Table 1: Summary of nano-formulated polyphenols for improved pharmacokinetics and use in cardiovascular therapy

Polyphenol	Nano-formulation	Process	Size (nm)	Entrapment efficiency	Study type	Major results	Ref
Quercetin	Nano-quercetin	Anti-solvent precipitation	170	-	In vitro dissolution study	Enhanced quercetin dissolution in simulated intestinal fluid	18
	PLGA nanoparticle	Electrohydrodynamic atomization	384.9	-	In vitro stability and release study	Sustained release for over 59 days.	19
	SLN	Emulsification and low temperature solidification	155.3	91.1%	In situ absorption study	Enhanced intestinal absorption and oral bioavailability	20
	PLGA nanoparticle	Solvent displacement	399.67±10.86	79.84±2.5%	In vitro release and anti-oxidant study	Higher free radical scavenging activity of encapsulated flavonoid	21
	Eudragit® E and PVA nanoparticle	Nanoprecipitation	81.9±0.26	99.9±0.59%	Development and in-vitro anti-oxidant activity of nanoparticles	Greater anti-oxidant activity of nano-formulation.	22
	Mesoporous silica nanoparticle	-	100-150	89.47±1.28%	In-vitro and In-vivo models of myocardial ischemia-reperfusion injury	Mesoporous silica nanoparticles intensified the activation of JAK/STAT pathway and more effectively inhibited myocardial injury	23
	PLGA nanoparticle	Oil-in-water emulsification	165±7.5	98.15%	In-vitro model of hypoxia-reoxygenation injury	Better flavonoid delivery to cardiomyocyte upon nano-encapsulation. Increased cell	27

						viability. Reduced mitochondrial oxidative stress.	
	Superparamagnetic silica and PLGA nanoparticle	Sol-gel technique	100-200	-	Fabrication and in vitro evaluation of nano biocarrier	Controlled drug release. Reduced infarct size.	30
Curcumin	SLN	Microemulsion technique	450	70%	Formulation and characterization of nanoparticles	Prolonged drug release up to 12h. Improved physical and chemical storage stability.	40
	PBCA (poly(butyl) cyanoacrylate) nanoparticles coated with poloxamer 188	Anionic polymerization using solvent evaporation method	178	77.99%	Physicochemical characterization and stability study	Controlled drug release with higher release at acidic pH. Increased storage stability.	41
	Liposome (lecithin-SLP-white and SLP-PC70)	-	263±86	68%	In vivo oral bioavailability and anti-oxidant activity	Improved bioavailability. Enhanced anti-oxidant effect	42
	PLGA-PEG blend nanoparticles	Single-emulsion solvent evaporation	<200	70%	Oral pharmacokinetic study	Prolonged drug release. 7.4-times increase in maximum plasma concentration. 55.5-times higher bioavailability of encapsulated curcumin compared to aqueous solution	43
	PLGA-PVA nanoparticle	Emulsion-diffusion-evaporation method	264±2	76.9%	In-vivo pharmacokinetic study	9-fold increase in oral	44

						bioavailability	
	CMC (carboxymethyl chitosan) nanoparticle conjugated with myocyte specific homing peptide	-	331.2	61.24%	In-vivo and in-vitro models of cardiac hypertrophy	Targeted delivery of drug at the hypertrophic myocyte. High cardiac bioavailability of drug even at a low dose. Improved cardiac functions and reduced apoptosis of hypertrophied cardiac cells.	46
	Curcumin nanoparticles	-	300 ± 50	-	Pulmonary arterial hypertension induced cardiac remodeling	Reduced right ventricular wall thickness and tissue weight. Mitigated cardiac expression of inflammatory proteins like TNF-α and IL-1β. Inhibited cardiac remodeling and oxidative stress.	47
	PEG-PDLLA (poly (ethylene glycol)-b-poly (DL-lactide)	-	<100	-	In-vitro palmitate induced cardiomyocyte injury	Mitigated cardiac apoptosis and attenuated oxidative stress and lipotoxic cellular damage through the AMPK pathway	48
	PEG-PDLLA nanoparticle (Monomethoxy	-	50	-	In-vitro cardio protection from palmitate induced	Anti-apoptotic and anti-oxidant effect	49

	poly (ethylene-glycol)-b-poly (DL-lactide))				apoptosis	reduced cardiomyocyte death. Anti-apoptotic effect mediated through inhibition of NADPH-mediated oxidative stress and ERS (endoplasmic reticulum stress)-related pathway.	
Curcumin-Nisin	PLA (poly Lactic Acid) nanoparticles	Double emulsion-diffusion-evaporation	284±17.9	-	Isoproterenol induced myocardial infarction	Reduced expression of cardiac and renal injury markers. Improved cardiac functions	50
Resveratrol-curcumin (5:1)	Pluronic® F-127 micelles	Solvent casting method	25.05	-	In-vitro doxorubicin induced cardiotoxicity	Alleviated doxorubicin induced cardiotoxicity by anti-apoptotic and anti-oxidant pathways.	45
Resveratrol-quercetin	Pluronic® F-127 micelles	Solvent casting method	22.34±0.15	-	In-vitro and in-vivo model of doxorubicin induced cardiotoxicity	Increased circulation time of enclosed molecules. Reduced oxidative stress and improved cell viability. Enhanced cardio protection.	73
	Sodium deoxycholate (SDC)- elastic	Thin lipid film method	149	97%	Formulation and characterization of dual-loaded liposome	Improved storage stability.	74

	liposome					Sustained release of drugs for 60h	
Resveratrol	PLGA nanoparticles	Emulsion evaporation	257.90± 8.29nm	20%	In-vivo Isoproterenol-induced myocardial infarction	Reduced oxidative stress. Reduced inflammatory damage. Upregulated eNOS and downregulated iNOS expression. Enhanced bioactivity and cardio protection.	71
	SLN (egg yolk lecithin, glyceryl monostearate)	Emulsion-diffusion	271.13	-	In vivo pharmacokinetic and dynamic effect on animal model of doxorubicin induced cardiotoxicity	Improved solubility and sustained release of the drug. Improved cardiac functions.	72
	SLN (Stearic acid, Phospholipon® 90 G)	Solvent diffusion-solvent evaporation method	134±7.6	88.9%	Oral pharmacokinetic study	Sustained drug release up to 120h. 8-fold increase in oral bioavailability	53
	Layer-by-layer nano-formulation (polyallylamine hydrochloride and dextran sulfate)	-	215.3±2.3	-	Oral bioavailability study	1.76-fold increment in plasma drug concentration. Improved chemical stability of resveratrol in simulated gastric and intestinal fluids.	57
	SLN (N-trimethyl chitosan graft	Emulsification and ultrasonication method	258.28±18.74	95.45±2.18%	In-vitro and in-vivo drug release study	Negligible drug release in simulated	55

	palmitic acid)					gastric fluid. Sustained drug release at intestinal pH. 3.8-fold increase in oral bioavailability	
	SLN and NLC	Hot homogenization	150-250	70%	In-vitro oral drug release study	Improved storage stability. Controlled drug release at gastrointestinal pH.	54
	Carboxymethyl chitosan	Emulsion cross-linking	155.3±15.2	44.5±2.2%	In vitro anti-oxidant and in vivo bioavailability study	Enhanced anti-oxidant activity. Increased solubility and bioavailability.	58
	Galactosylated PLGA nanoparticles	Solvent diffusion method	108.4	-	Pharmacokinetic study	Enhanced oral bioavailability by 335.7%.	60
	PLGA nanoparticles	Nanoprecipitation	90.35±1.2	78.25±1.2	Oral bioavailability study	10-fold increase in bioavailability	59
Baicalin	NLC (glycerol monostearate and medium chain triglyceride)	Emulsion-evaporation and low temperature solidification	244.7	59.51±0.57%	Formulation, in-vitro drug release and in vivo pharmacokinetic study	Sustained drug release for over 48h. Significantly improved plasma drug concentration and retention time. Enhanced oral bioavailability	89
	NLC (glycerol monostearate, polyethylene glycol monostearate and oleic acid)	Emulsion-evaporation and low temperature solidification	83.9	83.5%	In-vitro and in-vivo pharmacokinetic and biodistribution evaluation	Sustained release, improved AUC and plasma retention. Increased drug accumulation at the heart. Reduced infarct size.	90

EGCG (epigallocatechin-3-gallate)	Chitosan coated NLC	Phase-inversion technique	56.5±3.2	99%	In-vitro drug release, cytotoxicity and bioactivity study on macrophages	Improved drug stability. Increased cellular drug uptake. Reduced macrophage cholesterol content and monocyte chemoattractant protein-1 (MCP-1).	94
	Gold nanoparticles	-	40±5	48%	In-vitro stability, affinity and selectivity study towards smooth muscle and endothelial cells	Selective anti-proliferative and anti-migratory effect on smooth muscle cells with no toxic effect on endothelial cells. Cellular endocytosis of EGCG via the laminin receptor	93
	Chitosan-tripolyphosphate nanoparticles	-	440±37	-	In-vivo bioavailability study	1.5-fold increase in plasma and 2.3-fold increase in intestinal (jejunum) drug concentration. Enhanced oral bioavailability	95
Icariin	Monomethyl ether polyethylene glycol (mPEG)	-	143.3	32%	In-vitro model of myocardial ischemia	Prolonged drug release for 72h. Reduced ischemic cell damage. Improved cardiomyocyte activity under glucose and	100

						oxygen deprivation. Decreased myocardial apoptosis. Enhanced icariin bioactivity.	
Puerarin	SLN (monostearin and soy lecithin)	Solvent injection method	160	-	Oral pharmacokinetic study	Increased drug plasma concentration and Cmax with shorter Tmax. Higher cardiac and brain drug accumulation. 1.46-times higher bioavailability.	101
	Cyclic arginyl-glycyl-aspartic acid (RGD) peptide modified PEGylated SLNs	Solvent-evaporation method	70-110	88.9±3.1%	Pharmacokinetic and dynamic study on acute myocardial ischemia in-vivo	Drug accumulation at the ischemic myocardium. Longer plasma retention time. Improved therapeutic efficacy of puerarin.	103
Puerarin prodrug-tanshinone	Co-loaded SLN	Single emulsification-solvent evaporation method	112.6±3.1	86.7±3.3%	In-vitro and in-vivo evaluation of co-loaded nanoparticle	3.4-fold increase in heart drug concentration. Increased therapeutic efficacy of enclosed drugs. Reduced infarct size with dual loaded nanoparticles compared to single drug loaded SLN.	102
Tilianin	Nano-micelles	-	70	-	In-vitro model of myocardial	Improved anti-oxidant and	105

					hypoxia/reoxygenation injury	anti-apoptotic activity. Increased cardiac protection against ischemic injury.	
Wogonin	PLGA-PVA nanoparticles	-	194.82	74.89%	In-vivo model of isoproterenol induced myocardial infarction	Significantly reduced myocardial infarct size. Enhanced cardio protection by down-regulation of inflammatory markers and upregulation of cardioprotective proteins (Nrf2 and heme oxygenase-1)	104

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