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Review Article

From Bench to the Heart: Metal-Based Complexes and Nanoparticles as Pioneers in Cardio-Protection and Cardiovascular Management

Esraa Mohammad Haji*

Department of Pharmaceutical Chemistry, College of Pharmacy, University of Hafr Al Batin, Hafr Al Batin, SAUDI ARABIA.

ABSTRACT

Cardiovascular Disorders (CVDs) are the leading cause of mortality and disability worldwide. Nanotechnology involving metal complexes as drug delivery systems is gaining attention for its cardioprotective potential. This review article discusses the effects of specific metal complexes implicated in CVD treatment. Complexation of these metals with some ligands and co-ligands such as VOL, Olmesartan, Metallothionein, α-Methyldopa, ADR-925, EDTA, DOX, *p*-cymene, and phenanthroline exhibit promising upshots in treating CVDs. This review compiles some metallic Nanoparticles (NPs) such as AgNPs, CuO, ZnO, SA-SeNPs, and Se-NPs with more specific physical, chemical, and biological characteristics along with their biological significance and their outstanding effectiveness in cardioprotection due to their smaller size. The discussion also highlights the mechanisms of metal complexes and nanoparticles and their role in ischemia-reperfusion injury, along with an emphasis on the potential toxicity of these metal complexes. These complexes demonstrated enhanced pharmacokinetics, reduced side effects, and superior cardioprotective outcomes by selectively targeting ischemic and infarcted tissues. Hence, coordinated complexes prove more effective than their free metal ions or drugs. The groundbreaking potential of metal complexes redefines the domain of cardioprotective strategies.

Keywords: Cardiovascular diseases, Metal-based complexes, Nanomedicine, Cardio-protection, Toxicity.

Correspondence:
Dr. Esraa Mohammad Haji
Department of Pharmaceutical Chemistry, College of Pharmacy, University of Hafr Al Batin, 39524, Hafr Al Batin, SAUDI ARABIA.
Email: emhaji@uhb.edu.sa.

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INTRODUCTION TO CARDIO-PROTECTION AND METAL COMPLEXES

Cardiovascular diseases are some of the most prevalent health disorders worldwide. All types of cardiac damage, regardless of its nature, are connected with oxidative stress as a result of a lack of oxygen flow to the heart muscles. The imbalance between the development of Reactive Oxygen Species (ROS) and any antioxidant mechanisms results in oxidative damage which is known to prompt cardiac myocyte apoptosis in ischemia or reperfusion injury following a heart attack (Chang *et al*., 2023). Therefore, free radical scavengers are progressively being incorporated into protective strategies for patients suffering from coronary heart disease. Metal complexes are compounds that contain a metal ion at its center, bonded to surrounding molecules or ions, termed as ligands. They consist of a central metal atom surrounded by an array of molecules or ions that are coordinated (bonded) to it, forming a "complex." Coordination typically involves the donation of one or more pairs of electrons from the ligands to the metal atom (Gao *et al*., 2020). Various metals can form complexes. Transition metals are the most studied, including copper, cobalt, nickel, iron, palladium, platinum, ruthenium, and rhodium. Metal complexes exhibit a range of coordination numbers, geometries, oxidation states, catalytic activities, and different kinetics, which provide opportunities in different fields. As a result, metal-ligand complexes are being widely used in biochemistry, medicine, catalysis, imaging, drug delivery, and therapy among others in a field known as bio-inorganic chemistry (Kostova, 2024). Some metal-ligand complexes are compiled in this review as shown in Figure 1.

MECHANISMS OF CARDIO-PROTECTION BY METAL COMPLEXES

Several routes of action have been reported in cardiovascular protection (Figure 2). Despite the different structures of the metal complexes, in mechanistic studies, they uniformly protect the mitochondrial population from preconditioning stimuli against mitochondrial dysfunction due to cardiotoxic substrates. Redox-active metal complexes, including Cu^{2+} and Fe^{2+} can influence mitochondria and the temporary

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activation of the permeable mitochondrial transition channel (mPTP) in mitochondria exposed to hazardous circumstances (Hernández-Cruz *et al*., 2022). Metal complexes regulate mPTP opening by reducing oxidative stress, maintaining calcium homeostasis, and stabilizing mitochondrial bioenergetics. As Superoxide Dismutase (SOD) mimetics, they lower ROS levels, stabilize iron-sulfur proteins, and prevent excessive ROS production. These complexes compete with Ca^{2+} at mitochondrial sites, reducing mPTP-triggering Ca^{2+} overload. They also interact with mPTP components like cyclophilin D and Anthracyclines (ANT), altering their conformations to prevent pore formation. In ischemia-reperfusion injury, Adenosine Triphosphate (ATP) depletion and calcium overload induce mPTP opening. Transition metal complexes protect against cardiotoxicity by modulating ROS and mitochondrial permeability. Their cardioprotective effects have been studied *in vitro* and *in vivo*, showing direct modulation of bioenergetics and inhibition of mPTP opening (Korotkov, 2023).

THE ROLE OF METAL COMPLEXES IN THE TREATMENT OF CARDIOVASCULAR DISEASES

Research has also increasingly focused on low molecular weight oral platin complexes for dealing with CVDs in recent years (Yadav, 2021). For the treatment of cardiovascular disease with organometallic compounds, metal complexes of organic compounds containing cobalt have been studied (Kostić *et al*., 2024). To obtain and develop safe and orally active cardiovascular metal complex agents, diverse coordination compounds of antiarrhythmic drug amiodarone have been designed and characterized with transition and rare earth metals, including Co^{2+}, Cr^{3+}, Zn^{2+}, Rh^{3+}, Ru^{2+}, Pt^{2+}, and Cu^{2+}(Al-Jameel *et al*., 2024). Their molecular structure, dissolution, and bioavailability obtaining a new generation of cardiovascular drugs with transmetalation activity and favorable pharmacokinetic properties have been also studied. Metal coordination compounds such as $[C_{36}H_{50}BrN_2O_3S]$-$[Zn(CH_3SO_3)_2.2H_2O]$, $[C_{36}H_{50}BrN_2O_3S]$-$[Co(CH_3SO_3)_2.4H_2O]$, and $[C_{12}H_{15}N_3S]$-$[Cu(CH_3SO_3)_2.2H_2O]$ containing ammonium drugs and Zn(II), Co(III) and Cu^{2+} with 2-N, N-dimethylaminoethyl methacrylate, Co^{3+} with methacrylic acid and metoprolol, Fe^{3+} with propranolol, Zn^{2+} and Fe^{3+} with dithiocarbamate and phenothiazine antibiotics have been evaluated as possible ligands for the controlling action of CVDs. Additionally, the impacts of diamagnetic octahedral dioxidovanadium complex in diabetic rats, on cardiovascular failure (Booysen *et al*., 2015) were detected 1 (Figure 3). In former studies, the effects of a dioxidovanadium complex, *cis*-$[VO_2(oz)py]$ 1, were also assessed on the cardiovascular function of male Sprague-Dawley rats that suffered from diabetes, along with monitoring its capability to reduce glucose levels. It was anticipated that evaluating oxidative stress, cardiac fibrosis, Mean Arterial Pressure (MAP), lipid profile, and inflammatory markers would offer a more comprehensive understanding of how complex 1 affects cardiovascular function. Complex 1 mitigates hypertrophy by reducing the heart sizes of the diabetic control group. Complex 1 resulted in the lowering of transforming Growth Factor beta 1 (TGF-β1). Since left ventricular dysfunction & hypertrophy were associated with MAP, and decreased the level of TGFβ1. Additional research reveals that arrhythmias are caused by cardiac fibrosis (Grisanti, 2018).

The effects of oxovanadium complex of 2-[(2,4-dihydroxy benzylidene)hydrazine-1-[(N-(2 hydroxy benzylidene)](methyl) carbothioamide (VOL) (Yanardag *et al*., 2009) on the diabetic heart and aortic tissue was examined along with the *in vitro* suppression of Myeloperoxidase (MPO) and Lactate Dehydrogenase (LDH), antioxidant qualities, and lowering power. Ions of vanadium suppress MPO. Its valence states such as +2, +3, and + 4 interact pro-oxidatively with human neutrophils and effectively compete with MPO for hydrogen peroxide to promote the hydroxyl radical generation. Therefore, vanadium complexes are considered to be effective MPO inhibitors and a class of medications with a significant risk for cardiac side effects. By inhibiting the LDH and MPO enzymes, it was observed VOL also decreased oxidative stress. MPO and LDH exhibited non-competitive and mixed types of inhibition, respectively. Additional analysis revealed that VOL attaches itself to both enzymes somewhere other than the active center (Ertik *et al*., 2024).

The complexes (Zn-Telmisartan & Zn-Candesartan) exhibited a better affinity to the $Angiotensin^{2+}$ Receptors type 1 (AT1R), which are connected to a higher AT1R binding that balanced the blood pressure, as mentioned in previous work (Martinez *et al*., 2023). However, the novel chemical $[Zn(olme)(H_2O)_2]$ 2 (Figure 3) is also shown to have cardiac effects and antihypertensive activity. Complex 2 reduces interstitial myocardial fibrosis, which frequently coexists with Left Ventricle (LV) hypertrophy, and shows an increment in myocardial stiffness that impairs contractile performance. AT1R suppression prevents cardiac fibrosis by TGF-β1 production (Khan and Sheppard, 2006). In the spontaneously hypertensive rats SHR-untreated rats, it is verified that oxidative stress is linked to LV remodeling, and ZnOlme therapy reduced these alterations. Based on Glutathione (GSH) content, it blocks the restoration of redox homeostatic processes of ZnOlme AT1R. Whereas, a decrease in the ROS and oxidative damage was examined which causes boosting of antihypertensive effects of Zn complex 2.

Olmesartan complexation with Zn improved hemodynamics and strengthened cardiac protection by reducing oxidative stress, surpassing the benefits of olmesartan separately. It is investigated that Cadmium (Cd) alters the antioxidant defense state in cardiac tissue, which is linked to its adverse impact on heart functions. Inflammation and dyslipidemia are triggered caused by dysregulation of the lipid in the bloodstream. Food additives and eugenol supplements may protect cardiac tissue against oxidative cardiac impairment and dyslipidemia caused by Cd (Kumar and Sharma, 2024). Silver Nanoparticals (Ag NPs) synthesized with an aqueous extract of *Rumex alpinus* L. leaves, which are proven cardioprotective, stabilizing, and reducing agents. The nanoparticles have distinct progress to be used in the pharmaceutical industry to develop innovative formulations that avoid cardiotoxicity for various medicinal purposes. The effects of Ag NPs on isoproterenol-induced cardiotoxicity were observed in different areas (Xu *et al*., 2023).

Zinc Oxide Nanoparticles (ZnO NPs) are among the most studied NPs for drug distribution, cancer diagnostics, and rehabilitation. ZnO NPs effectively manage cardiovascular disease in obese rats. Additionally, ZnO NPs and zinc sulfate have cardiovascular defenses in diabetic rat models. ZnO NPs have been studied in another investigation to offer protection of the heart in irradiated rats. However, a previous study found that breathing in ultra-fine NPs caused MI cells to grow larger and disrupted their cell arrangement, which indicates that the particles hastened the pathological remodeling of the LV. ZnO NPs are also damaging to heart cells, therefore ingesting items containing (ZnO) may result in cardiac dysfunction and the development of cardiovascular issues. Furthermore, ZnO NPs cause cardiac malfunction and degenerative abnormalities, particularly at high doses (Hussein *et al*., 2024).

Metallothionein (MT) MT can also prevent doxorubicin-induced heart injury by neutralizing those, that are harmful and decreasing the levels of oxidative damage (Baltaci *et al*., 2018). Thiolate groups (-SH) present in MT, allow it to eliminate its free radicals. Cysteine ligands manifest their antioxidant properties, and the Zn–MT combination provides the molecular basis. likewise, Zn preserves heart tissue cells from oxidative injury by increasing MT expression and controlling Peroxiredoxin (Prx) synthesis. Previous studies have established Prx's antioxidant properties in adult rat hearts. Nitric Oxide Synthase (NOS) is a group of metalloenzymes that regulate arterial pressure, Coronary Artery Disease (CAD), and kidney function. Zn is used to stabilize the structure. ZnO nanoparticles inhibit vascular smooth muscle cell growth, aggregation of platelets, monocyte adherence, decreased cholesterol oxidation process, and cardiovascular inflammation while increasing vasodilation. Enhanced heart function is indicated by higher NO levels after ZnO NPs delivery (Tsutsui *et al*., 2008).

Likewise, Zn, α-Methyldopa (ZnMD), a novel metal combination containing the critical element Zn and the antihypertensive medication α-methyldopa, enhanced the biological characteristics of the original medicine. While MD alone might not offer the same amount of protection, ZnMD therapy showed a protective impact against oxidative stress in the heart. The structurally changed, medication therapy by Zn complexation [ZnMD(OH)$(H_2O)_2$] 3 see in (Figure 3) may affect the countenance of key proteins tangled in ROS formation and scavenging, thereby leading to a reduction in levels of ROS and coronary redox status. In general, ZnMD therapy might encourage a positive equilibrium between the concentrations of NO and ROS, which may help with the demonstrated antifibrotic and antihypertrophic effects combined with an enhancement of heart function in the rats receiving treatment. Acute Coronary Syndrome (ACS) patients had significantly lower plasma concentrations of the metals (Zn), (Mg), (Ca), (K), and (Ni) (Yin *et al*., 2017).

Zinc protects cardiomyocytes against IR stress in both *in vivo* and *in vitro* studies (Ischia *et al*., 2019), and it also lowers apoptotic markers, reduces O_2^{-t} generation, and increases ATP and LV pressure via decreasing oxidative stress into the cell caused by NADPH oxidase. Nonetheless, Israel Cancer Research Fund (ICRF) medications promote the production of dimers and could offer a way to reduce secondary oxidative chemistry in heart cells (Diop *et al*., 2000). The pathophysiology of chronic CVDs is linked to the alteration of Copper (Cu) homeostasis, which is caused by modified lipid metabolism through the formation of reactive oxidative chemicals. Prior studies have established a strong correlation between high Cu levels and the formation of ROS, facilitated by low-density cholesterols. The elevation is observed in heart hypertrophy in the rats exposed to Cu (Kumari *et al*., 2018). The pathophysiology of Cu-induced cardiac injury includes cardiomyocyte destruction, inflammatory cell infiltration, and vascular congestion. CuO NPs activate Activator protein-1, Nuclear Factor κb (NF-κB) transcription in the liver and kidneys and produce proinflammatory cytokines. The capacity of Cu to change the antioxidant balance has already documented that Cu-induced inflammation and cardiac inefficiency are caused by NF-κB transcription and activation (Ali *et al*., 2023).

A novel cardioprotective protective drug contains Cu NPs synthesized by *Berberis vulgaris* L. to study rats suffering from isoproterenol-induced myocardial ischemia. Drinking three to four cups of barberry syrup daily can help open blood vessels and cure heart failure due to Potassium (K) in barberries. The combined action of Cu NPs suppresses the inflammatory response to isoproterenol. Cu NPs inhibited the elevated levels of enzymes caused by isoproterenol therapy. Additionally, in the treated groups, the Cu NPs decreased the elevated heart-wet weight/body weight ratio. In other research, beneficial chemicals to preserve the heart muscle and lessen the damaged region have been delivered

via nanocarriers. Cu NPs exhibit cardioprotective effects that may be related to the activation & suppression of genes in mice having isoproterenol-induced myocardial ischemia. Applying Cu NPs reduces the expression of inflammatory cytokines and slows down cell death dramatically. The normalization of gene expression is associated with the advantageous effects of Cu NPs (Tu *et al*., 2023).

Arsenic (As) has therapeutic effects, but these are limited by its negative impacts on the body. However, its clinical use is restricted due to dose-dependent cardiotoxicity and hepatotoxicity, requiring careful monitoring. Additionally, arsenic and its Nanoparticles (NPs) have historically been used in traditional. Glioma cells are also given anti-cancer characteristics by ATO (Fang and Zhang, 2020). Both sodium alginate-decorated Selenium Nanoparticles (SA-SeNPs) and Selenium Nanoparticles (SeNPs) have the potential for use in several biological contexts, such as medication transport, antioxidant, and cardiovascular therapy. The capacity of Se-NPs to rummage ROS and shield the cells from oxidative impairment is responsible for its strong antioxidant qualities. ROS such as ·OH radicals, O_{2}·, and H_2O_2, can react with Se-NPs and change into less reactive forms. This feature of Se-NPs lessens the expanse of oxidative anxiety that takes place in biological units (Chatripour *et al*., 2016).

The besieged Fe nano-sized carriers act as active therapy that can be utilized to induce damage in cervical arteries and aortic aneurysms by attaching arginine glycose-amino-aspartate (Arg-Gly-Asp) to NPs (Kitagawa *et al*., 2017). This method was adopted in circulatory ailments including atrial diseases, Myocardial Infarction (MI), and heart attack. In addition, a publication demonstrates the activity of antibodies against nanoliposomes coupled with the Intercellular Adhesion Molecule-1 (ICAM-1). It is commonly observed that Anthracyclines (ANTs) may create ROS via different routes see Scheme 1. As it has been well addressed elsewhere, there is experimental evidence because iron (Fe) is crucial for inflammation and coronary artery disease caused by ANTs. The production of ANT-Fe complexes and the amplification of oxidative harms to bio-membranes consequent to *in vitro* studies is also observed. The damage mediated by the ANT-Fe complex was not susceptible to inhibition by traditional ROS scavengers. Later, isolated rat cardiomyocytes were used to

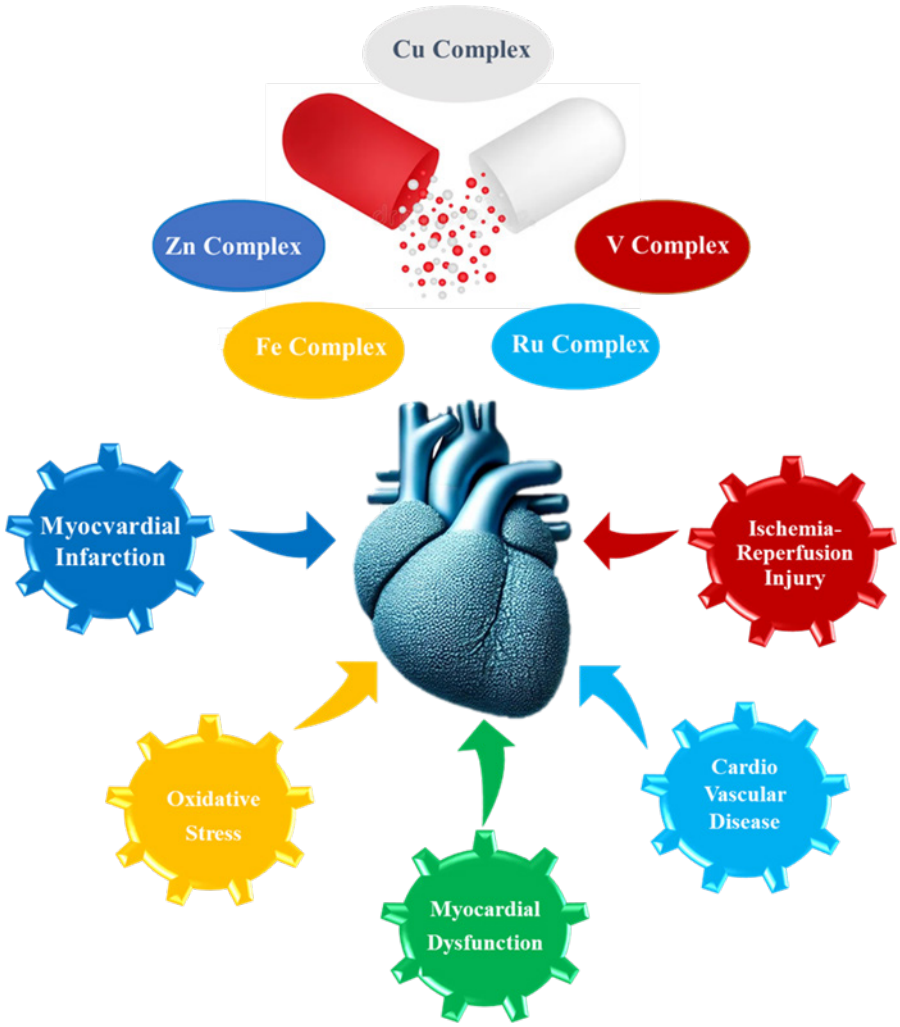


Figure 1: The role of some metal complexes in cardiac diseases.

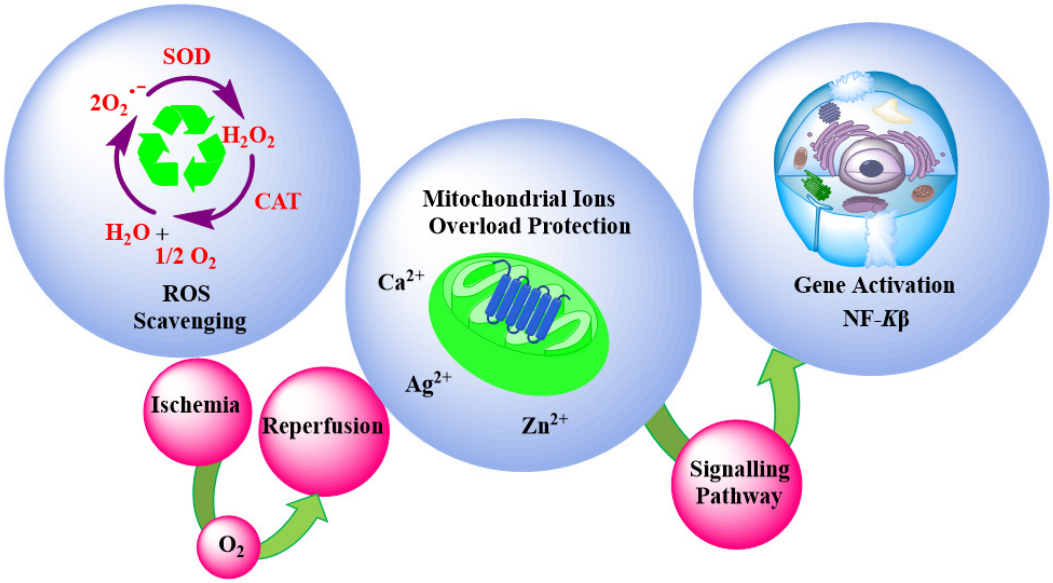


Figure 2: The mechanism of Ischemia-Reperfusion Injury and potential applications of organometallic complexes, ions, and coordination metals are categorized in this outlook according to their modes of action, which include Ca^{2+} uptake inhibitors, Zn^{2+} & Ag^{2+} role, and ROS degradation catalysts.

illustrate iron amplification of ANT cardiotoxicity (Kuang *et al.*, 2024).

The excretion of Lactate Dehydrogenase (LDH) along with variations in cell contractions have demonstrated that Fe loading significantly increases the toxic effects of Doxorubicin (DOX). Iron loading doubled the death rate, and caused substantial weight loss *in vivo* study, among DOX-treated rats (166). In both trials, the iron chelator Deferoxamine (DFO) was able to reverse the detrimental effects of iron on DOX cardiotoxicity. According to the hereditary model of the hemochromatosis condition in humans that causes an excess of iron in the body, mice defective in Hereditary Hemochromatosis genes (*Hfe*), showed a significant increase in susceptibility to DOX-induced cardiotoxicity (Miranda *et al.*, 2003). Dioxopiperazine rings are chemically hydrolyzed by Dexrazoxane (DEX) in hydrous solutions at appropriate pH and temperature, with a half-life of 9.3 hr Scheme 2.

Scheme 2 demonstrates the intermediates (B and C) produced with just one ring open, which further hydrolyze to the end product named di-amide of EDTA (ADR-925). Fe^{2+} accelerates the decomposition of the ring, resulting in hydrolytic intermediates to ADR-925, while Fe^{3+} has been shown to enhance the hydrolysis of DEX. It has also been shown that the latter process is significant at physiological quantities of Mg^{2+}, Ca^{2+}, Mn^{2+}, Cu^{2+}, and Zn^{2+} (BB *et al.*, 1998). Total hydrolysis of DEX yields ADR-925, which has a strong affinity for Fe^{2+} and Fe^{3+}. But even so, ADR-925 5 (Figure 3) remains a potent hexadentate iron chelator that works similarly to EDTA in chelating iron. This also holds for the hydrolytic products of other bis-dioxopiperazines. Fe(ADR-925) $H_2O]^+$ 4 and derivative Fe(EDTA)H_2O], the resultant complexes, have a deformed pentagonal bipyramidal geometry, and a water molecule occupies the seventh coordination site on the Fe^{3+} center (Diop *et al.*, 2000). Incredibly, it is thought that the volatile water molecule corresponding to Fe is responsible for the consequent production of hazardous hydroxyl radicals and redox-cycle characteristics of EDTA networks. Comparably, it has been noted that the Fe compound with ADR-925 has similar characteristics. ADR-925 is a more effective Fe chelator than ANTs, therefore it can effectively extract Fe^{3+} from the complex. It has also been reported that the intermediary products of hydrolysis (B and C) only in the tetradentate form also serve as iron chelators (Buss and Hasinoff, 1995).The intermediate (B & C) concentrations fell quickly after reaching their peak concentrations (Scheme 2).

Peroxide of lipids and other forms of biomolecular damage can be caused by the creation of ·OH, which can be catalyzed by this complex. Remarkably, when an oxidant and a reductant are present, [Fe (ADR-925)]$^+$ 5 generates ·OH. But the Fe-ICRF combination lessens the preference for the cell membrane, which eliminates the redox-active Fe and diminishes the damage caused by oxidation to the heart muscle. The lipid-based cell membrane is protected by dexrazoxane, although protein oxidative damage may also arise from complex FeICRF catalytic hydroxyl radical generation. Additionally, [Fe(ADR-925)]$^+$ 5 may target additional cellular locations, according to Malisza and Hasinoff (Pearlman, 1999). In the presence of molecular oxygen and ascorbic acid, [Fe(ADR-925)]$^+$ and its desmethyl derivative 5, (ICRF-247), called EDTA-*bisamide*[2] (Meščić Macan *et al.*, 2019), the hydrolysis product of (ICRF-154) generate ·OH that cleaves pBR322 plasmid. It is unclear if FeICRF complexes can encourage subsequent *in vivo*-based oxidative damage. FeICRF complexes provide

credence to moxo dimer formation that may contribute to the observed reduction in DNA scission for both $[Fe(ADR\text{-}925)]^+$ and 5 at higher concentrations and pH 7. Dimerization may lessen the generation of hydroxyl radicals and consequently secondary oxidative damage caused by FeICRF complexes; nevertheless, the monomer-dimer equilibrium is anticipated to be influenced by several circumstances, including *in vivo* concentration and the presence and concentration of a reductant. Other iron-chelating compounds are utilized, which may be more potent, selective, and less prone to redox activity than ADR-925, typically leading to only partial or no response (Štěrba *et al*., 2013).

Ruthenium amide complexes 6 (Figure 4), namely those containing *p*-cymene ligands, have been studied for their potential antitumor effects for a considerable time. A recent publication showed the presence of quercetin in a Ru *p*-cymene complex. The enzyme 3-Hydroxy-3-Methyl-Glutaryl-CoA Reductase (HMGR), is located in the endoplasmic reticulum and controls the initial steps of cholesterol production and was demonstrated to bind to the complex both *in vitro* and *in silico* studies (Cuccioloni *et al*., 2016). However, experiments on the HepG2 cell line revealed dose-dependent reductions that cultivated liver cells in cytoplasmic cholesterol. Remarkably, the complex [Ru(*p*-cym)(quercetin)Cl] exhibited activity that was equivalent to that of two model medications, such as simvastatin and pravastatin, and had a much greater curing effect than that of pure quercetin. Three compounds are the best investigated in the copper-based drugs belonging to the Cassiopeia (Cas) family, and toxicological studies allow for the inference of cardiotoxicity. Structures of Cas IIIEa7 [Cu (4,7-dimethyl-1,10-phenanthroline), 4,7-dimethyl-1,10-phenanthroline, acetylacetonato copper (II) nitrate], Cas IIIia8 [Cu(4,4′ dimethyl) (2,2′ -dipyridine) (acetylacetonate) aqua, 4,4-dimethyl-2,2′-bipyridine, acetylacetonato copper (II) nitrate] and Cas IIgly9 [Cu (4,7-dimethyl-1,10-phenanthroline) (glycinate) aqua, 4,7-dimethyl-1,10-phenanthroline, glycinato copper (II) nitrate] as shown in (Figure 4) (Bravo-Gómez *et al*., 2009).

The IIgly 9 and IIIEa 7 (with phenanthroline as a ligand) were two and seven times more powerful as inhibitors than IIIia 8 (with bipyridine as a ligand) on the respiratory activity due to the absence of the third aromatic ring may be the cause of a decrease in cardiotoxicity, it was noted in various *in vitro* and *in vivo* models. Cas alters the redox state and lowers membrane potential, which can result in thiol-dependent pore alterations that are connected to increased mPTP opening and cardiotoxicity (Silva-Platas *et al*., 2016). Table 1 provides an overview of previous research on the use of various metal-based compounds and their mechanisms in cardioprotective experiments.

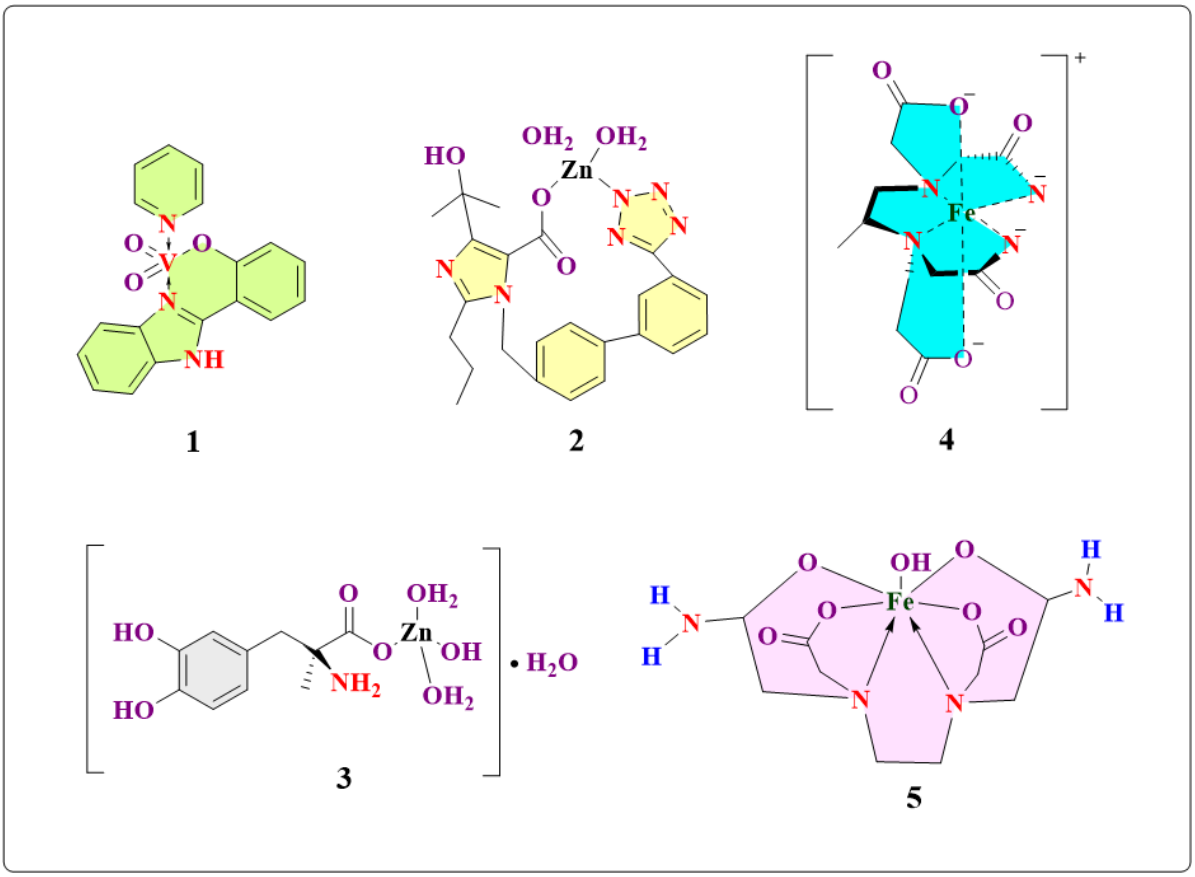


Figure 3: Zn(II), V(III), and Fe(IV) complexes that were used for the treatment of cardiovascular diseases.

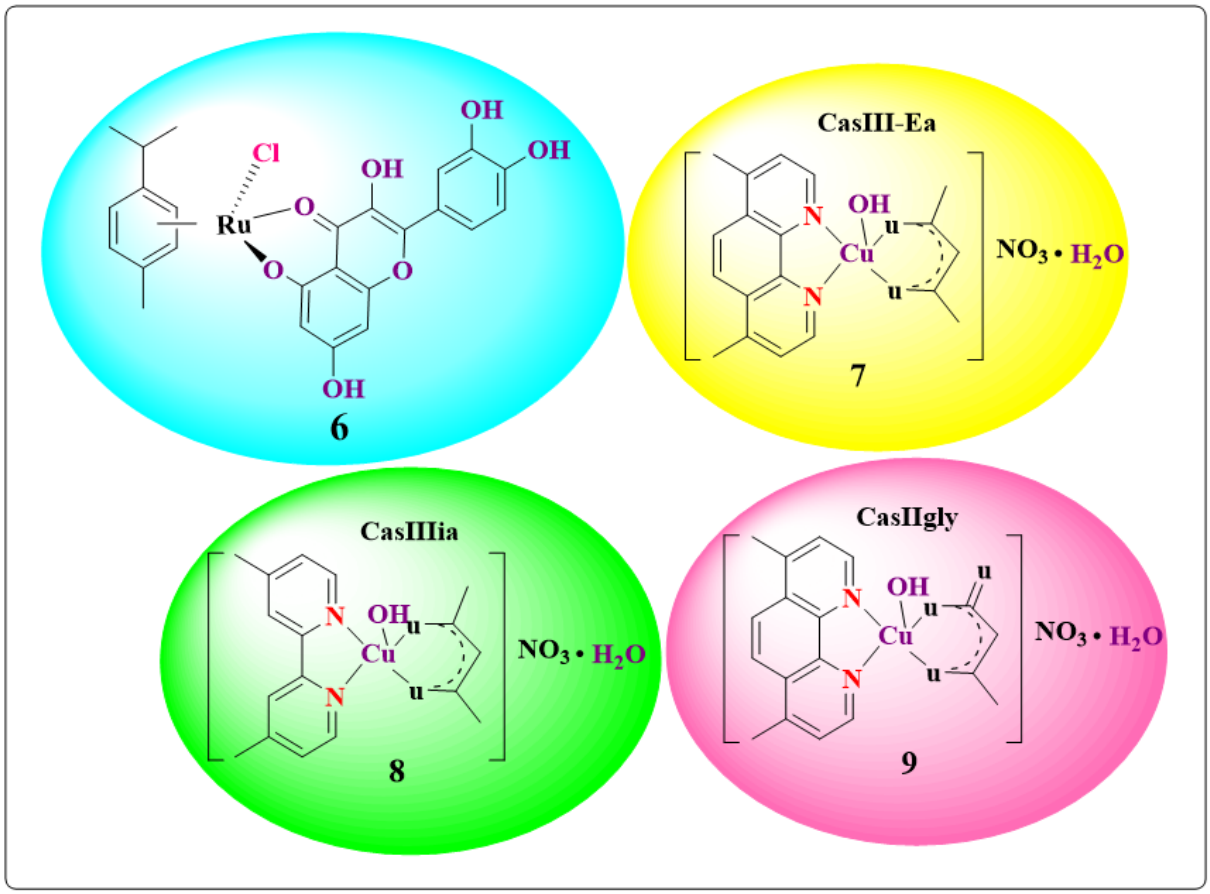


Figure 4: Structural representation of ruthenium complex 6. Structures of 7 Cas IIIEa [Cu (4,7-dimethyl-1,10-phenanthroline), 4,7-dimethyl-1,10-phenanthroline, acetylacetonato copper (II) nitrate], 8 Cas IIIia [Cu(4,4′ dimethyl) (2,2′ -dipyridine) (acetylacetonate) aqua, 4,4-dimethyl-2,2′-bipyridine, acetylacetonato copper (II) nitrate] and 9 Cas IIgly [Cu (4,7-dimethyl-1,10-phenanthroline) (glycinate) aqua, 4,7-dimethyl-1,10-phenanthroline, glycinato copper (II) nitrate].

METAL COMPLEXES IN ISCHEMIA-REPERFUSION INJURY

Metal complexes of *N*-heterocyclic carbenes, phenanthroline, porphyrins, and metallothioneins have shown promise in various models of ischemia-reperfusion injury. Their diverse mechanism of action has also been validated (Liu *et al.*, 2023). Myocardial Ischemia-Reperfusion (I-R) injury represents an acute type of cardiac injury, marked by elevated production of Reactive Oxygen Species (ROS) and the release of inflammatory mediators. This can be studied through *in vitro* and *in vivo* models, including isolated heart preparations and surgical models in small animals. Additionally, *ex vivo* models have been utilized to investigate the role of iron complexes in ischemia-reperfusion injury. Cardiomyocytes, which are highly aerobic, depend on the supply of ATP from mitochondria (Sagredo *et al.*, 2024).

Beyond that, cobalt metal induces free radical oxidation, which raises the levels of heme oxygenase and cytochrome P450, responsible for decreasing cellular respiration. The electrocardiographic abnormalities may have resulted in reduced cardiac contractility, which results from the prolonged $CoCl_2$ exposure-induced hypoxia/ischemia. Bisoprolol as well as diosmin were found to have the ability to normalize the redox state, reduce cell inflammation, and increase the anti-fibrotic and anti-apoptotic functions of heart cells towards $CoCl_2$-induced cardiotoxicity. Research on treatment advancements and preventative strategies is crucial due to the increasing prevalence of Ischemic Heart Disease (IHD) (Rai *et al.*, 2024). CAD-dependent cardiomyopathies and mitochondrial complex syndrome are linked to Ischemic Heart Failure (IHF) as one of its primary origins. IHF causes mitochondrial dysfunction due to a change in respiration from mitochondrial complex I (Figure 5) from state 3 to state 2. One possible therapeutic option is gene therapy, which aims to restore functioning Complex-I (CI) subunits. In addition, antioxidants targeting the mitochondria, like MitoQ, have been created to lessen ROS produced by the mitochondria and lessen the effects of ischemia-reperfusion damage (Smith and Murphy, 2011).

Despite not being redox-active, magnesium protects against ischemia-reperfusion damage and has some indirect antioxidant properties. Moreover, mitochondrial Fe causes ROS production, which in turn leads to myocardial IR impairment with the manifestation of cardiomyopathy. Mice with reduced lifespans

Table 1: Cardioprotective role of various metals, metal-based complexes, metal-based nanoparticles, metal-based salts, and other compounds, their mechanism in different experimental studies.

Metal	Metal-based Complexes	Metal-based Nanoparticles	General Items	Target Cells/ Tissue/ Cells/ Tissue/Some other active site	Cardioprotective Mechanism Followed	Experimental Model	References
Zn	Zn-Telmisartan, Zn-Candesartan, [Zn(olme)$(H_2O)_2$](2), [ZnMD(OH)$(H_2O)_2$](3),	ZnO NPs	Zinc sulfate, Zn-MT	Left ventricular	↓interstitial myocardial fibrosis ↑myocardial stiffness , ↓TGFβ1, ↓ROS, regulate PKC, ↓NF-κB, ↓ventricular arrhythmia, regulate Prxs, ↑ NO, Labile Zn+ ↑ under ischemia; Labile Zn^{2+} ↑ under reperfusion,Total Zn ↑ under IR	*in vivo* *in vitro*	(Dato *et al*., 2024; Mohamed *et al*., 2024; Restrepo Guerrero *et al*., 2024; Zhang and Zhao, 2015)
V	oxovanadium complex, (VOL), [VO_2(oz)py](1)			Left ventricular	↓oxidative stress ↓heart sizes,↓TGFβ1, ↓MPO, ↓LDH	*in vivo* *in vitro*	(Ertik *et al*., 2024; Mbatha *et al*., 2021)
Cd			Cd^{2+} ions	Cardiac tissue	alters the antioxidant defense dysregulation of the lipid, Inflammation and dyslipidemia malondialdehyde ↑(MDA), ↑(NO), ↑DNA oxidative damage marker 8-OHdG, ↓GSH, ↑ROS, ↓CoQ10 & LPO	*in vivo*	(Alruhaimi *et al*., 2023; Antar *et al*., 2024; Kumar and Sharma, 2024)
Ag		Ag NPs		Left ventricular	Improve Nrf2, downstream antioxidant enzymes, ↓apoptotic &inflammatory mediators	*in vivo*	(Xu *et al*., 2023)
Cu	Cu chelator (trientine), IIIEa (7), IIIia (8), IIgly (9)	CuO NPs		Heart tissues	↓heart hypertrophy, ↑inflammatory cell infiltration & vascular congestion, activate NF-κB, ↑PPAR-γ,pIKKα/β, p-IκB-α, and p-NF-κB,	*in vivo*	(Ali *et al*., 2023; Renu *et al*., 2023; Tu *et al*., 2023)
As		As NPs	Silibinin	Heart tissues	Protective role of heart mitochondria, treat acute promyelocytic leukemia	*in vivo*	

Metal	Metal-based Complexes	Metal-based Nanoparticles	General Items	Target Cells/ Tissue/ Cells/ Tissue/Some other active site	Cardioprotective Mechanism Followed	Experimental Model	References
Se		SeNPs, SA-SeNPs		Carotid arteries	↓oxidative stress, ↑GPx,catalase, SOD,		(Naveenkumar *et al*., 2024)
Fe	ANT-Fe complexes (4), Fe (ADR-925) $H_2O]^+$(5), Fe (EDTA)H_2O],		Deferiprone, Deferasirox, (ICL670A), SIH, Dp44mT	Heart muscles	Promote LDH, minimizing oxidative injury, contractile activity, Contractility, mitochondrial ultrastructure, Mortality,	*in vitro* *in vivo*	(Diop *et al*., 2000; Štěrba *et al*., 2013; Yang and Smith, 2023)
Ru	[Ru(p-cym) (quercetin)Cl](6)				lowering cholesterol activity, prevent blood vessel blockage,	*in vitro* *in silico* studies	(Santos and Braga, 2021)

Note: The upwards arrow ↑indicates the value is going up and the downward arrow ↓indicates the value is going down.

and poor cardiac function were caused by Fe excessive stress in cardiomyocytes. In studies of cardiac ischemia-reperfusion injury in mice, an increase in iron levels is observed. Following ischemia, there is also an increase in coronary outflow. Human total cholesterol levels, atherosclerosis risk, and cardiovascular death are all correlated with elevated serum Cu levels. A mouse model of myocardial ischemia-reperfusion damage that results in Cu recruitment and depletion. The animal exhibits a fifty-fold rise in Cu in its coronary outflow during ischemia. A low magnesium level may weaken the antioxidant defense response by reducing the protein production of crucial enzymes like Superoxide Dismutase 2 (SOD2) and catalase. However, prophylactic treatment with $MgSO_4$ looks beneficial in a rat model of ischemia-reperfusion injury (Zheltova *et al*., 2016).

TOXICITY OF METAL COMPLEXES

In general, metals are two-edged weapons. They are essential in preventing oxidative pressure, but they can also raise the production of ROS, which can then affect the NRF2 anti-inflammatory activation pathway. Zn reduces the generation of ROS in the mitochondria after reperfusion & $ZnCl_2$ increases myocardial oxidative phosphorylation in a rat heart damaged by IR. Although many metals and their complexes are used in cardiac disorders, researchers also described some adverse effects of heavy metals on cardiac tissues. However, Wilson's disease and the patient's livers are the main sites of Cu buildup because of a genetic mutation in the ATP7B gene (Padrilah *et al*., 2017). In the past, the protective benefits of melatonin on lung tissue in Cu-exposed rats are seen by decreased oxidative stress, tissue inflammation, and collagen buildup. Melatonin may protect biological components like lipids from Cu-induced oxidation. According to recent findings, Melatonin can treat cardiac damage as it chelates free Cu ions. The potential of Cu to cause cardiac injury in rats has not been examined before. Likewise, the impact of melatonin, free radical scavenger was investigated against Cu-induced heart damage. The ability of Melatonin to stop the progression of cardiac diseases has been thoroughly studied in many animal models due to its notable role in inhibiting oxidative stress and inflammatory signaling (Dominguez-Rodriguez *et al*., 2010).

In prior *in vitro* investigations, melatonin was reported to diminish Cu-mediated lipid peroxidation, and in ischemic rats, it inhibited fibrotic proteins that led to heart hypertrophy. Although Arsenic (As) has therapeutic effects, these are limited by its negative impacts on the body. This holds particularly true for the cardiovascular system. The cardiovascular system is especially susceptible to the harmful effects of As. Arsenic causes damage to the heart through a disturbance in mitochondrial function by increasing ROS and oxidative pressure, which contributes to heart-related problems. In certain animal models, extended consumption of Arsenic (As) has been demonstrated to cause cardiac dysregulation. As produces oxidative injury and inflammation in the vascular system, which causes cardiac issues, according to several animal studies (Ochoa-Martínez *et al*., 2019). They also reduce ROS levels and hypertension, both of which can lead to cardiovascular issues. Well-known risk factors for cancer Se-NPs have been shown to reduce chronic inflammation. Interaction with Cd has been connected to an increased risk of CVD because of its capacity to induce inflammation, oxidative stress, and heart injury. Heart hypertrophy, atherosclerosis, and myocardial infarction all have been related to Cd exposure (Das *et al*., 2021).

To assess the function of Coenzyme Q10 (CoQ10) and identify possible morphological and structural alterations that might develop in heart muscle after treatment with Cadmium Chloride ($CdCl_2$). Given that the Oxidative Stress (OS) and inflammation play a role in Cd cardiotoxicity. With an emphasis on participation of the Nuclear Factor kappa B (NF-κB)/reduced NLR family pyrin domain containing 3 (NLRP3) inflammasome axis, the protective effect of CoQ10 against Cd-induced OS and inflammation in rat hearts was investigated. The primary mechanism responsible for the cardioprotective effectiveness of CoQ10 was the prevention of OS. With OS involvement in Cd cardiotoxicity, it is significant to assume that CoQ10 antioxidant efficacy is the primary mechanism for its cardioprotective benefits. According to recent research, oxidative damage, reduced antioxidant enzyme activity, elevated ROS generation, and GSH depletion are the causes of Cd cardiotoxicity. Moreover, inflammatory reactions are linked to Cd cardiotoxicity in addition to OS. Inducing a series of inflammatory reactions, Cd causes an increase in pro-inflammatory cytokine production, which damages cardiac tissues further (Shen *et al*., 2018).

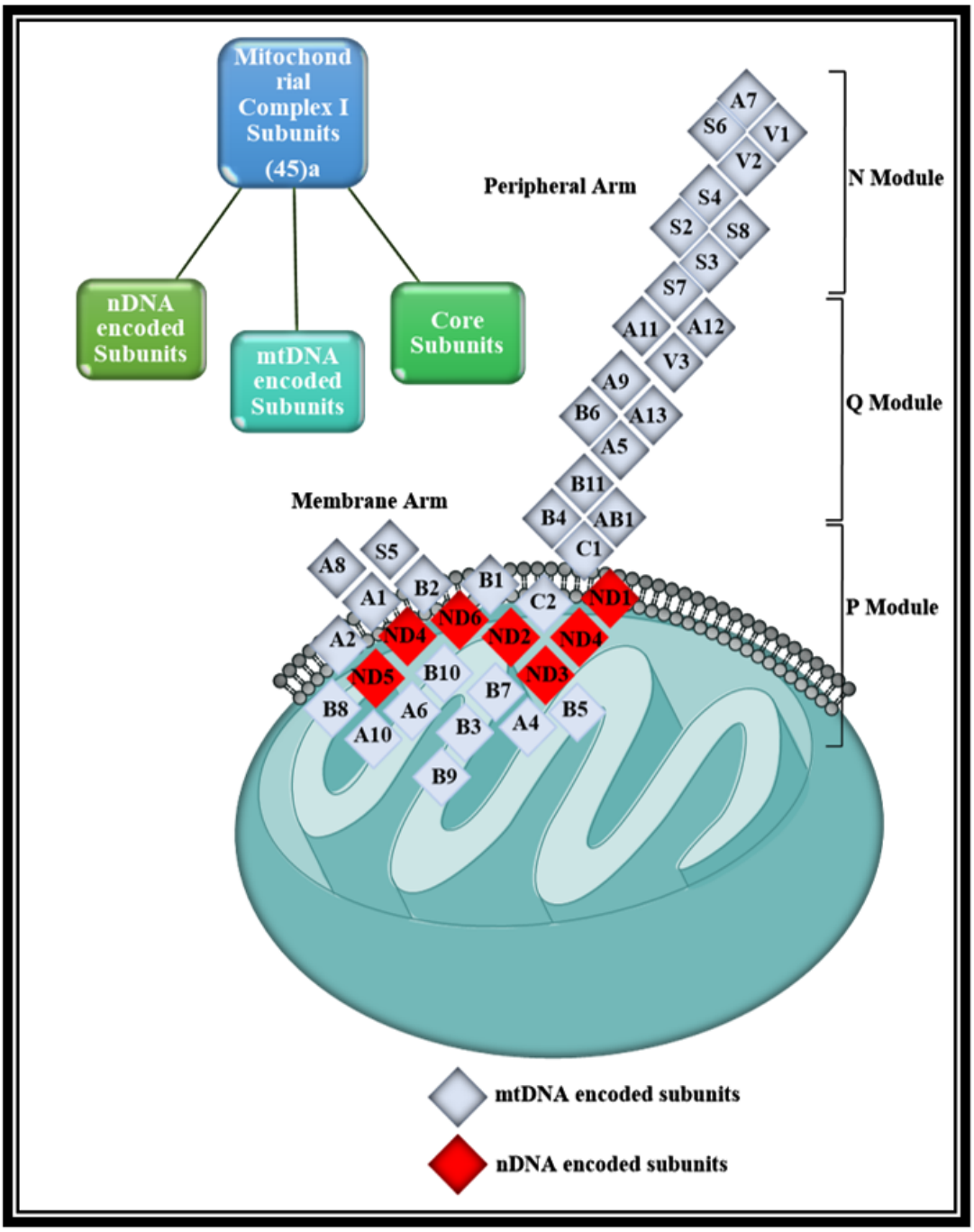
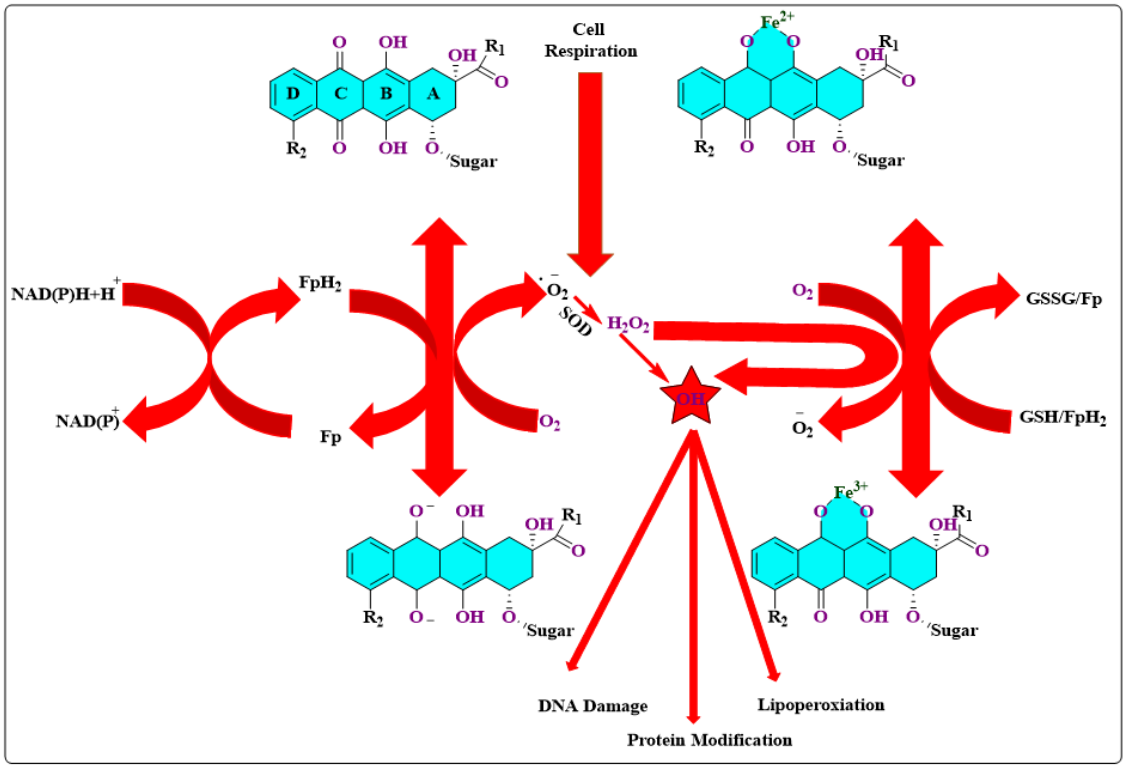
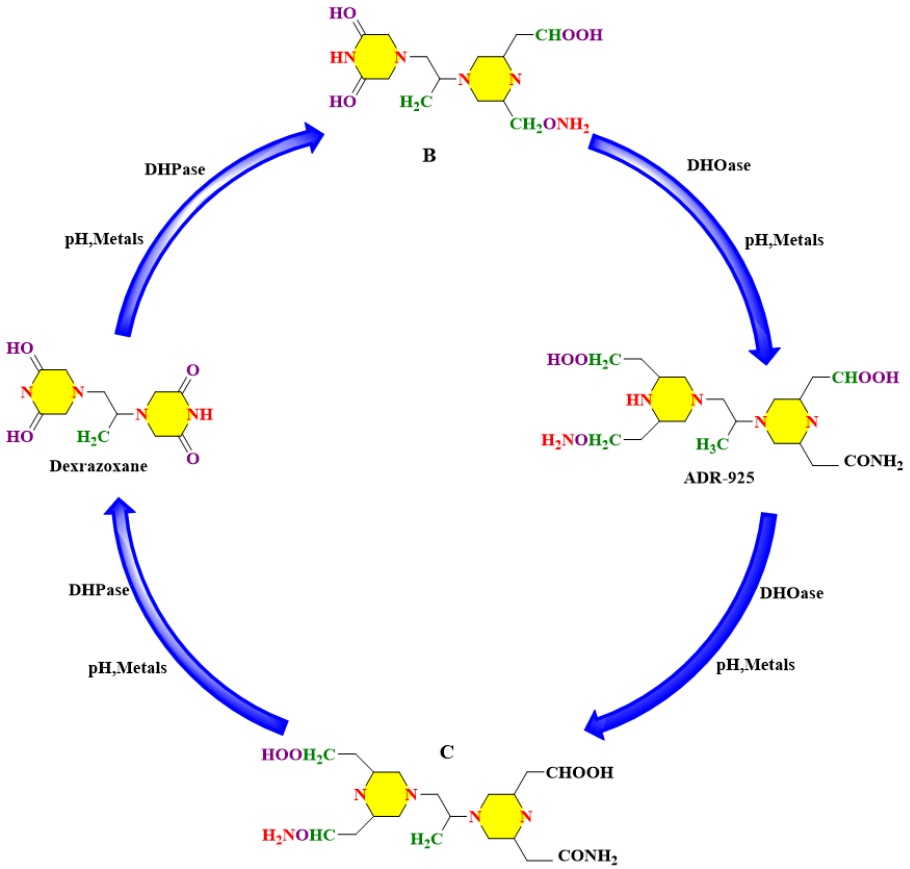


Figure 5: Structure of the mitochondrial complex I, together with its components (Rai *et al*., 2024).



Scheme 1: Principal routes of Fe- and anthracycline-catalyzed oxidative pressure are schematically represented (Šimůnek *et al*., 2009).



Scheme 2: Stepwise hydrolysis of dexrazoxane to intermediate metabolites B and C and iron chelating metabolite ADR-925.

CONCLUSION

Nanotechnology research utilizing metal complexes as drug delivery systems emerges as a pivotal area of exploration, particularly concerning their cardioprotective properties. The assessment of metal complexes such as Fe^{2+}, Co^{2+}, Zn^{2+}, Ru^{2+}, and Cu^{2+} complexes demonstrate their significant therapeutic potential in mitigating myocardial ischemia and related cardiac conditions. Fe^{2+} complexes have shown efficacy in reducing arrhythmia and bradycardia, while Co^{2+} and Cu^{2+} complexes highlight the importance of ligand coordination in enhancing cardioprotective effects. Ni^{2+} complexes mitigate cardiac toxicity, and Ru^{2+} complexes exhibit comparable activity to establish medications. These complexes demonstrated enhanced pharmacokinetics, reduced side effects, and superior cardioprotective outcomes by selectively targeting ischemic and infarcted tissues. Hence, coordinated complexes prove more effective than their free metal ions or drugs. The groundbreaking potential of metal complexes redefines the domain of cardioprotective strategies.

FUTURE DIRECTION

Further studies are needed to optimize metal complexes for efficacy and minimize potential toxic effects.

Research should focus on enhancing pharmacokinetics and maximizing the cardioprotective benefits.

Leveraging ischemic tissue targeting can drive innovation in advanced cardiac therapeutic strategies.

This review guides pharmacists in developing improved CVD treatments using metal-based nanomaterials.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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