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SYSTEMATIC REVIEW ARTICLE

Role of Organic and Inorganic Nanoparticles in the Drug Delivery System for Hypertension Treatment: A Systematic Review

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Abstract: ***Background*:** The present investigation was designed to systematically review the anti-hypertensive effects of all the organic and inorganic nanoparticles in the *in vitro, in vivo*, and clinical trials.

***Methods*:** The current study was carried out using 06-PRISMA guideline and registered in the CAMARADES-NC3Rs Preclinical Systematic Review and Meta-analysis Facility (SyRF) database. The search was performed on five English databases, including Scopus, PubMed, Web of Science, EMBASE, and Google Scholar, without time limitation for publications worldwide related to the anti-hypertensive effects of all the organic and inorganic nanoparticles without date limitation, so as to identify all the published articles (*in vitro*, *in vivo*, clinical, and case-control). Studies in any language were entered in the search step if they had an English abstract.

***Results*:** Out of 3602 papers, 60 including 25 were*in vitro* (41.7%), 17 *in vitro / in vivo* (28.3%), 16 *in vivo* (26.7%), and 2 *in vitro / ex vivo* (3.3%) up to 2020 met the inclusion criteria for discussion in this systematic review. The most widely used nanoparticles were organic nanoparticles such as polylactic acid, poly lactic-co-glycolic acid (PLGA), lipid, chitosan, *etc.*, followed by inorganic nanoparticles such as silver and palladium nanoparticles.

***Conclusion*:** This review demonstrated the anti-hypertensive effects of some organic and inorganic nanoparticles alone or in combination with the available anti-hypertensives. We found that organic nanoparticles such as PGLA and chitosan can be considered as preferred options in nanomedicine for treating high blood pressure. The results also showed these nanoparticles displayed antihypertensive effects through some mechanisms such as sustained release forms *via* increasing bioavailability, increasing oral bioavailability and improving oral and non-oral absorption, counteracting excessive superoxide, decreasing blood pressure, *etc.* However, further investigations are required to prove these effects, particularly in clinical settings, as well as their accurate possible mechanisms and toxicity.

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1. INTRODUCTION

In recent decades, Arterial Hypertension (AHT) or high blood pressure is well-known as one of the most significant agents for morbidity and mortality around the world. However, it causes nearly nine million deaths every year worldwide, especially in developing countries [1]. According to the World Health Organization's (WHO) reports, AHT was considered as a health condition that leads to a continuous increase in Blood Pressure (BP) inside the arteries of people [2]. While AHT can be asymptomatic in the early stages, it can lead to dangerous and even fatal complications, including heart failure, coronary artery disease, angina, myocardial infarction, thrombosis development, and cerebral hemorrhage in advanced and chronic or untreated stages [3, 4]. Nowadays, the most important ways to treating AHT are (i) to use synthetic drugs such as diuretics, beta blockers, calcium channel blockers, *etc.* and (ii) to change lifestyle such as regular exercise, reduce salt intake, maintain the ideal weight, *etc.* [5-7]. Due to some side effects of the existing synthetic drugs, the interest in novel strategies such as the use of medicinal herbs, nanomaterials, and combination therapy with high efficacy and low complications is increasing among physicians around the world [4, 8].

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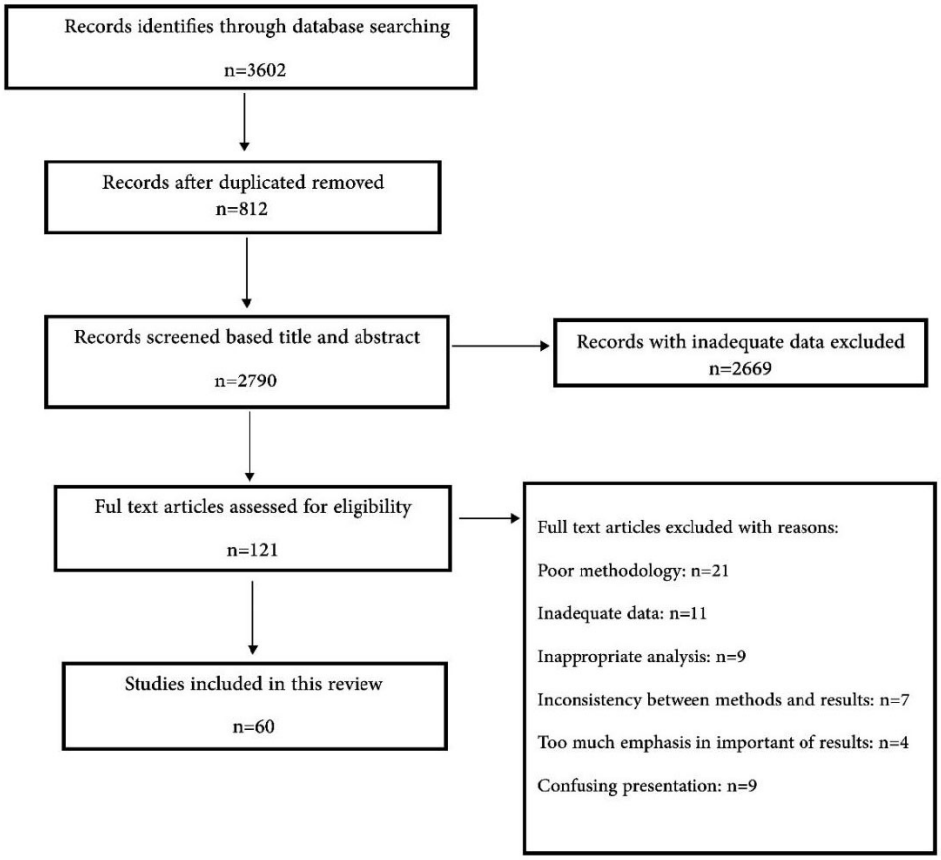

Fig. (1). Flowchart describing the study design process.

Nanomedicine is considered a relatively new field of science and technology that deals with nanometer-sized materials for medical purposes [9]. Nanomaterials are classically well-defined as those <100 nm in diameter, while particles up to 400 nm could exhibit some improved vascular permeability. To date, nanomedicine has a variety of diagnostic and therapeutic applications in modern medicine to diagnose, control, and treat a wide range of diseases such as cancers, gastrointestinal, pulmonary, cardiovascular, *etc.* [9]. Based on the type formulation of nanoparticles, several materials, such as polymeric nanoparticles or liposomes, could encapsulate high payloads of diagnostic or therapeutic purposes, while other materials, such as metal oxides, are able to append with a plethora of functional ligands [10].

Considering the use of nanoparticles to treat cardiovascular diseases, some studies have reported the anti-hepertensive effects of some inorganic nanoparticles (such as metal and metal oxide) and peptide- and polymer-based nanoparticles such as cationic peptides, synthetic cationic polymers, chitosan, *etc.* [11]. The present investigation was designed to systematically review the antihypertensive effects of all the organic and inorganic nanoparticles in *in vitro, in vivo*, and clinical trials.

2. MATERIALS AND METHODS

2.1. Study Design

The current study was carried out using 06-PRISMA guideline (Moher, Liberati Tetzlaff, & Altman, 2009) and registered in the CAMARADES-NC3Rs Preclinical Systematic Review and Meta-analysis Facility (SyRF) database. The search was performed in five English databases, including Scopus, PubMed, Web of Science, EMBASE, and Google Scholar, without time limitation for publications worldwide related to the anti-hypertensive effects of all organic and inorganic nanoparticles without date limitation, so that to identify all the published articles (*in vitro*, *in vivo*, clinical, and case-control).

2.2. Search Strategy

Studies in any languages were entered in the search step if they had an English abstract. The words and terms were used as a syntax with specific tags of each database. The searched words and terms were: “nanoparticles”, “antihypertensive”, “hypertension”, “blood pressure”, “metal nanoparticles”, “cardiovascular diseases”, “organic nanoparticles”, “inorganic nanoparticles”, “*in vitro*”, clinical”, “*in vivo*” (Fig. **1**).

2.3. Studies Selection

First, the studies were imported into the EndNote X9 software (Thomson Reuters, New York, NY, USA) and duplicate studies were deleted. Afterwards, three independent authors examined the title and abstract of the studies and the relevant studies were included for further analysis. The same authors carefully read the studies and the eligible studies with adequate inclusion criteria were selected. The corresponding author resolved any disagreement between the authors.

2.3.1. Inclusion and Exclusion Criteria

Inclusion criteria in this investigation were the studies evaluating the anti-hypertensive effects of all the organic and inorganic nanoparticles. The studies with inadequate information, only abstract, failure to match methods with results, and incorrect interpretation of the results were excluded from the current study.

2.3.2. Data Extraction

Three independent authors extracted information from the selected articles and, if needed, the differences were resolved by the corresponding author. The extracted data included nanoparticles, type of nanoparticles, being in combination or loaded with other drugs, type of study, and important results.

3. RESULTS AND DISCUSSION

Out of 3602 papers, 60 including 25 *in vitro* (41.7%), 17 *in vitro / in vivo* (28.3%), 16 *in vivo* (26.7%), and 2 *in vitro / ex vivo* (3.3%) up to 2020 met the inclusion criteria for discussion in this systematic review with the extracted data presented in (Table **1**). The most widely used nanoparticles were organic nanoparticles, such as PLGA, PLG, or poly (lactic-co-glycolic acid) and chitosan, *etc.*, followed by inorganic nanoparticles, such as silver and palladium nanoparticles.

Table 1. List of organic and inorganic nanoparticle to treat hypertension.

Nanoparticles (NPs)	In Combination/ Loaded with	Preparation Method	Type of Study	Outcome	Refs.
(Methoxy-polyethylene glycol)-b-poly(D,L-lactide-co-glycolide)-bpoly(L-lysine) NPs	Eudragit S100	Double emulsion method	*In vitro / In vivo*	The medium and high doses of orally administered VLPVPR nanoparticles reduced blood pressure for more than 30 hours, demonstrating that these nanoparticles have long-lasting and significant antihypertensive effects in spontaneously hypertensive rats.	[12]
1,3-Dicyclohexyl urea (DCU) nanosuspension	-	Aqueous in solution	*In vivo*	Nanosuspension formulations of DCU have been utilized for both intravenous injection and infusion to reach steady-state (Css) plasma concentrations in rat enabling the investigation of the target, chemistry space, and PK/PD in a timely manner without encountering efficacy results.	[13]
1,3-dicyclohexylurea nanosuspension	-	Dissolution process	*In vivo / In vitro*	The data confirm the antihypertensive effect of soluble epoxide hydrolase inhibition and demonstrate that greatly enhanced exposure of a low-solubility compound is achievable by oral delivery using a nanoparticle drug delivery system.	[14]
Carvedilol nanostructured lipid carriers (CAR-NLCs)	Stearic acid and oleic acid as lipid	Microemulsion followed the probe sonication	*In vivo*	*In vivo* antihypertensive study in Wistar rats showed significant reduction in mean systolic BP by CAR-NLCopt owing to the drug absorption through lymphatic pathways. In conclusion, the NLC formulation remarkably improved the oral bioavailability of CAR and demonstrated a promising perspective for oral delivery of poorly water- soluble drugs.	[15]
Carvedilol-Poly (Lactide-co-Glycolic acid) NPs	Carvedilol	Solvent evaporation technique	*In vitro*	formulation of carvedilol- Poly(Lactide-co-Glycolic acid) was able to improve physicochemical characteristics of the drug and possibly will enhance the antihypertensive effects of the drug following its oral administration.	[16]
Chitosan nanoparticles	Propranolol	Ionic gelation method	*In vitro*	Rheological parameters indicated a good stability of the optimised nanoparticle formulation. In-vitro drug release and cytotoxicity results showed sustained release of the drug till 24 hours along with less cytotoxicity.	[17]
Chitosan NPs	Bromelain	Ionotropic gelation method	*In vivo / In vitro*	The ACE-inhibitory biopeptides stabilized by chitosan nanoparticles can effectively reduce blood pressure for an extended period of time in hypertensive individuals.	[18]
Chitosan NPs	Losartan potassium	Ionic gelation technique	*In vitro*	No appreciable difference was observed in the extent of degradation of product during 60 days in which nanoparticles were stored at various temperatures. The developed formulation overcomes and could possibily be advantageous in terms of sustained release dosage forms of losartan potassium.	[19]

(Table 1) contd....

Nanoparticles (NPs)	In Combination/ Loaded with	Preparation Method	Type of Study	Outcome	Refs.
Chitosan NPs (CNPs)	Nebivolol (NEB)	Cross-linking method	*In vitro*	The *in vitro* release study revealed sustained release of drug for 72 h with 71.24% cumulative drug release. The promising results from the study revealed the applicability of chitosan in the formulation of NEB loaded CNPs.	[20]
Chitosan polymer	Captopril, amlodipine and valsartan	Ultra sonication method	*In vitro*	Here reported innovative AHT nano-ceuticals of polymeric origin can improve the oral administration of currently available hydrophobic drugs while providing the extended-release function.	[21]
Cyclodextrin NPs	Captopril (CAP)	Kneading method	*In vitro*	The inclusion complex of CAP and α-CD can function as a novel antihypertensive formulation that may improve therapeutic use of CAP by reducing its oral dose administration to once per day.	[22]
Eprosartan mesylate (EPM) nanopowder	-	Ultrasonic wave-assisted liquid-antisolvent technique.	*In vitro/ In vivo*	Results revealed pronounced antihypertensive potential of redispersed EPM nanopowder at 5-fold lower dose (12.4 mg/kg). In conclusion, the study indicates that nanopowder delivery might be the promising approach for providing enhanced oral bioavailability at lower dose.	[23]
Felodipine loaded eudragit® Rs100 nanoparticles	Felodipine	Solvent evaporation technique	*In vitro*	The prepared drug loaded nanoparticles showed slow release of the felodipine with reduced burst release in comparison with intact drug powder. Thus, the felodipine-eudragit® RS100 nanoparticles may provide an effective platform for nanotech drug delivery systems and the prepared formulation may further be used for *in vivo* study.	[24]
Folate-mediated lipid	Val-Leu-Pro- Val-Pro (VLPVP, VP5)	Emulsification-evaporation method	*In vitro / In vivo*	The promising results suggested that FA-VP5-LNPs could overcome the intestinal barrier and provide a potential strategy for enhancing peptide delivery and improve the antihypertensive effects.	[25]
Gal-polyethylene glycol polyethylenimine (G-PE)-ANG-shRNA NPs	-	GPE-AGT-shRNA complexes were prepared by vigorous mixing of GPE solution and plasmid solution of AGT shRNA or negative shRNA at a weight ratio of 30:1	*In vivo*	The study showed a significant decrease in systolic blood pressure (SBP). In conclusion, the present study showed that Angiotensinogen(ANG) -silencing had a significant inhibitory effect on hypertension and hypertensive-induced cardiac hypertrophy in spontaneously hypertensive rats.	[26]
Hydrochlorothiazide NPs	-	Antisolvent precipitation-solvent evaporation and emulsion solvent evaporation methods	*In vitro*	The selected sample of hydrochlorothiazide nanoparticles stabilized with carboxymethyl dextran sodium salt with particle size 2.6 nm was characterized additionally by Fourier transform mid-infrared spectroscopy and scanning electron microscopy. It was found that the solubility of this sample was 6.5-fold higher than that of bulk hydrochlorothiazide.	[27]
Irbesartan (IRB) -Pluronic® F-127 NPs	-	Supercritical fluid based on supercritical anti-solvent (SAS) technique	*In vitro*	The analysis of dissolution data indicated that enhanced drug dissolution can be achieved where the SDs in the supercritical fluid process consisted of pluronic nanoparticles. Finally, the SAS-SD formulation showed an increase in relative bioavailability than the pure IRB.	[28]
Isradipine nanoparticles	Isradipine	Solvent evaporation method.	*In vitro*	The results showed good sustained release of drug for upto 24 h. The PMMA (Poly-Methyl-Metha- Acrylate) isradipine NPs shows fall in blood pressure was delayed and reach 15272 mmHg at 1 h. The isradipinenanoparticles shows better bioavailability compare with solution form.	[29]
Lecithin/chitosan NPs	Hydrochlorothiazide (HCT)	Modified solvent evaporation method	*In vivo*.	*In vivo* activity in DOCA induced hypertensive rats demonstrates 1.5-fold percentage decrease in systolic blood pressure and a prolonged duration of action.	[30]
Lecithin/chitosan NPs	Ramipril	Solvent evaporation method	*In-vivo/ in-vitro*	The prepared lecithin/chitosan NPs represent an efficient new drug delivery system for oral administration of this poorly water soluble drug.	[31]

(Table 1) contd....

Nanoparticles (NPs)	In Combination/ Loaded with	Preparation Method	Type of Study	Outcome	Refs.
Lipid nanoparticles (YF4-L-NPs)	Antihypertensive peptides	Solvent evaporation method/membrane hydration-ultrasonic dispersion method	*In vitro / In vivo*	The optimal preparation of YF4-LNPs exhibited sustained release of YF4 *in vitro* and a 5 days long-term antihypertensive effect *in vivo*. The lipid nanoparticles for oral antihypertensive peptide delivery were successfully constructed, which might have a promising future for hypertension treatment.	[32]
Losartan Potassium nanoparticles	Losartan potassium	Microreactor precipitation method	*In vitro*	The design formulations showed the encapsulation efficiency within the range of 57.5 to 82.8% with sustained release profile of 77.2 to 100% over 12 h. The actual and predicted values of both the responses were close to each other. It is verified that the Box behnken factorial design provides a useful platform for the optimization of LP loaded nanoparticle by microreactor precipitation methodology.	[33]
Magnetic NPs:Fe3O4 NPs, FC (iron oxide coated with chitosan) and FCPE (iron oxide NPs	Chitosan-perindopril erbumine) (CPE)	Sonochemical method	*In vitro*	It is apparent that prindopril erbumine was released in a controlled manner with around 89% within about 93 h by phosphate-buffered solution at pH 7.4 and governed by first-order kinetics. Prindopri erbumine, iron oxide nanoparticles and its coated nanocomposite, FCPE were not toxic in a normal human fibroblast (3T3) cell line. Therefore, our nanocomposite containing prindopril erbumine is a possible alternative drug delivery method with minimal toxicity potential.	[34]
Magnetic poly(D,L-lactide) NPs	Aliskiren	Modified nanoprecipitation method	*In vivo*	Differential scanning calorimetry and infrared spectroscopy confirmed that aliskiren was successfully identified in the magnetic poly(D,L-lactide) nanoparticles. The *in vivo* experiments indicated that encapsulated aliskiren decreased blood pressure of the studied male spontaneously hypertensive rat even more significantly than common administered drug	[35]
Mesoporous Silica Nanoparticles (MSN)	Polypill: hydrochlorothiazid, amlodipine, losartan and simvastatin	Modified Stöber method	*In vitro*	Amlodipine, losartan and simvastatin were released from the polypillMSN-41 system in a controlled way. This would be a favourable behaviour when used clinically for avoiding quick pressure decrease. However, the diuretic hydrochlorothiazide was quickly released from our system in the first minutes, as is needed in hypertensive urgencies. In addition, an increase in the stability of amlodipine and hydrochlorothiazide occurred in the polypill-MSN-41 system.	[36]
Mesoporous silica nanoparticles (MS NPs)	Aminopropyl groups (AP-MSN)	Water soluble valsartan method	*In vivo*	Blood pressure monitoring in rats showed that the morning dosing of Diovan tablet efficiently controlled BP for just over 360 minutes whereas the effect of M-MSN lasted for more than 840 minutes.	[37]
Multi-wall lipid-core nanocapsule (MLNC)	Captopril and nanoencapsulating furosemide	Aqueous solution	*In vivo*	In conclusion, the formulation Capt (0.5)-Zn(25)-MLNC-Fur(0.45) proved to be suitable for hypertension treatment envisaging an important innovation.	[38]
Nano hydrochlorothiazide	-	Top-down method	*In vitro*	In this research, the association between Hctz treatment effects with the point of view of the fractal dimension of the drug was demonstrated to prove the properties of the drug in the body. In the near future, drug fractal studies can improve the development of new drugs and treatments with minimal cost than clinical approaches by linking chemistry, mathematical sciences and pharmaceutical sciences.	[39]
Nanoformulated superoxide dismutase: poly-L-lysine (PL-L50)-polyethylene glycol (PEG)/ copper/zinc superoxide dismutase (CuZnSOD): (PL-L50-PEG CuZnSOD Nanozyme)	-	Crosslinked method	*In vivo*	*In vivo* studies conducted in adult male mice demonstrate that hypertension established by chronic subcutaneous infusion of angiotensin II is significantly attenuated for up to 7 days after a single intracerebroventricular injection of nonreducible nanozyme. These data indicate the efficacy of nonreducible poly-l-lysine (PLL50)-polyethylene glycol (PEG) CuZnSOD nanozyme in counteracting excessive superoxide and decreasing blood pressure in angiotensin II -dependent hypertensive mice after central administration.	[40]
Nanovesicle of ceramide 2, stearic acid, behenic acid and cholesteryl sulfate containing oleic acid gel (NOVG)	Nitrendipineacid	Film hydration method	*Ex vivo/ In vivo*	NOVG-5 has shown the most favorable physicochemical properties and good permeation through skin providing good management of hypertension during crucial initial hours.	[41]

(Table 1) contd....

Nanoparticles (NPs)	In Combination/ Loaded with	Preparation Method	Type of Study	Outcome	Refs.
Nebivolol	Eudragit® RS100 polymer	Solvent evaporation (single emulsion) technique	*In vitro*	The *in vitro* drug release study of the prepared nanoparticles showed prolongation of drug release with reduced burst release in comparison with pure drug powder.	[42]
Novel nanoproliposomes of lercanidipine	-	Modified thin-film hydration method	*In vitro*	These findings suggest that nanoproliposomes are promising carriers in improving the oral bioavailability and bioactivity of lercanidipine, and can be an effective therapy in the management of hypertension.	[43]
Novel solid self-nanoemulsifying drug delivery systems (S-SNEDDS) of valsartan	Labrasol/ Tween 20	Response surface methodology employing 33-Box–Behnken design	*In vivo / In vitro*	The present studies demonstrated the bioavailability enhancement potential of porous carriers based S-SNEDDS for a BCS class II drug, valsartan.	[44]
Olmesartan medoxomil (OM): Nanoemulsion	-	Nanoemulsion strategy	*In vitro/ In vivo*	The result of the pharmacokinetic study showed 2.8-fold increase in area under the curve (AUC0–27) of olmesartan upon oral administration of OM nanoemulsion and sustained release profile. Subsequent, *in vivo* studies with nanoemulsion demonstrated better and prolonged control of experimentally induced hypertension with 3-fold reduction in conventional dose.	[45]
Omapatrilat/monolein-nanoparticles (omapatrilat/MO-NPs)	-	Emulsification-diffusion method	*In vivo*	The results indicated that the variables involved in the process did not have an influence on particle size, and that the former is directly determined by the amphiphilic properties of MO. When SHR were orally treated with omapatrilat/MO-nanoparticles, blood pressure was significantly reduced and completely normalized after three days. This effect was markedly higher than that observed with omapatrilat suspensions.	[46]
Palladium nanoparticle	Carbon paste electrode/terazosin	Electrochemical deposition method.	*In vitro*	The efficiency of palladium nanoparticle film on the surface of carbon paste electrode successfully proved for determination of terazosin in pharmaceutical sample and human serum sample with promising recovery results. The effect of some foreign species has been studied.	[47]
Poly (D, L-lactic-co-glycolic acid) polymer: PLGA NPs	Felodipine	Single emulsion solvent evaporation technique	*In vitro / In vivo*	The developed felodipine nanoparticles were prepared, characterized and could possibly be advantageous for prolonged drug release and improving the antihypertensive effect.	[48]
Poly (lactic-co-glycolic acid)[-PLGA] nanoparticles	Carvedilol (CVL)	Nanoprecipitation method	*In vitro*	CVL-loaded NPs were set up by economic nanoprecipitation method owing to the advantages of PLGA polymer accepted as the gold standard. This study aims to treat hypertension effectively by low dose of CVL in a prolonged release pattern.	[49]
Poly (lactic-co-glycolic acid) (PLGA)nanoparticle	Captopril (CAP) / valsartan (VAL)	Common nanoprecipitation fabrication technique	*In vivo*	The formulated nanoparticle could successfully provide sustained drug delivery to a targeted area of the body, which could help to decrease the number of doses for hypertensive treatment, and subsequently increase patient adherence.	[50]
Poly (lactic-co-glycolic acid) (PLGA) nanoparticles	Phe-Tyr dipeptide	Double emulsion (w/o/w) method	*In vitro*	This study presents properties of Phe-Tyr-PLGA NPs drug molecule that can provide insights for improved new drug design and formulation for the treatment of hypertansion disease.	[51]
Poly (lactic-co-glycolic acid) (PLGA) nanoparticles	Peptide/ guar-gum films	Double emulsion technique	*In vitro*	The combination of PLGA nanoparticles with guar-gum films represent a suitable alternative to conventional per os delivery systems, leading to an increased buccal permeability of carried antihypertensive peptide.	[52]
Poly (lactic-co-glycolic) acid (PLGA) NPs	Olmesartan medoxomil (OLM)	Simple one step electrospray method	*In vivo / In vitro*	The current study revealed that the OLM could be well encapsulated in OLM-PLGA, which could address the bioavailability issue of OLM and enhance its potency in the treatment of hypertension.	[53]
Poly-(lactic-co-glycolic) acid nanoparticle (PLGANPs)	Val-Leu-Pro- Val-Pro (VLPVP, VP5) peptides	Double-emulsion (W1/O/W2) solvent evaporation method	*In vivo*	This study illustrated that VP5-NPs might be worthy of further development and used as a potential therapeutic strategy for hypertension in the future.	[54]
Poly-e-caprolactone (PCL NPs)	Isradipine	Nanoprecipitation method	*In vitro*	These nanospheres will be a good candidate delivery system for oral administration, to reduce the initial hypotensive peak and to prolong the antihypertensive effect of the drug.	[55]

(Table 1) contd....

Nanoparticles (NPs)	In Combination/ Loaded with	Preparation Method	Type of Study	Outcome	Refs.
Polyethylene glycol (PEG) - coated magnetite NPs(Iron oxide nanoparticles (FNPs)	Perindopril erbumine (PE)	Coprecipitation method	*In vitro*	The decrease toxicity against mouse normal fibroblast (3T3) cell lines prospective of this nanocomposite together with controlled-release behavior provided evidence of the possible beneficial biological activities of this new nanocomposite for nanopharmaceutical applications for both oral and non-oral routes.	[56]
Poly□ε□caprolactone (PCL), polylactic and glycolic acid (1:1) copolymers (PLAGA), and Eudragit RL/RS (Eudragit) NPs	Nifedipine	Solvent evaporation method	*In-vivo/ in-vitro*	The nanoparticle nifedipine preparations represent sustained release forms with increased bioavailability, a less pronounced initial antihypertensive effect and a long-lasting action.	[57]
Polyionic hybrid nano drug: sodium alginate and chitosan	Captopril, amlodipine and valsartan	Cross-linking method	*In vitro*	Carbohydrate-based hybrid NCS offering high loading capacity, stability and sustained release of hydrophobic drugs can be excellent alternative to current antihypertensive therapeutics.	[58]
Polylactic acid (PLA) and poly(lactic-co-glycolic) acid (PLGA): nanocomposites	Shell of poly(N-isopropylacrylamide) (pNIPAM)	Single emulsion technique followed by an aqueous free radical precipitation polymerisation process	*In vitro*	Release pattern was attributed to the non-Fickian nature of the system, which suggested that the ramipril release was diffusion controlled. Overall, PLGA exhibited better characteristics than PLA as a drug carrier for ramipril adsorption over its matrix.	[59]
Polylactic acid (PLA)/chitosan (CS) NPs	Nifedipine	Emulsion method	*In vivo*	The *in vivo* test of PLA/CS nanoparticles loading nifedipine on mice was evaluated by the change in diastolic pressure, systolic pressure, arterial pressure and heart rate. The obtained results confirm that the PLA/CS nanoparticles loading nifedipine is suitable for applying in the treatment of hypertension patients lately.	[60]
Polylactic and glycolic acid copolymers (PLAGA NPs)	Felodipine	Nanoprecipitation method	*In vitro / Ex vivo*	NPs can be a suitable alternative to the current available therapy in hypertension and angina by enhancing the bioavailability.	[61]
Polylactide acid (PLA) NPS	Aliskiren	Modified nanoprecipitation method	*In vivo*	Nanoparticle-loaded aliskiren decreased vasoconstriction of the mesenteric artery and collagen content (by 11%), and cross-sectional area (by 25%) in the aorta compared to the powdered aliskiren group. In conclusion, nanoparticle-loaded aliskiren represents a promising drug with antihypertensive and cardioprotective effects.	[62]
Sericin NPs	Verapamil Hcl	Crosslinking method	*In vivo*	The nanoparticle form of verapamil had better bioavailability and good pharmacological actions, which might be beneficial for future formulation design perspective.	[63]
Silver nanoparticles (AgNPs)	-	Reducing silver nitrate (AgNO3) with gallic acid	*In vivo / In vitro*	These data suggest that hypertension intensified AgNPs-cardiotoxicity. Nevertheless, the precise mechanism of action is still under elucidation.	[64]
Silver nanoparticles modified with β-cyclodextrin (CD-S-Ag NPs)	Prazosin (PRH)/ losartan (LOS).	Reducing AgNO3 with βCD	*In vitro*	CD-S-Ag NP as a Surface-Enhanced Raman Scattering (SERS) substrate have great potential for the monitoring and determination of antihypertensive drugs, such as prazosin and losartan.	[65]
Solid lipid nanoparticles (ND-SLNs)	Nisoldipine	Hot homogenization followed by ultrasonication	*In vivo / In vitro*	In this study, a significant reduction in the systolic blood pressure was observed, which sustained for a period of 36 h when compared with a controlled suspension.	[66]
Solid lipid nanoparticles (SLNs)	Isradipine (ID)	Hot homogenization followed by ultrasonication method	*In vitro / In vivo*	Pharmacodynamic study of SLNs in fructose induced hypertensive rats showed a decrease in systolic blood pressure for 36h, when compared to suspension, which showed a decrease in systolic blood pressure for only 2 h. Thus, the results conclusively demonstrated the role of SLNs for a significant enhancement in pharmacodynamic effect of ID.	[67]
Solid lipid NPs	Isradipine	Ultra sonication method	*In vitro / In vivo*	The drug release from SLNs formulation found to be around 99% within 12 hours. Drug released from the nanoparticles was in the first order fashion and mechanism followed was diffusion and erosion.	[68]
Solid lipid NPs (SL NPs)	Candesartan cilexetil	Ultrasonication method	*In vivo*	Pharmacodynamic study of SLNs in hypertensive rats showed a decrease in systolic blood pressure for 48 h, while suspension showed a decrease in systolic blood pressure for only 2 h.	[69]

(Table 1) contd....

Nanoparticles (NPs)	In Combination/ Loaded with	Preparation Method	Type of Study	Outcome	Refs.
Solid lipid NPS (CLNs)	Candesartan cilexetil (CC)	Film homogenization technique	*In vivo*	The pharmacokinetic results indicated that the oral bioavailability of candesartan was obviously improved over 12-fold after incorporation into solid lipid nanoparticles. These results demonstrated that solid lipid nanoparticles have great potential for increasing oral bioavailability of lipophilic drugs, such as CC.	[70]
Solid–lipid nanoparticles (coated SLN)	Isradipine	Modification the homogenization followed by ultrasonication method	*In vivo / In vitro*	*In vivo* studies were revealed significantly at greater extent in (drug stability and solubility) oral absorption, which has shown potential entrapment efficiency (97.85% ± 1.02%) to improve biological activity against hypertension. Hence, nano-system of ISR against hypertension is achieved with consequent dose reduction with enhanced systemic bioavailability.	[71]

In total, 10 studies (16.7%) demonstrated the anti-hypertensive activities of PLGA or PLG nanoparticles in combination with various synthetic drugs such as nifedipine, felodipine, aliskiren, perindopril erbumine, isradipine, and olmesartan medoxomil.

Out of 60 papers included in this review, 7 papers (11.7%) had studied the anti-hypertensive effects of chitosan nanoparticles combined with a number of current drugs such as propranolol, bromelain, losartan potassium, nebivolol, captopril, ramipril, *etc.*

Totally, 6 studies (10.0%) showed *in vitro* and *in vivo* anti-hypertensive activities of solid lipid nanoparticles (ND-SLNs) combined with some synthetic drugs such as isradipine, candesartan cilexetil, and nisoldipine.

From 60 included papers, 4 (6.7%) exhibited the anti-hypertensive effects of metal nanoparticles, such as silver, palladium, and iron oxide nanoparticles combined with some of the existing drugs, such as prazosin and losartan.

High blood pressure is one of the most important risk factors that seriously increases the chances of getting some dangerous diseases such as heart disease, stroke, or other dangerous ones [72]. The common treatments for hypertension are altering many lifestyle risk factors, such as diet, exercise, consumption of alcohol and smoking, and use of medications such as diuretics, beta-blockers, angiotensin II receptor blockers, *etc.*, which could reduce blood pressure through different ways and mechanisms [5-7]. Recent studies have demonstrated that the use of these drugs could cause many challenges and limitations in dosing and the related adverse side effects, which could significantly bound their therapeutic properties [4, 8].

Nanomedicine and nanodelivery systems have been well defined as novel emerging sciences which use materials in the nanoscale range to help as means of diagnostic tools or to transport therapeutic medications for particular targeted positions in a well-ordered manner [11]. Today, it has been proven that nanomedicine shows many applications and benefits in treating many chronic diseases through site-specific and target-oriented delivery of exact medicines. The present study aims to systematically review the anti-hypertensive effects of all the organic and inorganic nanoparticles in *in vitro, in vivo*, and clinical trials [63].

In recent years, a wide range of nanoparticles such as inorganic, organic, metalic, and polymeric nanoparticles, including dendrimers, micelles, and liposomes, are regularly used to design the target-specific drug delivery systems. Although these nanoparticles are mostly tagged with drugs that have low solubility and absorption, their efficacy as drug delivery agents varies depending on the size, shape, and other biophysical and chemical features [73].

Polymeric nanomaterials with sizes ranging from 10 to 1000 nm are one of the most widely used types of nanoparticles with ideal properties in drug delivery systems [74]. Since polymeric nanoparticles have high biocompatibility and biodegradability possessions, a number of natural polymers (chitosan, alginate, *etc.*) and synthetic polymers (poly-L-lactic acid, poly(lactic-*co*-glycolic acid), polyvinyl alcohol, and polyethylene glycol, *etc.*) are broadly applied in the nanofabrication of nanoparticles [75]. In this review, several studies showed the beneficial application of polymeric nanoparticles as nanospheres and nanocapsules. These studies demonstrated that polymeric nanoparticles play a key role in the drug delivery systems for hypertension treatment through sustained release forms with increased bioavailability, less pronounced initial anti-hypertensive effect, and long-lasting action [57], improving the oral and non-oral administration of available hydrophobic and lipid drugs but indicating the stability and extended-release function [58], counteracting excessive superoxide, decreasing blood pressure [40], *etc.*

Recently, lipid nanoparticles have been widely applied in pharmaceutical nanotechnology, because of their key role in green chemistry. Lipid nanoparticles with a solid matrix are categorized into (i) solid lipid nanoparticle and (ii) nanostructured lipid carrier (NLC). The main role of lipid nanoparticles as drug delivery vehicles is to improve drug absorption, metabolism, and transportation in the gastrointestinal tract [76]. Here, we found anti-hypertensive effects of some lipid-based nanoparticles alone or along with the available anti-hypertensive drugs candesartan [70] and isradipine [71]. These studies have demonstrated that antihypertensive properties of lipid nanoparticles can be attributed to their activities in sustained release and increasing oral bioavailability of lipophilic drugs [32, 70], overwhelming the intestinal barrier, providing a likely strategy for improving peptide delivery, enhancing the antihypertensive effects [25], and increas-

ing oral absorption through lymphatic pathways, drug stability, and solubility [15, 71].

Metal nanoparticles, possessing some properties including small size, large surface area-to-volume ratio, varieties of metal, synthesis, varieties of fabrication techniques, inertness, and biocompatibility, have been used extensively both in pharmaceuticals and nanopharmaceuticals, such as immunodiagnostics, drug delivery, therapeutics, and gene transfer [77]. Here, we reported the anti-hypertensive activity of some of the metal nanoparticles, such as silver (Ag) and palladium nanoparticles [47, 64]. These studies have exhibited that these nanoparticles could play a key role as inhibitors of the soluble epoxide hydrolase and be a significant target for treatment against hypertension or inflammation. Recently, Fancher *et al.* (2019) demonstrated that a number of FDA-approved drugs loaded onto nanoparticles such as lercanidipine, felodipine, aliskiren, superoxide dismutase, *etc.* due to biocompatibility, biodegradability, and low toxicity might be described for further improvement as new agents for treating resistant hypertension [78].

CONCLUSION

This review demonstrated the anti-hypertensive effects of some organic and inorganic nanoparticles alone or in combination with the available antihypertensives. We found that the organic nanoparticles such as PGLA and chitosan can be considered as preferred options in nanomedicine for treating high blood pressure. The results also showed that these nanoparticles displayed anti-hypertensive effects through some mechanisms such as sustained release forms with increased bioavailability, increasing oral bioavailability and improving oral and non-oral absorption, counteracting excessive superoxide, decreasing blood pressure, *etc.* However, further investigations are required to prove these effects, particularly in clinical settings, as well as their accurate possible mechanisms and toxicity.

CONSENT FOR PUBLICATION

Not applicable.

STANDARDS OF REPORTING

PRISMA guidelines and methodologies were followed.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

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