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Review article

Therapeutic potential of nicorandil beyond anti-anginal drug: A review on current and future perspectives

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ABSTRACT

Nicorandil (NIC) is a well-known anti-anginal agent, which has been recommended as one of the second-line treatments for chronic stable angina as justified by the European guidelines. It shows an efficacy equivalent to that of classic anti-anginal agents. NIC has also been used clinically in various cardiovascular diseases such as variant or unstable angina and reperfusion-induced damage following coronary angioplasty or thrombolysis. Different mechanisms have been involved in the protective effects of nicorandil in various diseases, including opening of adenosine triphosphate-sensitive potassium (KATP) channel and donation of nitric oxide (NO). In recent years, NIC has been found to show numerous pharmacological activities such as neuroprotective, nephroprotective, hepatoprotective, cardioprotective, and testicular protective effects, among other beneficial effects on the body. The present review dwells on the pharmacological potentials of NIC beyond its anti-anginal action.

1. Introduction

Nicorandil (NIC) is a commonly known, safe anti-anginal drug which has been accepted for long-term chronic stable angina treatment in Japan and Europe [1]. The European Society of Cardiology has approved the use of NIC as one of the second-line therapies for chronic stable angina [2]. Reports on the role of NIC in angina have confirmed its protective effect on morbidity and mortality in Japanese coronary artery diseases patients [3,4]. Overall, systematic clinical trials have demonstrated effectiveness of NIC in the amelioration of effort angina and ischemic effects relative to β blockers and calcium antagonists with reduced hemodynamic disruption [5]. However, NIC treatment has not been correlated with a substantial decrease in blood pressure while combined with calcium antagonists or β receptor blockers [6]. Significantly, NIC serves as an effective anti-ischemic drug in patients with contraindications to β blockers, such as bradycardia and aggravated pulmonary disease [7]. Moreover, the adverse effects of NIC are negligible, including frequent headache and less frequent dizziness, gastrointestinal discomfort, flushing and malaise. NIC is associated with complications in respect of use in hypotension conditions or when combined with other vasodilators [8].

This review has been done to highlight and discuss the various therapeutic benefits of NIC, within and outside the context of drug

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Abbreviations

NIC	nicorandil
KATP	ATP-sensitive K^+ channels
cGMP	Cyclic guanosine monophosphate
Bax	Bcl-2-associated X protein
Bcl-2	B-cell lymphoma-2
COX2	Cyclooxygenase 2
ROS	reactive oxygen species
PCI	percutaneous coronary intervention
eNOS	Endothelial nitric oxide synthase
NF-κB	Nuclear factor kappa B
Nrf2	Nuclear factor erythroid 2–related factor 2
iNOS	Inducible nitric oxide synthase

repurposing, including amongst others its neuroprotective, nephroprotective, hepatoprotective, cardioprotective, testicular protective, anti-ulcer, and anti-inflammatory effects, beyond its use as an anti-angina drug.

2. Search strategies

To comprehensively explore the diverse facets of nicorandil, a literature search was conducted across various electronic databases, including PubMed, Web of Science, Scopus, and Google Scholar. The search was carried out using relevant keywords and combinations, such as nicorandil, cardioprotective activity of nicorandil, role of nicorandil in pulmonary disease, renal protective activity of nicorandil, neuroprotective activity of nicorandil, hepatoprotective activity of nicorandil, role of nicorandil in gastric ulcer, and nicorandil and COVID-19.

Inclusion criteria included studies detailing the pharmacotherapeutic properties of nicorandil, mechanisms of action of nicorandil, together with studies highlighting the dose and pharmacokinetic of nicorandil. Animal and human studies depicting such properties of nicorandil were added too. Articles that were written in English, contained relevant or substantial data, and articles in which the full text was accessible were also included.

3. Mechanism of action

NIC is an anti-anginal drug which has the dual unique features of nitrate and ATP-sensitive K^+ channel agonists [9]. The nitrate action of nicorandil dilates large coronary arteries in humans at low plasma concentration. NIC decreases coronary artery resistance with high plasma levels, which is correlated with enhanced opening of ATP-sensitive K^+ channels [10]. NIC promotes guanylate

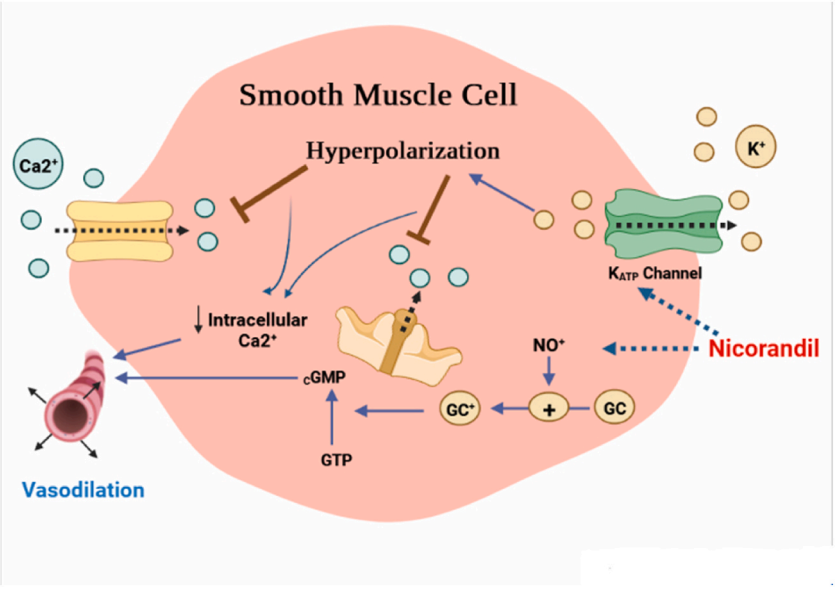

Fig. 1. Protective mechanism of action of nicorandil in different experimental models.

cyclase in order to improve cyclic GMP formation (cGMP). cGMP activates protein kinase G (PKG) which phosphorylate and suppress GTPase RhoA and decreases the activity of Rho-kinase. The down regulation of Rho-kinase allows the activity of myosin phosphatase to increase, which reduces the smooth muscle calcium sensitivity [11]. PKG also triggers the calcium pump of sarcolemma to take off activating calcium and operates on K^+ channels to facilitate K^+ efflux; the resultant hyperpolarization inhibits the voltage-gated calcium channels [12]. Fig. 1 shows the protective mechanism of action of nicorandil in different experimental models.

4. Dosage and pharmacokinetics

NIC is quickly and almost fully absorbed through the gastrointestinal system, reaching full plasma levels after 30–60 min and a fairly constant level after 4–5 days of normal therapy. Gastric absorption is delayed by food, but its pharmacokinetic properties are not significantly affected by age, chronic liver disease or chronic kidney disease. The half-life of NIC is nearly 52 min. NIC does not go through first-pass metabolism and has a linear dose-to-plasma concentration relationship at doses of 5–40 mg. Its oral bioavailability is more than 75 % and around 20 % of the drug is excreted in the urine. NIC is weakly bound to human plasma proteins (free fraction greater than 75%) and its mean residence time is close to 1.25 h.

Its anti-angina actions last about 12 h, requiring twice per day dose or 5 mg for patients susceptible to headache [13,14]. The minimum effective dose is recommended to prevent potential side effects, especially in the elderly. The therapeutic dose is usually 10–20 mg twice daily and the maximal dose is 30 mg twice daily. Unlike nitrates, tolerance tend not to occur to NIC, probably because of its dual mode of action [15,16]. Rebound angina is not produced by NIC [17].

5. Nicorandil and cardiac disease

Cardiovascular disorder (CVD) is the primary cause of mortality worldwide [18,19]. Hence, the search for various ways to reduce the mortality due to CVD remains one of the important objectives to attain. Chronic poor diet and lifestyle choices which lead to diabetes and obesity cause continuous rise in the occurrence of cardiac diseases [20]. NIC preserved cardiac cells from doxorubicin mediated cardio-toxicity through normalization of cardiac oxidative stress (shown by reduction in superoxide production, NF-κB expression and Caspase-3 activity) and maintained other biological parameters along with inducing improvement of cellular alterations in rats [21]. NIC relieved cardiomyocytes hypoxia/re-oxygenation induced cytotoxicity by up-regulation of ACAT1/OXCT1 action and metabolism of ketone bodies in in-vitro study [22]. Xing and team reported that NIC exerts its protective effect on ischemic heart failure rats as observed by the improvements of cardiac function and LV re-modelling. The mechanism might be in relation to the inhibitory effect of NIC on the protein level of Bax expression [23]. In another study, pre-administration of NIC suppressed coronary microembolization produced apoptosis of myocardial cells and enhanced cardiac function by blocking mitochondrial, as well as death receptor apoptotic pathways [24].

Liang and colleagues demonstrated the cardioprotective effects of NIC on myocardial injury after cardiac arrest by improving post-resuscitation myocardial impairment and energy metabolism, reducing myocardial histopathologic injury and inhibiting apoptosis [25]. In-vitro study revealed that NIC caused opening of the mitoKATP channel without involvement of the NO/cGMP-dependent pathway on HL-1 cardiomyocyte cell line against doxorubicin mediated oxidative stress [26]. NIC demonstrated a protective effect against reperfusion injury in rat heart without the presence of any co-morbidity like calcification [27].

NIC defended against stress mediated apoptosis in dystrophin-deficient cardiac myocytes and retained cardiac activity in the heart of mdx mouse susceptible to ischemia, as well as reperfusion injury [28]. Wei and his colleagues reported that NIC potentially exert a cardioprotective effect through opening of KATP channel and improvement of NCX1 by increasing intracellular cGMP in the heart of guinea pig [29]. Li and team demonstrated the pharmacological pre-conditioning and post-conditioning effect of NIC which protected hypercholesterolemic rat hearts against I/R meditated necrosis and apoptosis in a dose-dependent way. They found that the cardioprotective effects of NIC may be due to the pharmacological mechanisms of mitoKATP channel opening, a NO/sGC dependent mechanism, and regulation of apoptosis-related proteins; Caspase-3, Bax and Bcl-2 [30]. NIC enhanced post-ischemic contractile regeneration and substantially decreased myocardial infarction (MI) size in a dose-proportional manner and repressed the IR produced apoptosis plus ER stress in perfused rat hearts activating PI3K/Akt signal pathway [31]. Further, NIC triggers COX-2 by GATA-4 activation in the heart of rat by activation of KATP channel, as well as nitrate-like effects [32].

NIC ameliorated slowing of impulse conduction, balanced increase in Cx43 protein expression and decreased generation of electrically induced ventricular tachyarrhythmia in the mouse model of desmin-mediated cardiomyopathy [33]. NIC therapy has been reported to minimise mitochondrial dysfunction and apoptosis, and extended survival rate in HSPB5 R120G TG mice, inhibiting the enhancement of Bax, decreasing Bcl-2 and Caspase-3 activation [34]. NIC at 10 mg/kg had a cardioprotective effect by preserving mitochondrial function in a rat model of autoimmune myocarditis [35]. In-vitro study showed that NIC repressed Ang-II mediated generation of ROS, ERK phosphorylate, expression of ET-1 and cell proliferation, and also improved eNOS phosphorylation and NO concentration in cardiac fibroblasts of rat [36]. Raveaud and co-worker proposed that low-dose NIC therapy reduced or removed certain age-dependent alterations in arterial function and expanded the amount of elastic lamellae in the aortic wall, and also ameliorated mechanical relaxation and noradrenaline induced vasoconstriction in aged rats [37]. NIC exerted cardio-protective action, altering intracellular signalling pathways through balancing intracellular variations in c-GMP, PKC and p38-MAPK phosphorylation levels in rabbit heart against ischemic reperfusion damage [38]. Further, NIC controlled Bax, as well as Bcl-2 proteins in mitochondria and repressed mitochondrial death via the initiation of mitochondrial pathways and the NO-cGMP signalling pathway in hypoxic rat myocytes [39].

NIC defended against post-ischemic LV dysfunction by activating the mitochondrial KATP channels, eliminating hydroxyl radical,

and enhancing coronary flow in the isolated rat heart [40].

The cardioprotective effect of NIC has been investigated in combination with St. Thomas' solution on senile rat heart against ischemic reperfusion damage. NIC when combined with St. Thomas' solution could recover the left ventricular performance and showed an enhanced myocardial protecting effect on the ischemic senile myocardium [41]. The protective action of NIC was examined with different temperatures and the function of sarcolemmal, as well as mitochondrial KATP channels under ex-vivo conditions using contractile force (CF) and possible action potential duration (APD) as endpoints. NIC was able to retain contractile strength during hypothermic hypoxia and re-oxygenation comparatively better in both tested concentrations (0.1 and 1.0 mM) as compared to controls, as well as in groups administered the mitoKATP blocker, 5HD [42]. Sato et al. demonstrated that NIC has a direct cardio-protective action on heart muscles, triggered by the selective modulation of mitoKATP channels in intact rabbit cardiac myocytes [43].

NIC treatment before and during coronary blockage can result in preservation from ischemia/reperfusion induced arrhythmias, thereby reducing infarct size of myocardium and increasing survival rate in acute cardiac infarction in anesthetized rabbits [44]. Fang and team found that NIC, a KATP channel modulator, could imitate the effect of ischemic myocardial pre-conditioning by decreasing the region of myocardial infarction during ischemia/reperfusion damage in dogs [45]. NIC prevented mitochondrial Ca^{2+} overload by opening the mitoKATP channels and prevented impairment of mitochondrial Ca^{2+} homeostasis which further inhibited the death of rat ventricular myocytes [46]. It has been reported that NIC administration produced delayed cardio-protective action after 24 h against myocardial infarction and this effect was associated with increased expression of myocardial Bcl-2 and COX-2 in anesthetized rabbits [47]. NIC treatment improved survival rate and exerted cardio-protective and antiarrhythmic effects against I/R caused cardiac injury in the anesthetized rabbits by opening mitochondrial KATP channels [48].

Long period oral therapy with NIC following MI ameliorated left ventricular dilation and improved cardiac function in rats with reperfused MI [49]. Akao and colleagues demonstrated that NIC attenuated oxidative stress and inhibited apoptosis in cardiac myocytes, and elicited cardio-protective action due to opening of mitoKATP channels [50].

NIC has a cardio-protective role in Coronary microembolization (CME) that primarily includes activation of the PI3K/AKT signalling pathway and inhibition of CME produced cardiomyocyte apoptosis [51]. In another study, NIC prevented cardiac fibrosis in the heart of Type 2 diabetic rats and enhanced cardiac output by inhibiting fibrosis and by preventing apoptosis which is based on PI3K/Akt pathway [52].

NIC polarised the macrophages to M2 by inhibition of the RhoA/RhoA-kinase pathway leading to inhibition of cardiac myophibroblast fibrosis following myocardial infarction in rats [53]. Mohamed et al. found that NIC therapy synergistically increased the clinical effectiveness of bone marrow-derived mesenchymal stem cell (BM-MSC) transplantation during isoproterenol mediated myocardial injury in rats by providing a safe environment for BM-MSC [54]. Further, NIC decreased cardiovascular hypertrophy and retained cardiac activity in rats with diabetic cardiomyopathy, known to be mediated by reducing oxidative stress [55]. A recent study has shown that NIC therapy improved PAH-induced RV remodelling in rats, not only by reducing RV stress overload, but also by preventing apoptosis in cardiomyocytes by modifying mitoKATP channel in rats [56]. NIC has also been reported to prevent endothelial hyperplasia following catheter produced balloon damage in diabetic rats by reducing inflammation and inhibiting cell proliferation [57].

A randomized controlled clinical study of 100 patients has been performed for the cardio-protective action of NIC on CHD patients who had elective percutaneous coronary intervention (PCI). Intake of NIC prior to PCI can decrease the rate of no-flow occurrence, decrease myocardial damage and promote myocardial contractility [58]. In a randomized study of 62 stable patients undergoing elective PCI, intravenous NIC (6 mg bolus prior to PCI and 6 mg/h infusion for 24 h following PCI) led to a notably lower IMR instantly post-PCI compared to controls [59]. A previous randomised clinical investigation showed that the occurrence of peri-procedural myocardial damage and PCI-related myocardial infarction can be decreased by an oral single dose of NIC (10 mg or 20 mg) 2 h earlier than PCI [60]. NIC (20 mg once regularly for one week earlier, plus 6 months following PCI) therapy has been found to reduce PCI related myocardial damage and increase left ventricular ejection fraction in diabetic patients receiving PCI [61].

There is one small proof of concept randomized controlled study in the context of CABG surgery including 32 patients, whereby intravenous NIC infusion which began before bypass and persisted for 2 h following weaning off bypass showed beneficial cardioprotective action [62]. Long-term therapy of NIC has been shown to improve endothelial function remarkably in patients without prior coronary artery disease at 1 year follow up with concomitant documented reductions in oxidative injury and inflammatory markers [63].

A sub-analysis of previous study found that pre-administration with intravenous NIC prior to PCI significantly lowered complications with much improved results in AMI patients suffering stress hyperglycemia in both the early as well as late stages [64]. A meta-analysis of 17 clinical trials found that treatment with NIC increased ejection fraction of left ventricular and microvascular activity while combined with coronary reperfusion treatment in patients having acute myocardial infarction [65]. Kasama et al. showed that NIC has benefits on the cardiac sympathetic nerves, as well as remodelling in the setting of first anterior myocardial infarction in a clinical trial study of 58 patients [66].

Intravenous NIC pre-administration modulated ST-segment elevation and increased lactate metabolism during coronary angioplasty, meaning that NIC causes pharmacological pre-conditioning. One of the reliable metabolic factors of myocardial injury, troponin T, is also suppressed following coronary angioplasty and ST-segment elevation is suppressed during coronary angioplasty [67]. In the clinical study of 157 patients, NIC could help minimise the inflammatory reaction, suppress platelet activity, raise the level of myocardial antioxidation and enhance the clinical effectiveness of dysfunctional angina patients [68].

NIC, KATP channel agonist, reduced NF-kB activation, expression of adhesion molecule, and cytokine generation in patients having coronary artery bypass surgery [69].

In a clinical study of 60 patients, intracoronary treatment of NIC earlier than PCI remarkably suppressed the expression of pro-inflammatory factors and enhanced the anti-inflammatory factors after PCI [70]. Fig. 2 shows the therapeutic potential of nicorandil in cardiac dysfunction.

6. Hepatoprotective activity

Yamazaki et al. stated that in a porcine total hepatic vascular exclusion model, NIC preserved the liver from IR damage purely through KATP, and this benefit was fully countered by glibenclamide (GLB), with no substantial difference between IR and the combined NIC/GLB group [71]. NIC showed liver protective action that was evident in a rat model of non-alcoholic fatty liver disease (NAFLD) and this effect was associated with opening of KATP channel, nitric oxide donation, antioxidant, and anti-inflammatory activities [72].

Sattar et al. highlighted the beneficial role of NIC plus atorvastatin against CCl_4-mediated liver fibrosis in rats. They both exerted a marked anti-fibrotic action which could be due to their antioxidant, anti-inflammatory and anti-lipidemic activities by decreasing TNF-α, MPO and MDA content and elevating GSH, SOD and CAT [73]. NIC significantly reduced hepatic and renal biomarkers of damage and improved enzymatic and non-enzymatic antioxidants contents against doxorubicin mediated liver and kidney injuries [74].

The protective action of NIC (NO donor) has been explored on non-alcoholic fatty liver disease (NAFLD) induced by hypercholesterolemia and fatty diet in rats. Treatment with NIC in rats led to the reduction in the level of liver enzyme (AST and ALT), liver triglycerides, MDA, and TNF-α, along with the decline of insulin resistance and elevation of adiponectin, as well as expression of eNos gene [75].

7. Pulmonary disease

NIC decreased monocrotaline produced vascular endothelial injury and pulmonary arterial hypertension in rats by decreasing Caspase-3 expression and activating eNOS, PI3K/Akt and expression of Bcl-2 [76]. Oral administration of NIC has shown an important beneficial effect towards allergic asthma caused by ovalbumin and this action may be because of its abilities to ameliorate antioxidant status, diminish nitric oxide generation, and attenuate IL-13, as well as NF-κB signalling [77].

NIC enhances the levels of antioxidants probably through activation of Nrf2/HO-1 axis and inhibition of NF-kB mediated inflammatory pathway. In addition, NIC lowers fibrogenic factors such as aggregation of TGF-β and collagen, and also decreases iNOS expression and its derived NOx levels, contributing to modulation of silica mediated pulmonary inflammation plus fibrosis in rats [78].

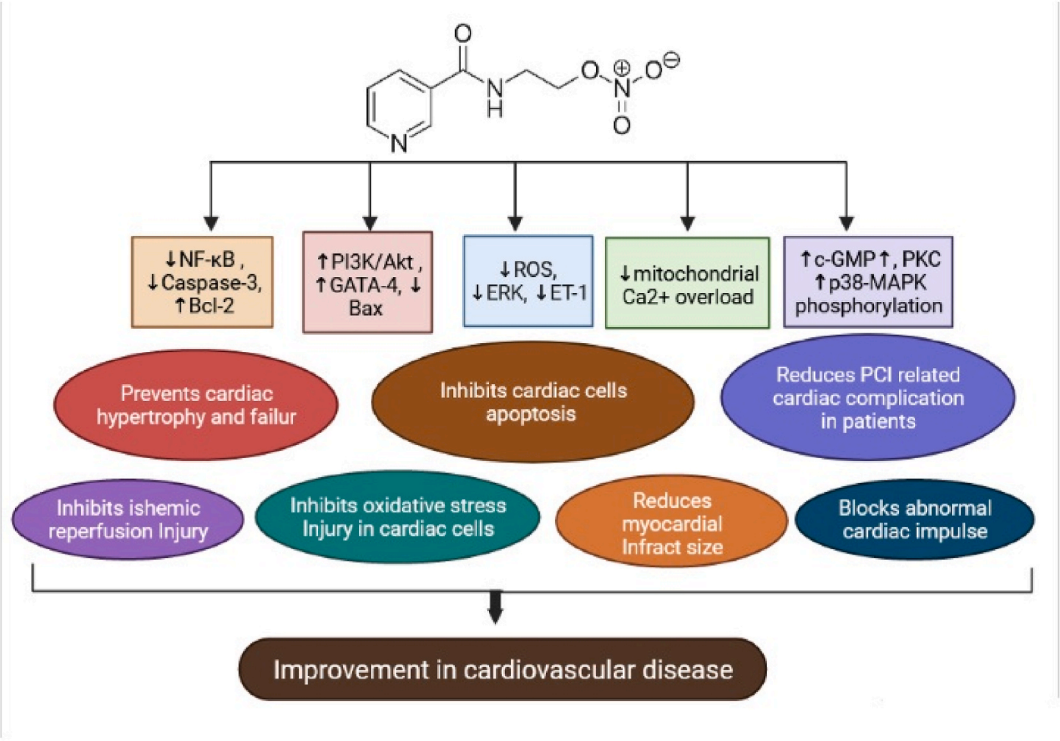

Fig. 2. The therapeutic potential of nicorandil in cardiac dysfunction. NIC inhibits the activity of NF-κB, Caspase-3, Bax, ROS, ERK, ET, Ca2+, and activates PI3K/Akt, Bcl-2, GATA-4, cGMP, PKC, p38-MAPK which shows beneficial outcome for cardiac arrhythmia, cardiac fibrosis, cardiac hypertrophy, and myocardial infarction.

NIC can exert pulmonary protective effect through its antioxidant along with anti-inflammatory properties against bleomycin produced pulmonary fibrosis in rats. It has capacity to decrease overall NOx, iNOS, HIF-1 alpha and TXNIP lung levels and has ability to enhance eNOS pulmonary expression [79].

In the rabbit, NIC showed a beneficial effect by inhibiting apoptosis in the non-ventilated lung that had contracted and re-expanded, while single lung ventilation and this action is mediated due to inhibition of Caspase-3, down regulation of NF-κB and triggered activation of PI3K/Akt pathway [80]. NIC relieved LPS mediated lung injury by preserving endothelial cells owing to blocking apoptosis, preventing endothelial inflammation, as well as minimizing oxidative stress in mice [81].

NIC protects human pulmonary arterial endothelial cells from hypoxia mediated apoptosis by inhibiting the mitochondrial and death receptor pathways and aiding preservation of endothelial function by restoring eNOS expression. This protective effect is hypothesized to be associated with deactivation of p38 MAPK via mitoKATP channels [82].

8. Renal protective activity

NIC has been shown to protect kidneys from cyclosporine caused nephrotoxicity targeting endothelial dysfunction in rats and ameliorated the underlying molecular disturbance of HIF-1α/VEGF/eNOS pathway induced by cyclosporine [83]. NIC offers a possible preventive role against adenine-induced vascular and renal dysfunction in rats, which may be due to modulation of vascular calcification, regulation of Nrf2 and eNOS genes in aortic tissues [84].

NIC mitigated DOX-induced cell death and inflammation by inhibition of oxidative stress triggered activation of TLR4/MAPKp38/NF-κB signalling pathways [85]. The present review article is the first work to assess the therapeutic potential of NIC against partial unilateral ureteral obstruction (PUUO). NIC treatment can reduce the oxidative stress by raising the activity of the serum antioxidant enzymes, reducing lipid peroxidation, and changing the concentrations of nitric oxide synthase in the tissue of the renal tubules after PUUO [86].

NIC has shown beneficial effect by maintaining the number of podocytes and decreasing the excretion of urinary albumin in the CKD rat model. The defence process includes the elimination of oxidative stress, which is likely to be induced via the KATP pathway [87]. NIC possess a renal protecting action against proximal tubule injury following I–R injury to the rat kidney and this effect is based on its dual action as an opener of KATP channel and as NO donor [88].

NIC restored glomerular disease in streptozotocin-induced diabetic eNOSKO mice and directly minimized oxidative stress in podocytes by KATP channel facilitatory action via independent effect of NO [89]. Tamura et al. proposed that NIC has a podocyte protecting action that maintains the podocytes number and decreases the excretion of urinary albumin in a rat model of chronic renal disease. The protective mechanism is based on decreasing oxidative stress, which is likely to be triggered by the ATP-sensitive potassium channel [90]. NIC consistently infused intravenously at 1 mL/kg/h starting at 4 h even before operation and lasting for 24 h after surgery may have a beneficial nephroprotective role towards contrast-induced nephropathy (CIN) in patients with poor renal function [91].

Fan and co-worker found that in patients having renal insufficiency, the oral therapy of NIC (10 mg, t.i.d) could reduce CIN [92]. Zhang et al. explored administering NIC prophylactically for patients with low renal failure undergoing PCI and found that it could reduce developing CIN [93]. Meta-analyses performed by Li et al. and Wang et al. have indicated that NIC would minimise the occurrence of CIN in patients exposed to contrast medium [94,95].

9. Neuroprotective activity

NIC exerted neuroprotective action in chronic cerebral hypoperfusion mediated vascular dementia in mice by opening of KATP channels [96]. NIC elicited a neuroprotective role in deep hypothermic low flow produced I/R damage via suppressing apoptosis by activation of the PI3K/Akt1 signalling pathway [97]. NIC was studied directly to assess the beneficial effect on cerebral blood flow (CBF) in mice; experimental dose of NIC increased CBF without affecting systemic hemodynamics and this effect was found to be mediated by both the NO pathway and opening of KATP channel [98].

NIC has exerted anti-apoptotic action towards neurotoxicity in SH-SY5Y by upregulation of Bcl-2 levels and downregulation of Bax and Caspase-3 expression, and also further stimulation of the PI3K/Akt/CREB signalling pathway [99].

A DHLF mouse model has been explored in which NIC ameliorated cerebral histopathology, repressed neuronal apoptosis, enhanced expression of Bcl-2 and decreased expression of Bax; these effects were found to be produced by the PI3K/Akt1 signalling pathway [100]. NIC exerted potential neuroprotective role in cerebral I/R injury induced by STZ mediated Type 1 diabetes in rats by reducing cerebral infarction volume and level of Caspase-3 [101].

NIC attenuated ischemia-induced disruption of BBB and brain edema, and showed a substantial reduction in infarction volume, possibly through up-regulation of Nrf2 [102]. NIC protected from neuro-inflammation damages in astrocytes by opening KATP channels, minimizing ER stress and inflammation, thus protecting astrocytes against oxygen-glucose deprivation (OGD) mediated injury [103].

10. Bowel disease

NIC showed an anti-inflammatory effect by inhibiting the release of inflammatory mediators, such as tumour necrosis factor-alpha, primarily via donation of NO and to a smaller extent through opening of KATP channel [104]. NIC attenuated experimentally produced inflammatory bowel disease (IBD) by a dosage that has no major effect on BP and a pathway that is partly or fully independent of KATP

channels, as seen on co-administration of glibenclamide (GLB). It could be that the upregulation of eNOS, the generation of NO, as well as its antioxidant potential by nicotinamide moiety may be primarily responsible for its effects in the remission of IBD [105].

11. Reproductive organ injury

NIC intervention has been reported to successfully prevent the occurrence of cyclophosphamide mediated testicular injury in rats where modulation of the KATP channel plays a remarkable role in the beneficial outcome of NIC [106]. NIC elicited a protective effect against ovarian I/R produced injury in rats by increasing antioxidant level, reducing inflammation and inhibiting apoptosis; this support depends at least partially on the KATP channel [107].

12. Pain and inflammation

NIC in experimental rat models of nociceptive as well as inflammatory pain activated opioid pathway and naltrexone reduced the anti-nociceptive effect of NIC [108]. Morais et al. evaluated the anti-nociceptive effect of NIC in paclitaxel induced rat model of neuropathic pain. They found that NIC activated serotonergic, as well as opioidergic pathway to elicit analgesic effect [109].

The analgesic action of NIC in the spinal cord and dorsal root ganglion of rats with chronic postsurgical pain has been demonstrated by ameliorating the expression of p120 [110]. Zhang et al. demonstrated that NIC retained macrophage M1/M2 state in M1 and M2 cell models by blocking monocyte development into mature macrophages, decreasing M1 phenotypic transition, and increasing M2 phenotype transition to produce anti-inflammatory actions [111].

The possible anti-arthritic effect of NIC and theophylline on experimentally produced RA in rats have been explored and the outcome showed that 15 mg/kg NIC daily along with 20 mg/kg theophylline daily possess better anti-arthritic action associated to modification of JAK/STAT/RANKL signalling pathway [112]. NIC has been investigated for anti-arthritic action against Complete Freund's Adjuvant (CFA) produced arthritis model of rat and it exerted promising anti-arthritic potential by modulating TLR4 signalling [113].

The anti-inflammatory effect of NIC has been investigated against carrageenan produced experimental pleurisy in mice and this effect was found to be mediated by lowering of the neutrophil accumulation and inhibition of generation of inflammatory agents [114].

13. Endothelial dysfunction

Eguchi et al. have shown that endothelial cell mitochondria play a decisive role in the thrombus formation mechanism. Reactive oxygen species (ROS) promote the thrombus formation process that is modulated by NIC following endothelial damage caused by $FeCl_3$ in the mouse testicular artery [115]. NIC has been shown to produce protective role in human coronary artery endothelial cell damage and to prevent the development of Sirolimus produced thrombus due to its antioxidant action [116].

NIC plays a major cardioprotective role in hyperhomocysteinemia mediated coronary microvascular dysfunction, predominantly by triggering the PI3K/Akt/eNOS signalling pathway [117]. NIC has a protective effect on DOX-induced HUV endothelial cells apoptosis through ATF3 induced NRF2/HO-1 signalling, p53 lowering and reactive oxygen production, and mitigation of Bcl-2 inhibition [118].

14. Skeletal muscle

NIC increases muscle function by modifying fatigue in the slow skeletal muscle fibre of chicken by its impact not only as a mitoKATP channel activator but also as a NO donor and antioxidant [119]. The protective effect of NIC in skeletal muscle at the mitochondrial level by ambivalent modulation of complexes III and IV resulted in increased mitochondrial ROS generation at a level that is not deleterious to biomolecules like membrane lipids [120].

15. Gastric ulcer and intestinal injury

NIC pre-administration demonstrated a higher preventive index in acute ulceration caused by indomethacin (89.8 percent) and alcohol (77.7 percent) by decreasing oxidative stress, raising NO concentrations, down-regulating ulcerogen-induced TNF-α elevation, and covering the gastric mucosa from leukocyte infiltration and tissue congestion [121]. NIC exerted antiulcer action on aspirin plus pylorus ligation and ethanol mediated gastric ulcers in rats and this could be associated with the opening of KATP channels, suppression of acid secretion, improvement of mucin activity, and amelioration in gastric mucosal blood flow [122].

NIC produced gastroprotective effect through KATP channel opening, free radical scavenging, PGE_2 elevation, decline of proteolytic activity and acid output, and avoidance of the detrimental increase of nitric oxide [123]. The gastric mucosa was substantially shielded from indomethacin-induced lesion by NIC. The mechanism involved in the defense is primarily KATP channel opening which results in reduced gastric acid secretion and proteolytic action, NO donation, reduced lipid peroxidation, and normalization of the harmful acceleration of gastric mucosal nitrites levels [124]. Superior mesenteric artery (SMA) blood flow and tissue blood flow following small intestinal IR damage and mucosal harm were all improved by NIC [125].

16. Lung injury

NIC elicited a protective effect via inhibiting apoptosis in non-ventilated lung collapse and re-expansion during one-lung ventilation (OLV) in the rabbit. It acted on mitoKATP through the PI3K/Akt signalling pathway [126].

17. Conclusion

Nicorandil (NIC) was initially introduced to therapeutic practise over 40 years ago. Today, NIC is used to address a variety of diseases and its tolerability and utility across a wide range of ailments is well proven. Information from many preclinical and clinical trials indicates that NIC might have cellular protective actions mediated through molecular mechanisms that include opening of adenosine triphosphate-sensitive potassium (KATP) channels or donation of nitric oxide (NO). In recent years, NIC has been associated with several beneficial actions, such as renoprotective, hepatoprotective, neuroprotective, cardioprotective, ulcer protective, anti-inflammatory, and other effects beyond its anti-anginal action. In several cadioprotective and neuroprotective studies, NIC showed anti-apoptotic effects by activation of Bcl2, HSP70, CDK5, ERK, AKT pathway and inhibition of Caspase-3, Bax, ROS, and endoplasmic reticulum stress. This review has provided details of various therapeutic benefits of nicorandil, outside its established use as an anti-angina medication, with the discussion of the underlining mechanisms of action.

18. Future perspective

NIC appears to be a pleiotropic drug with numerous modes of action and protective effects against a variety of disease models based on all of the previously described effects. Because inflammation and oxidative stress are the primary factors in practically all human illnesses, medicines that may inhibit these pathways are predicted to be useful in a variety of disease states. NIC has been shown to have these effects, hence this review on the different pharmacological actions of this drug.

Recent reviews have shown that NIC may be useful in SARS-CoV-2 virus infection due to its anti-inflammatory and anti-fibrotic properties [127,128]. The pathology of SARS-CoV-2 virus infection has been associated with exaggerated patient inflammatory response, oxidative stress, and consequent endothelial dysfunction with further induction of fibrosis and coagulopathy. NIC has been reported to have the potential to abort the pathogenicity of SARS-CoV-2 virus infection owing to its antioxidant and anti-inflammatory properties, maintenance of endothelial cells integrity and diminished fibrosis and coagulopathy process [127].

Safari et al. [128] reported on evolving experimental presentations on the beneficial effects of mesenchymal stem cell (MSC) against SARS-CoV-2 virus infection and prevention of the onset of multi-organ failure. According to the authors, MSCs and their derived exosomes have the potential to reduce SARS-CoV-2-induced inflammatory response via positive impact on immune cell function and cytokine expression. NIC, through its modulation of inflammation, cell injury, and death in the lungs of SARS-CoV-2 virus infected patients (associated with inhibition of ROS generation and apoptosis) is able to protect MSCs against hypoxia-induced apoptosis [128]. Thus, the combination of MSCs transplantation and NIC administration has the potential to enhance MSCs survival in inflamed microenvironment with enhanced therapeutic benefits in SARS-CoV-2 infection.

Data availability statement

This is a review article; hence, no associated data has been generated and none is relevant for deposition into a publicly available repository.

CRediT authorship contribution statement

Dhirendra Singh: Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Randhir Singh:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Abidemi James Akindele:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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