Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Vol 13 [10] September 2024: 01-06

Online ISSN 2277-1808
Journal's URL: http://www.bepls.com
CODEN: BEPLAD

REVIEW ARTICLE **OPEN ACCESS**

Nicorandil: Varied Actions and Benefits

Madhura Shirishkumar Bhosale[1], Shraddha Yadav*[1], Shruti Vimal[2], Mandar Ambike[3]
[1]Department of pharmacology; Symbiosis Medical College for Women & Symbiosis University Hospital and Research Centre, Symbiosis International (Deemed University), Pune, India
[2]Department of pathology; Symbiosis Medical College for Women & Symbiosis University Hospital and Research Centre, Symbiosis International (Deemed University), Pune, India
[3]Department of anatomy; Symbiosis Medical College for Women & Symbiosis University Hospital and Research Centre, Symbiosis International (Deemed University), Pune, India
Corresponding Author: Shraddha Yadav
Email Address: madhura.bhosale@smcw.siu.edu.in

ABSTRACT
Nicorandil, a well-established antianginal agent, is recommended as a second-line treatment for chronic stable angina in European guidelines, demonstrating efficacy comparable to classic antianginal agents. Its clinical application extends to various cardiovascular diseases, including variant or unstable angina and reperfusion-induced damage following coronary interventions. The protective effects of nicorandil involve different mechanisms, either through adenosine triphosphate-sensitive potassium (KATP) channel opening or nitric oxide (NO) donation. The prevalence of these mechanisms depends on nicorandil dosage, disease location, and the functionality of the specific mechanism. Experimental models indicate that nicorandil's protection is primarily attributed to KATP channel opening in myocardial and pulmonary fibrosis, renal injury, and glomerulonephritis. Conversely, NO donation dominates as a protective mechanism in hepatic fibrosis and inflammatory bowel diseases. Recognizing the predominant mechanism in different conditions is crucial for the optimal use of nicorandil, providing valuable insights into recommended dosage for specific diseases.
Keywords: *Nicorandil, cardiovascular diseases, therapeutic mechanisms*

Received 09.06.2024 Revised 19.07.2024 Accepted 30.08.2024

INTRODUCTION

Nicorandil stands as a well-established and secure antianginal agent, granted approval for long-term therapy in the management of chronic stable angina in both Japan and Europe [1]. The positive impact of nicorandil on mortality and morbidity among patients with coronary artery disease (CAD) has been underscored by the Japanese CAD and the Impact of Nicorandil in Angina studies [2,3]. Recognizing its efficacy, the European Society of Cardiology recommends nicorandil as a second-line treatment for chronic stable angina [4]. Comparative clinical trials have consistently demonstrated the comparable efficacy of nicorandil in ameliorating effort angina and ischemic symptoms when compared to β blockers and calcium antagonists. Remarkably, this improvement is achieved with minimal hemodynamic disturbance [5]. Furthermore, nicorandil exhibits a notable advantage by serving as an effective anti-ischemic agent for patients unable to use beta blockers due to contraindications such as bradycardia or exacerbated pulmonary disease [7]. Crucially, the pharmacokinetic profile of nicorandil suggests its safety for individuals undergoing anticoagulant therapies or those with renal or hepatic impairments [8]. The incidence of side effects is minimal, with headaches being a common occurrence, and less frequent side effects including dizziness, gastrointestinal upset, flushing, and malaise. It is important to note that nicorandil is contraindicated in cases of hypotension and should not be used concurrently with other vasodilators [9]. Nicorandil has found clinical application across various cardiovascular conditions, including variant angina (coronary vasospasm), unstable angina, and reperfusion-induced damage following coronary angioplasty or thrombolysis [6,10]. In a clinical study addressing refractory angina, Nicorandil demonstrated significant improvements in frequency, duration, electrocardiographic perturbations, and patients' adverse reactions [11]. A noteworthy meta-analysis of 17 clinical trials revealed that Nicorandil, when used in conjunction with coronary reperfusion therapy for acute myocardial infarction (AMI), led to enhanced left ventricular ejection fraction and improved microvascular function [12]. Long-term Nicorandil therapy exhibited positive effects on left ventricular remodelling and

myocardial sympathetic nerve activity in AMI patients post-reperfusion therapy [13]. Additionally, Nicorandil, as an adjunct to coronary angioplasty, demonstrated superior clinical and functional outcomes for patients with anterior AMI compared to angioplasty alone. This improvement was attributed to reduced myocardial injury, enhanced microvascular function, and a lower rate of no-reflow [14]. Intravenous Nicorandil was found to decrease QT dispersion and ventricular fibrillation in patients following successful coronary angioplasty [15]. However, caution is warranted as preoperative use of Nicorandil before coronary artery bypass graft may lead to severe vasodilation and a drop in blood pressure, particularly when influenced by various potentiating factors during surgery. Consequently, it is advisable to discontinue Nicorandil therapy at least three days before admission for an operation [6].

Pharmacological Actions of Nicorandil

Nicorandil functions as an opener for adenosine triphosphate-sensitive potassium (KATP) channels and acts as a nitric oxide (NO) donor. Its cardio protective effects stem from various mechanisms, encompassing the enhancement of myocardial blood perfusion, reduction in preload and afterload, protection against ischemic damage, anti-arrhythmic effects, prevention of calcium overload, energy-modulating actions, and anti-inflammatory, antiapoptotic, and antiproliferative effects [16,17]. Remarkably, nicorandil achieves improvements in cardiac function without impacting blood pressure (BP), cardiac conduction, or contraction. The antianginal and anti-ischemic effects of nicorandil are attributed to the dilation of coronary arteries and the reduction of myocardial oxygen demand, primarily by influencing afterload and, to a lesser extent, preload. Nicorandil is recognized as a balanced vasodilator, affecting both arterial and venous blood vessels. Notably, the impact of nicorandil on preload may be less than that observed with nitrates, owing to a significant decrease in systemic vascular resistance that tends to increase venous return [6,16,18].

Nitric Oxide Donation

The administration of Nicorandil elevates the level of nitric oxide (NO) by initiating a reaction between its nitrate group and the sulfhydryl group within the cells of vascular smooth muscle. Subsequently, this process either activates guanylate cyclase or promotes the release of NO. As a result, there is an augmentation of cGMP levels accompanied by a decrease in intracellular calcium, ultimately leading to the relaxation of vascular smooth muscle cells [18].

KATP Channel Opening

Nicorandil acts as an opener of the ATP-sensitive potassium (KATP) channel, a channel sensitive to the adenosine triphosphate/adenosine diphosphate ratio, reflecting the cell's energy status. This channel exhibits diverse actions depending on its type and tissue specificity, found at both sarcolemmal and mitochondrial levels in myocardial cells and vascular smooth muscle cells [17,19,20]. Nicorandil specifically activates the receptors Kir6.2/sulfonylurea receptor 2A (SUR2A) and Kir6.2/SUR2B, demonstrating its specificity for KATP channels in cardiac and smooth muscles. Notably, it has no observable effect on insulin secretion, indicating good tolerability in diabetic patients [21]. Sarcolemmal KATP channels in cardiomyocytes link electrical activity to metabolic and energy states, modulating action potential duration. Opening these channels during ischemia results in action potential shortening and reduced myocardial work [22]. In vascular smooth muscle, opening sarcolemmal KATP channels induces hyperpolarization, leading to the closure of voltage-sensitive calcium channels, reduced calcium influx, and intracellular calcium, ultimately causing myosin light chain dephosphorylation and vascular smooth muscle relaxation [6,23]. These channels also play a role in maintaining basal vascular tone in mesenteric and coronary arteries [24]. Nicorandil's NO donation and KATP channel opening contribute to its vasodilatory properties. Notably, KATP channel opening primarily dilates peripheral and coronary resistance arterioles at low doses, while its NO donating property predominantly dilates epicardial coronary arteries and veins at high doses [25-27]. The lack of tolerance with nicorandil administration compared to nitrates is attributed to its KATP channel opening effect rather than its nitrate activity [17].

KATP Channel Opening

Nicorandil activates ATP-sensitive potassium (KATP) channels, influencing cellular energy status. Specific to cardiac and smooth muscles, it activates Kir6.2/SUR2A and Kir6.2/SUR2B receptors. This action shortens action potentials during ischemia in cardiomyocytes and induces vascular smooth muscle relaxation. In vascular smooth muscle, KATP channel opening causes hyperpolarization, closing calcium channels, reducing calcium influx, and promoting relaxation. This process maintains basal vascular tone.

Nicorandil's NO donation and KATP channel opening drive its vasodilatory effects. At low doses, it primarily dilates peripheral and coronary resistance arterioles, while at high doses, it predominantly dilates epicardial coronary arteries and veins. Unlike nitrates, the lack of tolerance with nicorandil is linked to its KATP channel opening, not its nitrate activity [17].

Different Mechanisms in Various Disease Conditions

The protective effects of nicorandil involve diverse mechanisms, with the prevalence of KATP channel opening or NO donation contingent on the nicorandil dose, the location of diseased conditions, and the functionality of the specific mechanism.

Male and Female Reproductive Diseases

Nicorandil exhibits significant efficacy in addressing functional disorders induced by asymmetric dimethylarginine-induced preeclampsia in animals. The activation of KATP channels appears to predominantly contribute to these effects, as evidenced by the partial reduction in nicorandil's impact with glibenclamide[52]. Furthermore, nicorandil's ability to relax uterine muscle, primarily achieved through KATP channels, holds potential for improving placental microcirculation [53]. In the context of male impotency, nicorandil demonstrates notable effectiveness. Through in vitro experiments, it was found to relax corpora cavernosal smooth muscle mainly via KATP channel opening and, to a lesser extent, through NO donation. Its vasodilative action on the deep cavernous artery primarily involves guanylate cyclase stimulation [54,55].

Cardiovascular Diseases

Nicorandil demonstrates its beneficial impact on stunned myocardium in anesthetized dogs by directly activating KATP channels. This cardioprotective effect is impeded by pretreatment with glibenclamide, a KATP channel blocker [38]. Furthermore, nicorandil's role in preventing cardiac fibrosis involves KATP channel opening, as evidenced by its attenuation of myocardial infarction (MI)-induced cardiac fibrosis in rats. This effect is hindered by the addition of glibenclamide, which acts as both a KATP channel blocker and a vasorelaxant through NO generation [39].In various experimental models of myocardial injury, such as ischemia-reperfusion (IR), nicorandil provides cardioprotection through the opening of mitochondrial KATP channels, a phenomenon known as pharmacological preconditioning [36,41]. Pharmacological preconditioning with a lower oral dose of nicorandil selectively opens mitochondrial KATP channels and offers enhanced cardioprotection against biochemical changes and ventricular arrhythmias induced by IR [42]. Experiments on ventricular myocytes confirm the role of mitochondrial KATP channels, rather than their sarcolemmal counterparts, as the target for nicorandil's cardioprotective action [43]. Nicorandil also mitigates mitochondrial dysfunction in experimentally induced heart failure by improving mitochondrial oxidative stress status, energy production capacity, and inhibiting ultrastructural changes, apoptotic signaling pathways, and DNA fragmentation [33]. Its protective effect against doxorubicin-induced reactive oxygen species (ROS) in the HL-1 cardiomyocyte cell line is attributed to mitochondrial KATP opening, not NO donation [32]. Crucially, pharmacological preconditioning with nicorandil enhances the efficacy of bone marrow-derived mesenchymal stem cell (BM-MSC) transplantation after isoproterenol-induced myocardial damage. This is achieved by creating a supportive environment for BM-MSC, improving their survival and homing, and reducing factors of inflammation, fibrogenesis, and apoptosis that could impede cell-based therapy [44].

Bowel Diseases

Nicorandil improves experimentally induced inflammatory bowel disease (IBD) using a dose that does not significantly affect blood pressure. Its mechanism, partially or entirely independent of KATP channels (as observed with coadministration of glibenclamide), involves the upregulation of endothelial nitric oxide synthase (eNOS), the production of nitric oxide (NO), and its antioxidant potential through its nicotinamide moiety. These factors contribute significantly to the remission of IBD [37]. Nicorandil also exhibits anti-inflammatory effects by inhibiting the release of inflammatory mediators, such as tumor necrosis factor-alpha. This effect is primarily attributed to NO donation and, to a lesser extent, KATP channel opening [51].

Pulmonary Diseases

Nicorandil has been shown to alleviate monocrotaline-induced endothelial damage and pulmonary arterial hypertension in rats. This effect is primarily attributed to KATP channel opening, with an additional contribution from its nitric oxide (NO)-releasing property. The confirmation of these beneficial effects involved the use of glibenclamide and N omega-nitro-L-arginine methyl ester (L-NAME), an inhibitor of NO synthase, which blocked nicorandil's effects [45]. In contrast, the activation of KATP channels plays a major role in nicorandil's positive impact against pulmonary fibrosis induced by cyclophosphamide in rats. The concurrent administration of glibenclamide completely nullified the effects provided by nicorandil in this context [46].

Hepatic Diseases

Nicorandil has demonstrated effectiveness as a therapeutic approach against experimentally induced liver fibrosis by bile duct ligation. Its protective effects on biochemical and histological changes were fully reversed when co-administered with L-NAME. In contrast, glibenclamide coadministration offered less protection compared to nicorandil alone. These findings suggest that nicorandil's protection against

hepatic fibrosis is primarily associated with its role as a nitric oxide (NO) donor and, to a lesser extent, its KATP channel opening [50].

Renal Diseases

Nicorandil exhibits beneficial effects in various experimental models of renal diseases. In diabetic eNOS-deficient mice, it significantly reduces renal injury and urinary albumin excretion, with the protective mechanism excluding the role of nitric oxide (NO) donation. The reduction of oxidative stress, likely initiated through KATP channel opening, constitutes a key element of this protective mechanism, as evidenced by its attenuation with the use of glibenclamide[47]. Nicorandil also safeguards podocytes in the kidney from hyperglycemia-induced oxidative stress by activating KATP channels and stimulating manganese superoxide dismutase (MnSOD) expression in the mitochondria [48]. Additionally, it ameliorates renal injury induced by unilateral ureteral obstruction in rats by increasing renal NO and reducing transforming growth factor-beta. The renoprotective effects are compromised by L-NAME coadministration [49].

CONCLUSION

In diverse diseased or clinical conditions, understanding the predominant mechanism behind nicorandil's therapeutic or protective effects is crucial. This insight can provide valuable information for the appropriate utilization of the medication and the determination of its recommended dose tailored to specific diseases.

REFERENCES

1. Roland E. (1993): Safety profile of an anti-anginal agent with potassium channel opening activity: An overview. *Eur Heart J*. ;14 Suppl B:48-52.
2. Walker A, McMurray J, Stewart S, Berger W, McMahon AD, Dargie H, et al. (2006): Economic evaluation of the impact of nicorandil in angina (IONA) trial. *Heart*. ;92: 619-24.
3. Horinaka S, Yabe A, Yagi H, Ishimitsu T, Yamazaki T, Suzuki S, et al. (2010): Effects of nicorandil on cardiovascular events in patients with coronary artery disease in the Japanese coronary artery disease (JCAD) study. *Circ J*. ;74: 503-9.
4. Task Force Members, Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, et al. (2013): ESC guidelines on the management of stable coronary artery disease: The task force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J*. 2013;34:2949-3003.
5. Ferrari R, Pavasini R, Camici PG, Crea F, Danchin N, Pinto F, et al. (2019): Anti-anginal drugs-beliefs and evidence: Systematic review covering 50 years of medical treatment. *Eur Heart J*.;40: 190-4.
6. Falase B, Easaw J, Youhana A. (2001): The role of nicorandil in the treatment of myocardial ischaemia. *Expert Opin Pharmacother*. ;2: 845-56.
7. Morishita S, Maeba H, Takehana K, Shiojima I. (2017): Nicorandil was an effective treatment option for a patient with bland-white-garland syndrome. *Intern Med*.;56: 2295-9.
8. Frydman A. (1992): Pharmacokinetic profile of nicorandil in humans: An overview. *J Cardiovasc Pharmacol*. ;20 Suppl 3:S34-44.
9. Dunn N, Freemantle S, Pearce G, Wilton LV, Mann RD. (1999): Safety profile of nicorandil – Prescription-event monitoring (PEM) study. *Pharmacoepidemiol Drug Saf*. ;8: 197-205.
10. Krumenacker M, Roland E. (1992): Clinical profile of nicorandil: An overview of its hemodynamic properties and therapeutic efficacy. *J Cardiovasc Pharmacol*.;20 Suppl 3:S93-102.
11. Li Y, Liu Y, Peng W, Wang B, Geng T, Xu Z. (2018): Therapeutic effect and safety of nicorandil in treatment of refractory angina pectoris. *Int J Clin Exp Med*.;11: 6993-8.
12. Iwakura K, Ito H, Okamura A, Koyama Y, Date M, Higuchi Y, et al. (2009): Nicorandil treatment in patients with acute myocardial infarction: A meta-analysis. *Circ J*.;73: 925-31.
13. Kasama S, Toyama T, Sumino H, Kumakura H, Takayama Y, Ichikawa S, et al. (2007): Long-term nicorandil therapy improves cardiac sympathetic nerve activity after reperfusion therapy in patients with first acute myocardial infarction. *J Nucl Med*. ;48: 1676-82.
14. Ito H, Taniyama Y, Iwakura K, Nishikawa N, Masuyama T, Kuzuya T, et al. (1999): Intravenous nicorandil can preserve microvascular integrity and myocardial viability in patients with reperfused anterior wall myocardial infarction. *J Am Coll Cardiol*. ;33: 654-60.
15. Ueda H, Nakayama Y, Tsumura K, Yoshimaru K, Hayashi T, Yoshikawa J. (2004): Intravenous nicorandil can reduce the occurrence of ventricular fibrillation and QT dispersion in patients with successful coronary angioplasty in acute myocardial infarction. *Can J Cardiol*. ;20: 625-9.
16. Kinoshita M, Sakai K. (1990): Pharmacology and therapeutic effects of nicorandil. *Cardiovasc Drugs Ther*. ;4: 1075-88.
17. Schmid JP, Schroeder V. (2005): Nicorandil-review of pharmacological properties and clinical applications. *Heart Drug*.;5:220-9.
18. Taira N. (1987): Similarity and dissimilarity in the mode and mechanism of action between nicorandil and classical nitrates: An overview. *J Cardiovasc Pharmacol*. ;10 Suppl 8:S1-9.
19. Escande D, Henry P. (1993): Potassium channels as pharmacological targets in cardiovascular medicine. *Eur Heart*

J. ;14 Suppl B:2-9.
20. Tamargo J, Caballero R, Gómez R, Valenzuela C, Delpón E. (2004): Pharmacology of cardiac potassium channels. *Cardiovasc Res*.;62: 9-33.
21. Zhang M, Zhang H, Liu C, Li X, Ling M, Wang Z, et al. (2018): Myocardial protective effects of nicorandil on rats with type 2 diabetic cardiomyopathy. *Med Sci Monit Basic Res*.;24: 141-5.
22. Nichols CG, Lederer WJ. (1991): Adenosine triphosphate-sensitive potassium channels in the cardiovascular system. *Am J Physiol*. ;261:H1675-86.
23. Kreye VA, Lenz T, Theiss U. (1991): The dualistic mode of action of the vasodilator drug, nicorandil, differentiated by glibenclamide in 86Rb flux studies in rabbit isolated vascular smooth muscle. *Naunyn Schmiedebergs Arch Pharmacol*. 1991;343: 70-5.
24. Daut J, Klieber HG, Cyrys S, Noack T. (1994): KATP channels and basal coronary vascular tone. *Cardiovasc Res*. 1994;28: 811-7.
25. Holzmann S. (1983): Cyclic GMP as possible mediator of coronary arterial relaxation by nicorandil (SG-75). *J Cardiovasc Pharmacol*.;5:364-70.
26. Lefer DJ, Lefer AM. (1988): Studies on the mechanism of the vasodilator action of nicorandil. *Life Sci*. ;42:1907-14.
27. Holzmann S, Kukovetz WR, Braida C, Pöch G. (1992): Pharmacological interaction experiments differentiate between glibenclamide-sensitive K+ channels and cyclic GMP as components of vasodilation by nicorandil. *Eur J Pharmacol*. ;215: 1-7.
28. Das B, Sarkar C, Karanth KS. (2001): Effects of administration of nicorandil or bimakalim prior to and during ischemia or reperfusion on survival rate, ischemia/reperfusion-induced arrhythmias and infarct size in anesthetized rabbits. *Naunyn Schmiedebergs Arch Pharmacol*. ;364: 383-96.
29. Holmuhamedov EL, Wang L, Terzic A. (1999): ATP-sensitive K+ channel openers prevent Ca2+ overload in rat cardiac mitochondria. *J Physiol*.;519: 347-60.
30. Crestanello JA, Doliba NM, Babsky AM, Doliba NM, Niibori K, Whitman GJ, et al. (2002): Ischemic preconditioning improves mitochondrial tolerance to experimental calcium overload. *J Surg Res*. ;103:243-51.
31. Kim JS, Jin Y, Lemasters JJ. (2006): Reactive oxygen species, but not Ca2+ overloading, trigger pH- and mitochondrial permeability transition-dependent death of adult rat myocytes after ischemia-reperfusion. *Am J Physiol Heart Circ Physiol*. ;290:H2024-34.
32. Asensio-López MC, Soler F, Pascual-Figal D, Fernández-Belda F, Lax A. (2017): Doxorubicin-induced oxidative stress: The protective effect of nicorandil on HL-1 cardiomyocytes. *PLoS One*. ;12:e0172803.
33. Ahmed LA, El-Maraghy SA. (2013): Nicorandil ameliorates mitochondrial dysfunction in doxorubicin-induced heart failure in rats: Possible mechanism of cardioprotection. *Biochem Pharmacol*. ;86(9):1301-10.
34. Sasaki N, Sato T, Ohler A, O'Rourke B, Marbán E. (2000): Activation of mitochondrial ATP-dependent potassium channels by nitric oxide. *Circulation*. ;101(4):439-45.
35. Nakano A, Liu GS, Heusch G, Downey JM, Cohen MV. (2000): Exogenous nitric oxide can trigger a preconditioned state through a free radical mechanism, but endogenous nitric oxide is not a trigger of classical ischemic preconditioning. *J Mol Cell Cardiol*.;32(6):1159-67.
36. Tsuchida A, Miura T, Tanno M, Sakamoto J, Miki T, Kuno A, et al. (2002): Infarct size limitation by nicorandil: Roles of mitochondrial K(ATP) channels, sarcolemmal K(ATP) channels, and protein kinase C. *J Am Coll Cardiol*. ;40(8):1523-30.
37. Hosseini-Tabatabaei A, Esmaily H, Rahimian R, Khorasani R, Baeeri M, Barazesh-Morgani A, et al. (2009): Benefit of nicorandil using an immunologic murine model of experimental colitis. *Cent Eur J Biol*. ;4(1):74-85.
38. Auchampach JA, Cavero I, Gross GJ. (1992): Nicorandil attenuates myocardial dysfunction associated with transient ischemia by opening ATP-dependent potassium channels. *J Cardiovasc Pharmacol*. ;20(5):765-71.
39. Lee TM, Lin SZ, Chang NC. (2018): Nicorandil regulates the macrophage skewing and ameliorates myofibroblasts by inhibition of RhoA/Rho-kinase signalling in infarcted rats. *J Cell Mol Med*. ;22(2):1056-69.
40. Chan W, Yao X, Ko W, Huang Y. (2000): Nitric oxide mediated endothelium-dependent relaxation induced by glibenclamide in rat isolated aorta. *Cardiovasc Res*.;46(1):180-7.
41. Mizumura T, Nithipatikom K, Gross GJ. (1996): Infarct size-reducing effect of nicorandil is mediated by the KATP channel but not by its nitrate-like properties in dogs. *Cardiovasc Res*. ;32(2):274-85.
42. Ahmed LA, Salem HA, Attia AS, Agha AM. (2011): Pharmacological preconditioning with nicorandil and pioglitazone attenuates myocardial ischemia/reperfusion injury in rats. *Eur J Pharmacol*.;663(1-3):51-8.
43. Sato T, Sasaki N, O'Rourke B, Marbán E. (2000): Nicorandil, a potent cardioprotective agent, acts by opening mitochondrial ATP-dependent potassium channels. *J Am Coll Cardiol*. ;35(2):514-8.
44. Mohamed SS, Ahmed LA, Attia WA, Khattab MM. (2015): Nicorandil enhances the efficacy of mesenchymal stem cell therapy in isoproterenol-induced heart failure in rats. *Biochem Pharmacol*. ;98(3):403-11.
45. Sahara M, Sata M, Morita T, Hirata Y, Nagai R. (2012): Nicorandil attenuates monocrotaline-induced vascular endothelial damage and pulmonary arterial hypertension. *PLoS One*. ;7(2):e33367.
46. Ahmed LA, El-Maraghy SA, Rizk SM. (2015): Role of the KATP channel in the protective effect of nicorandil on cyclophosphamide-induced lung and testicular toxicity in rats. *Sci Rep*. ;5:14043.
47. Tanabe K, Lanaspa MA, Kitagawa W, Rivard CJ, Miyazaki M, Klawitter J, et al. (2012): Nicorandil as a novel therapy for advanced diabetic nephropathy in the eNOS-deficient mouse. *Am J Physiol Renal Physiol*.;302(9):F1151-60.
48. Tamura Y, Tanabe K, Kitagawa W, Uchida S, Schreiner GF, Johnson RJ, et al. (2012): Nicorandil, a K(ATP) channel opener, alleviates chronic renal injury by targeting podocytes and macrophages. *Am J Physiol Renal Physiol*. ;303(3):F339-49.

49. Masunaga A, Ito K, Asano T, Tsuda H, Asano T.(2018): Nicorandil increases renal nitric oxide (NO), decreases transforming growth factor (TGF)-β, and ameliorates renal injury in unilateral ureteral obstruction (UUO) in rats. *J Urol*. ;199(4 Suppl):e115.
50. Mohamed YS, Ahmed LA, Salem HA, Agha AM. (2018): Role of nitric oxide and KATP channel in the protective effect mediated by nicorandil in bile duct ligation-induced liver fibrosis in rats. *Biochem Pharmacol*. ;151: 135-42.
51. Hosseini-Tabatabaei A, Abdollahi M. (2008): Potassium channel openers and improvement of toxic stress: Do they have role in the management of inflammatory bowel disease? *Inflamm Allergy Drug Targets*. ;7(2):129-35.
52. Stupakova EG, Lazareva GA, Gureev VV. (2018): Correction of morphofunctional disturbances arising when modeling preeclampsia with resveratrol and nicorandil. *Res Results Pharmacol*. ;4(2):59-71.
53. Hong SH, Kyeong KS, Kim CH, Kim YC, Choi W, Yoo RY, et al. (2016): Regulation of myometrial contraction by ATP-sensitive potassium (KATP) channel via activation of SUR2B and Kir 6.2 in mouse. *J Vet Med Sci*. ;78(8):1153-9.
54. Hedlund P, Holmquist F, Hedlund H, Andersson KE. (1994): Effects of nicorandil on human isolated corpus cavernosum and cavernous artery. *J Urol*. ;151(4):1107-13.
55. Lee SW, Wang HZ, Christ GJ. (1999): Characterization of ATP-sensitive potassium channels in human corporal smooth muscle cells. *Int J Impot Res*. ;11(4):179-88

CITATION OF THIS ARTICLE

Madhura Shirishkumar B, Shraddha Y, Shruti V, Mandar A. Nicorandil: Varied Actions & Benefits. Bull. Env. Pharmacol. Life Sci., Vol 13 [10] September 2024: 01-06.