REVIEW

Current Advances in the Use of Nanophytomedicine Therapies for Human Cardiovascular Diseases

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Abstract: Considering the high prevalence of cardiovascular diseases (CVDs), the primary cause of death during the last several decades, it is necessary to develop proper strategies for the prevention and treatment of CVDs. Given the excessive side effects of current therapies, alternative therapeutic approaches like medicinal plants and natural products are preferred. Lower toxicity, chemical diversity, cost-effectiveness, and proven therapeutic potentials make natural products superior compared to other products. Nanoformulation methods improve the solubility, bioavailability, circulation time, surface area-to-volume ratio, systemic adverse side effects, and drug delivery efficiency of these medications. This study intended to review the functionality of the most recent nanoformulated medicinal plants and/ or natural products against various cardiovascular conditions such as hypertension, atherosclerosis, thrombosis, and myocardial infarction. Literature review revealed that curcumin, quercetin, and resveratrol were the most applied natural products, respectively. Combination therapy, conjugation, or fabrication of nanoparticles and nanocarriers improved the applications and therapeutic efficacy of herbal- or natural-based nanoformulations. In the context of CVDs prevention and/or treatment, available data suggest that natural-based nanoformulations are considerably efficient, alone or in blend with other herbal/synthetic medicines. However, clinical trials are mandatory to elucidate the safety, cardioprotective effect, and mechanism of actions of nanophytomedicines.

Keywords: cardiovascular diseases, medicinal plants, natural products, nanoformulation, nanoparticles

Introduction

Cardiovascular diseases (CVDs) are among the most significant and evergrowing concerns during the last several decades, accounting as the most lethal diseases worldwide. Approximately 17.7 million deaths were associated with CVDs in 2015 worldwide, corresponding to about 31% of all global death. Based on the World Health Organization (WHO) report, nearly 7.4 and 6.7 million deaths are caused by coronary heart diseases and stroke, respectively.[1] The most common controllable risk factors for CVDs include a high degree of psychosocial factors, over-consumption of alcohol, the elevated value of low-density lipoprotein (LDL) and cholesterol, hypertension, insufficient consumption of fruits and vegetables, diabetes mellitus, abdominal obesity, smoking, and the lack of regular physical activity.[2,3] Combination of cholesterol, fat, calcium, and other harmful substances can form plaques, leading to atherosclerosis or hardening of the arteries. Depending on which vessels are affected by this process, cerebrovascular disease, coronary artery disease, cardiac arrhythmias, and the subsequent development of heart failure

can occur.[4] Although various kinds of therapies have emerged to control CVDs, most of them have not been sufficient to prevent or significantly reduce CVDs progression and prevalence. Considering the proven side effects of current therapies, the development of novel therapeutic strategies is emerging.[5] Given the significance of nanotechnology, especially in medicine, it may be an innovative tool to prevent or cure CVDs.[6]

Since a long time ago, herbal products have been extensively utilized to tackle severe diseases. Besides, many pharmaceutical products are derived from plants.[7,8,9] Enormous chemical diversity, low toxicity, therapeutic potentials, and cost-effectiveness make natural compounds precious to being exploited for discovering new therapeutic agents.[7,10,11]

Nanoformulation is a practical therapeutic approach to diminish the probable side effects of medications and enhance drug delivery efficiency.[12] Encapsulation of natural products and their derivatives provides unique advantages, including reduced systemic adverse side effects, enhanced biosafety, high solubility and bioavailability of drugs, extended circulation time, and restricted accumulation in target organs.[13,14] Different features of target organs can indicate the specific types of nanostructures that have to be designed to cure diseases. Diverse organic and inorganic nanostructures, including nanoparticles (NPs), have been developed to deliver phytochemicals such as curcumin, emodin, gymnemic acid, tilianin, puerarin, berberine, quercetin (QUE), scutellarin, magnolol, breviscapine, resveratrol, baicalin, naringenin, and so on.[13,15] However, therapeutic applications of some natural products such as nano-curcumin or nano-resveratrol have been clarified. Data are nonetheless inadequate when it comes to CVDs.[16,17] Considering the high prevalence of CVDs, the current study aimed to review the probable therapeutic advantages of nanophytomedicine for CVDs treatment. This article introduces medicinal plants and natural products that are favorable for CVDs prevention or treatment, along with the recent advances of natural-/herbal-based nanoformulations, as efficient carriers for drug delivery against CVDs.

Study Design

Data were collected using several electronic databases, including Scopus, PubMed, and Google Scholar. Relevant in vitro and in vivo studies investigating the effects of natural-/herbal-based nanoformulations for CVDs management were collected until July 2020. This comprehensive review was performed using the following keywords: "cardiovascular disease", "cardiovascular disorder", "hypertension", "atherosclerosis", "thrombosis", "myocardial infarction", "coronary artery disease", "pulmonary arterial hypertension", "stroke", "ischemia reperfusion injury", "nanophytomedicine", "nanophytochemical", "natural product", "herbal extract", "medicinal plants", "nanomaterials", "nanoparticles", "nanoemulsion", "liposome", "micelle" in title/abstract/keywords. To harmonize data, non-English language articles were excluded.

Medicinal Plants and Phytochemicals in Cardiovascular Diseases

Medicinal plants are defined as a medicine derived from parts of plants or a whole plant and constructed as a crude or purified form to treat or prevent disease. Phytochemicals or plant-derived natural products are chemicals that are produced through primary or secondary metabolism. The plants are a reservoir of primary or secondary metabolites that generally have biological activity and are suitable for pharmacological studies.[18] A large group of medicinal plants known as alternative therapies for CVDs treatment is listed in Table 1. For example, it has been demonstrated that saponin components of *Panax notoginsenoside*, including ginsenoside Rg1, ginsenoside Rg3, ginsenoside Rb1, and notoginsenoside R1, can inhibit thrombosis, protect from ischemic myocardial cells, expand peripheral vessels, and prevent ischemic brain damage, etc.[19] Moreover, cardioprotective activities of some phytochemicals such as silymarin, cyclovirobuxine D, withanolides, curcumin, berberine, naringenin, tilianin, QUE, baicalin, resveratrol, allicin, and myricitrin were documented in various studies.[20–34] Curcumin, a naturally phytoconstituent isolated from *Curcuma longa* rhizomes, was shown to have significant cardioprotective effects, including prevention of myocardial infarction, stroke, aortic aneurysm, and atherosclerosis.[29,30] Also, it has been reported that anti-angiogenic drugs like allicin (significant phytochemicals present in garlic) might significantly involve the reproduction of clots in arteries that may cause a heart attack or stroke.[25,35] QUE is a flavonoid present in different fruits and vegetables such as apples, citrus fruits, onions, and tea.[36] Polymeric NPs of QUE considerably inhibited atherosclerosis.[22] Myricitrin as a flavonol glycoside displayed anti-inflammatory, antioxidant, and anxiolytic effects. It can prevent vein endothelial cell dysfunction by regulating antioxidant enzyme

Table 1 Medicinal Plants and Their Phytochemical Components Applied in the Treatment of CVDs

Plant Name	Family	Phytochemicals	Actions	Reference
Ginkgo biloba	Ginkgoaceae	Iron-based superoxide dismutase, sesquiterpenes, catechin, diterpen lactones, ascorbic acid, flavonol, flavones glycosides, ginkgolides, myricetin, quercetin, carotenoids	Antistress activities, antiaging, cytotoxic, antiulcer, anticoagulant, antidepressant, hepatoprotective, memory enhancer, anti-inflammatory, antimicrobial, antioxidants	[181,182]
Nerium oleander	Apocynacea	Dambonitol, deacetyloleandrin, 16-acetyl gitoxigenin, oleandrigenin, scopoletin, scopolin, oleandrin, ursolic acid, adyresin, odoroside, neriantin, gitoxigenin, digitoxigenin, oleanolic acid, nerium F, nerium D, neriodin, karabin, oleandrose, neriodorein, uzarigenin, oleanolic acid, tannic acid	Cardioprotective agent, antioxidants	[183]
Terminalia arjuna	Combretaceae	Tannins, triterpenes, flavonoids, triterpenes, arjunic acid, freidelin, b-sitosterol, polyphenols, arjunetin	Cardioprotective agent, antioxidants, antimicrobial	[184,185]
Sesbania grandiflora	Fabaceae	Minerals, amino acids, nicotinic acid, riboflavin, vitamin A, C	Cardioprotective activities, antiinflammatory, antimicrobial	[186]
Centella asiatica	Apiaceae	Asiatic acid, asiaticoside, triterpenes, bacogenin, hydrocotylin, hersaponin, sitosterol, vallarine, phenols, tannins	Cardioprotective activities, anti-inflammatory, antimicrobial, wound healing	[187]
Tinospora cordifolia	Tinospora	Berberine, diterpenoid lactones, sesquiterpenoids, glycosides, steroids, palmarin, columbin, chasmanthin, gilosterol, giloinin, tinosporol	Cardioprotective activity, antioxidant	[188,189]
Bombax ceiba	Bombacaceae	Sesquiterpenoids, n-triacontanol, naphthoquinone, glycosides, lupeol, sitosterol, flavonoids, tannins	Cardioprotective activity, antioxidant, antimicrobial	[190,191]
Sonchus asper	Asteraceae	Proanthocyanidin, sesquiterpenes, phenols, tannins, niacin, thiamine, riboflavins, alkaloids, flavonols, flavonoids, protein amino acids, vitamins, minerals	Cardioprotective activity, antitumor, anti-inflammatory	[192,193]
Zingiber officinale	Zingiberacae	6-Gingerol, 6-shogaol, 8-gingerol, 10-gingerol.	Cardioprotective impacts against stroke and heart diseases, antimicrobial	[79]
Syzygium cumini	Myrtaceae	Phenols, tannins, flavonoids, terpenes	Cardioprotective, and antioxidant activities, anti-inflammatory	[61]
Prunus spp.	Rosaceae	Phenols	Cardioprotective, and antioxidant activities, anticancer anti- inflammatory,	[194]
Paeonia emodi	Paeoniaceae	Tannins, terpenoids, carbohydrates, phenolics	Cardioprotective, antioxidant, anti-inflammatory, antimicrobial activities	[195]
Pinus merkusii	Pine	Saponins, triterpenoids, glycosides, alkaloids, flavonoids, polyphenols	Cardioprotective, anti-inflammatory activities	[78]
Dracocephalum moldavica	Labiatae	Rosmarinic acid, luteolin, tilianin	Cardioprotective, antioxidant activities	[69]
Panax notoginsenoside	Araliaceae	Ginsenoside Rg1, ginsenoside Rg3, ginsenoside Rb1, notoginsenoside R1	Cardioprotective, anti-inflammatory activities	[19]

activity, reducing malondialdehyde and H_2O_2-induced oxidative damage.[26,37] It has been demonstrated that encapsulation of berberine (an isoquinoline quaternary alkaloid) into liposomes could improve its efficacy by protecting cardiac function against myocardial infarction in vivo.[31]

Nanoformulations as a Novel Drug Delivery Approach in Cardiovascular Diseases

The stability, solubility, bioavailability, dissolution rate, and absorption are essential parameters affecting the efficiency of any drug in vivo. Nanotechnology can eliminate physical and biological barriers by applying nanophases and nanostructures at different science branches, mainly in nanomedicine and nano-based drug delivery systems.[38] In the context of drug delivery, there are two main categories for nanostructured nanocarrier systems: organic nanocarriers (ie, micelle and vesicle nanocarriers, liposomes, polymeric nanogels, and dendrimers) and inorganic NPs (ie, metallic NPs like iron oxide and gold NPs, carbon nanotubes, quantum dots (QDs), and mesoporous silica NPs).[39]

Drug targeting means the ability of a drug molecule to accumulate at the sites of action, leading to a higher therapeutic index. Among various drug-targeting approaches, magnetic drug targeting (as a nanoparticle-based delivery system) is very useful.[40,41] Functionalization of magnetic nanoparticles (MNPs) is possible through coating with different agents, including polymers, proteins, silane (or organosilane), silica, and other materials. For example, through supplying many amine groups, silanes construct an ideal system to tune the surface functionality of the Fe3O4 NPs for protein conjugation. To enhance the stability of NPs against oxidation, surface coating with different polymers might be helpful.[42]

In the context of CVDs, a broad spectrum of therapeutic products is available for heart treatment following an ischaemic episode. Direct intramyocardial injection or intracoronary catheterization are common routes for delivering therapeutics to the myocardium with more certainty.[43] Despite the positive outcomes of intramyocardial injection, it is an invasive technique that can severely damage the heart. On the other hand, intracoronary catheterization can induce embolization. Therefore, systemic intravenous injection of drugs is a superior alternative. This process is less invasive and provides a suitable condition for adequate drug circulation in the cardiovascular system.[43]

Non-functionalized therapeutics are unable to target the heart specifically and are often cleared in reticuloendothelial organs. Therefore, drug encapsulation inside NPs enhances their persistence and circulatory half-lives compared with free form. For example, in hypertensive disease, intraduodenal administration of solid lipid NPs (SLN) loaded with nitrendipine (a calcium channel blocker) leads to three to four times more bioavailability than conventional formulations.[44] SLNs are new favorable lipid-based nanocarriers that incorporate drugs in a solid hydrophobic core.[39]

In atherosclerosis, ruptures of macrophage-rich atherosclerotic plaques in the coronary arteries are the main reason underlying the sudden onset of acute coronary syndromes. Generally, targeted therapeutic interventions may inhibit macrophages' actions and reduce dose-dependent adverse effects in remote organs. For instance, receptor-specific targeted vesicles loaded with statins, the most common cholesterol-lowering drugs, enhanced the possibility of high-dose treatment with efficient delivery and selective inhibition of highly active macrophages in vulnerable plaques.[45]

In acute myocardial infarction treatment, the limited regenerative capacity of cardiomyocytes and their slight ability for self-repair usually lead to permanent heart injuries. Hence, stem cell therapy is a useful approach to treat CVDs, but only less than 10% of the transplanted stem cells can remain at the targeted site.[46] To overcome these drawbacks, iron oxide super-paramagnetic NPs have gained more attention. These NPs can be used in the orientation and proliferation tracking of stem cells.[47]

In thrombosis, systemic fibrinolytic therapy for recanalization of occluded vessels by intravenously-administration of the tissue plasminogen activator (tPA) was shown to have low efficacy and many side effects. In the rat model, magnetic NPs for tPA orientation to the target site enhanced the drug accumulation in the thrombus region. In another study, NPs operationalized with PPACK, a selective and irreversible thrombin inhibitor, improved circulation time, and antithrombotic activity of PPACK in an animal model.[48]

Medicinal Plant-Based Nanoformulation for Cardiovascular Diseases

Given the morbidity and mortality caused by CVDs, researchers have focused on discovering novel compounds

and pharmacological targets to prevent or cure such conditions. Up to date, many medicinal plants have been traditionally used by the public as natural alternatives to synthetic drugs without any proof from clinical trials.[49] Therefore, scientists are interested in developing natural products with validated efficacy and safety. Numerous herbal-based products are described to prevent and control CVDs.[50] Various parts of the plants, from roots to flowers, have been used in this field.[51]

Furthermore, many drugs have been derived from herbal medicine's chemical constituents to develop commercial therapies for CVDs.[52] Advances in nanomedicine and drug delivery systems improved the safety and efficacy of medicinal plant-based nanoformulations for CVDs.[53,54] The following sections discuss the characteristics of medicinal plant-based nanoformulations that have been used for CVDs prevention or treatment. Physicochemical characteristics of NPs loaded with different medicinal plants and natural products for the treatment of CVDs are listed in Table 2. A schematic figure has also been provided to illustrate how nanophytomedicines affect CVDs (Figure 1).

Rabdosia rubescens

Rabdosia rubescens, also known as donglingcao, is a native herb from North China.[55] In pathological conditions, P-selectin, an effector on activated human platelets, transfers from the α-granule to the platelets membrane's surface and is converted into the soluble P-selectin (sP-selectin) in the blood circulation, which ultimately leads to platelet aggregation and thrombosis. Therefore, the downregulation of sP-selectin has been considered to treat both inflammation and thrombosis.[56,57] The capability of the aqueous extract of *R. rubescens* leaves (AERL) was investigated to determine the in vivo inhibition of thrombosis formation, in vitro platelet aggregation, and the in vitro P-selectin expression. AERL dose-dependently inhibited thrombosis in rats, inhibited platelet aggregation, and downregulated platelet sP-selectin release. Docking analysis exhibited that rosmarinic acid, the antithrombotic ingredient of AERL, was responsible for the downregulation of P-selectin expression. The minimal oral dose of AERL that inhibited thrombosis was 25 mg/kg. The potency of AERL inhibiting thrombin-induced platelet aggregation was twofold, tenfold, and twelvefold higher than that of AERL inhibiting platelet aggregation induced by arachidonic acid, adenosine diphosphate, and platelet-activating factor, respectively. It was also reported that

0.5 mg/mL of AERL forms NPs (53–159 nm in diameter) in rat plasma.[58]

Syzygium cumini

Syzygium cumini (*S. cumini*) is an evergreen tropical tree belonging to the Myrtaceae. Seeds of *S. cumini* have anti-diabetic and gastro-protective properties. Previous studies have shown that the methanolic extract of *S. cumini* seeds was rich in phytochemicals with high antioxidative potential.[59,60] The same extract reduced mitochondrial membrane potential and collagen content. It caused excessive production of reactive oxygen species (ROS) in H9C2 cardiomyocytes, thereby suppressing the high glucose-induced stress.[61,62] Respecting this extract's antidiabetic and cardioprotective properties, the potential cardioprotective effect of *S. cumini* silver NPs (SmSNPs) was evaluated in glucose-induced cardiac stress in vitro. Silver NPs with higher safety were used to improve the delivery system and enhance the therapeutic potential of *S. cumini* against diabetic cardiomyopathy. SmSNPs were morphologically polydispersed and were consisted of irregular spherical contours. Restoration in cell size, nuclear morphology, and lipid peroxide formation observed following the treatment of glucose-stressed H9C2 cardiac cells with SmSNPs. SmSNPs were stable, crystalline, and pure.

Meanwhile, they suppressed glucose-induced cardiac stress through cellular integrity maintenance and reduced oxidative damage. The HPLC analysis of the methanolic seed extract (MSE) has revealed that it was rich in QUE, p-coumaric acid, gallic acid, 3,4-dihydroxy benzoic acid, caffeic acid, sinapic acid, ferulic acid, kaempferol, chlorogenic acid, and p-hydroxybenzoic acid. The antioxidant assessment demonstrated that SmSNPs were more active than the *S. cumini* MSE alone. Pretreatment of glucose-stressed cells with SmSNPs restored the cell size and converted both the nuclear enlargement and DNA fragmentation to the normal state. Overall, administration of SmSNPs protected cardiac cells against glucose-induced stress by scavenging free radicals, maintaining cellular and nuclear integrity, and inhibiting lipid peroxide formation.[63]

Cherry

It is well known that cherries are rich in polyphenols, including flavonoids and anthocyanins. These polyphenols have been frequently used against human diseases such as cancers, heart disease, and diabetes.[64,65] Beconcini et al investigated the ability of cherry extract (CE)-loaded NPs

Table 2 Physicochemical Characteristics of NPs Loaded with Different Medicinal Plants and Natural Products for the Treatment of CVDs

Medicinal Plants and Phytochemicals	Nanoformulatin	Average Size (nm)	PDI	Zeta Potential (mV)	Encapsulating Efficiency (%)	Ref
Ginger extract	Polyurethane sample with ginger extract	90±9	~0.7	+27.8±4.1	~82.9	[84]
Syzygium cumini seeds	*Syzygium cumini* Ag NPs	~40–100	–	−19.6 ± 0.5	–	[63]
Dracocephalum moldavica L.	TFDM-SLNs	104.82±0.24	0.21±0.97	−28.7±1.94	Luteolin, rosmarinic acid, and tilianin of the optimal TFDM-SLNs formulation were 83.98±1.05, 87.01±0.83, and 88.82 ±0.58, respectively	[72]
Paeonia emodi	Pe.EA40-AuNPs	203.4 ± 4.72	0.32 ± 0.01	–	–	[75]
Curcumin	Curcumin nanoemulsion	42.93 ±29.8	0.36 ± 0.04.	−0.12 ±0.50	89.89 ± 8.18%	[90]
Curcumin	Curcumin/P	~30	–	–	–	[91]
Curcumin	Curcumin- polymer-based nanoparticle	30–100	–	–	–	[96]
Curcumin	AC-Lipo	192±0.8	–	6.78±0.99	79.33±3.61	[102]
Curcumin	Curcumin-mesoporous silica material	216.9± 7.6	~ 0.4	–	42 ± 2.3	[107]
Curcumin	Curcumin-PEG-PDLLA	~50	–	−14.9	–	[108]
Curcumin	PLGA nanoparticle-encapsulated curcumin		–	−29	–	[112]
Curcumin	Curcumin/CMC-peptide	331.2	–	+11.2	–	[94]
Curcumin	Curcumin-loaded PEG-PDLLA NPs	57.09±4.52	0.19	0.44±0.018	82.3±3.71	[110]
Curcumin-nisin	Curcumin-nisin poly lactic acid NP	284.0 ± 17.9	–	–	–	[105]
Cherry extract	CE-loaded NPs based on quaternary ammonium chitosan S-protected thiolated derivative	344.9 ± 17.8 339.9 ± 68.2	0.52 ± 0.08 0.50 ± 0.09	14.8 ±0.3 15.8 ± 0.5	78.4 ± 4.5 79.8 ±0.6%	[66]
Cherry extract	FITC-QA-Ch NPs FITC-QA-Ch-S-pro NPs FITC-PLGA NPs	191.5 ±3.7 235.4 ±3.2 201.4 ±5.7	0.30 ±0.02 0.24 ±0.02 0.06 ±0.05	7.0 ±0.9 5.5 ±0.8 7.9 ±0.1	–	[68]
Cherry extract	PLGA NP + CE 100 PLGA NP + CE 250 PLGA NP + CE 420 PLGA NP + CE 840	216.0 ± 2.6 216.8 ± 4.9 208.4 ± 4.9 206.1±1.8	0.06 ± 0.03 0.06 ± 0.02 0.05 ± 0.02 0.06 ± 0.03	−11.0±1.23 −10.9±1.04 −12.6±0.87 −8.36±1.07	– 64.8 ± 2.3 43.9 ±4.6 79.8 ± 6.2	[67]
Pinus merkusii	Chitosan-*Pinus merkusii*	201.8±14.6	–	–	–	[78]
Ginsenoside Rg3	P-Rg3	49.44 ± 0.15	0.339±0.001	–	96.47 ± 1.92	[115]

(Continued)

Table 2 (Continued).

Medicinal Plants and Phytochemicals	Nanoformulatin	Average Size (nm)	PDI	Zeta Potential (mV)	Encapsulating Efficiency (%)	Ref
Panax notoginsenoside	PNS-HLV	337.8 ± 40.2	–	−44.7±0.51	R1: 57.5 ± 1.1 Rb1: 83.1 ± 1.7 Rg1: 40.5 ± 1.8	[119]
Salvianolic acid B and *panax notoginsenoside*	RGD-S/P-LPNs	139.5 ± 4.1	0.16 ± 0.04	−32.4 ± 3.7	Sal B: 90.3 ±3.7 PNS: 89.1 ± 3.2	[121]
Berberine	BB-lip	~0.11	~0.048	–	–	[31]
Tilianin	Tilianin-loaded PEG-PPS micelles	~70	–	−2.73	–	[134]
Puerarin	PUE@PEG-PE micelles	~16.0		−24.1 ev	68.7	[139]
Puerarin	PUE@TPP/PEG-PE micelles	~17.1	<0.2	−6.24	~85.5	[140]
Puerarin	RGD/PEG-PUE- SLN	110.5±3.4	0.23±0.03	−26.2±1.8	85.7±2.7	[143]
Naringenin	Naringenin lipid nanoemulsions	~200	~0.2	–	–	[131]
Baicalin	BN-PEG-NLC	83.9±1.6	0.21±0.06	−32.1±1.8	83.5±1.2	[153]
Quercetin	mRQ	22.34 ± 0.15	0.111 ± 0.001	–	–	[148]
Quercetin	Quercetin-loaded PLGA	343.5±25.4	–	–	–	[22]
Quercetin	PLGA-quercetin	165 ± 75	–	−28 8 ± 1 2	98 15 ± 0 5	[149]
Breviscapine	Bre-LE	225.3±8.8	0.221±0.020	−29.6±1.5	94.5±0.6	[161]
Resveratrol	RSV-NC	207±0.03	0.12±0.04	−7.15± 0.19	99.54±1.02	[156]
Resveratrol	mRC	25.05 ±0.53	0.059 ±0.01	–	–	[157]
Resveratrol	RS-SLN	~ 271.13	–	−25.8±0.33	–	[158]
Epigallocatechin-3-Gallate	L-Enano	104.8±0.4	0.18±0.020	−20.30±1.5 −21.81 ± 1.18	~96	[173]
Epigallocatechin-3-Gallate	CSNLCE	53.5 ± 1.6 53.5 ± 1.6	0.19 ± 0.01 0.19 ± 0.01	13.3 ± 1.0 13.3 ± 1.0	~99	[174]
Magnolol	Magnolol NPs	75.6±1.7	0.241±0.023	–	~96.4	[169]
Magnolol	EPC- encapsulated magnolol (0.01 mg/mL) DPPC- encapsulated magnolol (0.01 mg/mL)	54.7 27.5	–	–	74.13±1.86 64.26 ±2.92	[168]
Tanshinone IIA	Discoidal recombinant HDL Spherical recombinant HDL	138.2 ± 5.1 132.6 ± 4.8	– –	_18.2 ±0.6 _35.6 ± 0.8	93.3 ± 1.5 98.5 ± 1.2	[178]

(*Continued*)

Table 2 (Continued).

Medicinal Plants and Phytochemicals	Nanoformulatin	Average Size (nm)	PDI	Zeta Potential (mV)	Encapsulating Efficiency (%)	Ref
Tanshinone IIA	TPP-TPGS/TN/LPNs	~140	0.16±0.03	~−10	~ 90	[179]
Tanshinone IIA	IIA-NP	100–200	<0.25	_7.12 ± 0.07	61.30 ± 1.96	[180]

Abbreviations: Ag, argentums (silver); TFDM-SLNs, total flavonoid extract from *D. moldavica* L. solid lipid nanoparticles; Pe.EA40-AuNPs, P. emodi ethyl acetate fraction-gold nanoparticles; curcumin/P, curcumin/PBLG-PEG-PBLG (poly (gamma-benzyl-L-glutamate)-poly(ethylene glycol)-poly(gamma-benzyl-L-glutamate) (PBLG-PEG-PBLG)); AC-Lipo, liposomes loaded with atorvastatin calcium and curcumin; curcumin-PEG-PDLLA, curcumin-poly(ethylene glycol) methyl ether-block-poly(D,L- lactide); curcumin/CMC-peptide, curcumin encapsulated by carboxymethyl chitosan (CMC) nanoparticle conjugated to a myocyte-specific homing peptide; curcumin-loaded PEG-PDLLA NPs, curcumin-loaded monomethoxy poly (ethylene glycol)-*b*-poly (DL-lactide) nanoparticles; PLGA, poly lactic-*co*-glycolide; CE, cherry extract; FITC-QA-Ch NPs, fluorescein isothiocyanate-quaternary ammonium chitosan nanoparticles; FITC-QA-Ch-S-pro NPs, fluorescein isothiocyanate-quaternary ammonium chitosan S-protected thiolated derivative; P-Rg3, Rg3-loaded Pluronic F127 micelles; PNS-HLV, panax notoginsenoside-loaded core-shell hybrid liposomal vesicles; RGD-S/P-LPNs, arginyl-glycyl-aspartic acid–salvianolic acid B/panax notoginsenoside-loaded lipid-polymer hybrid nanoparticles; BB-lip, berberine liposomes; PEG-PPS, poly(propylene sulfide)-*co*-poly(ethylene glycol); PUE@PEG-PE, puerarin-loaded 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000]; TPP, triphenylphosphonium; RGD/PEG-PUE- SLN, RGD-modified and PEGylated solid lipid nanoparticles loaded with puerarin; BN-PEG-NLC, baicalin-loaded PEGylated nanostructured lipid carriers; mRQ, resveratrol and quercetin in Pluronic® F-127 micelles; Bre-LE, breviscapine lipid emulsion; RSV-NC, resveratrol nanocapsule; mRC, resveratrol–curcumin at a molar ratio of 5:1 in F127 micelles; RS-SL, a solid lipid nanoparticle loaded with resveratrol; L-Enano, ligand-epigallocatechin-3-gallate-loaded nanoparticles; CSNLCE, chitosan-coated EGCG encapsulated nanostructured lipid carriers; EPC, 1,2-diacyl-*sn*-glycero-3-phosphocholine; DPPC, 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine; TPP-TPGS/TN/LPNs, triphenylphosphonium-D-α-tocopheryl polyethylene glycol 1000 succinate surface-modified, tanshinone-loaded LPNs; IIA-NP, tanshinone IIA nanoparticles.

to improve the resistance of endothelial cells against oxidative stress.[66] CE-loaded NPs were prepared using both quaternary ammonium chitosan (NP1; QA-Ch-NP) and an S-protected thiolated derivative (NP2; QA-Ch-S-pro-NP). The CE-encapsulated NPs protected human umbilical vein endothelial cells (HUVECs) against oxidative stress, and both types of NPs improved the CE permeation parameters compared with control. Of course, CE-loaded NP2 reduced ROS production more effectively than CE-loaded NP1 and free CE.[66] It was also shown that CE polyphenols encapsulated in chitosan derivatives (Ch-der) mucoadhesive NPs were more effective antioxidant protectors than PLGA NPs. When higher therapeutic doses are needed, PLGA NPs are preferred due to less cytotoxicity.[67] It is also reported that similar to dexamethasone, CE can reduce the production of inflammatory cytokines. The anti-inflammatory properties of CE, either encapsulated in NPs PLGA or Ch-der or free form, have been evaluated on lipopolysaccharide (LPS)-stressed HUVECs. CE-loaded QA-Ch-NPs were the most effective NPs, by increasing the in vitro anti-inflammatory activity of CE through reducing the secretion of prostaglandin E_2, tumor necrosis factor-alpha (TNF-α), and interleukin 6 (IL-6) cytokines, and by enhancing the IL-10 level. CE-loaded QA-Ch-NPs also declined the nucleotide-binding domain and leucine-rich repeat receptor family, pyrin domain-containing protein 3 inflammasome, and nitric oxide, which was implicated in the internalization of the extract into HUVECs.[68] Therefore, nanoformulation can protect CE from degradation in the gastrointestinal tract.

Dracocephalum moldavica

Dracocephalum moldavica L. belongs to the Labiatae family. It was shown to have therapeutic efficacy for hypertension, atherosclerosis, and coronary heart disease. Total flavonoid of *D. moldavica* (TFDM) include tilianin, luteolin, and rosmarinic acid, which play critical roles in *D. moldavica* pharmacological action.[69–71] In another study, the effectiveness of TFDM solid lipid NPs (TFDM-SLNs) were investigated against coronary artery occlusion-induced myocardial ischemia-reperfusion injury rats.[72] The central composite design and response surface method were used to optimize the formulation of TFDM-SLNs. TFDM-SLN-treated group showed smaller infarct size, lower LDH activity, and lower CK level, indicating an improved cardioprotective effect of TFDM-SLN compared with TFDM alone. Administration of the TFDM-SLN improved the integrity of the myocardial membrane and fibers while significantly reduced the IL-1β and TNF-α levels.[72]

Paeonia emodi

Paeonia emodi Wall. Ex Royle. belongs to the Paeoniaceae family. It has been used for the treatment of cardiac diseases such as atherosclerosis, hypertension, congestive heart failure, and palpitations.[73] Ibrar et al reported cardioprotective activity of *P. emodi* ethyl acetate fraction (Pe.EA) in the reduction of alanine aminotransferase (ALT), AST, LDH, and CPK. Pe.EA also possessed antithrombosis, free radical scavenging, and antihyperlipidemic effects.[74] In another study, Pe gold NPs significantly
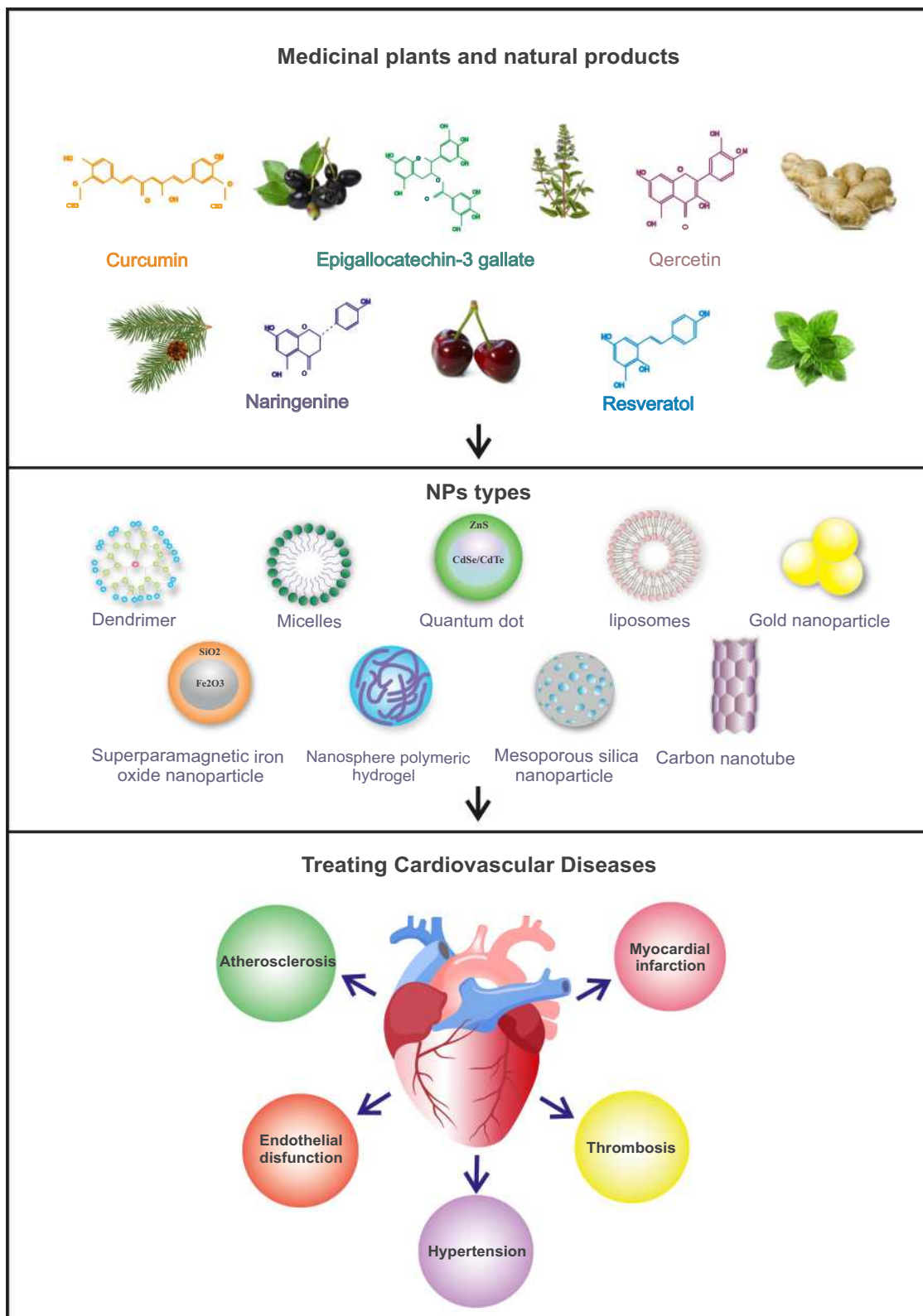
Figure 1 A schematic figure illustrating the effect of nanophytomedicine on cardiovascular diseases.

reduced lipid profile, ALT, AST, CPK, LDH, and DNA damage in mice.[75]

Pinus merkusii

Pinus plant contains phytochemicals such as polyphenols, lignans, alkaloids, flavonoids, saponins triterpenes, glycosides, sterols, and triterpenoids.[76,77] It was shown that administration of chitosan-*P. merkusii* extract NPs (400 mg/kg BW) significantly decreased the LDH, MDA, and CK-MB levels in heart tissue. These NPs also considerably increased the SOD and GPx levels and inhibited the formation of ROS and oxidative damage in myocardial cells. Thus, *Pinus* NPs could prevent lead acetate-induced cardiac cell damage through scavenging free radicals and enhancing antioxidant enzymes.[78]

Ginger

The ginger extract, derived from the rhizome of *Zingiber officinale*, is being used against heart diseases and stroke, bacterial infections, malabsorption, nausea, vomiting, and indigestion.[79] Verma et al reported the protective effect of ginger powder against CVDs could be associated with enhancement of fibrinolytic activity and decrease of lipid peroxidation in atherosclerosis-induced rabbits.[80] Synergetic effects of ginger powder and nifedipine have also been shown on antiplatelet aggregation in hypertensive patients.[81] Furthermore, the beneficial effects of chemical components of ginger on blood glucose levels, blood pressure, and lipid concentrations have been stated.[82,83] A mixture of polyester- and polyether-urethanes (PU) and the ethanolic extract of ginger root (containing 6-shogaol, 6-gingerol, 8-gingerol, and 10-gingerol) was used to prolong the time of the constant release of the extract from NPs. The membrane penetration of ginger extract-polymer NPs was assessed using a polyvinylidene fluoride artificial membrane. It was shown that the PU NP degradation started after 2 days. The extract passed through this membrane after 3–4 days. The rise of stability against hydrolysis could explain the delayed degradation due to encapsulation. The products were heat resistant up to 280°C, and the PU NPs with and without ginger extract did not irritate murine skin in vivo testing. Borcan et al proposed that PU NPs could be a cardiovascular protector.[84]

Natural Product-Based Nanoformulations for Cardiovascular Diseases

Flavonoids, phenolic acids, hydroxyl cinnamic acids, organosulfides, alkaloids, carotenoids, isoflavones, anthocyanins, terpenes, and phytosterols are the main categories of phytochemicals. These phytochemicals have a broad spectrum of medical values against different diseases. Antioxidative, antiangiogenic, antiischemic, antihypercholesterolemic, inhibition of platelet aggregation, and anti-inflammatory activities of isoflavones, QUE, catechin, resveratrol, carotenoids, and sulforaphane have been stated for cardioprotection and reduction of CVDs.[84,85] This review has also provided a brief overview of recent advances in natural product-based nanodrugs to treat CVDs. The mechanisms of action of nanophytomedicines are illustrated in Figure 2.

Curcumin

It was comprehensively reviewed that curcumin exerts antioxidant activity and is functional against oxidative stress-induced damages.[86–89] Rachmawati et al evaluated the antihypercholesterolemic and antihypertensive effects of curcumin nanoemulsion in vitro using acetylcholinesterase (ACE) and 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGR) assay kits. The results revealed that nanoemulsified curcumin slightly increased its inhibitory effect on ACE compared with pure curcumin. Furthermore, curcumin nanoemulsion increased the HMGR inhibition, representing its antihypercholesterolemic activity.[90] In another study, the encapsulation of curcumin into multipolymer poly (gamma-benzyl -L-glutamate)-poly(ethylene glycol)-poly (gamma-benzyl -L-glutamate), known as PBLG-PEG-PBLG, improved its water solubility, biological activity, and dispersion in aqueous solutions in a diabetic cardiomyopathy model. In vivo administration of curcumin/P enhanced the serum levels of H2S and $Ca^{2+}i$ content in myocardial cells and upregulated the expression of cystathionine-γ-lyase, calmodulin, and calcium-sensing receptor. Furthermore, curcumin and curcumin/P significantly reduced diabetic cardiomyopathy and alleviated pathological and morphological destruction of myocardial cells.[91] Cardioprotective effects of curcumin NPs were also shown in ISO-induced AMI in diabetic rats, attributed to their antioxidant and anti-inflammatory features.[92] On the other hand, two nanoformulation of curcumin; 1) curcumin encapsulated in
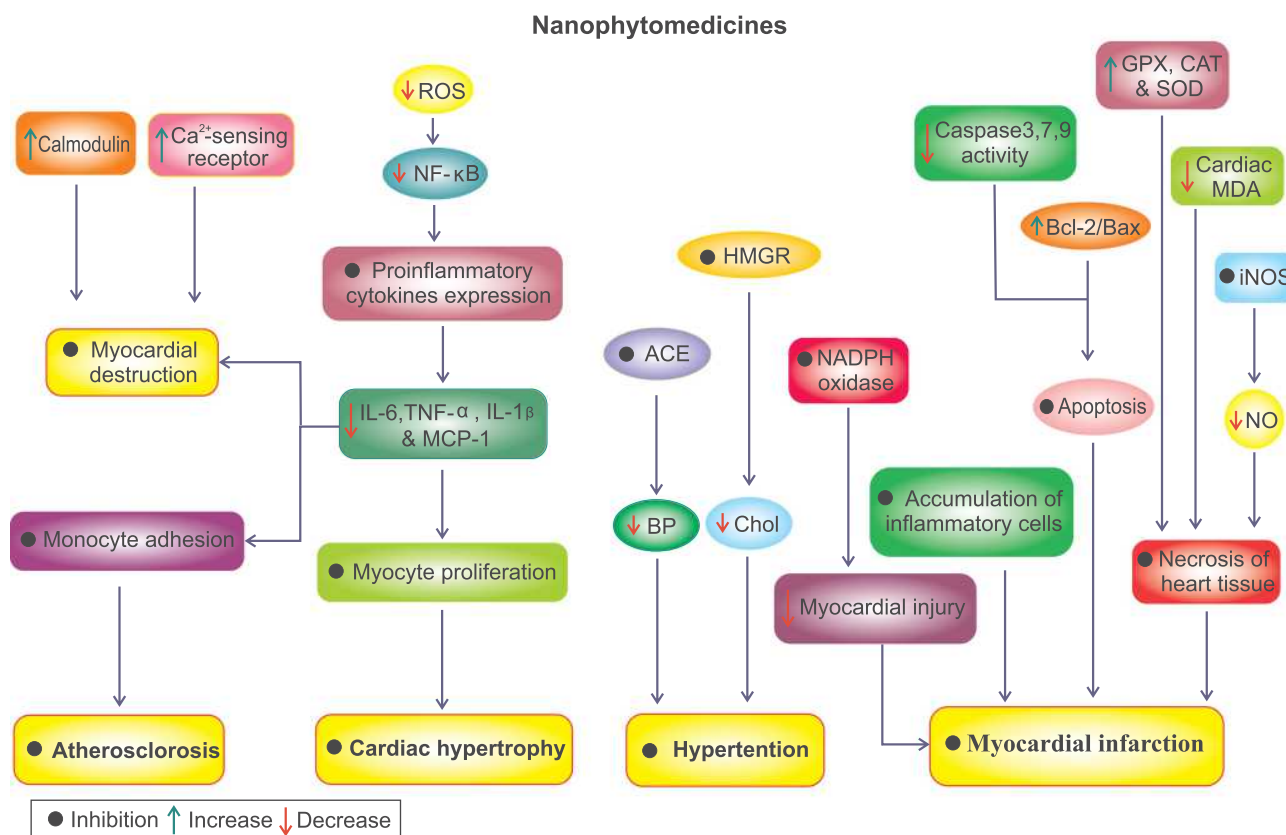
Nanophytomedicines

Figure 2 The nanophytomedicines mechanism of action in CVDs therapy.
Abbreviations: ROS, reactive oxygen species; NF-κB, nuclear factor kappa B; ACE, acetylcholinesterase; HMGR, 3-hydroxy-3-methylglutaryl coenzyme Areductase; BP, blood pressure; Chol, cholesterol; IL-6, interleukin 6; IL-1β, interleukin 1β; TNF-α, tumor necrosis factor-alpha; MCP1, monocyte chemotactic protein 1; iNOS, inducible nitric oxide synthase; SOD, superoxide dismutase; GPX, glutathione peroxidase; CAT, catalase; NADPH oxidase, nicotinamide adenine dinucleotide phosphate oxidase; MDA, malondialdehyde.

poly (glycidyl methacrylate) NPs alone (Cur-PGMA), and 2) curcumin in combination with a peptide targeting the α-interacting domain of L-type Ca^{2+} channel (Cur-AIDPGMA); were investigated against ischemia-reperfusion injury in rat hearts.[93] Both NPs were found effective against ischemia-reperfusion-induced oxidative stress and myocardial injury. Another study revealed that curcumin encapsulation in carboxymethyl chitosan NPs (Cur-CMC) increased its bioavailability, maintained its bioactivity, and reduced cardiac hypertrophy in a rat model.[94] Curcumin NPs were used for the treatment of monocrotaline-induced pulmonary arterial hypertension in the rat model. Treatment with curcumin NPs (50 mg/kg i. p.) attenuated the development of right ventricular hypertrophy, decreased right ventricle weight to the bodyweight ratio, decreased right ventricle mRNA expression of TNF-α, and IL-1β, and diminished oxidative stress.[95]

Pretreatment with curcumin polymer-based NPs solution (nC) and curcumin solution (Cs) was investigated in ISO hydrochloride (ISO)-induced myocardial infarction

rats. Neither Cs nor nC influenced systolic or diastolic blood pressure values before or after ISO administration. Pretreatment with different doses of Cs and nC increased RR interval and reduced the heart rate before ISO administration. However, the mechanism by which curcumin reduced the heart rate remained unknown. The highest dose of Cs and nC (200 mg/kg bw) was more effective for cardioprotection.[96] Pretreatment of Cs and nC reduced lipid peroxidation, myocardial levels of MDA, nitric oxide, and total oxidative status. A lower level of nitric oxide was obtained in nC pretreated rats. Administration of both Cs and nC lowered the serum LDH, ALT, and AST levels in ISO-induced rats, but nC was more active.[96] Lipopolymer hybrid NPs of curcumin have also been used to protect against QT prolongation.[97] In another investigation by Boarescu et al, pretreatment of rats with Cs and nC reduced severe myocardial tissue damage, myofibrillar degeneration, interstitial edema, and accumulation of inflammatory cells and necrosis.[98] Overall, the administration of nC was suggested to prevent the

extension of myocardial tissue damages in acute myocardial infarction.

Inflamed endothelium is involved in atherosclerosis development and targets antiatherosclerosis therapy to treat hyperlipidemia and/or inflamed endothelial cells. Atorvastatin calcium, an antiatherosclerosis drug, acts through reducing plasma lipids and intimal hyperplasia, promoting intimal regeneration, and inhibiting the intimal smooth muscle cell accumulation.[99,100] As mentioned, the antiatherosclerosis activity of curcumin is attributed to its anti-inflammatory and antioxidant activities.[101] Combination of atorvastatin calcium and curcumin synergistically reduced atherosclerosis and diminished the side effects of atorvastatin in both in vitro and in vivo models.[102] Another study showed that E-selectin-binding (Esb) peptide-modified PEG-1, 2-distearoyl-*sn*-glycerol-3-phosphoethanolamine (DSPE) (Esb-PEG-DSPE) liposomes loaded with atorvastatin and curcumin (T-AC-Lipo) inhibited E-selectin and the intercellular cell adhesion molecule-1 gene expression; increased antioxidative effects; and led to much weaker fluorescence staining of IL-6 and monocyte chemotactic protein 1 (MCP1) in comparison with either single-drug treatment. T-AC-Lipo treatment also reduced total cholesterol and LDL. Overall, it was demonstrated that T-AC-Lipo can reduce atherosclerosis by decreasing lipid deposition.[102] Administration of nano-curcumin and aged garlic extract (AGE) reduced advanced glycation end products (AGEPs) and oxidative stress in streptozotocin-induced diabetic rats. Nano-curcumin and AGE suspension attenuated myocardial cell deaths, myocardial fibrosis, and cardiac inflammation by inhibiting oxidative stress and AGEPs accumulation in diabetic heart tissues. Although nano-curcumin upregulated the Mn-SOD and downregulated the AGEPs gene expressions, AGE was more potent.[103]

Nisin, an antimicrobial peptide, induced cell cycle arrest and apoptosis while reducing the head and neck squamous cell carcinoma cells.[104] A nanoformulation of nisin and curcumin was used to improve their delivery, stability, bioavailability, and pharmacological activity for CVDs treatment. Curcumin-nisin nanoparticle (CurNisNp) was found non-toxic and well-tolerated in mammals. Pretreatment of myocardial infarction of ISO-induced guinea pigs with CurNisNp (21 mg/kg) improved ECG patterns, suppressed the serum myeloperoxidase activity, reduced ROS and MDA levels, and downregulated cardiac troponin I expression in the heart. Moreover, CurNisNp improved the hypertrophy index, necrosis, myofibril

thickness, and loss of transverse striations.[105] In another study, a surfactant-soluble oral drug delivery system (DDS) was prepared to increase the curcumin absorption. DDS curcumin reduced perivascular fibrosis, myocardial cell diameter, and hypertrophy following myocardial infarction in rats. Pretreatment with DDS curcumin (0.5 mg/kg/d, oral) significantly reduced the posterior wall thickness and improved the rats' systolic function.[106] The effect of curcumin-loaded mesoporous silica NPs (MSNs) was assessed against doxorubicin-induced cardiotoxicity in rats. Pretreatment with curcumin-MSNs significantly protected myocardium from the toxic effects of repeated administration of doxorubicin by reducing the level of MDA and increasing SOD, GSH, and catalase levels in cardiac tissue. Curcumin-MSNs pretreated groups showed lower ALP levels, CPK, MDA, and LDH than those only treated with doxorubicin. The histology of heart tissues demonstrated more preservation of myofibrils and the cytoplasm vacuolization in the curcumin-MSNs+doxorubicin treated group. The cardioprotective activity of curcumin-MSNs could be attributed to enhanced bioavailability and its significant antioxidant and anti-inflammatory activities.[107]

According to another study conducted by Li et al, exposure of cardiomyocytes to curcumin NPs, decreased cell apoptosis, intracellular ROS levels, and the activity of Rac1. Besides, curcumin NPs suppressed the expression of $gp91^{phox}$, $p22^{phox}$, $p47^{phox}$, and $p67^{phox}$, which were induced by palmitate. Curcumin NPs significantly increased Bcl-2/Bax ratio, glucose-regulated protein 78, and C/EBP homologous protein expression in cardiomyocytes. Administration of curcumin NPs also inhibited apoptosis, decreased ROS generation and MDA content, increased SOD activity, and attenuated NADPH oxidase isoforms in cardiomyocytes. It was concluded that the endoplasmic reticulum stress-related signaling pathway probably mediated NADPH-induced oxidative stress inhibition. Therefore, curcumin NPs were suggested as possible drug formulations to improve lipid toxicity-induced myocardial injury.[108,109] These effects might be implicated in regulating the expression of specific proteins and activation of the adenosine monophosphate-activated protein kinase signaling pathway.[110] The effect of curcumin-loaded magnetic hydrogel nanocomposite (Cur-NIPAAM-MAA-NP) was also investigated against doxorubicin-induced cardiac toxicity in rats. Cardioprotective activity of Cur-NIPAAM-MAA-NP was approved by decreasing the atrial natriuretic peptide,

B-type natriuretic peptide, and β-myosin heavy-chain gene expression as heart failure markers.[111] It was also shown that the administration of curcumin-loaded lipid nanoemulsions (CmLN), conjugated with a nano-arginine peptide (R9CmLN), had low hemolytic activity and low cytotoxic effect on human endothelial cells. It has recently been reported that PLGA-curcumin NPs effectively improved cardiovascular responses by reducing liver fat deposition and improving oral bioavailability of curcumin.[112] In another study, curcumin NPs prevented the CK-MB leakage from cardiomyocytes in ISO-induced myocardial infarction in rats. The serum levels of IL-6, TNF-α, MCP-1, IL-1α, and IL-1β did not increase after the induction of myocardial infarction.[98] Administration of curcumin capped gold loaded poly (lactic-coglycolic acid) nanoparticles (CAu-PLGA Nps) inhibited cardiac hypertrophy via increasing solubility, bioavailability, and absorption, improving resistance to enzymatic degradation and drug delivery efficiency in a rat model. CAu-PLGA Nps also increased survival rate, preserved myocardial function, and protected animals against cardiac toxicity and heart failure through their antiapoptotic, antioxidant, and anti-inflammatory properties.[113] Together, nano curcumin is a potent natural product formulation for treating a wide range of CVDs such as atherosclerosis, hypertension, myocardial infarction, diabetes, cardiac hypertrophy, and cardiomyopathy.

Ginsenoside Rg3

Ginsenoside Rg3 (Rg3), an active constituent of *Panax ginseng*, possesses anti-inflammatory, immunomodulatory, antioxidant, and anti-aging activities in different diseases.[114–116] Rg3 loaded in Pluronic F127 micelles (P-Rg3) effectively reduced doxorubicin-induced mortality, preserved the peak aortic blood velocity, and decreased the levels of atrial natriuretic peptide and B-type natriuretic peptide in C57/BL mice.[115] P-Rg3 significantly reduced the myocardial levels of LDH, CK, and CK-MB, thereby preserving cardiac membrane integrity compared to those in the doxorubicin group. P-Rg3 decreased apoptosis; suppressed the mRNA expression of Bax and increased Bcl-2; decreased caspase 3 and caspase 9 proteins expressions; alleviated mitochondrial swelling and crista reduction, and maintained mitochondrial arrays; decreased the levels of ROS and calcium overload; increased ATP content and reduced mtDNA copy number compared with those in the doxorubicin group. P-Rg3 was more effective than Rg3 at protecting the heart against doxorubicin-induced

cardiotoxicity and prevented depolarization of the mitochondrial membrane in H9C2 cells. The basal respiration, mitochondrial maximal respiration capacity, ATP production, and mitochondrial spare respiratory capacity were also markedly increased in P-Rg3-treated cells. This study indicated that co-administration of the polymeric micellar encapsulated natural products with chemotherapeutic agents increased their efficacy, decreased their toxicity, and was more effective than drug administration alone.[115]

Panax notoginsenoside

Panax notoginsenoside (PNS) is the primary active component of *P. notoginseng*.[117] PNS is poorly absorbed after oral administration.[118] Combination of PNS with a liposomal system [encapsulation of methyl ether poly (ethylene glycol)-poly(lactide-*co*-glycolide) (mPEG-PLGA)-based NPs] enhanced the entrapment efficiency. It postponed releasing the significant components of PNS, including ginsenoside R1, ginsenoside Rb1, ginsenoside Rg1, and ginsenoside Rd. Treatment with PNS-core-shell hybrid liposomal vesicles (HLV) significantly decreased the serum levels of LDH, MDA, H2O2, and increased SOD pituitrin-induced myocardial ischemia in rats versus the control group. In other words, PNS-HLV decreased infarction volume and improved biochemical parameters by improving its physicochemical properties.[119] Salvianolic acid B (Sal B), isolated from the roots of *Salvia miltiorrhiza*, has been reported to protect the cardiovascular system through mechanisms mentioned previously by Deng et al 2015.[120] A lipid-polymer hybrid NPs (LPNs) system was designed to assess the effect of SalB and PNS co-delivery on acute myocardial ischemia.[121] The modified LPNs were stable in serum and prolonged the plasma circulation time. Combinational therapy virtually reduced the infarct size due to sustained release of drugs from the carriers, providing lasting anti-apoptotic effects for up to 72 h. In another study, the arginyl-glycyl-aspartic acid (RGD) peptide ligand was used to promote the myocardial infarction zone. RGD-Sal B and PNS-loaded system were stable and could enhance the in vivo therapeutic efficacy of both drugs and were not toxic against H9c2 cardiomyocytes.[122]

Berberine

Berberine, derived from *Berberis* spp., is a small fluorescent isoquinoline quaternary alkaloid. Berberine reduces triglycerides levels and systolic blood pressure.[123,124]

Despite potent anti-inflammatory, antioxidative, and cardioprotective activities of berberine, its application is limited due to low solubility in aqueous buffers, short half-life in blood circulation, and low absorption rate in the intestine.[31,125,126] In a mouse model of myocardial infarction, liposomal encapsulation of berberine improved its solubility, reduced adverse cardiac remodeling, and preserved left ventricular ejection. Furthermore, berberine encapsulation into long-circulating liposomes enhanced the accumulation of the compound in infarcted heart tissue and improved its local delivery and treatment efficacy.[31]

Naringenin

Naringenin is a flavanone existing in vegetables and citrus fruits such as orange and grapefruit. Its antioxidant, anti-inflammatory, anti-hyperglycemic, and anti-mutagenic activities have been reported previously.[32,127,128] Several strategies have been used to improve the pharmacokinetics of naringenin, including a combination of naringenin with cyclodextrin or liposome and incorporating this compound into chitosan core-shell NPs coated with alginate.[129,130] Given the anti-inflammatory effects of naringenin and hesperetin, they are incorporated into PEGylated lipid nanoemulsions coupled with a vascular cell adhesion molecule 1 recognizing peptide to enhance their efficacies and to reduce endothelial cell inflammation. This combination inhibited adhesion and transmigration of monocyte to or through endothelial cells, reduced nuclear translocation of nuclear factor kappa B (NF-κB), produced MCP1, and ultimately reduced endothelium inflammation.[131]

Tilianin

Tilianin, a natural flavonoid compound extracted from *Dracocephalum moldavica*, has been used to treat cardiovascular conditions such as coronary heart disease, hypertension, atherosclerosis, and myocardial ischemia.[33,132,133] An amphiphilic block polymer [(propylene sulfide)-co-poly(ethylene glycol) (PEG-PPS)], has been designed to encapsulate tilianin. PEG-PPS could scavenge ROS due to sulfur atoms in its PPS block.[134,135] The pharmacological effect of tilianin-loaded micelles (TLMs) on hypoxia-reoxygenation (H/R) induced H9c2 cardiomyocytes was investigated in a study. Upon the addition of some oxidants, tilianin was released from TLMs in vitro. Pretreatment of H/R- induced H9c2 cardiomyocytes with TLMs, reduced the LDH levels, preserved the ROS production, increased cell viability, and significantly reduced the MDA level in the cardiomyocytes. Toll-like receptor 4

and NF-κB p65 protein expressions were also reduced according to the Western blot analysis. Despite the presence of relatively low drug loading capacity and cytotoxicity of high concentrations of polymer, TLMs could reduce the contents of IL-1 and TNF-α and decreased the apoptosis rate of H9c2 cardiomyocytes versus H/R condition.[134]

Puerarin

Puerarin (PUE), a primary active ingredient derived from *Radix puerariae*, acts as an antioxidant and has been widely used to improve CVDs.[136–138] 1,2-Distearoyl-*sn*-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000] (PEG-PE) micelles were used to fabricate PUE-loaded PEG-PE (PUE@PEGPE) micelles and were assessed against ISO-induced apoptosis H9c2 cells. These micelles improved the bioavailability of PUE and extended its circulation time. PUE@PEG-PE pretreatment reversed the adverse effects of ISO, increased Bcl-2 expression while alleviating the caspase 3 activity and Bax expression in H9c2 cells. PEG-PE micelles enhanced the protective effects of PUE against ISO-induced apoptosis in H9c2 cells, also extended the drug delivery to H9c2 cells.[139] Consistent with this report, Li et al synthesized a PEG-PE copolymer containing a single terminal lipophilic triphenylphosphonium (TPP) cation to enhance the delivery efficacy of a mitochondrial targeting ligand. This copolymer was incorporated into PEG-PE to facilitate the penetration of NPs through the mitochondrial membrane. Administration of PUE-loaded TPP/PEG-PE (PUE@TPP/PEG-PE) micelles enhanced the anti-apoptosis effect of PUE in ISO-induced H9c2 Cells, which was associated with higher delivery of PUE into the mitochondria.[140] PUE@TPP/PEG-PE micelles enhanced the intracellular uptake of the desired drug in the ischemic zone. The system reduced the ROS level, Bax expression, and caspase-3 activity while increasing the Bcl-2 expression. Overall, PUE@TPP/PEG-PE micelles were suggested as a potent nanocarrier system to treat acute myocardial infarction. RGD peptide is another targeting moiety used for the targeted delivery of NPs loaded with therapeutics.[141] Yu et al reported intra-myocardial injections of RGD modified alginate, thereby enhancing angiogenesis.[142] Considering the adverse effects of direct myocardial injection, such as invasive, volume-limitation, and sometimes causing further injury to the myocardium, Dong et al designed a novel RGD/PEGylated solid lipid NPs loaded with PUE (RGD/PEG-PUE-SLN) to deliver

more drugs to the infarct zone. RGD/PEG-PUE-SLN was a favorable carrier for cardioprotective drug delivery in myocardial infarction treatment.[143,144]

Quercetin

Quercetin, a flavonoid isolated from various citrus fruits, tea, onions, and apples, exerts significant antioxidant, anti-inflammatory, and antihypertensive activities.[36,145,146] Quercetin-loaded phosphatidylcholine liposomes (PCLs) found protective against myocardial injuries induced by peroxynitrite by directly acting as both the scavenger and decomposer of endogenously formed peroxynitrite ions and thereby could restore the normal myocardial contractility in both anesthetized animals and isolated tissues.[147] In another study, polymeric micelles loaded with a combination of resveratrol and quercetin were used to assess their cardioprotective actions against doxorubicin-induced cardiotoxicity. This combination was effective in attenuating the cardiotoxicity in both in vivo and in vitro experiments.[148] Besides, Giannoulia et al fabricated a quercetin-loaded polymeric PLGA NPs by electrohydro-dynamic atomization process to improve its drawbacks and prevent atherosclerosis. Quercetin demonstrated excellent potential for preventing atherosclerosis and other CVDs, attributed to its biphasic release (24 hours and 59 days, respectively) from NPs.[22] It is also reported that the delivery of quercetin-loaded PLGA NPs into H9c2 cells led to the preservation of mitochondrial function and ATP synthesis in hypoxia-reoxygenation conditions, which was attributed to suppression of oxidative stress.[149] Wang et al built PLGA-covered polymeric superparamagnetic nano-silica@PLGA (SiN@PLGA) loaded with quercetin to improve its low water solubility and control the medication discharge from the nanocarriers. The manufactured nanocomposite guaranteed secure and controlled release of the quercetin, permitting cell enlistment, attachment, expansion, and articulation of heart proteins in local myocardium.[150]

Baicalin

Baicalin, one of the significant bioactive flavone glucuronides derived from *Scutellaria Radix*, was shown to exert anti-inflammatory and antioxidant activities. Baicalin was also shown to suppress the expression of many inflammatory chemokines and cytokines.[151] It has been used to alleviate diabetes and CVDs.[23,152] Various nanosized formulations have been used to overcome low hydrophilicity, short half-life, and poor absorption of baicalin following

oral administration.[153] Baicalin-loaded PEGylated nanostructured lipid carriers (BN-PEG-NLC) prolonged its plasma circulation time, enhanced its delivery to the ischemic area of the heart, and reduced the infarct size in the acute myocardial infarction model. PEG-NLC was suggested as an effective biocompatible carrier for heart-targeted drug delivery of baicalin.

Resveratrol

Resveratrol is a polyphenol commonly found in berries, grapes, and peanuts with a broad spectrum of pharmacological activities such as cardioprotective, anticancer, antioxidant, antiangiogenic, and immunomodulatory.[154,155] Shahraki et al synthesized resveratrol-loaded nanocapsules and assessed the effect of this nanoformulation in mice with fat diet-induced metabolic syndrome. Synthesis of resveratrol nanocapsule has also been reported using poly-caprolactone, a biodegradable polymer. Administration of resveratrol nanocapsules significantly reduced both the systolic and diastolic blood pressures and alleviated insulin resistance in mice due to reduced whole-body fat.[156] Since both curcumin and resveratrol can act as chemosensitizers and antioxidant agents, Carlson et al used their polymeric micellar co-delivery to lessen doxorubicin-induced cardiotoxicity. Encapsulation of curcumin and resveratrol in F127 micelles increased their aqueous solubility; resveratrol by 29.6-fold, and curcumin by 1617-fold. Improved cardioprotection in H9C2 cells, either when curcumin and resveratrol were used as free drugs or when they were loaded in micelles with doxorubicin, was implicated in ROS scavenging and apoptosis prevention.[157] In another study, administration of resveratrol-loaded solid lipid NPs significantly increased the heart rate, ejection fractions, and fractional shortening in doxorubicin-induced cardiotoxicity mice. The myocardial fibers were also arranged regularly, and a few vacuole degenerations were seen in the myocardial cells.[158]

Breviscapine

Breviscapine, a flavone glucuronide isolated from a traditional Chinese herb, *Erigeron breviscapus*, is commonly used to treat coronary heart disease, angina pectoris, and cerebral infarction. It was also shown favorable for CVDs by removing blood stasis and promoting blood circulation.[159] Scutellarin, the primary active component of Breviscapine, has limitations such as poor chemical stability, low aqueous solubility, and short biological half-life.[160] A lipid emulsion formulation loaded with

Breviscapine exhibited desirable sustained release. It was safe for intravenous administration while being chemically and physically stable for 6 months at room temperature. This formula also increased the amount and prolonged the retention time of Breviscapine in the heart, which would be beneficial in CVDs therapy.[161]

Magnolol

Magnolol (5,5′-diallyl-2,2′-dihydroxy biphenyl), a bioactive compound isolated from *Magnolia Officinalis*, has been used to inhibit cell growth, induce cell apoptosis, and treat various inflammatory diseases.[162–166] It was evidenced that magnolol suppresses the expression of TNF-induced vascular cell adhesion molecule 1 (VCAM-1) in endothelial cells.[167] It was stated that encapsulated magnolol in either 1,2-diacyl-*sn*-glycero-3-phosphocholine (EPC) liposome or 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine (DPPC) liposome inhibited the proliferation of vascular smooth muscle cells (VSMCs). The inhibitory effect of encapsulated magnolol was higher than the pure magnolol. Also, magnolol-EPC was more effective than DPPC liposome.[168]

HUVECs were used to investigate the anti-inflammatory mechanisms of magnolol NPs. In vitro administration of magnolol NPs was shown to suppress the activity of TNFα-induced VCAM-1 promoter. They attenuated TNFα-induced VCAM-1 mRNA and protein expressions in endothelial cells, mediated by the protein kinase B (AKT), extracellular signal-regulated kinases (ERK), and NF-κB signaling pathways. Furthermore, in vivo administration of magnolol NPs, effectively suppressed TNF-α-induced VCAM-1 expression on the aortic endothelium. Overall, magnolol NPs could be a potentially useful therapeutic nanoformulation to treat inflammatory diseases and atherosclerosis.[169]

Epigallocatechin

(−)-Epigallocatechin-3-gallate (EGCG) includes 25–55% of the total catechins in green tea.[170] It was demonstrated that EGCG prevented atherosclerosis formation by decreasing inflammatory responses and cholesterol accumulation in macrophages.[171,172] Zhang et al developed EGCG-loaded NPs (Enano) using alpha-tocopherol acetate (as an antioxidant), kolliphor HS15 (a commonly used nonionic solubilizer), and phosphatidylcholine. Then, a ligand-Enano (L-Enano) was prepared via incorporating KOdiA-PC (a CD36-targeted ligand found on oxLDL) on the surface of Enano. The final product, CD36-targeted L-Enano, significantly improved the stability of EGCG, exhibited a higher binding affinity for macrophages, enhanced the macrophage-EGCG content, and decreased the macrophage mRNA levels and protein secretion of MCP-1 in human monocytic THP-1 cells. CD36-targeted NPs were proposed as carriers for targeted delivery of antiatherogenic compounds to intimal macrophages to prevent or mediate atherosclerosis.[173] Chitosan-coated EGCG exhibited similar results as encapsulated nanostructured lipid carriers.[174]

Tanshinone

Tanshinone IIA (TA), a lipophilic pharmacologically active compound derived from the *Salvia miltiorrhiza* Bunge rhizome, is of interest for CVDs therapy. TA exhibited significant therapeutic effects, including vasodilatory potential, scavenger activity, the preventive effect on endothelial dysfunction, retarding effect on macrophage-derived foam cells formation, and the inhibitory effect on the proliferation and migration of vascular smooth muscle cells.[175,176] Low solubility, short half-life, poor bioavailability, and low oral bioavailability are the major drawbacks of this compound.[177] To improve the clinical delivery of TA, several methodologies were developed. For example, both discoidal and spherical recombinant HDL (d-rHDL and s-rHDL) loaded with TA have a high affinity towards atherosclerotic lesions than normal vessel walls. Moreover, based on the pharmacodynamic studies, both TA-d-rHDL and TA-s-rHDL presented higher antiatherogenic activities than conventional TA nanostructured lipid carriers (TA-NLC), TA liposomes (TA-L), and commercially available preparation sulfotanshinone sodium injection. TA-s-rHDL found more potent than TA-d-rHDL.[178] In another study, lipid-polymeric nanocarriers of tanshinone IIA, TA/LPNs exhibited superior mitochondrial-targeted efficacy in compatibility and therapeutic features than free TA and TA/NPs.[179] Furthermore, it was demonstrated that monomethoxy-poly (ethylene glycol)-poly (lactic acid)-D-α-tocopheryl polyethylene glycol 1000 succinate (mPEG-PLA-TPGS) nanoparticle loaded with tanshinone IIA limited the infarct expansion and reduced adverse cardiac remodeling and dysfunction.[180] Collectively, TA-s-rHDL, TPP-TPGS/TA/LPNs, and TA/mPEG-PLA-TPGS nanoparticles could be exploited as a novel approach to improve atherosclerotic lesions and myocardial IR injury in patients with MI.

Conclusion

Given the prevalence of CVDs, efficient strategies seem necessary for either prevention or treatment approaches. Data from past decades signified the therapeutic potential of many herbal and natural compounds against CVDs, with lower side effects than chemical drugs. Herbal extracts' antioxidant and anti-inflammatory properties are the critical characteristics that make them favorable candidates for CVDs treatment. Efficient and controlled delivery of drugs into the target sites of action and improving their physicochemical features are the primary purposes of natural-based nanoformulation. Therefore, nano carrier-based drug delivery systems have been applied to sustain and control drug release, avoid drug degradation, improve bioavailability, and prolong drug residence time in the systemic circulation. The current review provides an overview of the probable therapeutic advantages of nanophytomedicine for CVDs treatment, along with recent advancements in this field. As presented, the efficacy of nanoformulations of herbal extracts and their bioactive phytochemicals is significantly higher than conventional formulations. The preparation methods and the type of nanoformulation affect their chemical characteristics and functionalities. To date, many nanoformulations have been applied and investigated in both in vitro and in vivo conditions against CVDs. However, their applications in clinical states are still on the way, and it is necessary to translate the outputs of these studies into clinical trials. According to the literature, ISO-induced cardiac hypertrophy, myocardial infarction, doxorubicin-induced cardiotoxicity, hypertension, atherosclerosis, and diabetic cardiomyopathy were the most common methodologies were used to assess nanophytomedicines. Curcumin, quercetin, and resveratrol were the most applied natural products, respectively.

On the other hand, liposome nanocarriers were the most used technique for nanoformulation. Anti-hypercholesterolemic and antiatherosclerotic effects of curcumin, besides its cardioprotective properties, propose it as the most interesting cardioprotective compound. In vitro and in vivo experiments have revealed that combination therapy (eg, atorvastatin and curcumin; resveratrol and quercetin; curcumin and nisin) is more efficient due to their synergistic effects. Fabrication of NPs or nanocarriers by techniques such as PEGylating solid lipid NPs loaded with therapeutic agents or coating them with superparamagnetic nano-silica improves the drug penetration into the target tissue, thereby enhancing its therapeutic efficacy.

Prospects

Although numerous cardioprotective drugs have been utilized to prevent and treat CVDs, researchers have focused on herbal or natural-based nanoformulations due to their higher solubility, bioavailability, and efficiency, lower side effects, and having the potential to be more specific by targeted delivery to the cardiovascular tissue. Encapsulation of natural- or herbal-based medications in NPs enhances their antioxidant and anti-inflammatory activities, increases their bioavailability, and improves their efficiency. Innovative targeted nanophytomedicines are recommended as valuable alternatives for the management of CVDs. Although several natural-based nanoformulations have been tested in both in vitro and in vivo, clinical trials are warranted. The safety profiles (eg, allergic responses, DNA damage, excitotoxicity, and neuroinflammation) of nanophytomedicines have to be assessed. Overall, therapeutic applications of nanophytomedicines in CVDs are still in their initial phases.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors have no conflicts of interest to declare for this work.

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