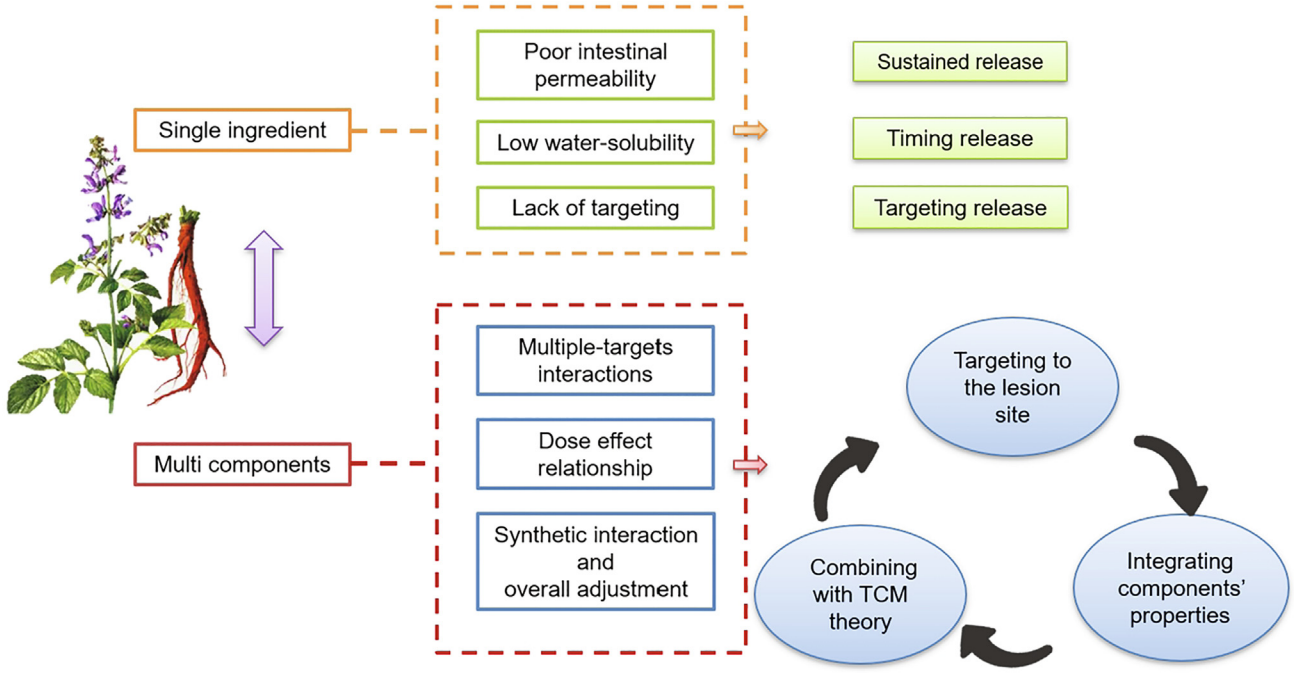


Fig. 1. Marketed preparations and DDSs in studies (top), challenges and strategies can be taken into account in DDSs design (bottom) for Danshen.

DSS was also investigated to have protective effects on cardiac ischaemia/reperfusion (IR) injury. The mechanisms involved in the inhibition of autophagy and apoptosis through activating mammalian target of rapamycin (Fan et al., 2016). Down-regulation of maternally expressed gene 3 in cardiomyocytes H9c2 cells contributed to the cardioprotective function of Sal B (Yang et al., 2019). The mechanisms of Danshen for cardio-protection were multi-targets and complex. There were evidences that Sal B regulates multi-targets relative to apoptosis pathway in acute myocardial infarction rats, such as regulation of 33 proteins, inhibition of poly polymerase-1 pathway, integrity improvement of heart tissue mitochondrial and nucleus (Xu et al., 2011). Reduced angiotensin converting enzyme (ACE) expression and increase of ACE2 via AT1R/p38 MAPK pathway were conductive to protection effects of RA on cardiac dysfunction and fibrosis (Liu et al., 2016). Considerable cardioprotective effects of DHT I, CPT and Tan IIA were related with inhibition on arachidonique ω-hydroxylase (Wei et al., 2016), regulation of NO synthesis (Oche et al., 2016) and inhibition of PTEN expression (Zhang et al, 2016b), respectively. The wide clinical application of Danshen in cardiovascular diseases is mainly due to its superior cardiovascular protection. Further studies examining the multi-targets and complex mechanisms on cardiovascular system are conductive to novel DDSs design and clinic use of Danshen.

2.2. Anti-tumor activity

Chinese medicine theory holds that, when cancer diseases occur, blood stasis syndrome happens throughout the course of tumor development (Wang et al., 2015). As a representative herb

for blood-activating and stasis-resolving, Danshen is widely used in anti-tumor Chinese medicine prescriptions. The anti-tumor mechanisms involved in inhibition of tumor cell growth, angiogenesis, metastasis, apoptosis and cell cycle arrest (Zhu et al., 2016; Jiang et al., 2017; Tsai, Yang, Wu, Pang, & Huang, 2011).

Both DSS and Tan IIA displayed anti-lung cancer activity on non-small cell lung cancer (NSCLC) (Tao et al., 2014; Son et al., 2016; Cao, Wang, Li, Zhang, & Qiao, 2018; Cheng & Su, 2010). Methanol extract of Danshen induced apoptosis of NSCLC Glc-82 cells through mitochondrial pathway (Ye et al., 2017). Sal B significantly reduced the tumor volume of human breast cancer adenocarcinoma through enhancing apoptosis and angiogenesis (Katary, Abdelsayed, Alhashim, Abdelhasib, & Elmarakby, 2019). DHT I targeted breast cancer stem cells via apoptosis pathway (Kim et al., 2019). Tan I also presented potent anti-breast cancer activity via down-regulating biomarker Aurora A expression and function (Gong, Li, Abdolmaleky, Li, & Zhou, 2012). Evidences proved that Tan I, Tan IIA, DHT I and CPT all induce apoptosis in HepG2 cells (Lee, Chiu, & Yeung, 2008; Lee, Liu, & Yeung, 2009). Possible mechanisms of HepG2 cytotoxicity were caspases activation, intracellular glutathione perturbation. In addition to the above, anticarcinogenic activity of active ingredients in Danshen was also shown on oral squamous cell carcinoma (Wei et al., 2018), glioblastoma cells (Chen et al., 2018; Kumar, Radin, & Leonardi, 2019), ovarian cancer cells (Jiang et al., 2017), etc. Further investigations should be carried on developing Danshen as an effective and safe agent to prevent and treat kinds of cancers.

2.3. Neuroprotective effect

Oxidative stress includes free radical generation, mitochondrial dysfunction and the immune-inflammation may play important roles in neurodegenerative disorders (Bhat et al., 2015; Wang, Wen, Huang, Chen, & Ku, 2006). Danshen was demonstrated to have neuroprotective effects on AD and PD (Habtemariam, 2018). DSS showed neuronal protection on zebrafish (Chong et al., 2013) and could pass the blood brain barrier (BBB) in rat (Yu et al., 2011). Sal B was proved to display neuroprotective and antidepressant actions via up-regulation of Nrf2 antioxidant signaling pathway (Zhang et al., 2018) and over-activated NLRP3 (Jiang et al., 2017). High affinity inhibition of acetylcholinesterase, alleviated memory decline in β-amyloid-induced AD mouse model, suggested that DHT I, Tan IIA and CPT may be potential therapeutic drugs for AD (Cheung, Gary, Shiomi, & Rosenberyy, 2013; Maione et al., 2018). Positive experimental results provided us a protective potential of Danshen in the treatment of neurodegenerative disorders.

2.4. Antioxidative and anti-inflammatory activity

As for inflammatory diseases, enhanced reactive oxygen species (ROS) at the damaged area is observed (Arulselvan et al., 2016). Overload of ROS may lead to cell damage and health problems. Infiltration of inflammatory cell and production of inflammatory cytokine were inhibited by Sal B (Liu et al., 2018c). Water/ethanol extracts of Danshen displayed great anti-inflammatory effects both *in vitro* and *in vivo* (Liu et al., 2018b; Luo et al., 2019; Gao et al., 2018). The potential mechanism may associate with mitochondrial anti-oxidative defense system. Studies on anti-inflammatory/oxidative mechanisms provided Danshen a promising herb to treat inflammatory vascular diseases.

2.5. Anti-fibrosis activity

Continuous progress of fibrosis can cause organ structure destruction, functional decline, and even organ failure, which threatening human health and life severely. Danshen is proved to cause anti-fibrosis actions. Administration of DSS reduced fibrosis and inhibited 2,3-dioxygenase I expression in rat hepatic fibrosis model (Cao et al., 2019). RA was investigated to protect against myocardial infarction induced cardiac fibrosis (Liu et al., 2016). Sal B treatment increased expression of Nrf2 in fibroblastic foci areas (Liu et al., 2018a). Danshen was regarded as a potential alternative or complimentary agent to treat and prevent hepatic fibrosis in studies.

3. Challenges for DDSs development of Danshen

The combined effect of multiple active compounds in Danshen via multi-targets is relative to pharmacokinetic property and bioavailability of each ingredient (Yang et al., 2014). However, the physicochemical properties of each single component in Danshen are different. DSS and Sal B are hydrophilic ingredients, while show poor intestinal permeability (Zhou, Chow, & Zuo, 2009). Tan ⅡA has extremely low water-solubility (2.8 ng/mL) (Li, Liu, Zeng, & Zheng, 2008) and extensive First Pass Effect (Wang et al., 2019; Yan, Li, Li, Zhang, & Liu, 2015).

Physicochemical properties discussed above result in the low bioavailability of single components and multi-components in Danshen. Moreover, complexity and challenges in pharmacokinetic and pharmaceutical studies are extremely ascribed to mutual effects of active ingredients in Danshen (Lai et al., 2011). Both hydrophilic and hydrophobic ingredients in Danshen exerted strong pharmacological effects. Poor solubility and low dissolution rate limit the clinical application, including primary components among phenolic acid and TANs, such as Sal B, DSS, DHT I, Tan I, Tan IIA and CPT. Lots of DDSs like nanoparticles, pellets, micelles and liposomes therefore were designed for Danshen to improve the bioavailability, pharmaceutical effects, even for targeting ability or permeating blood brain barrier (BBB) of active components.

4. Strategies applied in delivering single component from Danshen

To improve the bioavailability of active constituents in Danshen, DDSs for single component such as nanoparticles, liposomes, pellets, had been developed (Table 1). Sustained/controlled DDSs designed for Danshen significantly prolonged the drug duration in blood circulation, thus improved bioavailability and enhanced efficacy were obtained. Furthermore, DDSs based on nanotechnology and nanomaterials successfully delivered drugs site-specifically to disease focus or targeted tissue, even into target cells.

4.1. Nanoparticles

Nanoparticles can improve the solubility and dissolution rate of drugs due to its small particle size and large surface area. More and more nanomaterials are applied in the therapy of various diseases, especially incurable cancer (Pérez-Herrero & Fernández-Medarde, 2015). Transferrin, antibodies, hyaluronic acid and other targeting peptides are conjugated to the surface of nanoparticles so as to improve the target ability for enhancing drug efficacy (Zhi, Yang, Yang, Fu, & Zhang, 2020; Xie, Shen, Anraku, Kataoka, & Chen, 2019). DDSs designed based on improving effect of therapeutic drugs provide the promising strategy for disease.

Nanoparticles are an effective tool to overcome some limitations of TCMs in clinical application, especially in bioavailability and bioactivity *in vivo* and undesirable side effects. Besides, nanoparticles in delivering active ingredients from TCMs perform targeting of effects, sustained release, enhanced biological barrier

Table 1
DDSs for single component from Danshen.

Drug delivery systems		Materials	Drugs	Advantages	References
Nanoparticles	Mesoporous silica nanoparticles	Rhodamine B; SBA-15-structured mesoporous silica	Sal B	Sustained-release property; high Sal B release rates; no visible cytotoxicity; good blood compatibility	(He et al., 2010)
	Polymeric nanoparticles	PLGA, cardiolipin, DSPE-PEG (2000)-CA, FITC, PAAM	RA, CUR	High loading efficiency; no significant toxicity; higher BBB permeability coefficient	(Kuo & Tsai, 2018)
	Poly (ethyl cyanoacrylate) nanoparticles	Monomer ECA, HCl, dextran 70000, anhydrous glucose, Tween 80	Sal B	High encapsulation efficiency; sustained release	(Grossi et al., 2017)
	PLGAnanoparticles	PLGA, biotin-PEG-NH_2, DCM, DCC, NHS, PVA	DHT I	Small particle size; narrow size distributions; sustained release property	(Luo et al., 2018)
	PEGylated nanoparticles	D, L-lactide, methoxy PEG-PLA/maleimide PEG-PLA, Sn $(Oct)_2$	Tan IIA	Better brain delivery efficacy; small particle size; high encapsulation efficiency	(Liu et al., 2013)
	Gold nanoparticles	$KAuCl_4$, PEI, β-CD	Tan IIA, α-mangostin	Low cytotoxicity; enhanced efficacy	(Qiu et al., 2016)
	Solid lipid nanoparticles	Soy lecithin, lipid matrix, Tween 80, sodium dehydrocholate	CPT	Improved bioavailability; stable	(Hu et al., 2010)
	Targeted nanoparticles	mPEG-PLGA-PLL-cRGD, F68,	Tan IIA	Even size distribution; stable; extended drug releasing time; improved tumor-targeting activity	(Wang et al., 2014)
Liposomes	Liposomes	P90G, cholesterol, PEG 2000	Sal B	Narrow size distribution; eliminate irreversible adsorptive loss; ameliorat drug delaying	(Isacchi et al., 2011)
Emulsion	Microemulsion	Phospholipid, glycerol, pluronic F68	Tan IIA	Safe used for iv injection; enhance antitumor effect	(Ma et al., 2013)
	Lipid emulsion	Soybean oil, MCT, soybean lecithin, Poloxamer 188, glycerol	Tan IIA	Enhanced efficacy; reduced systematical toxicity; physico-chemically stable	(Chu et al., 2012)
	Nanoemulsion	Ethyl oleate, oleic acid, IPM, GTCC, Capryol 90, lactoferrin-mPEG5000	Tan I	Stable with a smaller droplet size in nano-range; efficient delivery of drugs to brain	(Wu et al., 2019)
Pellets	Pellets	Sodium caprate, MCC, PVP, Eudragit RS30D/RL30D	DSS	Prolonged release; improved oral bioavailability	(Yu et al., 2017)
	Pellets	PVP, poloxamer 188, Opadry II, PVAc, PVA-PEG	Tan IIA	Stable and improved efficacy; chronotherapeutic modified-release.	(Yan et al., 2015)
	Phospholipids complex loaded pellets	Lipoid S100, chloroform	Sal B	Improved lipo-solubility and permeability; great oral bioavailability	(Li et al., 2013)
	Proliposomes loaded pellets	Lipoid S100, cholesterol, mannitol, carrageenan	PD	Enhanced encapsulation efficiency; sustained release	(Zhang et al., 2016a)
Micelles	Micelles	TPGS-g-PLGA, Pluronic F68	Tan IIA	Improved bioavailability; mono-dispersed; small particle size; high encapsulation efficiency; highly stable; sustained release; enhanced anti-cancer effects	(Zhang et al., 2014)

permeability, improved efficacy by co-delivery of active ingredients or therapeutic agents.

4.1.1. Nanoparticles for hydrophilic ingredients in Danshen

Because of oral administration of Danshen or most of TCMs in most cases, low and variable bioavailability usually limits their clinical application, which is influenced by physicochemical properties, physiological barriers and biochemical barriers. In recent years, lots of researches studied nanocarriers to improve the stability of drugs and thus enhanced their oral bioavailability. Nanocarriers altered their absorption, distribution, metabolism and elimination.

Sal B at the purity of 88.2% was loaded in nanoparticles coated with Tween 80 by emulsion polymerization method. They could successfully cross the BBB and sustain Sal B release in 8 h for protecting central nervous system without long-term administration toxicity (Grossi et al., 2017). The DDS of rhodamine B covalently grafted SBA-15-structured mesoporous silica nanoparticles (MSNs-RhB) was developed for anti-ROS/hepatic fibrosis by loading Sal B (SAB) (He et al., 2010). Large pore sizes, high specific surface areas and large pore volumes allow MSNs-RhB to hold SAB with high loading capacities and release SAB in a more sustained way, which talent SAB@MSNs-RhB more remarkable time and dose dependent inhibition effect on ROS level and proliferative activity of hepatic stellate cell LX-2 than free SAB. Both SAB@MSNs-RhB and free SAB did not display visible cytotoxicity in a broad concentration range of 0.5–100 μmol/L. In AD pathology, the early stage of tau protein hyperphosphorylation at S2020 in neurons can be activated by p-p38 kinase and destabilizes microtubule-bound soluble tau protein and forms tau protein aggregates, leading to impaired axonal transport. Polymer nanoparticles PAAM-CL-PLGA grafted with surface 83–14 monoclonal antibody (MAb) was loaded with RA and curcumin (CUR). Free RA-CUR did not show significant effect on reduction in the expressions of p-p38 and p-S202 in β-amyloid (Aβ) insulted SK-N-MC cells, while 83–14 Mab-RA-CUR-PAAM-CL-PLGA nanoparticles could easily cross the BBB and considerably inhibit the expressions of p-p38 and p-S202 after induction with Aβ and recover their expressions to normal level, which provided us a promising DDS to permeate BBB and reduce neurotoxicity (Kuo & Tsai, 2018).

In view of unstable and subject to degradation and oxidation of hydrophilic ingredients, especially Sal B, which brought about the reduced clinical effectiveness, nanoparticles could be taken as choices. Higher bioavailability and longer duration of hydrophilic constituents were obtained after takeing nanoparticles as DDSs.

4.1.2. Nanoparticles for hydrophobic ingredients in Danshen

Cationic bovine serum albumin conjugated Tan IIA PEG nanoparticles (CBSA-PEG-TIIA-NPs) were obtained through double emulsion/solvent evaporation (Liu, An, Jin, Liu, & Wang, 2013). After intravenous administration of CBSA-PEG-TIIA-NPs and free Tan IIA solution, CBSA-PEG-TIIA-NPs showed a prolonged circulation time of Tan IIA which could be measured in plasma even after 24 h, while Tan IIA was not detected in plasma of animals injected with Tan IIA solution after 6 h. CBSA-PEG-TIIA-NPs could successfully across BBB and obviously ameliorate infarct volume, neurological deficit and histopathological severity, which showed remarkable neuroprotective effects on cerebral ischemia rat model. However, free Tan IIA could not cumulate in brain to exert curative effect due to poor permeability across BBB. Additionally, Tan IIA was loaded into mPEG-PLGA-PLL-cRGD nanoparticles (TNPs) using emulsion-evaporation method (Wang et al., 2014). TNPs had an average diameter of 190 ± 42 nm, high encapsulation efficiency (EE) and drug loading (DL). TNPs had a slow rate of Tan IIA release *in vitro*, and the amount of released Tan IIA from TNPs increased to 75.3% at 120 h, which was less than 98.6% release of free Tan IIA. Beyond that, the area under the concentration curve (AUC) and elimination half-life of TNPs in mouse plasma were significantly higher than free Tan IIA. TNPs remarkably inhibited liver cancer cells HepG2 *in vitro* and could be effectively internalized by HepG2 hepatoma cells compared to that in the free Tan IIA group. Complex AuNPs/PEI/CD loaded with Tan IIA was prepared by using gold citrate, PEI and sulphated β-cyclodextrin (CD), which exerted high EE and enhanced efficacy at safe level (Qiu et al., 2016). Gold complexes with Tan IIA were very active on prostate cancer cell line PC-3 with IC_{50} of 6.0 μmol/L, which provided us a nanoparticle platform designed for prostate cancer chemotherapy.

D I -BPA-NPs were prepared using PLGA functionalized with polyethylene glycol (PEG) and biotin to form copolymers (BPA), DHT I (D I) was encapsulated in BPA. The release of DHT I from D I -BPA-NPs presented a biphasic release pattern. In the first 12 h, a burst release appeared and followed by a sustained release. It could significantly inhibit the proliferation of Hela cells compared with free D I, which showing a potential of application in anticancer therapy (Luo et al., 2018). CPT solid lipid nanoparticles (SLNs) were produced by ultrasonic and high pressure homogenization method (Hu, Xing, Meng, & Shang, 2010). CPT exhibited sustained release from SLNs. In pharmacokinetics study, SLNs containing 1% sodium dehydrocholate showed a relatively high C_{max} (7.94 ± 1.52 ng/mL) in rats. The oral bioavailability of CPT was improved due to the protection of the drug from metabolism by embedding CPT into a solid lipid matrix. Nanoparticles loaded with hydrophobic ingredients in Danshen extremely improved the oral bioavailability. Controlled/sustained release and enhanced pharmacological effects of active ingredients could be realized.

4.2. Liposomes

Lipid bilayer vesicles resemble biological membranes of liposomes contribute to the advantage of controlled composition and good biocompatibility (Carita, Eloy, Chorilli, Lee, & Leonardi, 2018). PEGylated liposomes, ligand targeted liposomes, drug-loaded liposomes and other various liposomes are explored and developed (Allen & Cullis, 2013).

Sal B loaded PEGylated liposomes were prepared using hydration method with optimized particle size, morphology, EE and polydispersity index (PDI) (Isacchi et al., 2011). After intraperitoneal administration of Sal B PEGylated liposomes, the Sal B plasma concentration in rats was 388 ± 1.3 μmol/L, which was 4-fold more than free Sal B and conventional liposomes without PEGylated. Sal B-loaded PEGylated liposomes shifted the maximum of anti-hyperalgesic activity 30 min after administration *versus* 15 min of Sal B-loaded conventional liposomes and the effect was still significant at 45 min. PEGylation is a commonly used way to protract the half-life of nanocarriers. Apart from PEGylation, proteins, peptides or exogenous magnetic materials also can be applied to liposomes with the aim of targeting disease lesions and enhancing therapeutic effects. It provided us PEGylated or other modified liposomes to improve bioavailability and prolong biological activities of Danshen.

4.3. Emulsions

Emulsions, microemulsions and nanoemulsions are widely used in DDSs to improve the stability and maintain effectiveness of active components. They have the ability to solubilize drugs of varied lipophilicity, enhance stability and permeability, improve the drug absorption and bioavailability, etc. Microemulsions could be applied in various administration routes, such as oral, intravenous, transdermal administration. Tan IIA was capsulated into a microemulsion (ME), which enhanced the antitumor effect of Tan IIA against hepatocellular carcinoma (HCC) cells through up-regulating the mRNA and protein levels of Bax, caspase-3 and down-regulating Bcl-2 *in vitro* H22 cells and *in vivo* H22 tumor-bearing mice (Ma, Fan, Yu, Xin, & Zhang, 2013). Lipid emulsion of Tan IIA (Tan IIA-LE) was developed for intravenous administration (Chu et al., 2012). Tan IIA-LE displayed well physicochemical stability at room temperature in dark without venous irritation and acute toxicity. Furthermore, it displayed remarkable antitumor activity on human hepatoma cell lines *in vitro*.

Tan I nanoemulsion (TS I -NE) modified with brain targeting ligand (Lactoferrin, Lf) was developed to improve the BBB permeability (Wu et al., 2019). The average particle size of nanoemulsion was 21.11 ± 0.03 nm, with high affinity across the BBB. About 30% Tan I was released from TS I -NE within 72 h, which suggested a sustained release. The increased transport of TS I -NE was contributed to the binding of Lf to transferrin receptors on the surface of BBB. Absorption and bioavailability of poorly water-soluble TANs were improved after being packaged into emulsions. Meanwhile, emulsions offer great stability and high solubilization ability for both hydrophilic and hydrophobic ingredients, which improve the drug delivery *in vivo*.

4.4. Pellets

Pellets are spherical, free flowing granules and are in the size range from 500 to 1500 μm (Xia, Shi, Fang, & Wang, 2018). They are advantaged in desirable flowability and high surface area (Zaman et al., 2016).

In terms of poor intestinal absorption of DSS, sodium caprate was added to improve bioavailability in pellets core. DSS loaded pellets cores were coated with Eudragit RS30D/RL30D to realize sustained release (Yu et al., 2017). DSS pellets were dispersion layered spherical characteristic in steady with improved efficacy. Tan IIA sustained release pellets were also developed by coating with polyvinyl acetate (PVAc) and polyvinyl alcohol (PVA)-PEG using fluidized bed technology (Yan et al., 2015). In pharmacokinetic studies, relatively high Tan IIA plasma concentrations in 8–12 h after oral administration suggested that Tan IIA pellets produce a sustained release *in vivo*. Time to maximal efficacy of Tan IIA was equal to time to peak drug concentration. Tan IIA was released slowly from pellets and could continuously stimulate NO secretion in vascular endothelial cells, which had better efficacy in treating variant angina. Additionally, in order to decrease the hepatic first-pass metabolism of PD, pro-liposomes were prepared as pellet cores, and PD sustained release pellets was obtained. Relative bioavailability (200%) of PD was achieved compared with pure agents. The PD pro-liposomes pellets also displayed desires plasma

Table 2
DDSs for multi-components from Danshen.

Drug delivery systems		Materials	Drugs	Advantages	References
Tablets	Multiple release drug bilayer tablets	MCC, PVPP, L-HPC, HPMC, CP934p, and lactose	Hydrophilic extract from Danshen, and Lipophilic extract from Danshen	Characteristics of quick release and slow release *in vitro*	(Peng et al., 2010)
	Osmotic pump tablets	PEO, PVPP, PVP, CA, DBP, PEG 400, and NaCl	Hydrophilic extract from Danshen, and lipophilic extract from Danshen	Constant speed and completed controlled release	(Zheng et al., 2013)
	Two-step release tablets	HPMC, PEG 4000, lactose, CMS, succinic acid, MCC, NaCl, and Pearlitol	Hydrophilic extract from Danshen, and lipophilic extract from Danshen, PNS, borneol	Zero-order release and pulse release	(Yuan et al., 2014)
Solid dispersions	Solid dispersions	PEG 6000, poloxamer 188, and PVP K30	Total TANs	Increased solubility and dissolution rate of Tan IIA and CPT	(Zhai et al., 2017)
	Solid dispersions	PVP10, and F127	Lipophilic extract from Danshen	Increased release of lipophilic components	(Xiong et al., 2011)
	Solid dispersions	GMS, and PEO	Total TANs	Increased dissolution and sustained release of TANs	(Chen et al., 2013)
Emulsions	Emulsions	soybean phospholipid, poloxamer 188, and glycerin	Tan ⅡA and Sal B	Long-term stability and loading of Tan ⅡA and Sal B simultaneously	(Wang et al., 2014)
Solid self-microemulsions	Solid self-microemulsions	Maisine 35–1, and IPM	Lipophilic extract from Danshen, and hydrophilic extract from Danshen	Improved oral bioavailability and storage stability	(Bi et al., 2016)
Liposomes	Liposomes	Phospholipid, and cholesterol	Total salvianolic acids	Sustained release of total salvianolic acids	(Zhang et al., 2007)
		Soybean phospholipid, and cholesterol	Glycyrrhetinic acid, Sal B, and Tan IIA	Increased bioavailability and water solubility	(Lin et al., 2014)
Hydrogel	Hydrogel	Octa-peptide FHFDFHFD	TANs	Increased loading capacity, sustained drug release and better anticancer capability	(Yin et al., 2017)

concentration–time course for angina chronotherapy (Zhang et al., 2016a). Phospholipids complex of Sal B (PC-Sal B) was prepared by using Lipoid S100, and then PC-Sal B was loaded in pellets, which attached improved lipid solubility, permeability and great oral bioavailability to Sal B. PC-Sal B pellets could significantly promote the penetration of Sal B acrossing the foam cell membrane (Li, Liu et al, 2013). Pellets accelerated the absorption rate and oral bioavailability of drugs. Controlled/sustained release property synchronized plasma drugs concentration with the body biorhythm of patients, which well prevented and cured diseases.

4.5. Others

Despite DDSs mentioned above, other DDSs such as micelles were also used to enhance the effects and bioavailability of single ingredient in Danshen. Tan IIA was loaded in TPGS-g-PLGA/Pluronic F68 mixed micelles (TAN) through thin film hydration technology (Zhang et al., 2014). Compared with 94% Tan IIA released from free Tan IIA solution after 16 h, only 70% released from mixed micelles 96 h later, which demonstrated a sustained release behavior of mixed micelles. Besides sustained release, prolonged circulation time of Tan IIA during 48 h in plasma contributed to longer retention and increased accumulation of Tan IIA in tumor tissue.

5. Strategies applied in delivering multi-components from Danshen

In view of the multi-components and multi-targets effectiveness of TCMs, drug delivery of multi-components remains a major challenge to the DDSs design of Chinese herb medicine. To date, tablets (Liu & Shi, 2011), capsules (Xiang, Yang, Chen, & Pan, 2019), dropping pills (Guo et al., 2012), and injections (Zhang, 2016) for multi-components from Danshen extract have been studied and used clinically. However, they lack high capacity, targeting, and controlled release rates.

Recently, many studies have focused on DDSs able to compensate for drug defects mentioned above (Table 2). They showed great efficacies in prolonging the drug retention time, decreasing the frequency and enhancing the compliance of patient.

5.1. Sustained/controlled-release formulations

Sustained/controlled-release formulations in which the drug can be released at or near a rate of grade zero to maintain effective blood concentration, and achieve long-term effects, playing an important role in applications because of their sustained drug release, long-lasting efficacy and less side effects.

Compound Danshen released double-layer tablets composed of Danshen, Sanqi and Bingpian was prepared. Water-soluble and fat-soluble parts of Danshen were added into quick release layer (treating symptoms) and slow release layer (addressing the root cause), respectively. Water-soluble parts of Danshen, microcrystalline cellulose (MCC), crosslinked polyvinylpyrrolidone (PVPP), and amylum were mixed and prepared into granules, then Bingpian, $mSiO_2$-nH_2O, PVPP and low-substituted hydroxypropyl cellulose (L-HPC) were added into granules and mixed well as quick release layer. Likewise, the slow release layer was prepared as follows: fat-soluble parts of Danshen, *Panax notoginseng* saponins, carbomer, hydroxypropyl methyl cellulose (HPMC), hydroxypropyl cellulose (HPC) and lactose were mixed and prepared into granules and then Bingpian, magnesium stearate were added and mixed well. *In vitro* Sal B release in compound Danshen released double-layer tablets, T_{50} and T_d were 0.66 min and 1.83 min respectively, which were significantly faster than commercially available Fufang Danshen Tablets (T_{50} = 21.92 min, T_d = 26.99 min) and ordinary tablets (T_{50} = 20.79 min, T_d = 26.70 min). As index

component of slow release layer, gindenoside Rg1 released from double-layer tablets slowly (completely released in simulated gastric fluid after 12 h). Excellent characteristics of quick and slow release allowed Compound Danshen double-layer tablets to address both symptoms and the root cause of diseases (Peng et al., 2010).

Multi-components osmotic pump tablets were prepared via loading hydrophilic and lipophilic extracts from Danshen, with sodium chloride as permeability promoter, dibutyl phthalate as plasticizer, and PEG-400 as pore-forming agent to achieve constant, complete and controlled drug release (Zheng, Du, Yan, & Wu, 2013).

Furthermore, the two-step release system (TSRS) composed of effervescent osmotic pump tablet and pulsed-released tablet was prepared to achieve zero-order and pulse release. The prescription of osmotic pump tablets were composed of sodium chloride and mannitol as permeability promoters, HPMC as blockers and PEG 4000 as pore-making agents, while the pulse tablets were composed of pill core (lactose, sodium carboxymethyl starch, succinic acid and microcrystalline cellulose), isolation layer, swelling layer, controlled release layer (Yuan et al., 2014). Diurnal rhythm of CHD was taken into account, zero-order and pulse release resulted in TSRS more adapted to prevent and cure CHD.

5.2. Solid dispersions

The production of solid dispersions is a technique for improving the dissolution rate and bioavailability of hydrophobic drugs by dispersing the drugs into solid-state hydrophilic carriers with an increased surface area. In addition, appropriate carriers can also enable controlled or sustained release of the drug.

Three hydrophilic excipients including PEG 6000, poloxamer 188 and polyvinylpyrrolidone (PVP) K30 were used to prepare total TANs solid dispersions at different ratios by solvent method respectively, which all significantly increased solubility and dissolution rate of Tan ⅡA and CPT (Zhai, Li, Lenon, Xue, & Li, 2017). Moreover, the combined use of PVP10 and poloxamer 127 significantly increased the release of lipophilic components in the solid dispersion for Danshen extract prepared by spray drying method (Xiong, Zhen, & Wang, 2011).

TANs solid dispersions prepared with glycerin monostearate (GMS) and polyethylene oxide (PEO) as excipients by solvent melting method exhibited excellent release characteristics *in vitro*. The accumulative drug-release percent *in vitro* at 12 h was over 90%, and the results from the phase analysis indicated that the tanshinone composition existed in carriers as amorphous state (Chen et al., 2013). As an intermediate dosage form, solid dispersions can be prepared into a variety of preparations according to agent properties and clinical needs. The dripping pills prepared by TANs solid dispersions could achieve requirements of immediate release *in vitro* (Li, Cui, Wu, an& Li, 2013). Moreover, the solid dispersion micro-pellets prepared by TANs solid dispersions are able to enhance the solubility of TANs to improve its absorption *in vivo* (Yu, Jia, Shi, & Xiao, 2013).

5.3. Emulsions

Emulsions are supposed to enhance the stability and capacity of active constituents. The feasibility of simultaneously loading both lipophilic and hydrophilic components of Danshen in emulsion was studied. Soybean phospholipid and poloxamer 188 were added to hydrophilic (Sal B) solution. Liposoluble component Tan ⅡA was dissolved in chain oil for injection and slowly dropped into aqueous phase with stirring at high speed. Soybean phospholipid and poloxamer 188 were used as emulsifiers and glycerin as isosmotic regulator. Optimal and stable biphasic drug-loading emulsion was obtained after high pressure homogenization, which provide basis for display therapeutic effects of Danshen adequately (Wang et al., 2014).

A novel solid self-microemulsified DDS (S-SMEDDS) containing both lipophilic and hydrophilic extracts from Danshen has been designed to improve oral bioavailability and storage stability. Aqueous extracts were dissolved in distilled water together with a mixture of mannitol and dextran-40. The lipophilic extracts were dissolved in oil phase with continuous stirring in a mixture of (Maisine 35–1 + Isopropyl myristate), (Cremophor RH40 + Solutol HS15) and Transcutol P. S-SMEDDS was acquired by adding oil phase mixture to aqueous phase mixture and continuously stirred. The relative bioavailability was calculated by dividing AUC_{0-t} value of DSS, Sal B, CPT and Tan ⅡA for S-SMEDDS and drug suspensions. For each drug, the AUC for S-SMEDDS was significantly larger than that for suspension (DSS: 822.43 ± 91.70 *versus* 471.51 ± 52.11; Sal B: 801.23 ± 148.55 *versus* 484.02 ± 65.14; CPT: 39.52 ± 9.91 *versus* 7.92 ± 2.31; Tan ⅡA: 65.04 ± 14.07 *versus* 6.93 ± 0.92). The novel S-SMEDDS increased the dissolution rate and improved the oral bioavailability of hydrophilic and lipophilic drugs in Danshen (Bi, Liu, Di, & Zu, 2016).

5.4. Liposomes

Lipophilic components are loaded into the phospholipid bilayers, hydrophilic components loaded into the hydrophilic core to form the drug-loaded liposomes. Certainly, liposomes are supposed to improve the solubility with the high loading capabilities, and protect the encapsulated agents from the external media. Moreover, the high capacity allows the delivery for several biologically active components and macromolecules (e.g. DNA, peptides, proteins and imaging agents). Reverse-phase evaporation technique was chosen to prepare total salvianolic acids liposomes, which had the properties of high encapsulation rate, small particle size and sustained release (Zhang, Zhang, Han, & Wang, 2007).

Sal B, Tan ⅡA and glycyrrhetinic acid (GA) were co-encapsulated into liposomes (GTS-lip) with enhanced bioavailability and water solubility of the compounds. In this study, Tan ⅡA and GA, the hydrophobic constituents, were incorporated into phospholipid bilayers by employing the film hydration method, and the pH-gradient method was then used to load the hydrophilic constituent Sal B. The mean diameter of GTS-lip was 191.3 ± 6.31 nm, and EE of Sal B, Tan ⅡA and GA was (96.03 ± 0.28)%, (80.63 ± 0.91)% and (88.56 ± 0.17)%, respectively. A total of 90% Sal B was released in the initial 5 h from drug solution while GTS-lip released 30%. The multi-components in GTS-lip were then demonstrated synergistic effects on the inhibition of hepatic stellate cell proliferation (Lin et al., 2014).

Advantages of high capacity, loading hydrophilic and lipophilic components at the same time, surface modification for liposomes provide us a promising DSS for loading multi-components of TCM.

5.5. Others

In addition to the formulations of multi-components mentioned earlier, hydrogel has also been used to enhance the solubility, stability and sustained release. The self-assembled and gelated octapeptide FHFDFHFD was chosen as DDS for Tan ⅡA and TANs, which showed increased loading capacity, sustained release and improved anticancer capability (Yin et al., 2017). More attention and efforts should be paid to designing more effective DDSs for TCMs multi-components in the future. Strategies based on pharmaceutics technologies will be developed to solve challenges encountered in DDSs design.

6. Discussion

6.1. Construction of DDSs based on single- and multi-component for TCMs

Numerous single components in TCMs including Danshen are shown to possess strong pharmacological effects. An appropriate DDS can be constructed based on physicochemical property and pharmacokinetics of active ingredient. For single component drug loading, improvement of the limitation for drug-like properties (e.g., low solubility, dissolution rate, permeability, bioavailability, lack of targeting, etc.), enhancement of drug efficacy, and more precise treatment strategies (e.g., targeting, timing and sustained release, photo-thermal combination therapy, etc.) are challenges that need to be addressed. Therefore, DDSs with high capacity, improved solubility and targeted ability may be concerned in the future. Solid dispersion, inclusion compound, microencapsulation, microspheres, nanoparticles, liposomes and other novel preparations could be ideal selections to load single components.

Clinical effects of TCMs mainly benefit from multi-components, multi-targets and overall regulation of body. Single component usually cannot represent the clinical curative effect. Components unit could be introduced in DDSs designing for TCMs (Jia et al., 2018). A group of representative active ingredients with similar structure and effects is regarded as the component unit, DDS construction of which is similar to single component. Therefore, multiple preparation technologies can be applied in and more than one DDS combined to construct multiple DDSs for TCMs multi components units. For multi-components drug loading, tablets, solid dispersions, emulsions, liposomes are potential DDSs due to their co-delivery for both hydrophilic and lipophilic components, enhancement of solubility and dissolution rates, and high drug loading-capacity. To overcome the low solubility and dissolution rates of TCMs, solid dispersions have shown better results than other formulations. Although solid dispersion technology has been relatively mature and preparation excipients have been greatly developed, the stability of solid dispersion is still a major challenge, and the aging process will still exist, leading to a decline in dissolution during long-term storage. The remarkable feature of emulsions and liposomes delivery system is that it can co-encapsulate drugs with different solubility properties to improve drug dissolution and bioavailability, and even produce synergistic effect, which is more effective than unencapsulated drugs. Moreover, liposomes can achieve targeted therapy after functional modifications, providing the possibility of precise therapy. However, controlling the proportions of different drugs in the DDS remains a challenge.

6.2. Construction of DDSs based on property of TCMs components

To great extent, clinical effects are influenced by bioavailability of drugs, while the bioavailability is related to physicochemical properties and physiological factors. According to solubility and permeability, TCMs components could be classified into components I (high solubility and permeability), components Ⅱ (low solubility and high permeability), components III (high solubility and low permeability) and components Ⅳ (low solubility and permeability) (Yu, Liu, Zhang, Sun, & Jia, 2012). Superfine grinding technology, pellets, solid dispersion, inclusion compound and microemulsion/self-microemulsion can extremely improve solubility of component. To improve the permeability of TCMs component, liposomes, absorption enhancer, microemulsion/self-microemulsion, phytosome can be a consideration. In addition, sustained/controlled/immediate-release pellets, nanoparticles and other formulations could be prepared according to the biopharmaceutics, pharmacokinetics characteristics of active ingredients and orders of priority in diseases.

6.3. Construction of TCMs DDSs for targeted lesion areas

Targeted formulations allow TCMs functional substances to display stronger therapeutic effects and lower toxicity. Target delivery of TCMs active ingredients is divided into three types, passive targeting, active targeting and physicochemical targeting. Passive targeting is benefit from retention of particles in body. Nanoparticles with small particle size are able to reach tumor tissue passively because of high tumor vascular permeability and enhanced permeability and retention effect (EPR) (Pei et al., 2017). Active targeting preparations are obtained by loading drugs into modified carriers. Ligands modified drug carriers are the most common active targeting DDSs on the basis of cell surface receptors at lesion areas. Physicochemical targeting is realized by using physicochemical methods. Magnetic materials, pH and temperature sensitive carriers are used with the aim of taking effect at specific areas.

Except for targeting ways mentioned above, some channel ushering TCMs such as *Cyathulae Radix* (Niuxi in Chinese), *Bupleuri Radix* (Chaihu in Chinese), *Platycodonis Radix* (Jiegeng in Chinese), Bingpian, etc. exert synergic effect compatible with monarch drug in a prescription. For instance, Jiegeng and *Mori Cortex* (Sangbaipi in Chinese) possess the property of ushering functional substances to lung, Bingpian could take along active ingredients up to brain. The application of channel ushering TCMs in DDSs designing is a significant strategy to target lesion areas and enhance the therapeutic effects.

6.4. Construction of DDSs based on TCM theory

TCMs are characteristic in multi-components, multi-targets and acts curative effect at the overall level of body. Whether the multiple components units could represent the whole functional substances and therapeutic effect, or the construction and clinical effect of DDSs for TCMs multi-components fully reflect TCMs function characteristics remains great disputes. Thus, the further research of complete evaluation systems for TCMs multi-components and its DDSs are required.

To prevent the tendency of TCMs pharmacy transforms to western medicine pharmacy, the development of TCMs pharmacy must be adhere to under the theoretical system of TCM, such as holistic viewpoint, dialectical therapy, compatibility theory and properties theory. It is necessary to further improve the formulation design theory under the guidance of TCM theories and strengthen the research on the basic theories of TCM Pharmacy.

Furthermore, the complex ingredients and design of multi-components DDSs for TCMs require the interdisciplinary crossing and integrative development. Through the combination of network pharmacology, functional material basis, pharmacokinetics, modern pharmaceutics, multi-components DDS and quality control research, we can effectively solve the problems of TCMs preparations, and develop innovative TCMs DDSs that have the same efficacy as the original medicines (Wang, Gu, Feng, & Jia, 2015). It provides us a promising direction and theoretical basis for TCMs preparations. Due to the multi-components, and -targets, it is difficult to illuminate the complex mechanisms of TCMs. DDSs for TCMs should deliver active ingredients as many as possible, which target the lesion areas with a high drug accumulation. Moreover, the quantity and its relationship between TCMs active ingredients or individual medicines serve as the basis of therapeutic effect. It is the also promising perspective for us to develop DDSs for TCMs through adjusting the quantity ratio of multi-components with the aim of receiving best therapeutic effect in future.

7. Conclusion

Up to now, multiple coating technology, layered tablets and osmotic pump technology are used to realize the programmed release of multiple component units. Traditional preparations like tablets, capsules are the most studied DDSs for multi-components delivery. Huge challenges remain in new formulations or nanotechnology applied in the component unit or multiple unit delivery. However, it is hard for us to clarify the relationship of dose–effect, substances taking effect and mechanisms of action in multiple units. The nanotechnology delivery for TCMs multi-component is limited in a group of active components, one/two ingredients extracted from TCMs or monomer composition combined with western medicine, hardly any research studied the preparations for Chinese herbal compound prescription.

In summary, DDSs presented in this review provide us a clue for the DDSs development of TCMs. Nanoparticles based on nanomaterials and nanotechnology show distinct superiority than traditional preparations. Furthermore, DDSs development of Danshen even for TCMs should focus on solving the following problems: 1) improve the bioavailability of active compounds; 2) develop novel DDSs for TCMs under the guidance of TCM theories; 3) explore and design nanomaterials or conjugation of ligands for targeting diseases. With the development of pharmaceutics and modernization of TCMs, more effective DDSs with low toxicity will be designed for TCMs in the future.

Declaration of Competing Interest

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

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References

Allen, T. M., & Cullis, P. R. (2013). Liposomal drug delivery systems: From concept to clinical applications. *Advanced Drug Delivery Reviews, 65*(1), 36–48.

Arulselvan, P., Fard, M. T., Tan, W. S., Gothai, S., Fakurazi, S., Norhaizan, M. E., & Kumar, S. S. (2016). Role of antioxidants and natural products in inflammation. *Oxidative Medicine and Celluar Longevity, 2016*, 5276130.

Bhat, A. H., Dar, K. B., Aness, S., Zargar, M. A., Masood, A., Sofi, M. A., & Ganie, S. A. (2015). Oxidative stress, mitochondrial dysfunction and neurodegenerative diseases; a mechanistic insight. *Biomedicine & Pharmacotherapy, 74*, 101–110.

Bi, X. L., Liu, X., Di, L. Q., & Zu, Q. (2016). Improved oral bioavailability using a solid self-microemulsifying drug delivery system containing a multicomponent mixture extracted from *Salvia miltiorrhiza*. *Molecules, 21*(4), 456.

Cao, G., Zhu, R. Y., Jiang, T., Tang, D. X., Kwan, H. Y., & Su, T. (2019). Danshensu, a novel indoleamine 2,3-dioxygenase1 inhibitor, exerts anti-hepatic fibrosis effects via inhibition of JAK2-STAT3 signaling. *Phytomedicine, 63* 153055.

Cao, Y. G., Chai, J. G., Chen, Y. C., Zhao, J., Zhou, J., Shao, J. P., ... Liu, X. Q. (2009). Beneficial effects of danshensu, an active component of *Salvia miltiorrhiza*, on homocysteine metabolism via the trans-sulphuration pathway in rats. *British Journal of Pharmacology, 157*(3), 482–490.

Cao, Y. F., Wang, S. F., Li, X., Zhang, Y. L., & Qiao, Y. J. (2018). The anticancer mechanism investigation of Tanshinone II_A by pharmacological clustering in protein work. *BMC Systems Biology, 12*(1), 90.

Carita, A. C., Eloy, J. O., Chorilli, M., Lee, R. J., & Leonardi, G. R. (2018). Recent advances and perspectives in liposomes for cutaneous drug delivery. *Current Medicinal Chemistry, 25*(5), 606–635.

Chen, W., Wang, N., Li, R. C., Xu, G. F., Bao, G., Jiang, H. T., & Wang, M. D. (2018). Salvianolic acid B renders glioma cells more sensitive to radiation via Fis-1-mediated mitochondrial dysfunction. *Biomedicine & Pharmacotherapy, 107*, 1230–1236.

Chen, X. Y., Zhang, Z. H., Yu, D. H., Liu, D., Jin, H. F., & Yang, S. L. (2013). Studies on sustained release solid dispersion of tanshione composition. *Chinese Traditional and Herbal Drugs, 44*(17), 2391–2396.

Cheng, C. Y., & Su, C. C. (2010). Tanshinone ⅡA may inhibit the growth of small cell lung cancer H146 cells by up-regulating the Bax/Bcl-2 ratio and decreasing mitochondrial membrane potential. *Molecular Medicine Reports, 3*(4), 645–650.

Cheung, J., Gary, E. N., Shiomi, K., & Rosenberyy, T. L. (2013). Structures of human acetylcholinesterase bound to dihydrotanshinone I and territrem B show peripheral site flexibility. *ACS Medicinal Chemistry Letters, 4*(11), 1091–1096.

Chong, C. M., Zhou, Z. Y., Razmovski-Naumovski, V., Cui, G. Z., Zhang, L. Q., Sa, F., ... Lee, S. M. (2013). Danshensu protects against 6-hydroxydopamine-induced damage of PC12 cells *in vitro* and dopaminergic neurons in zebrafish. *Neuroscience Letters, 543*, 121–125.

Chu, T., Zhang, Q., Li, H., Ma, W. C., Zhang, N., Jin, H., & Mao, S. J. (2012). Development of intravenous lipid emulsion of tanshinone IIA and evaluation of its anti-hepatoma activity *in vitro*. *International Journal of Pharmaceutics, 424*(1–2), 76–88.

Fan, G. W., Yu, J. H., Asare, P. F., Wang, L. Y., Zhang, H., Zhang, B. L., ... Gao, X. M. (2016). Danshensu alleviates cardiac ischaemia/reperfusion injury by inhibiting autophagy and apoptosis via activation of mTOR signalling. *Journal of Cellular and Molecular Medicine, 20*(10), 1908–1919.

Gao, H. W., Huang, L. T., Ding, F., Yang, K., Feng, Y. L., Tang, H. Z., ... Yang, S. L. (2018). Simultaneous purification of dihydrotanshinone, tanshinone I, cryptotanshinone, and tanshinone IIA from *Salvia miltiorrhiza* and their anti-inflammatory activities investigation. *Scientific Reports, 8*, 8460.

Gao, L., Siu, P. M., Chan, S. W., & Lai, C. W. K. (2017). Cardiovascular protective effects of salvianic acid A on *db/db* mice with elevated homocysteine level. *Oxidative Medicine and Cellular Longevity, 2017*, 9506925.

Gong, Y., Li, Y. L., Abdolmaleky, H. M., Li, L. L., & Zhou, J. R. (2012). Tanshinones inhibit the growth of breast cancer cells through epigenetic modification of Aurora A expression and function. *PLoS One, 7*(4) e33656.

Grossi, C., Guccione, C., Isacchi, B., Bergonzi, M. C., Luccarini, I., Casamenti, F., & Bilia, A. R. (2017). Development of blood-brain barrier permeable nanoparticles as potential carriers for salvianolic acid B to CNS. *Planta Medica, 83*(5), 382–391.

Guo, Y. M., Zhang, C., Cha, Q. L., Cheng, W. N., Jiang, M., & Lv, A. P. (2012). "Compound Salvia Droplet Pill" for treatment of coronary heart disease: A systematic review. *Acta Univesitatis Traditions Medicalis Sinensis Pharmacologiaeque Shanghai, 26*(03), 24–31.

Habtemariam, S. (2018). Molecular pharmacology of rosmarinic and salvianolic acids: Potential seeds for Alzheimer's and vascular dementia drugs. *International Journal of Molecular Sciences, 19*(2), 458.

He, Q. J., Zhang, J. M., Chen, F., Guo, L. M., Zhu, Z. Y., & Shi, J. L. (2010). An anti-ROS/hepatic fibrosis drug delivery system based on salvianolic acid B loaded mesoporous silica nanoparticles. *Biomaterials, 31*(30), 7785–7796.

Hu, L. D., Xing, Q. B., Meng, J. A., & Shang, C. (2010). Preparation and enhanced oral bioavailability of cryptotanshinone-loaded solid lipid nanoparticles. *AAPS PharmSciTech, 11*(2), 582–587.

Isacchi, B., Fabbri, V., Galeotti, N., Bergonzi, M. C., Karioti, A., Ghelardini, C., ... Bilia, A. R. (2011). Salvianolic acid B and its liposomal formulations: Anti-hyperalgesic activity in the treatment of neuropathic pain. *European Journal of Pharmaceutical Sciences, 44*(4), 552–558.

Jia, X. B., Yang, B., Feng, L., Shi, X. H., Wang, H., & Liu, L. G. (2018). Research frontiers of Chinese medicine pharmaceutics: Foundations and key issues of components preparation technology. *Acta Pharmaceutica Sinica, 53*(12), 1943–1953.

Jiang, G. Q., Liu, J., Ren, B. Y., Zhang, L., Owusu, L., Liu, L. K., ... Li, W. L. (2017). Anti-tumor and chemosensitization effects of cryptotanshinone extracted from *Salvia miltiorrhiza* Bge. on ovarian cancer cells *in vitro*. *Journal of Ethnopharmacology, 205*, 33–40.

Jiang, P., Guo, Y. J., Dang, R. L., Yang, M. Q., Liao, D. H., Li, H. D., ... Xu, P. F. (2017). Salvianolic acid B protects against lipopolysaccharide-induced behavioral deficits and neuroinflammatory response: Involvement of autophagy and NLRP3 inflammasome. *Journal of Neuroinflammation, 14*(1), 239.

Katary, M. A., Abdelsayed, R., Alhashim, A., Abdelhasib, M., & Elmarakby, A. A. (2019). Salvianolic acid B slows the progression of breast cancer cell growth via enhancement of apoptosis and reduction of oxidative stress, inflammation, and angiogenesis. *International Journal of Molecular Sciences, 20*(22), 5653.

Kim, S. L., Choi, H. S., Kim, J. H., Jeong, D. K., Kim, K. S., & Lee, D. S. (2019). Dihydrotanshinone-Induced NOX5 activation inhibits breast cancer stem cell through the ROS/Stat3 signaling pathway. *Oxidative Medicine and Cellular Longevity, 2019*, 9296439.

Kumar, V., Radin, D., & Leonardi, D. (2019). Studies examining the synergy between dihydrotanshinone and temozolomide against MGMT+ glioblastoma cells *in vitro*: Predicting interactions with the blood-brain barrier. *Biomedicine & Pharmacotherapy, 109*, 386–390.

Kuo, Y. C., & Tsai, H. C. (2018). Rosmarinic acid- and curcumin-loaded polyacrylamide-cardiolipin-poly(lactide-co-glycolide) nanoparticles with conjugated 83–14 monoclonal antibody to protect beta-amyloid-insulted neurons. *Materials Science & Engineering C-Materials for Biological Applications, 91*, 445–457.

Lai, X. J., Liu, H. Q., Li, J. S., & Cai, B. C. (2011). Progress in the pharmacokinetics and interactions between components of salvianolic acids. *Chinese Journal of New Drugs, 20*(14), 1287–1291.

Lee, W. Y. W., Chiu, L. C. M., & Yeung, J. H. K. (2008). Cytotoxicity of major tanshinones isolated from Danshen (*Salvia miltiorrhiza*) on HepG2 cells in

relation to glutathione perturbation. *Food and Chemical Toxicology, 46*(1), 328–338.
Lee, W. Y. W., Liu, K. W., & Yeung, J. H. K. (2009). Reactive oxygen species-mediated kinase activation by dihydrotanshinone in tanshinones-induced apoptosis in HepG2 cells. *Cancer Letters, 285*(1), 46–57.
Li, J., Liu, P., Liu, J. P., Yang, J. K., Zhang, W. L., Fan, Y. Q., ... Zhang, W. J. (2013). Bioavailability and foam cells permeability enhancement of Salvianolic acid B pellets based on drug-phospholipids complex technique. *European Journal of Pharmaceutics and Biopharmaceutics, 83*(1), 76–86.
Li, L., Feng, Y., Hong, Y. L., Lin, X., & Shen, L. (2018). Recent advances in drug delivery system for bioactive glycosides from traditional Chinese medicine. *American Journal of Chinese Medicine, 46*(8), 1791–1824.
Li, N., Cui, H. M., Wu, P., & Li, X. F. (2013). Optimization of preparation technology of tanshinone solid dispersion dripping pills. *Chinese Journal of Experimental Traditional Medical, 19*(03), 8–12.
Li, S. C., Liu, J. P., Zeng, Z. Z., & Zheng, Y. X. (2008). Study on the solubility and permeability of tanshinoneⅡA and on the excipients increasing the solubility and permeability. *Lishizhen Medicine and Materia Medica Research, 19*, 1724–1726.
Li, Z. M., Xu, S. W., & Liu, P. Q. (2018). *Salvia miltiorrhiza* Burge (Danshen): A golden herbal medicine in cardiovascular therapeutics. *Acta Pharmacologica Sinica, 39*(5), 802–824.
Lin, J. H., Wang, X. L., Wu, Q., Dai, J. D., Guan, H. D., Cao, W., ... Wang, Y. R. (2014). Development of salvianolic acid B-tanshinone II A-glycyrrhetinic acid compound liposomes: Formulation optimization and its effects on proliferation of hepatic stellate cells. *International Journal of Pharmaceutics, 462*(1–2), 11–18.
Liu, C. J., & Shi, J. Y. (2011). Progress on pharmacological action and clinical application of compound Danshen Tablet in recent years. *Food and Drug, 13*(11), 434–437.
Liu, H. M., Ma, S. L., Xia, H. R., Lou, H. X., Zhu, F. L., & Sun, L. R. (2018a). Anti-inflammatory activities and potential mechanisms of phenolic acids isolated from *Salvia miltiorrhiza* f. alba roots in THP-1 macrophages. *Journal of Ethnopharmacology, 222*, 201–207.
Liu, M., Xu, H. Y., Zhang, L., Zhang, C., Yang, L. C., Ma, E. L., ... Li, Y. C. (2018b). Salvianolic acid B inhibits myofibroblast transdifferentiation in experimental pulmonary fibrosis via the up-regulation of Nrf2. *Biochemical Biophysical Research Communications, 495*(1), 325–331.
Liu, Q. F., Tian, J. W., Xu, Y. N., Li, C. M., Meng, X. J., & Fu, F. H. (2016). Protective effect of RA on myocardial infarction induced-cardiac fibrosis via AT1R/p38 MAPK pathway signaling and modulation of the ACE2/ACE ratio. *Journal of Agricultural and Food Chemistry, 64*(35), 6716–6722.
Liu, Q. M., Lu, J. Y., Lin, J. R., Tang, Y. L., Pu, W. L., Shi, X. G., ... Wu, W. Y. (2019). Salvianolic acid B attenuates experimental skin fibrosis of systemic sclerosis. *Biomedicine & Pharmacotherapy, 110*, 546–553.
Liu, Q. M., Shi, X. G., Tang, L. Y., Xu, W. H., Jiang, S., Ding, W. F., ... Wu, W. Y. (2018c). Salvianolic acid B attenuates experimental pulmonary inflammation by protecting endothelial cells against oxidative stress injury. *European Journal of Pharmacology, 840*, 9–19.
Liu, X., An, C. Y., Jin, P., Liu, X. S., & Wang, L. H. (2013). Protective effects of cationic bovine serum albumin-conjugated PEGylated tanshinone IIA nanoparticles on cerebral ischemia. *Biomaterials, 34*(3), 817–830.
Luo, J. J., Meng, X. F., Su, J. Y., Ma, H., Wang, W., Fang, L. M., ... Chen, T. F. (2018). Biotin-modified polylactic-co-glycolic acid nanoparticles with improved antiproliferative activity of 15,16-dihydrotanshinone I in human cervical cancer cells. *Journal of Agricultural and Food Chemistry, 66*(35), 9219–9230.
Luo, J. M., Zhang, L., Zhang, X. Y., Long, Y. Y., Zou, F., Yan, C. Y., & Zou, W. (2019). Protective effects and active ingredients of *Salvia miltiorrhiza* Bunge extracts on airway responsiveness, inflammation and remodeling in mice with ovalbumin-induced allergic asthma. *Phytomedicine, 52*, 168–177.
Luo, J., Song, W. J., Yang, G. Y., Xu, H., & Chen, K. J. (2015). Compound Danshen *(Salvia miltiorrhiza)* dripping pill for coronary heart disease: An overview of systematic reviews. *American Journal of Chinese Medicine, 43*(1), 25–43.
Ma, H., Fan, Q., Yu, J., Xin, J. L., & Zhang, C. (2013). Novel microemulsion of tanshinone IIA, isolated from *Salvia miltiorrhiza* Bunge, exerts anticancer activity through inducing apoptosis in hepatoma cells. *American Journal of Chinese Medicine, 41*(1), 197–210.
Maione, F., Piccolo, M., De Vita, S., Chini, M. G., Cristiano, C., De Caro, C., ... Bifulco, G. (2018). Down regulation of pro-inflammatory pathways by tanshinone IIA and cryptotanshinone in a non-genetic mouse model of Alzheimer's disease. *Pharmacological Research, 129*, 482–490.
Oche, B., Chen, L., Ma, Y. K., Yang, Y., Li, C. X., Geng, X., ... Wang, H. (2016). Cryptotanshinone and wogonin up-regulate eNOS in vascular endothelial cells via ERα and down-regulate iNOS in LPS stimulated vascular smooth muscle cells via ERβ. *Archives of Pharmacal Research, 39*(2), 249–258.
Pang, H. Q., Wu, L., Tang, Y. P., Zhou, G. S., Qu, C., & Duan, J. A. (2016). Chemical analysis of the herbal medicine *Salviae miltiorrhizae Radix* et *Rhizoma* (Danshen). *Molecules, 21*(1), 51.
Peng, C. C., Zhen, Q., Hu, P. Y., Pan, J. J., Lai, C. H., & Yang, M. (2010). Drug release of compoound salvia multi-components released double-layer tablet. *Chinese Traditional Patent Medicine, 32*(01), 39–43.
Pei, Q., Hu, X. L., Liu, S., Li, Y., Xie, Z. G., & Jing, X. B. (2017). Paclitaxel dimers assembling nanomedicines for treatment of cervix carcinoma. *Journal of Controlled Release, 254*, 23–33.
Pérez-Herrero, E., & Fernández-Medarde, A. (2015). Advanced targeted therapies in cancer: Drug nanocarriers, the future of chemotherapy. *European Journal of Pharmaceutics and Biopharmaceutics, 93*, 52–79.
Qiu, S. H., Granet, R., Mbakidi, J. P., Brégier, F., Pouget, C., Micallef, L., ... Sol, V. (2016). Delivery of tanshinone ⅡA and α-mangostin from gold/PEI/cyclodextrin nanoparticle platform designed for prostate cancer chemotherapy. *Bioorganic & Medicinal Chemistry Letters, 26*(10), 2503–2506.
Ren, J., Fu, L., Nile, S. H., Zhang, J., & Kai, G. Y. (2019). *Salvia miltiorrhiza* in Treating cardiovascular diseases: A review on its pharmacological and clinical applications. *Frontiers in Pharmacology, 10*, 753.
Son, B., Jun, S. Y., Seo, H., Youn, H., Yang, H. J., Kim, W., ... Youn, B. (2016). Inhibitory effect of traditional oriental medicine-derived monoamine oxidase B inhibitor on radioresistance of non-small cell lung cancer. *Scientific Reports, 6*, 21986.
Tao, L., Wang, S., Zhao, Y., Sheng, X. B., Wang, A. Y., Zheng, S. Z., & Lu, Y. (2014). Phenolcarboxylic acids from medicinal herbs exert anticancer effects through disruption of COX-2 activity. *Phytomedicine, 21*(11), 1473–1482.
Tsai, M. Y., Yang, R. C., Wu, H. T., Pang, J. H. S., & Huang, S. T. (2011). Anti-angiogenic effect of Tanshinone IIA involves inhibition of matrix invasion and modification of MMP-2/TIMP-2 secretion in vascular endothelial cells. *Cancer Letters, 310*(2), 198–206.
Wang, A. Y., Tao, L., Lu, Y., Lin, Y. P., Chen, W. X., & Zhou, L. (2015). Research progress on intervention by *Salviae Miltiorrhizae Radix* et *Rhizoma* on angiogenesis of tumor and ischemic disease. *Chinese Traditional and Herbal Drugs, 46*(9), 1399–1404.
Wang, C. F., Gu, J. F., Feng, L., & Jia, X. B. (2015). Development of innovative structural components of Chinese medicine by multidisciplinary crossing. *China Journal of Chinese Materia Medica, 40*(13), 2496–2502.
Wang, D. Q., Zhang, S. S., Tang, H., Jiang, C. P., Wang, B. W., & Liu, J. P. (2019). Development of sustained-release pellets to modulate the *in vivo* processes of the main active components of Danshen: A pharmacokinetic and pharmacodynamic evaluation. *Phytomedicine, 58* 152793.
Wang, J. Y., Wen, L. L., Huang, Y. N., Chen, Y. T., & Ku, M. C. (2006). Dual effects of antioxidants in neurodegeneration: Direct neuroprotection against oxidative stress and indirect protection via suppression of glia-mediated inflammation. *Current Pharmaceutical Design, 12*(27), 3521–3533.
Wang, X. H., Morris-Natschke, S. L., & Lee, K. H. (2007). New developments in the chemistry and biology of the bioactive constituents of Tanshen. *Medicinal Research Reviews, 27*(1), 133–148.
Wang, Y., Song, D. Q., Costanza, F., Ji, G., Fan, Z. Z., Cai, J. F., & Li, Q. (2014). Targeted delivery of tanshinone IIA-conjugated mPEG-PLGA-PLL-cRGD nanoparticles to hepatocellular carcinoma. *Journal of Biomedical Nanotechnology, 10*(11), 3244–3252.
Wang, Y. Y., Li, X., Lai, X. J., Li, W., Yang, Y. J., Chu, T., & Mao, S. J. (2014a). Development of biphasic drug-loading lipid emulsion of *Salvia miltiorrhiza* and its quality evaluation. *China Journal of Chinese Materia Medica, 39*(19), 3749–3752.
Wei, J., Wu, J., Xu, W., Nie, H., Zhou, R. Q., Wang, R., ... Wu, J. Y. (2018). Salvanic acid B inhibits glycolysis in oral squamous cell carcinoma via targeting PI3K/AKT/HIF-1α signaling pathway. *Cell Death Disease, 9*(6), 599.
Wei, Y. D., Xu, M. J., Ren, Y., Lu, G., Xu, Y. M., Song, Y. Y., & Ji, H. (2016). The cardioprotection of dihydrotanshinone I against myocardial ischemia-reperfusion injury via inhibition of arachidonic acid ω-hydroxylase. *Canadian Journal of Physiology and Pharmacology, 94*(12), 1267–1275.
Wu, Y. M., Zhang, B., Kebebe, D., Guo, L. L., Guo, H., Li, N., ... Liu, Z. D. (2019). Preparation, optimization and cellular uptake study of tanshinone I nanoemulsion modified with lactoferrin for brain drug delivery. *Pharmaceutical Development and Technology, 24*(8), 982–991.
Xia, Y., Shi, C. Y., Fang, J. G., & Wang, W. Q. (2018). Approaches to developing fast release pellets via wet extrusion-spheronization. *Pharmaceutical Development and Technology, 23*(5), 432–441.
Xiang, W. Z., Yang, Q. F., Chen, L. P., & Pan, Q. (2019). Clinical Study of Danshen Shuxin Capsule combined with Diltiazem in treatment of refractory angina pectoris with blood stasis type. *Chinese Archives of Traditional Chinese Medicine, 37*(06), 1494–1496.
Xie, J. B., Shen, Z. Y., Anraku, Y., Kataoka, K., & Chen, X. Y. (2019). Nanomaterial-based blood-brain-barrier (BBB) crossing strategies. *Biomaterials, 224* 119491.
Xiong, X. L., Zhen, Y., & Wang, Y. T. (2011). Application of solid dispersion combined with carriers for *in vitro* release of multi-components from Danshen extract. *Chinese Traditional and Herbal Drugs, 42*(01), 50–55.
Xu, L. L., Deng, Y. P., Feng, L. X., Li, D. F., Chen, X. Y., Ma, C., & Guo, D. A. (2011). Cardio-protection of salvianolic acid B through inhibition of apoptosis network. *PLoS One, 6*(9) e24036.
Xu, W., Xing, F. J., Dong, K., You, C. Y., Yan, Y., Zhang, L., ... Wang, K. (2015). Application of traditional Chinese medicine preparation in targeting drug delivery system. *Drug Delivery, 22*(3), 258–265.
Yan, H. X., Li, J., Li, Z. H., Zhang, W. L., & Liu, J. P. (2015). Tanshinone ⅡA - loaded pellets developed for angina chronotherapy: Deconvolution-based formulation design and optimization, pharmacokinetic and pharmacodynamic evaluation. *European Journal of Pharmaceutical Sciences, 76*, 156–164.
Yang, B., Zheng, C. Y., Yu, H. C., Zhang, R., Zhao, C., & Cai, S. L. (2019). Cardio-protective effects of salvianolic acid B on oxygen and glucose deprivation (OGD)-treated H9c2 cells. *Artificial Cells Nanomedicine and Biotechnology, 47*(1), 2274–2281.

Yang, Y., Zhang, Z. Q., Li, S. P., Ye, X. L., Li, X. G., & He, K. (2014). Synergy effects of herb extracts: Pharmacokinetics and pharmacodynamic basis. *Fitoterapia, 92*, 133–147.

Ye, Y. T., Zhong, W., Sun, P., Wang, D., Wang, C., Hu, L. M., & Qian, J. Q. (2017). Apoptosis induced by the methanol extract of *Salvia miltiorrhiza* Bunge in non-small cell lung cancer through PTEN-mediated inhibition of PI3K/Akt pathway. *Journal of Ethnopharmacology, 200*, 107–116.

Yin, Y. J., Wu, C., Wang, J. L., Song, F. J., Yue, W. Q., & Zhong, W. Y. (2017). A simply triggered peptide-based hydrogel as an injectable nanocarrier of tanshinone ⅡA and tanshinones. *Chemical Communications, 53*(3), 529–532.

Yu, D. H., Jia, X. B., Shi, Y. Q., & Xiao, W. (2013). Pharmacokinetics of main components in *Salvia Miltiorrhizae Radix* et *Rhizoma* diterpene quinones composition and its solid dispersion micro-pellets in rats *in vivo*. *Chinese Traditional and Herbal Drugs, 44*(07), 851–857.

Yu, D. H., Liu, D., Zhang, Z. H., Sun, E., & Jia, X. B. (2012). Design technology of traditional Chinese medicine component and formulation. *China Journal of Chinese Materia Medica, 37*(19), 2993–2996.

Yu, P. P., Zhang, S. S., Zhang, W. L., Yang, J. K., Lu, J., & Liu, J. P. (2017). Tanshinol sustained-release pellets with absorption enhancer: Optimization, characterization, pharmacokinetics and pharmacodynamics. *Drug Development and Industrial Pharmacy, 43*(7), 1093–1102.

Yu, P. F., Wang, W. Y., Eerdun, G., Wang, T., Zhang, L. M., Li, C., & Fu, F. H. (2011). The Role of P-glycoprotein in transport of Danshensu across the blood-brain barrier. *Evidence Based Complementary and Alternative Medicine, 2011* 713523.

Yuan, Y., Dai, M., Zhou, W. L., Xie, Y. P., Li, Y. B., & Hou, S. X. (2014). Preparation process of two-step release drug delivery system of compound Danshen. *Chinese Traditional Patent Medicine, 36*(01), 72–76.

Zaman, M., Saeed-Ul-Hassan, S., Sarfraz, R. M., Batool, N., Qureshi, M. J., Akram, M. A., ... Danish, Z. (2016). Pellets and pelletization: Emerging trends in the pharma industry. *Acta Poloniae Pharmaceutica, 73*(6), 1415–1425.

Zhai, X. F., Li, C. G., Lenon, G. B., Xue, C. C. L., & Li, W. Z. (2017). Preparation and characterisation of solid dispersions of tanshinone IIA, cryptotanshinone and total tanshinones. *Asian Journal of Pharmaceutical Sciences, 12*(1), 85–97.

Zhang, C. Y. (2016). Research progress and industrialization countermeasure of *Salvia miltiorrhiza* injections. *Chinese Traditional Patent Medicine, 38*(7), 1585–1590.

Zhang, J. M., Li, Y. B., Fang, X. F., Zhou, D. M., Wang, Y. T., & Chen, M. W. (2014). TPGS-g-PLGA/Pluronic F68 mixed micelles for tanshinone IIA delivery in cancer therapy. *International Journal of Pharmaceutics, 476*(1–2), 185–198.

Zhang, L. H., Zhang, Z. R., Han, L. M., & Wang, J. X. (2007). Preparation and pharmaceutical properties of total salvianoic acids liposomes. *Fudan University Journal of Medical Sciences, 24*(03), 391–395.

Zhang, S. S., Yan, H. X., Yu, P. P., Xia, Y. L., Zhang, W. L., & Liu, J. P. (2016a). Development of protocatechualdehyde proliposomes-based sustained-release pellets with improved bioavailability and desired pharmacokinetic behavior for angina chronotherapy. *European Journal of Pharmaceutical Sciences, 93*, 341–350.

Zhang, X. S., Wu, Q., Lu, Y., Wan, J. R., Dai, H. B., Zhou, X. M., ... Wang, J. (2018). Cerebroprotection by salvianolic acid B after experimental subarachnoid hemorrhage occurs via Nrf2- and SIRT1-dependent pathways. *Free Radical Biology and Medicine, 124*, 504–516.

Zhang, Y., Akao, T., Nakamura, N., Duan, C. L., Hattori, M., Yang, X. W., & Li, J. X. (2004). Extremely low bioavailability of magnesium lithospermate B, an active component from *Salvia miltiorrhiza*, in rat. *Planta Medica, 70*(2), 138–142.

Zhang, Z., Li, Y. M., Sheng, C. Q., Yang, C. F., Chen, L. P., & Sun, J. H. (2016b). Tanshinone ⅡA inhibits apoptosis in the myocardium by inducing microRNA-152-3p expression and thereby downregulating PTEN. *America Journal of Translational Research, 8*(7), 3124–3132.

Zheng, J. F., Du, P. P., Yan, H. B., & Wu, Q. (2013). Preparation of multi-components osmotic pump tablets of Danshen *(Radix Salviae Miltiorrhizae)* and release *in vitro*. *Journal of Beijing University of Traditional Chinese Medicine, 35*(06), 394–398.

Zhi, D. F., Yang, T., Yang, J., Fu, S., & Zhang, S. B. (2020). Targeting strategies for superparamagnetic iron oxide nanoparticles in cancer therapy. *Acta Biomaterialia, 102*, 13–34.

Zhou, L. M., Zuo, Z., & Chow, M. S. (2013). Danshen: An overview of its chemistry, pharmacology, pharmacokinetics, and clinical use. *Journal of Clinical Pharmacology, 45*(12), 1345–1359.

Zhou, L. M., Chow, M. S. S., & Zuo, Z. (2009). Effect of sodium caprate on the oral absorptions of danshensu and salvianolic acid B. *International Journal of Pharmaceutics, 379*(1), 109–118.

Zhu, Z. J., Zhao, Y., Li, J. B., Tao, L., Shi, P. L., Wei, Z. H., ... Lu, Y. (2016). Cryptotanshinone, a novel tumor angiogenesis inhibitor, destabilizes tumor necrosis factor-alpha mRNA via decreasing nuclear-cytoplasmic translocation of RNA-binding protein HuR. *Molecular Carcinogenesis, 55*(10), 1399–1410.