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# Recent insights into the biological activities and drug delivery systems of tanshinones

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**Abstract:** Tanshinones, the major lipid-soluble pharmacological constituents of the Chinese medicinal herb Tanshen (*Salvia miltiorrhiza*), have attracted growing scientific attention because of the prospective biomedical applications of these compounds. Numerous pharmacological activities, including anti-inflammatory, anticancer, and cardio-cerebrovascular protection activities, are exhibited by the three primary bioactive constituents among the tanshinones, ie, tanshinone I (TNI), tanshinone IIA (TNIIA), and cryptotanshinone (CPT). However, due to their poor solubility and low dissolution rate, the clinical applications of TNI, TNIIA, and CPT are limited. To solve these problems, many studies have focused on loading tanshinones into liposomes, nanoparticles, microemulsions, cyclodextrin inclusions, solid dispersions, and so on. In this review, we aim to offer an updated summary of the biological activities and drug delivery systems of tanshinones to provide a reference for these constituents in clinical applications.

**Keywords:** tanshinones, biological activities, drug delivery systems, bioavailability, solubility

## Introduction

Tanshen, also known as *Salvia miltiorrhiza*, red sage, Chinese sage, or danshen, is widely used in traditional Chinese medicine for the treatment of cerebrovascular and cardiovascular diseases, as well as inflammatory diseases.<sup>1</sup> Tanshinones are the major liposoluble constituents of Tanshen and consist of abietane type-diterpene quinone pigments.<sup>2</sup> The primary bioactive constituents among the tanshinones are tanshinone I (TNI), tanshinone IIA (TNIIA), and cryptotanshinone (CPT) (Figure 1), which have attracted special attention for possessing various pharmacological effects, including anti-inflammatory, anticancer, and cardio-cerebrovascular protection activities.<sup>3,4</sup> TNIIA, which has been studied from the 1930s, has potential effects against diabetes, neurodegenerative diseases, and cardiac hypertrophy.<sup>5</sup> In addition to the anti-inflammatory and anticancer effects, TNI also enhances the ability to memorize and learn and ameliorates memory impairment.<sup>6–8</sup> Recently, a number of studies have been published concerning the modification, biosynthesis, metabolism, pharmacological actions, and therapeutic applications of tanshinones.<sup>5,9–15</sup> However, the poor water solubility and low oral bioavailability of tanshinones have limited their clinical applications. There have been no reviews that focused on the drug delivery systems of tanshinones to date. To give summary of current research progress of tanshinones, the organization of this review is as described later. First of all, the review outlines the various pharmacological of tanshinones (Figure 2), which indicates the high medicinal value of them. Then, the development of drug delivery systems for tanshinones are discussed, including liposomes, solid dispersion, and nanoparticles (NPs), which has been used to solve the poor bioavailability of tanshinones. Finally, we make a conclusion of our personal perspectives on the directions for developing tanshinone.



P-gp and suppressing its pump activity.<sup>48–51</sup> The clinical use of TIIA for cancer treatment has been reported in a patient with acute promyelocytic leukemia, who had no response to all-trans retinoic acid (ATRA) (20 mg, three times per day) for 14 days, and they achieved a complete remission after treated with TIIA (30 mg, oral, two times per day) for 12 weeks.<sup>52</sup> Cancer-related clinical trials of TIIA and tanshinone-containing traditional Chinese medicine formulas were well presented in this review.<sup>53</sup>

## Anti-inflammatory activities

TNIIA has shown remarkable anti-inflammatory activity by inhibiting the expression of inflammatory mediators, including interleukin (IL)-1 beta, IL-6, and tumor necrosis factor (TNF)-alpha, in an estrogen receptor subtype-dependent manner in murine macrophage RAW264.7 cells pretreated with lipopolysaccharide (LPS).<sup>54</sup> Additionally, TNIIA suppresses LPS-induced nuclear factor kappaB (NF-κB) activation through the inhibition of the NF-κB-inducing kinase/IkappaB alpha kinase (NIK/IKKalpha), ERK1/2, p38, and c-Jun N-terminal kinase (JNK) pathways.<sup>55</sup> Recently, data from a protein interaction network analysis have suggested that the anti-inflammatory effect of TNIIA may result in part from activating TNF receptor-associated factor (TRAF) 2/3/6 and inhibiting the toll-like receptor (TLR) signaling pathway.<sup>56</sup> TNI significantly inhibited the activity of group IIA secretory phospholipase A<sub>2</sub> (GIIA) to thereby block prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) formation in LPS-activated macrophages and exhibited in vivo anti-inflammatory activity in rats with adjuvant-induced arthritis and carrageenan-induced paw edema.<sup>57</sup> TNI and CPT also significantly inhibit IL-12 production in LPS-activated macrophages and interferon-γ production in lymph node cells.<sup>58</sup>

## Other pharmacological activities

Tanshinones are known as natural antioxidants by forming a quinone adduct of the lipid radical to form a stabilized radical.<sup>2</sup> TNIIA is able to prevent the DNA damage in liver cells resulting from lipid peroxidation by scavenging lipid free radicals and breaking the peroxidation chain reactions.<sup>59</sup> Preincubation with TNIIA significantly decreases the H<sub>2</sub>O<sub>2</sub>-induced death of ECV-304 human umbilical vein endothelial cells and J774 macrophages.<sup>60,61</sup> In addition, TNI activated the NF-E2 p45-related factor 2 (Nrf2)-dependent antioxidant response by preventing ubiquitination-mediated Nrf2 degradation and protected against As (III)-induced lung damage in vitro and in vivo.<sup>62</sup> TNI inhibited peroxynitrite-induced DNA damage by diminishing the 5,5-dimethyl-1-pyrroline

*N*-oxide-hydroxyl (DMPO-OH) radical adduct signal from peroxynitrite.<sup>63</sup> Tanshinones also have potent antiosteoporotic activities by targeting different pathways in the bone remodeling cycle.<sup>64</sup> It has been demonstrated that TNIIA, TNI, and CPT have obvious inhibitory effects on osteoclast differentiation.<sup>65</sup> It was found in further experiments that TNIIA inhibits osteoclast differentiation through blocking Akt, ERK, and NF-κB activation and downregulating the expression of c-Fos and nuclear factor of activated T-cells (NFATC1), cytoplasmic, calcineurin-dependent 1, which all are induced by receptor activator of NF-κB ligand.<sup>66,67</sup> Furthermore, TNIIA also suppressed bone resorption of differentiated osteoclasts.<sup>67</sup> Notably, TNIIA and TNI have insulin-sensitizing effects and enhance the ability of insulin to promote the tyrosine phosphorylation of the insulin receptor and the activation of the downstream ERK, Akt, and glycogen synthase kinase-3 beta (GSK-3β) kinases in Chinese hamster ovary cells and 3T3-L1 adipocytes.<sup>68</sup> It has been shown that CPT has potent antibacterial activity against a wide range of Gram-positive bacteria in a reactive oxygen species (ROS)-dependent manner<sup>69</sup> and has the potential to treat Alzheimer's disease as an inhibitor of acetylcholinesterase.<sup>70</sup> Particularly, major tanshinones such as TNIIA, TNI, and CPT are able to competitively inhibit the metabolism of CYP1A2 substrates,<sup>71</sup> and TNIIA and CPT are efficacious pregnane X receptor (PXR) agonists that induce CYP3A4 expression, suggesting that attention should be paid when tanshinones are used in combination with drugs metabolized by CYP1A2 and CYP3A4.<sup>72</sup> Recently, TNIIA, TNI, and CPT were found to be specific and selective inhibitors for the SARS-CoV cysteine proteases 3CL<sup>pro</sup> and PL<sup>pro</sup>, but did not exert significant inhibitory effects against other proteases, including chymotrypsin, papain, and HIV protease.<sup>73</sup> Moreover, TNIIA could inhibit tat-induced HIV-1 transactivation through redox-regulated AMPK/NAMPT pathway.<sup>74</sup>

## Drug delivery systems

Despite the multiple pharmacological effects of TNIIA, the poor water-solubility and low dissolution rate of this compound result in low oral bioavailability and have hampered the clinical application of TNIIA.<sup>75</sup> To tackle this problem, various methods have been developed, including the preparation of STS, the water-soluble derivative of TNIIA, the preparation of TNIIA in discoidal and spherical high-density lipoproteins, and the development of drug delivery systems for TNIIA.<sup>5</sup> To date, many studies have focused on loading TNIIA into liposomes or NPs, microemulsions, cyclodextrin (CD) inclusion, and solid dispersions.<sup>76–80</sup> In addition,

preparations of TNI and CPT with better intestinal absorption have been studied in recent years due to the unsatisfactory clinical effects of these agents, which have been attributed to their low levels of biological utilization;<sup>81,82</sup> these preparations include solid dispersion and solid lipid NPs.<sup>81,83</sup> Table 1 shows the various drug delivery systems of tanshinones.

## Liposomes

Liposomes are closed spherical vesicles composed of a lipid bilayer and have attractive properties, including biocompatibility, biodegradability, low clearance rates, and low toxicity.<sup>84</sup> To establish a highly efficient delivery system with multiple functions, more than one therapeutic drug can be entrapped within the aqueous liposomal interior or embedded into the liposomal membrane, depending on the characteristics of the drug and the process of encapsulation.<sup>85</sup> Because of these benefits, liposomes were used to encapsulate glycyrrhetic acid (GA), salvianolic acid B (SB), and TNIIA, enhancing the bioavailability and water solubility of the compounds, which then exerted synergistic effects on the inhibition of hepatic stellate cell (HSC) proliferation.<sup>76</sup> In this study, TSIIA and GA, the hydrophobic constituents, were incorporated into phospholipid bilayers by employing the film hydration method with probe sonication, and the pH-gradient method was then used to load the hydrophilic constituent SB, which finally yielded the GA-TNIIA-SB compound liposomes (GTS-lip) with cholesterol and soybean phospholipids. Eventually, the encapsulation efficiency of these drugs was >80% with little difference among the individual compounds. This study demonstrated that GTS-lip could suppress the proliferation of HSC with a sustained-release effect more effectively than a mixed solution of GA, TNIIA, and SB, which may promote the clinical application and therapeutic activities of tanshinones.<sup>76</sup> The outstanding advantage of the liposomal drug delivery system is the ability to co-encapsulate different drugs to exert synergistic effects in a sustained-release manner, which is more efficient than treatment with unencapsulated drugs. However, a challenge still exists in controlling the ratio of different drugs to produce an improved healing efficacy.

## Emulsions

Emulsions are a class of formulation consisting of two immiscible phases stabilized by a surfactant<sup>86</sup> and are widely used to enhance the stability of active constituents, thereby maintaining their effectiveness.<sup>87</sup> In previous studies, lipid emulsions,<sup>88</sup> microemulsions,<sup>89</sup> and nanoemulsions<sup>90</sup> of soybean phospholipid, pluronic F68 (F68), glycerol, oleic acid,

lecithin, and so on were used to produce TNIIA formulations with long-term stability and obvious anticancer activity.

However, nanoemulsions have proved to have higher bioaccessibility, stability, and optical clarity than conventional emulsions;<sup>91,92</sup> nanoemulsions are similar to microemulsions that are monodispersed spherical droplets with thermodynamic stability as well as excellent solubility properties.<sup>93,94</sup> In recent years, a series of studies have been reported regarding the preparation processes, quality control, and evaluation profiles of tanshinone microemulsions.<sup>89,90,95–97</sup> TNIIA was encapsulated into a microemulsion, consisting of F68, phospholipid, ethyl oleate, and glycerol, which had an antitumor effect on hepatoma H22 cells and mice.<sup>89</sup> Moreover, another TNIIA microemulsion with a mean droplet size of  $32.25 \pm 6.59$  nm was prepared to improve the bioavailability in rat small intestine. The results of the absorption in small intestine of TNIIA microemulsion showed that TNIIA microemulsion could improve the absorption of TNIIA in rat small intestine with the influence of the water-phase ratio (TNIIA microemulsion) to the absorption coefficient.<sup>97</sup> Additionally, TNIIA nanoemulsions were formed with an average particle size of 95.6 nm and an excellent entrapment efficiency of 99.3%, which showed potent cytotoxicity with 103.4-fold greater than TNIIA alone against T24 human bladder cancer cells in a time- and dose-dependent manner.<sup>90</sup> It was also reported that a tanshinone microemulsion possessed cytotoxic effects on the human leukemia cell line K562/ADM,<sup>95</sup> and a method of establishing the high performance liquid chromatography fingerprints of tanshinone microemulsions has been developed to control the quality.<sup>96</sup>

Although TNIIA emulsions have excellent long-term stability and anticancer activity, it is not convenient enough to prepare the emulsions with more than four types of materials, which may hinder the application of TNIIA emulsions with unsatisfactory bioavailability.

## CD inclusion

CD and its derivatives, including  $\alpha$ -CD,  $\beta$ -CD,  $\gamma$ -CD, and 2-hydroxypropyl-beta-cyclodextrin (HP- $\beta$ -CD), have a cage-like supramolecular structure and the ability to form inclusion complexes with various molecules; these complexes have been used as drug carriers in a number of applications, such as nasal administration, oral drug delivery, and dermal drug delivery, to enhance the stability, solubility, and bioavailability of the drugs.<sup>98</sup> Hence, the inclusion complexes of TNIIA or TNI and CDs were obtained via coprecipitation and lyophilization to enhance the level of biological utilization, and the results proved that HP- $\beta$ -CD had a greater stability than  $\beta$ -CD.<sup>99</sup> Furthermore, the transport mechanism



Table 1 Various drug delivery systems of tanshinones

Drug delivery systems	Materials	Drugs	Advantages	Disadvantages
Liposomes	Cholesterol, soybean phospholipid	TNIIA, SB, and GA	Codelivery of three drugs to exert synergistic effects	Difficult to control the ratio of the drugs
Emulsion	Soybean phospholipid, pluronic F68, oleic acid, glycerol	TNIIA	Long-term stability and obvious anticancer activity	More than four kinds of materials may hinder the application of TNIIA emulsions
Lipid emulsion	Soybean lecithin, soybean oil and medium-chain triglyceride, pluronic F68, glycerol	TNIIA		
Microemulsion	Phospholipid, ethyl oleate, pluronic F68, glycerol	TNIIA		
Nanoemulsion	Tween 80, lecithin, etc	TNIIA		
Cyclodextrin inclusion	2-Hydroxypropyl-beta-cyclodextrin	TNIIA or CPT	Enhancement of gastrointestinal tract absorption of drugs	The temperature of cyclodextrin inclusion should be controlled critically
Solid dispersion	Nano-CaCO <sub>3</sub> , pluronic F68	TNIIA	Higher stability and superior oral bioavailability with potent pharmacological effects	No long circulation function to have higher efficacy against cancer
	Nano-hydroxyapatite	TNIIA		
	Low molecular weight chitosan	TNIIA		
	Copovidone	TNIIA		
	Porous silica	TNIIA		
	Povidone K-30	TNIIA, TNI or CPT		
	Poloxamer 407	TNIIA, TNI or CPT		
Nanoparticles	Nano-silica, pluronic F68	TNIIA		
	Polyvinylpyrrolidone K30, pluronic F68	TNIIA		
	Poly(D,L-lactide-co-glycolide acid)	TNIIA, SB, and PNS		
	Cationic bovine serum albumin, PEGylated poly(lactic acid)	TNIIA	Sustained release of drugs and long circulation time in the human body with excellent pharmacological activities	No targeted delivery system with better cell uptake of drugs and minimal systemic side effects
	Pluronic F68 coating solid lipid nanoparticles	TNIIA		
	Poly(lactic acid)	TNIIA	Sustained release of drugs	No targeted delivery for better pharmacological effects
Pellets	Polyvinyl acetate and poly(vinyl alcohol)-poly(ethylene glycol) graft copolymer	TNIIA		
	Polyvinylpyrrolidone, pluronic F68	TNIIA		
	Hydroxypropyl methylcellulose, surelease	TNIIA		
Micelles	D-alpha-tocopheryl polyethylene glycol succinate-graft-poly(D,L-lactide-co-glycolide), pluronic F68	TNIIA	Long circulation time and high bioavailability	No targeted delivery for better pharmacological effects

**Abbreviations:** TNIIA, tanshinone IIA; SB, salivianolic acid B; GA, glycyrrhethinic acid; CPT, cryptotanshinone; TNI, tanshinone I; PNS, panax notoginsenoside; PEG, polyethylene glycol.

of TNIIA-HP- $\beta$ -CD was found by the recirculation intestinal perfusion technique<sup>100</sup> to be passive transport with no particular absorption site for TNIIA in vivo, and the permeability rate of TNIIA-HP- $\beta$ -CD through the intestinal epithelial membrane was seven times higher than that of free TNIIA, indicating that the TNIIA-HP- $\beta$ -CD complex enhanced the gastrointestinal tract absorption of TNIIA.<sup>77</sup> In addition, inclusion complexes of CPT with HP- $\beta$ -CD (inclusion ratio 1:1) were prepared by the wet grinding method, which significantly improved the dissolution of CPT.<sup>101</sup>

## Solid dispersions

The production of solid dispersions is a technique for improving the dissolution rate and bioavailability of poorly water-soluble drugs by dispersing the drugs into solid-state hydrophilic carriers with an increased surface area.<sup>102</sup> Therefore, solid dispersions of TNIIA, TNI, and CPT have been applied to improve the dissolution, stability, and bioavailability of these tanshinones. There are various types of carriers being used to prepare solid dispersions of TNIIA via the solvent technique or spray-drying method, such as combinations of polyvinylpyrrolidone (PVP)-K30 and F68,<sup>103</sup> nano-silica and F68,<sup>104</sup> poloxamer 407 or povidone K-30,<sup>81</sup> porous silica,<sup>105</sup> copovidone (PVP-S630),<sup>106</sup> low molecular weight chitosan (LMC),<sup>17</sup> nano-CaCO<sub>3</sub>, and F68.<sup>80</sup> Among TNIIA-poloxamer407, TNIIA-HP- $\beta$ -CD, and TNIIA-PVP-K30, the best dissolution rate of TNIIA solid dispersions was TNIIA-poloxamer407.<sup>81</sup> In addition, TNIIA-PVP-S630 had better dissolution rates than TNIIA-silica NPs and TNIIA-nano-silica-F68.<sup>104–106</sup> Moreover, TNIIA-PVP-S630 at a proportion of 1:10 improved the solubility up to 100% at 30 minutes and could be stored for 3 months with no change in the dissolution or components and little moisture absorption, which was better than TNIIA-poloxamer407.<sup>106</sup> Moreover, LMC and TNIIA (weight ratio 9:1) were used to prepare a solid dispersion that increased the dissolution rate by 368.2% compared to free TNIIA, which could enhance the absorption rate and oral bioavailability.<sup>17</sup> It was also reported that ternary solid dispersions that were composed of F68, nano-CaCO<sub>3</sub>, and TNIIA demonstrated high dissolution rates and stability, representing a promising method to prepare solid dispersions.<sup>80</sup> Despite the benefits of solid dispersions mentioned earlier, it is necessary to obtain long-lived circulation within the human body and greater efficacy against cancer.

## Nanoparticles

NPs, loosely defined as particles with 1–100 nm diameters,<sup>107</sup> can enhance the solubility and dissolution rate of drugs by

decreasing the particle size and enlarging the surface area.<sup>105</sup> Therefore, a number of polymeric carriers have been used to prepare NPs of TNIIA with better bioavailability, such as poly(D,L-lactic-co-glycolic acid) (PLGA),<sup>108,109</sup> polylactic acid (PLA),<sup>110</sup> F68,<sup>111</sup> and cationic bovine serum albumin (CBSA)-conjugated PEGylated PLA.<sup>78</sup> NPs of TNIIA-loaded PLGA (TNIIA-PLGA-NPs) had good biocompatibility and high absorption with preventive effects in the neointimal hyperplasia of the rabbit carotid artery after intimal denudation.<sup>109</sup> Furthermore, it is more efficient to prepare TNIIA-PLGA-NPs by the nanoprecipitation method instead of the emulsion evaporation method, resulting in particles with average diameters of 225 nm, an entrapment efficiency of 95.49%, a drug loading of 2.03%, and drug recovery rate of 38.42%.<sup>108</sup> Another type of material, PLA, was used to prepare novel NPs of TNIIA (TNIIA-PLA-NPs) by a single oil-in-water emulsion/solvent evaporation method, and the resulting particles had a significant dose- and time-dependent growth-inhibitory effect on hepatomas with sustained release in vitro and in vivo, which had 2.69-fold survival time of mice bearing hepatoma tumor than TNIIA.<sup>110</sup> Despite the enhanced bioavailability and water solubility of TNIIA with the NPs mentioned earlier, it is more efficient to modify the NPs to obtain an extended circulation within the human body. As a result, TNIIA NPs were modified with PEG (polyethylene glycol)<sup>78</sup> and F68<sup>111</sup> to enable an extended circulation within the human body with potent pharmacological activities. TNIIA PEGylated nanoparticles (PEG-TNIIA-NPs) were prepared using the double emulsion/solvent evaporation technique and then conjugated with CBSA through the maleimide function, finally forming CBSA-PEG-TNIIA-NPs with a long circulating time of 7.89 hours and better uptake efficiency in the brain than a TNIIA solution. The study also indicated that CBSA-PEG-TNIIA-NPs, which exhibited significant neuroprotective effects in ischemic stroke, could suppress microglial activation, inhibit neutrophil infiltration, and downregulate multiple pro-inflammatory cytokines via the regulation of p38 MAPK and PPAR signaling pathways.<sup>78</sup> Moreover, solid lipid NPs of CPT were prepared by an ultrasonic and high-pressure homogenization method to improve the low bioavailability with soy lecithin and Tween 80 as emulsifiers.<sup>83</sup> Although TNIIA NPs have greater bioavailability as well as water solubility and a long circulation time in the human body with excellent pharmacological effects, it would be promising to prepare polymeric NPs of TNIIA with the capability of targeted delivery, which has attracted much attention due to the enhanced cell uptake of drugs with minimal systemic side effects.<sup>112</sup>

## Others

In addition to the formulations of TNIIA mentioned earlier, pellets<sup>113</sup> and micelles<sup>114</sup> have also been used to enhance the solubility and stability of TNIIA. Several materials were applied to the TNIIA pellets with sustained release, including hydroxypropyl methylcellulose (HPMC) and surelease,<sup>113</sup> PVP and F68,<sup>115</sup> polyvinyl acetate (PVAc), and poly(vinyl alcohol)-poly(ethylene glycol) (PVA-PEG) graft copolymer.<sup>116</sup> In addition, D-alpha-tocopheryl polyethylene glycol succinate-graft-PLGA (TPGS-g-PLGA) copolymer and F68 were used to form mixed micelles with improved bioavailability and prolonged circulation times against hepatocellular carcinoma.<sup>114</sup> However, neither of these formulations had a targeted delivery system for the improved cellular uptake of TNIIA.

## Conclusion

To overcome the low bioavailability of tanshinones, many methods have been used to improve the solubility and dissolution rates as well as prolong the circulating times of these compounds; in particular, solid dispersion and NPs have shown better results than other formulations. In recent research, most of the formulations have had no tissue specificity. To enhance the pharmacological effects of TNIIA, it is necessary to design a type of drug preparation with components that actively target tumor tissue or other parts of the body. Despite the high dissolution rates of tanshinones obtained by these novel techniques, there has been little development in the clinical application of these formulations due to the complex process to produce the formulations and the lack of further research of TNIIA formulations on clinical trials, which is the ultimate goal in pharmaceutical research. In addition, it is necessary to clarify the light sensitivity of TNIIA in future research, and the development of TNIIA preparations may in part be driven by this lack of information. In conclusion, it is expected that with more and more effort for developing drug delivery systems of tanshinones and their clinical application, formulations of tanshinones can make a breakthrough and better therapy in the future.

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## Disclosure

The authors report no conflicts of interest in this work.

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