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**Review Article**

# Multifarious Effects Of Benidipine In Vitro And In Vivo - A Review

**Vishnupriya S*[1], Dhinesh M.[2] , Anjitha P. S.[3] , Eniya A. A.[4]**

*[1]M Pharm, Assistant Professor, Department of Pharmacy Practice, PSG College of Pharmacy, 2295+PCJ, Peelamedu, Avinashi Rd, Coimbatore, Tamil Nadu- 641004.*
*[2-4]Doctor of Pharmacy, Student, PSG College of Pharmacy,2295+PCJ, Peelamedu, Avinashi Rd, Coimbatore, Tamil Nadu- 641004.*

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## ABSTRACT

**BACKGROUND:**
Worldwide, around 25% of individuals suffer from Hypertension is an elevated blood pressure in arteries. Benidipine is an anti-hypertensive drug and it is a long-acting agent. It blocks all the L,N and T-type calcium channels.

**MAIN TEXT:**
Other than anti-hypertensive action, benidipine has other pharmacological effects. In-vivo basic research has shown that benidipine has anti-oxidative properties,stimulatesnitric oxide production, promotes osteoblast differentiation, prevents the formation of mesangial cells, prevents the proliferation of smooth muscles in the vascular system, and safeguards the kidney and muscular tissue of the heart. The purpose of the review is to study the effects of benidipine in in-vitro and in-vivo and its beneficial actions in different disease states.

**CONCLUSION:**
Benidipine is therapeutically well effective such as Reno-protective, Cardioprotective, and Neuro-protectivehas a stronger inhibitory impact on ureteric contractility in the distal ureter also effective in osteogenesis and osteoporosis conditions

## INTRODUCTION

**BACKGROUND:**

Hypertension is an elevated blood pressure in arteries, affecting about 25% of adults globally.It has led to significant health issues, causing a 43%increase in healthy life years lost between 1990 and 2015, resulting in 9.4 million deaths and 212 million lost healthy life years annually.1Benidipine is an orally active drug.2Benidipine is a dihydropyridine- derived long-acting CCB used in humans for many years as an anti-hypertensive medication. Benidipine is

***Corresponding Author:** Vishnupriya S.
**Address**: *M Pharm, Assistant Professor, Department of Pharmacy Practice, PSG College of Pharmacy, 2295+PCJ, Peelamedu, Avinashi Rd, Coimbatore, Tamil Nadu- 641004.*
**Email** : vishnupriyasakthivel1996@gmail.com
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effectively inhibits the L type, N type and T type calcium channels.3Benidipine has potent and long-lasting anti-hypertensive activity due to its high affinity for the DHP binding site on vascular L-type Ca2+channels,inhibition of tachycardia via T-type Ca2+channels,and suppression of catecholamine release from sympathetic nerve via N-type Ca2+channels.4It differs from other calcium channel blockers in that after oral administration, maximum concentration(T max)was reached in short time. In humans, dogs and rats, benidipine was highly bound to plasma proteins (more than 98%).5 In-vitro and In-vivo basic research has shown that benidipine has anti-oxidative activity,stimulatesNO production, inhibits adhesion molecule expression, promotes osteoblast differentiation, inhibits proliferation of vascular smooth muscles, inhibits the growth of mesangial cells, and protects the myocardium.2 This study reviews the relationship between the effects of benidipine and its pharmacological effects in in-vitro and in-vivo.

**MAIN TEXT:**

## THERAPEUTIC EFFECTS OF BENIDIPINE: INVIVO:

### EFFECT ON BONE:

A noticeable change in bone formation in tooth extraction sockets was seen after the administration of Benidipine. .An oral bacterial infection of the bone is a hallmark of the disease MRONJ.Benidipine accelerates the healing of gingival soft tissue and enhances its bone healing.In rats, Benidipine was injected once near MRONJ like regions in tooth extraction socket and the resultant alteration in the necrosed extraction socketwere examined using histologyandμCT studies. TheμCT examination revealed the development of new bone within the extraction socket. In rats with MRONJ-like symptoms, a topical and single injection of BD reduced the exposed and necrotic bone surface and enhanced the formation of new bone.6Furthermore, osteoporosis, a significant clinical concern that has been linked to high blood pressure and its adverse effects on bone development. Benidipine was investigated for its impact on bone marrow stromal cells (BMSC) and bone formation under osteoporotic conditions. In an animal model using ovariectomized (OVX) mice, which simulates postmenopausal osteoporosis, Benidipine treatment increased the expression of β-catenin and LDL receptor-related protein 5 (LRP5), indicating stimulation of BMSC osteogenesis through the WNT signaling pathway. Micro-CT evidence showed that Benidipine significantly prevented bone loss in OVX mice. Additionally, BD up-regulated the expression of alkaline phosphatase (ALP), runt-related transcription factor 2 (RUNX2), and osteocalcin (OCN), further supporting its role in promoting bone development and formation. This suggests that Benidipine could be a viable option for treating postmenopausal patients with hypertension and osteoporosis.7

### EFFECT ON BRAIN:

Cerebral ischemia damage is one of the life-threatening disease. The approach of management for cerebral ischemia injury is to restore blood re-perfusion as soon as possible. However, the act of re-perfusion may cause brain injury, cerebral edema, haemorrhaging of the brain, and neuronal death. This event is known as ischemia/re-perfusion.Benidipine treatment reduced the level of lipid peroxidation and exhibited antioxidant and anti-apoptotic propertiesand significantly reduced cerebral infarction in rats with ischemia/re-perfusion damage. Benidipine neuroprotective effects were detectable histopathologically in the tissues of the cerebral cortex. This beneficial effect could be attributed to increased brain tissue antioxidant capacity and reduced overproduction of inflammatory cytokines.8 Regarding epilepsy, patients often suffer from seizures, and it can affect their quality of life. Generalized tonic-clonic seizures are a common and serious type. In

epilepsy treatment, neuroprotection is crucial alongside seizure control. Various antiepileptic drugs act on mechanisms such as GABA modulation, synaptic vesicles, and ion channels (sodium, calcium, potassium). Valproic acid, which influences GABA metabolism and ion channels, is one such drug. Benidipine, a calcium channel blocker, may prevent neurodegeneration by reducing calcium influx into cells. In a study investigating Benidipine's potential in epilepsy, an experimental model was created using pentylenetetrazol, and different doses of benidipine or combinations with valproic acid were administered to rats. Antiepileptic effects were similar across groups, but the Benidipine 4 mg/kg group notably reduced IL-1 levels. The lowest TNF-alpha levels were observed in the valproic acid + benidipine 2 mg/kg group. Overall, Benidipine exhibited both antiepileptic and neuroprotective activity, making it a promising and cost-effective therapy for epilepsy.3

**EFFECT ON HEART:**

Ischemia followed by re-perfusion leads to intracellular calcium overload, and pre-ischemia treatment with calcium antagonists reduces size of the infarct and improves recovery. Apoptosis is regulated by intrinsic and extrinsic pathways. The extrinsic pathway involves procaspase-8 activation by ligands like Fas and TNFR1. The intrinsic pathway is triggered by mitochondria, leading to cytochrome c release and caspase activation. Benidipine, a vasodilating calcium antagonist, reduces cytosolic calcium levels, myocardial apoptosis, and enhances cardiac contractile performance in ischemia/re-perfusion. In rats, benidipine reduces caspase-9 activation and cytochrome c release, leading to less apoptosis, with no impact on caspase-8. It increases ERK1/2 activity and duration, but p38 MAPK remains unaffected. Calcium channel blockers contribute to cardio protection in MI/R by preventing post-ischemic myocardial apoptosis.9

Benidipine's cardio-protective effects are primarily linked to its ability to inhibit calcium currents, which helps prevent myocardial damage induced by intracellular calcium excess during myocardial ischemia and re-perfusion. Reactive oxygen species generated during re-perfusion lead to intracellular Ca2+ accumulation and lipid peroxidation, causing cell membrane damage and functional disturbances. Benidipine, a dihydropyridine calcium antagonist, serves as an antioxidant and helps preserve vascular endothelial cell function during ischemia and re-perfusion in rat arteries. In isolated perfused rat hearts, Benidipine demonstrated a reduction in myocardial damage during ischemia and re-perfusion. The study also assessed Benidipine's impact on H2O2-induced myocardial damage in rat isolated hearts, emphasizing the relevance of its antioxidant activity within therapeutic dose ranges. Notably, Benidipine's L-type Ca2+-channel blocking activity enhances coronary blood flow and decreases heart mechanical function. Its high lipophilicity allows efficient membrane accumulation, resulting in sustained vasorelaxant effects in isolated coronary arteries, even after drug removal. These findings suggest that myocardial membranes can consistently deposit Benidipine, enhancing its cardio-protective effectiveness. In isolated rat cardiac tissue, Benidipine exhibits preventive properties against H2O2-induced damage, indicating additional mechanisms beyond calcium antagonism, including antioxidant activity, contribute to its cardio-protective benefits.10

**EFFECT ON KIDNEY:**

Chronic renal failure (CRF) develops inexorably to end-stage kidney disease. The leukocytes mostly contain delayed rectifier K + channels (Kv1.3) in their plasma membranes, and the channels play important roles in the cell cycle. Benidipine is an effective Kv1.3 channel inhibitor. Benidipine has pharmacological activity in

delaying the advancement of renal fibrosis since it isover-expressed in leukocytes in advanced CRF. Benidipine, was found to successfully decrease the in-situ proliferation of leukocytes (white blood cells) in the renal of rats with severe CKD. This suggests that Benidipine had a direct effect on lowering the immunological response within the kidneys. This implies that Benidipine has a beneficial impact on reducing in-situ leukocyte proliferation and decreasing the evolution of renal fibrosis. Also Benidipine is known to have reno-protective effects in kidneys with glomerular disorders by reducing proteinuria and inhibiting the development of glomerulosclerosis. In terms of the mechanism, it has been shown that benidipine, which inhibits L- and T-type calcium channels in the renal vasculature, widens both the afferent and efferent glomerular arterioles and reduces glomerular hypertension.11 According to reports, the impact on T channel is higher than that on the L channel, offering tremendous potential for kidney protection. Rho kinase activity was shown to be inhibited by inhibiting the T calcium channel, and this is crucial for podocyte effacement in immune complex-mediated glomerular disease and other renal disorders. Rho kinase 1 (ROCK1) activity may be inhibited by blocking T channels to preserve diabetic kidney and lessen epithelium-mesenchymal trans-differentiation and fibrosis. By inhibiting Rho kinase activity, benidipine decreases epithelium mesenchymal trans differentiation. For the protein expressions of ROCK1, -SMA, and E-cadherin, as well as for the quantification of ROCK1 mRNA, PCR and blotting techniques were used. Without changing blood sugar or blood pressure, benidipine can considerably suppress NAG activity, lower urine protein and Serum creatinine levels, raise Ecadherin expression, decrease the expression of p-MYPT1, ROCK1, and -SMA, and increase the expression of p-MYPT1 and -SMA. This showed that benidipine suppressed ROCK1 activity, partially preventing Epithelium-mesenchymal transdifferentiation (EMT). Independent of its ability to reduce blood pressure, benidipine has a protective impact on the diabetic nephropathy.12 According to the hyper-filtration theory, both diabetic and non-diabetic kidney disease advance in part due to a rise in glomerular capillary pressure. Proteinuria harms kidney and stimulates mesangial and tubular protein overload, which promotes inflammation which eventually leads to glomerulosclerosis and tubulointerstitial fibrosis. Benidipine would therefore appear due to its antiproteinuric action. Benidipine considerably lower heart rate,when given to individuals with mild-to-moderate stage CKD, benidipine reduced plasma levels of aldosterone without affecting serum levels of Na and K. Benidipine would therefore on to decreasing blood pressure by preventing the synthesis of aldosterone. Ultrafiltration of proteins through the glomerular basement membrane causes proteinuria. Therefore, it would be expected that by reducing the production of aldosterone, benidipine would provides renoprotection. Benidipine appears to have these properties, which make the medication more beneficial for slowing the course of renal failure and reducing organ and tissue damage in individuals with hypertension and CKD.13 A significant risk factor for cardiovascular disease has been identified as CKD. The advancement of renal disease is thought to cause moderate renal impairment and proteinuria to increase hypertension, and further impair kidney function. Dilating the efferent arterioles and lowering intraglomerular pressure are two mechanisms by which certain dihydropyridine CCBs are known to preventkidneyimpairment. A long-acting CCB known as benidipine (hydrochloride) has been shown to increase the kidney's ability to produce nitric oxide (NO) and reduce intraglomerular pressure by widening efferent arterioles. Benidipine significantly decreased home SBP and

DBP at the measured time-points compared pretreatment, showing the dependable anti-hypertensive impact of the medications. Benidipine showed anti-hypertensive effects on HBP in both the morning and the evening. Changes in serum creatinine levels and eGFR, a marker of renal function, are used to determine the reno-protective impact of benidipine. Cardiovascular events in hypertensive individuals may be attributed to the presence of concurrent hypertension and renal illness. In terms of the mechanism, benidipine may also have an inhibitory impact on the T-type calcium channel that contributes to its reno-protective effects.Benidipine was said to provide remarkably significant decreases in proteinuria. Comparing benidipine to other CCBs, it has a favorable effect on renal function, pointing to the potential therapeutic advantages of benidipine as an anti-hypertensive medication with a reno-protective effect. Benidipine's reno-protective effects may be brought about by its ability to inhibit T-type calcium channels.14

**EFFECT ON MUSCLE:**

In this study, the research focused on the impact of benidipine on mouse airway smooth muscle (ASM), which has significant effect in the pathophysiology of asthma due to its involvement in airway constriction. Benidipine's effectiveness in relaxing ASM was assessed through various experiments. Male BALB/c mice were used, and their tracheas were collected and subjected to tissue tension tests. High K+ (80 mM)-induced precontraction was employed as a standard measure of ASM contraction. Benidipine had a dose-dependent ability to relax both high K+ and ACh-induced precontraction by inhibiting Ca2+ influx through L-type voltage-dependent Ca2+ channels (LVDCCs) and non-selective cation channels (NSCCs). Furthermore, the study found that Benidipine’s effects were long-lasting and challenging to reverse, making it a promising candidate for potential medical applications in treating airway hyper-responsiveness associated with asthma.4

**EFFECT ON HYPEREMIA PATIENTS:**

In patients with essential hypertension benidipineimproves forearm reactive hyperemia.Improving endothelial function may be critical in lowering cardiovascular morbidity. Calcium antagonists have anti-endothelial properties. In this clinical investigation, we looked at how individuals with hypertension, results in dysfunction in the endothelial cells, responded to the calcium antagonist benidipine. Benidipinehas been demonstrated to have a favorable preventive impact on endothelial cells. Benidipine substantially lowered both SBP and DBP when it was used to evaluate blood flow response at the same time. Reactive hyperemia ratio significantly increased after 8 weeks of benidipine administration. Benidipinewas shown in the current study that increase endothelial function as measured by strain-gauge plethysmography. Benidipine may potentially have a direct impact that is unrelated to the blood pressure drop, even though it is thought that this action is mediated via the lower blood pressure. Overall, It showed that benidipine directly affected endothelial dysfunction brought on by hypertension. Given that HGF protects against endothelium damage, Benidipine’s higher circulating levels of HGF may aid in the resolution of endothelial dysfunction.15

**IN VITRO:**

**EFFECT ON HEART:**

In atherosclerosis, Foam cells develop because of monocyte-derived macrophages invading the arterial wall and accumulating cholesterol. Vascular cell adhesion molecule-1 (VCAM-1, CD104) and intracellular cell adhesion molecule-1 (ICAM1, CD54), as well as chemokines like interleukin-8 and monocyte chemo-attractant protein -1 (MCP-1), are all highly abundant in atherosclerotic plaque.One of Benidipine's

pleiotropic properties is anti-oxidative action. To examine, the impact of benidipine on the expression of chemokines and surface adhesion molecules in human aortic endothelial cells (HAECs). The adherence of THP-1 cells to HAECs induced by TNF-a or interleukin-1b was considerably reduced after pretreatment with benidipine for 24 hours. Benidipine only slightly inhibited expression of ICAM-1 mRNA, whereas it significantly suppressed the increase in VCAM-1 mRNA in a concentration-dependent manner. Additionally, benidipine significantly decreased the amount of MCP-1 and IL-8 that HAECs produced. Western blotting of inhibitory nuclear factor- κB (IκB) phosphorylation and luciferase reporter experiment showed that benidipine suppressed the redox-sensitive transcriptional nuclear factor- κB (NF-κB) pathway. Benidipine may have anti-inflammatory properties and protective or therapeutic effects, not only for hypertension but also atherosclerosis.16

**EFFECT ON BONE:**

Older adults who are additionally predisposed to specific pathological disorders relating to the bones still struggle with hypertension as a serious health issue. Hip fractures and osteoporosis are other prevalent diseases that affect a sizable section of the elderly population and are characterized by bone loss and poor skeletal health conditions. It has been established that anomalies in bone mass are associated to hypertension. Therefore, it has long been hypothesized that Anti-hypertensive medications may be helpful to simultaneously enhance osteogenesis and modify bone health. MC3T3-E1 cells were grown in a humid incubator at 37°C with 5% CO2 in minimal necessary media with 10% fetal bovine serum (FBS; Gibco) and 100 U/ml streptomycin/penicillin (Sigma-Aldrich). Cells were passaged using 0.25% trypsin (Sigma-Aldrich) when cell density reached 80% and the cell culture medium was changed every 3 days. 5×103 MC3T3-E1 cells per well were planted into 96-well plates and incubated for 12 hours. Final concentrations of the BD solution were added. Negative control cells and blank wells were created using cells that had not received Benidipine treatment. The MTT assay and cell cycle assay revealed that Benidipine substantially and dose-dependently enhances the proliferation of MC3T3-E1 cells, laying the groundwork for subsequent osteogenic differentiation. It was shown that Benidipine inhibits the potential function of osteoclasts in vitro. Benidipine also enhances the proliferation, osteogenic differentiation, and maturation of mice pre-osteoblasts. However, to maximize the effectiveness of pure Benidipine in inducing osteogenesis in local applications, a well-designed drug delivery method is necessary.17

**EFFECT ON URETER:**

The effects of the Benidipine on the contractility of proximal and distal caprine (goat) ureters. They used the goat ureter due to its anatomical and physiological similarities to the human ureter.The ureters were dissected into proximal and distal sections, and the serosa was removed. These sections were then cut into smaller strips and kept in an organ bath with mammalian Ringer solution at 40°C. Benidipine was prepared in a stock solution and was shown to inhibit ureteral activity in vitro, with a stronger effect in the distal ureter compared to the proximal ureter.For the first time, the study revealed the dose-response relationship of benidipine on ureter contractility. Benidipine decreased distal ureter contractility at lower dosages, maybe due to the existence of more L-type calcium channels in the lower ureter.Overall, research suggests that benidipine has potential in treating ureteric stones, especially in facilitating the clearance of stones in the distal ureter.18

**CONCLUSION:**

Benidipine is a long-acting calcium channel blocker used to treat hypertension. Apart from its

anti-hypertensive activity, Benidipine provides multiple effects on animals. It shows that, benidipine is therapeutically well effective drug and provides Reno-protective, Cardio protective, Neuro-protective effect and has a stronger inhibitory impact on ureteric contractility in the distal ureter, protective impact ondiabetic nephropathy, reduces glomerular hypertension also effective in osteogenesis and osteoporosis conditions. As Benidipine is a newly emerging drug more research investigations are needed to define the effects of benidipine on humans and animals.

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