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Research Article

Evaluation of the Efficacy and Safety of Nanotechnology-Based Herbal Formulations for Hypertension Management

Ni Wayan Nanda Nirmala Sari

Universitas Udayana, Indonesia
Corresponding Author, Email: nandanirmala43824@gmail.com

Abstract

The use of herbal preparations as antihypertensive therapy continues to expand alongside advances in drug delivery technologies, particularly through nanotechnology-based approaches. This article discusses the impact of nanotechnology-based herbal formulations on enhancing the efficacy and safety of hypertension therapy, based on findings from recent studies. Nanoformulations of natural compounds such as curcumin, black garlic, red ginger, garlic, Phaleria macrocarpa, and Rauvolfia serpentina have been shown to improve bioavailability, stability, and antihypertensive activity compared to conventional extracts. Their main mechanisms include inhibition of the angiotensin-converting enzyme (ACE), increased nitric oxide (NO) production, and improvement of antioxidant status, which collectively contribute to the protection of hypertension target organs. Nano-delivery systems also offer better safety profiles with minimal toxicity. These findings indicate that nanoherbal preparations hold promise as more effective and safer complementary therapies for hypertension management. However, most studies remain limited to in vitro and preclinical in vivo experiments, highlighting the need for further investigations, including pharmacokinetic and clinical trials, to confirm their long-term benefits and safety.

Keywords: Nanotechnology, Hypertension, Nanoherbal, Nanomedicine.

INTRODUCTION

Hypertension is a major global health problem with a steadily increasing

prevalence. According to the World Health Organization (WHO, 2023), an estimated 1.28 billion people worldwide suffer from hypertension, with poor control rates in many countries, and this number is projected to rise to more than 1.56 billion by 2025 (Chockalingam et al., 2006). This condition significantly contributes to an increased risk of coronary heart disease, heart failure, and kidney failure (Kaban et al., 2025). In Indonesia, the prevalence of hypertension is also on the rise, creating a heavy economic and social burden on the healthcare system. Data from the World Health Organization (WHO, 2023) and recent epidemiological reviews reveal that fewer than half of hypertensive patients receive adequate treatment, and the proportion achieving recommended blood pressure control remains low. This underscores the urgent need for new and more effective management strategies.

Conventional pharmacological therapies (ACE inhibitors, ARBs, beta-blockers, calcium channel blockers, and diuretics) are indeed effective in lowering blood pressure and reducing the risk of complications; however, their clinical use is often limited by side effects that compromise quality of life and adherence (e.g., acute kidney injury associated with ACE inhibitors/ARBs, lipid abnormalities induced by diuretics or beta-blockers, and the frequent requirement for long-term combination therapy to achieve efficacy and adherence) (Erdine, 2010; Mansfield et al., 2016; Messerli et al., 2008). Moreover, patients' adherence to long-term medication regimens tends to decline, reducing the real-world effectiveness of therapy. These challenges have spurred the search for safe, effective, and patient-friendly alternative and complementary approaches (WHO, 2023). Alongside conventional pharmacological therapies, herbal medicines have long been considered as complementary treatments. Several plants, such as garlic, celery, and Hibiscus sabdariffa, have been reported to exert antihypertensive effects through mechanisms including vasodilation, diuretic action, and antioxidant activity (Damayanti, 2024).

Although many phytochemicals exhibit biological activity, their application remains limited due to poor absorption and distribution, low bioavailability, and suboptimal target specificity. These limitations reduce their effectiveness and often necessitate large doses to achieve therapeutic effects. Furthermore, some compounds are unstable and easily degraded in acidic conditions, further constraining their clinical potential (Dewi et al., 2022).

Nanotechnology has emerged as an innovative approach in drug delivery

systems, including for herbal bioactive compounds. Nanotechnology-based formulations have been shown to enhance stability, improve bioavailability, and enable more specific delivery to target sites within the body (Putri et al., 2025). For example, curcumin nanoemulsions have been demonstrated to improve the stability, solubility, and bioavailability of the active compound. In vitro and in vivo studies further indicate that curcumin nanoemulsions possess stronger antihypertensive effects compared to traditional forms. Thus, nano-herbal formulations can strengthen pharmacological potential relative to conventional extracts (Rachmawati et al., 2016).

Most studies to date remain limited to in vitro or preclinical investigations, while comprehensive evaluations of long-term safety, pharmacokinetics, and toxicity profiles are still scarce. Harnessing natural resources through nanotechnology not only supports the development of more effective and safer antihypertensive therapies but also provides strategic opportunities for Indonesia by leveraging its rich diversity of medicinal plants. Nanotechnology offers solutions to the limitations of conventional herbal preparations, such as low bioavailability and stability, while also reducing dependence on synthetic drugs, many of which are still imported.

This topic is critical for review, as existing research has largely been restricted to in vitro experiments, with relatively few studies evaluating in vivo efficacy or long-term safety. Therefore, a comprehensive review is required to identify opportunities and challenges toward clinical application. Accordingly, this review aims to summarize current advancements while highlighting research gaps that warrant further exploration.

METHOD

This study employed a comprehensive literature review method aimed at analyzing, evaluating, and examining various publications related to nanoherbal formulations and their impact on efficacy and safety in the management of hypertension. The review focused on scientific articles published between 2016 and 2025, both nationally and internationally, to ensure that the data used were relevant and up to date. Literature sources were retrieved from leading scientific databases, including PubMed, ScienceDirect, and Google Scholar, using specific keywords such as nano-herbal, antihypertension, nanoparticle, and hypertension.

Mendeley software was utilized for reference management to support structured

and systematic citation and bibliography compilation. Data analysis was conducted using a qualitative approach, taking into account key aspects of each study reviewed. Articles identified through the databases were screened in stages, beginning with a review of titles and abstracts to assess their relevance to the research theme. Articles that met the inclusion criteria were then examined in full to evaluate the appropriateness of their methodology, findings, and relevance to research on the use of nanoherbals in hypertension therapy. Conversely, articles falling under the exclusion criteria—such as non-academic publications, those unrelated to the topic, or those lacking sufficient information—were excluded from the analysis to ensure that the review remained aligned with the objectives of the study.

RESULT AND DISCUSSION

Hypertension is still primarily managed with conventional therapies such as ACE inhibitors, ARBs, beta-blockers, CCBs, and diuretics. While effective in lowering blood pressure and reducing complications, these therapies are often associated with adverse effects, including acute renal dysfunction, lipid profile alterations, and the need for long-term combination therapy that decreases patient adherence (Erdine, 2010; Mansfield et al., 2016; Messerli et al., 2008). Herbal remedies, such as garlic, celery, and Hibiscus sabdariffa, have long been used as complementary antihypertensive therapies through mechanisms involving vasodilation, diuretic effects, and antioxidant activity (Damayanti, 2024). However, their clinical application is limited by pharmacokinetic weaknesses, including low bioavailability, poor solubility, instability, and nonspecific distribution, with some phytochemicals easily degraded under acidic conditions, requiring high doses for therapeutic effects (Dewi et al., 2022).

Nanotechnology offers an innovative solution to these limitations. Nano-delivery systems, such as curcumin nanoemulsions, improve solubility, stability, and bioavailability, thereby enhancing pharmacological potential (Rachmawati et al., 2016). Both in vitro and in vivo studies demonstrate that nanoherbal formulations are more effective in reducing blood pressure than conventional extracts, acting through ACE inhibition, increased nitric oxide (NO) production, and improved antioxidant status (Putri et al., 2025). Beyond efficacy and safety, nanotechnology-based herbal formulations also hold strategic value in utilizing Indonesia's abundant medicinal resources while reducing dependence on imported synthetic drugs (Putri et al., 2025;

WHO, 2023). Evidence from multiple studies highlights that nanoformulations of curcumin, black garlic, red ginger, garlic, Phaleria macrocarpa, and Rauvolfia serpentina improve bioavailability, stability, and antihypertensive effectiveness compared to conventional preparations.

Table 1. Summary of Research Results Related to the Efficacy of Nanoherbal as an Antihypertensive

Types of research	Research methods	Test Compound	Research result	Ref.
in vivo	Formulation of curcumin in the form of nanoemulsion (Curcumin Nanoemulsion, C-NE), in vivo test on male Wistar rats with Deoxycorticosterone acetate (DOCA)-salt induced hypertension model, as well as comparison using free curcumin and captopril.	Curcumin in Nanoemulsion form (C-NE)	In DOCA-salt-induced hypertensive male Wistar rats, oral administration of curcumin nanoemulsion (C-NE) significantly decreased SBP, DBP, and MAP ($p<0.01$), suppressed ACE and Ang II, increased antioxidants (GSH, SOD, catalase), decreased MDA, and improved histopathology of the heart, kidney, and aorta, with effectiveness superior to free curcumin and close to captopril.	(Ishaq *et al.*, 2023)

in vivo	Formulation of black garlic extract in the form of nanoemulsion (Black Garlic Nanoemulsion, BG-NE), in vivo test on male Wistar rats with Deoxycorticosterone acetate (DOCA)-salt induced hypertension model, as well as comparator using black garlic extract (BGE) and lisinopril.	Black garlic extract (BGE) and black garlic extract nanoemulsion (BG-NE) containing organosulfur compounds (DAS, DADS, DATS), phenolics (gallic acid, p-coumaric acid), and flavonoids (quercetin).	In male Wistar rats with DOCA-salt-induced hypertension, oral administration of Black Garlic Nanoemulsion (BG-NE) significantly reduced blood pressure, especially at high doses, with effectiveness greater than that of black garlic extract (BGE) and approaching that of lisinopril ($p<0.01$). BG-NE also increased bradykinin, NO, and antioxidant activity (GSH, SOD, catalase), decreased Ang II, aldosterone, and MDA, improved cognitive function, and improved kidney and brain histopathology.	(Chen *et al*., 2021)
in vivo	Black garlic nanoemulsions were prepared with carrier oil, surfactants, and co-surfactants, characterized (particle size, PDI, zeta potential, stability), and then tested in DOCA-salt hypertensive rats with normal controls and captopril. Evaluations included blood pressure, ACE activity, Ang II, antioxidant biomarkers (SOD, catalase, GSH, MDA), and histopathology of the heart, kidney, and aorta.	Black garlic extract (Allium sativum L. var. single clove, Black Garlic Extract, BGE) in conventional and nanoemulsion (BG-NE) forms, with a positive comparator in the form of the standard antihypertensive drug captopril.	BG-NE showed significant antihypertensive effects by reducing SBP, DBP, and MAP, suppressing ACE and Ang II activities, increasing antioxidants (SOD, catalase, GSH) and reducing MDA, improving the histopathological structure of organs, and providing better results than BGE and approaching the effects of captopril.	(Sutiningsih *et al*., 2022)

in vivo	Nano-herbal Phaleria macrocarpa was prepared by high-energy milling, tested on prednisone-induced preeclampsia rats (1.5 mg/kgBW/day) and 6% NaCl, with various doses (180, 360, 720 mg/kgBW), compared to negative, positive, and nifedipine controls, and evaluated through blood pressure, organ weight, body weight, and hematological parameters (CBC).	Nano-herbal extract of Phaleria macrocarpa (Phaleria macrocarpa fruit), with a positive comparison to nifedipine (a standard antihypertensive drug).	The results of the study showed that nano-herb Phaleria macrocarpa significantly reduced systolic and diastolic blood pressure in a preeclampsia rat model equivalent to nifedipine, with a high dose (720 mg/kgBW) providing the strongest effect in the form of improving hematological parameters (leukocytes, erythrocytes, Hb) and organ protection (placenta, liver, heart), without causing significant systemic toxicity.	(Simanjuntak & Rumahorbo, 2024)
in vivo	This true experimental study with a pretest-posttest control group administered 250 mg of dopamet (2×/day) ± 0.5 g of black garlic extract nanoparticles (1×/day) for 14 days, with blood pressure evaluation (SBP, DBP, MAP) every 7 days as well as pre-post intervention GSH levels.	Black garlic extract nano particles (BG-NE).	Black garlic extract nanoparticles were proven to be effective in significantly reducing systolic and diastolic blood pressure (p=0.000) and have the potential to increase GSH levels, although the increase was not statistically significant (p=0.313).	(Aldo Dkk., 2024,)
in vivo	Red ginger extract from ethanol maceration was formulated into a nanoemulsion with VCO, Tween 80, PEG 400, and water titration, then tested in vivo on UUO model mice with control and treatment groups, using blood pressure parameters (SBP, DBP) through tail plethysmography and serum ACE levels with ELISA.	Red ginger extract (RGE) nanoemulsion containing flavonoids (especially quercetin), gingerol, and shogaol.	RGE nanoemulsion measuring ~33 nm (PI 0.268) at a dose of 360 mg/200 g BW significantly reduced systolic (142→107 mmHg) and diastolic (106→84 mmHg) blood pressure and serum ACE levels (10.8%), although the effect was still lower than captopril (20.9%), so it has the potential as a natural antihypertensive through the ACE inhibition mechanism.	(Hanifah *et al.*, 2021)
in vivo	T The mice were divided into control and treatment groups, then given Allium	Nanoemulsion of Allium	Garlic nanoemulsion significantly lowered blood pressure, suppressed ACE	(Alam *et al*., 2017)

	sativum extract nanoemulsion at varying doses, compared with captopril. The parameters measured were blood pressure, nitric oxide (NO) levels, ACE activity, and biomarkers of oxidative stress.	sativum (garlic) extract.	activity, increased NO levels, and improved antioxidant status in hypertensive rats. Its effects were superior to those of the conventional extract, although slightly inferior to those of captopril.	
in vitro	Ethanol extraction of Rauvolfia serpentina roots, nanosuspension formulation using the HPMC-based antisolvent precipitation method, optimization using CCD-RSM, characterization (DLS, zeta potential, SEM), and in vitro assay of ACE inhibitory activity and human erythrocyte hemolysis.	Rauvolfia serpentina root extract is rich in alkaloids (reserpine, ajmalicine, serpentine, ajmaline, deserpidine, yohimbine), as well as flavonoids and phenolics.	Nanosuspension of Rauvolfia serpentina showed ACE inhibition of 73.99% (vs crude extract 83.11% and captopril 83.33%) and was safer because it did not cause hemolysis, thus potentially increasing bioavailability as an antihypertensive therapy.	(Touqeer *et al*., 2022)
in vitro	Formulation of curcumin in the form of nanoemulsion with SNEDDS system based on GMO, Tween 20, and PEG 400 through ultrasonic sonication, followed by physical characterization (droplet size, PDI, zeta potential, entrapment efficiency, charge capacity) and in vitro testing of antihypertensive (ACE inhibition) and antihyperlipidemic (HMG-CoA reductase inhibition) activities using spectrophotometric methods."	Curcumin (pure) and curcumin in nanoemulsion form, with comparators captopril (ACE inhibitor) and pravastatin (HMG-CoA reductase inhibitor).	The results of the study showed that curcumin nanoemulsion had higher ACE inhibitory activity than pure curcumin although still lower than captopril, while the HMG-CoA reductase inhibitory activity was much stronger, approaching pravastatin, so it can be concluded that curcumin nanoemulsion is able to increase pharmacological effects both as antihypertensive and antihyperlipidemic.	(Rachmawati *et al*., 2016)

Ishaq et al. (2023) demonstrated that curcumin nanoemulsion (C-NE) enhanced

antihypertensive efficacy in DOCA-salt–induced hypertensive Wistar rats. Compared to free curcumin, C-NE improved absorption, bioavailability, and stability, resulting in significant reductions in systolic, diastolic, and mean arterial pressure. The effects were mediated by ACE inhibition, reduced angiotensin II, improved antioxidant markers (GSH, SOD, catalase), decreased MDA, and histopathological protection of the heart, kidneys, and aorta. The antihypertensive activity of C-NE was superior to free curcumin and comparable to captopril.

Similarly, Chen et al. (2021) reported that black garlic nanoemulsion (BG-NE) showed stronger blood pressure–lowering effects than conventional black garlic extract (BGE) in DOCA-salt–induced hypertensive rats. BG-NE significantly reduced SBP, enhanced NO and bradykinin levels, suppressed Ang II and aldosterone, improved antioxidant defenses, and reduced oxidative stress. Behavioral and histological analyses revealed cognitive improvements and renal and brain tissue protection, with efficacy approaching lisinopril.

In line with these findings, Sutiningsih et al. (2022) confirmed that BG-NE was more effective than BGE, lowering SBP, DBP, and MAP, inhibiting ACE and Ang II, enhancing antioxidant activity, and protecting cardiac, renal, and vascular tissues. The effects were markedly stronger than conventional extracts and nearly equivalent to captopril, suggesting that black garlic nanoformulations may serve as a more effective natural antihypertensive therapy.

Simanjuntak & Rumahorbo (2024) reported that nano-herbal Phaleria macrocarpa significantly enhanced antihypertensive efficacy in a preeclampsia rat model induced by prednisone and NaCl. Using high-energy milling, the nanoformulation improved absorption and stability, reducing systolic and diastolic blood pressure at high doses (720 mg/kg BW). It also improved hematological parameters and protected vital organs (placenta, liver, heart) without systemic toxicity, showing comparable effects to nifedipine.

Aldo et al. (2024) demonstrated that black garlic nanoparticles (BG-NE) improved antihypertensive outcomes in patients receiving dopamet therapy. In a true experimental pretest–posttest control design, BG-NE significantly reduced systolic and diastolic blood pressure ($p=0.000$) compared with controls. Although the increase in glutathione (GSH) as an antioxidant biomarker was not statistically significant ($p=0.313$), the findings suggest enhanced antihypertensive efficacy and potential

antioxidant benefits.

Hanifah et al. (2021) showed that red ginger nanoemulsion (RGE-NE) improved pharmacological activity in a unilateral ureteral obstruction (UUO) hypertensive rat model. With particle size 33 nm and PI 0.268, RGE-NE (360 mg/200 g BW) significantly reduced SBP (142 → 107 mmHg) and DBP (106 → 84 mmHg) ($p<0.05$), alongside a 10.8% reduction in serum ACE levels. Although less effective than captopril (20.9%), these results confirm ACE inhibition as the mechanism and highlight RGE-NE's potential as a natural antihypertensive alternative.

Alam et al. (2017) showed that Allium sativum nanoemulsion enhanced its antihypertensive efficacy compared to conventional extracts. In hypertensive rat models, the nanoformulation improved solubility, stability, and bioavailability, leading to significant blood pressure reduction, ACE inhibition, increased nitric oxide (NO), and improved antioxidant status. Although slightly less effective than captopril, nano-garlic demonstrated superior pharmacological activity over crude extracts.

Touqeer et al. (2022) developed a nanosuspension of Rauvolfia serpentina root extract using antisolvent precipitation with HPMC, aiming to improve stability and safety. While ACE inhibition (73.99% at 5 mg/mL) was slightly lower than crude extract (83.11%) and captopril (83.33%), the nanosuspension showed no hemolysis on human erythrocytes, unlike the crude extract (4.27%). These findings highlight nanosuspension as a safer and more bioavailable alternative for antihypertensive therapy.

Rachmawati et al. (2016) reported that curcumin formulated via a Self-Nanoemulsifying Drug Delivery System (SNEDDS) produced 43 nm droplets with high entrapment efficiency and uniform morphology. The nanoemulsion enhanced ACE inhibitory activity compared to pure curcumin, though lower than captopril, and showed markedly stronger HMG-CoA reductase inhibition, approaching pravastatin. This indicates improved solubility and stability, with strengthened antihypertensive and antihyperlipidemic effects.

Various studies have shown that nanotechnology-based herbal formulations can enhance antihypertensive efficacy by improving bioavailability, solubility, and stability of active compounds. Nanoformulations of curcumin, black garlic, garlic, red ginger, Rauvolfia serpentina, and Phaleria macrocarpa demonstrated stronger pharmacological effects than conventional extracts, including reductions in SBP, DBP, and MAP, ACE inhibition and Ang II suppression, enhanced antioxidant activity (SOD, catalase, GSH),

and decreased oxidative stress (MDA). Some studies also reported protective effects on target organs (heart, kidneys, aorta, brain, placenta), along with cognitive and hematological improvements. Antihypertensive effects often approached standard drugs like captopril or nifedipine, though sometimes slightly lower. Additional benefits included improved safety, as in R. serpentina nanosuspensions that caused no hemolysis. However, most evidence remains limited to in vitro and preclinical in vivo studies, with gaps in pharmacokinetics, biodistribution, long-term toxicity, and clinical validation. Further work on formulation optimization, early-phase trials, and production standardization is needed to advance nanoherbals as safe, effective, and competitive alternatives to standard antihypertensive drugs.

CONCLUSION

Based on the literature review, nanotechnology-based herbal formulations show strong potential to improve the efficacy and safety of hypertension therapy compared with conventional extracts, mainly through enhanced bioavailability, stability, and targeted delivery. In vitro and in vivo studies confirm that nanoformulations of curcumin, black garlic, red ginger, garlic, Rauvolfia serpentina, and Phaleria macrocarpa significantly reduce blood pressure, inhibit ACE and Ang II, boost antioxidant activity, and protect target organs, with effectiveness approaching standard drugs such as captopril and nifedipine. Additional benefits include improved safety, exemplified by R. serpentina nanosuspensions that did not cause hemolysis, unlike crude extracts. The novelty of this review lies in integrating recent findings on nanoherbals for hypertension while highlighting opportunities and challenges for clinical application. Thus, the objective to evaluate their efficacy and safety as alternative antihypertensive therapies was achieved, providing both theoretical insights for nanotechnology-based drug development and practical contributions to advancing safe, effective, and competitive herbal innovations.

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