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AN OVERVIEW ON USAGE OF CO-RELEASING MOLECULE (CORM) AS DIVERSE PHARMACOLOGICAL AGENT.

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Abstract: Carbon monoxide (CO), which is produced as a By-product of heme oxidation by the heme oxygenase(HO) enzyme imparts cytotoxicity in the biological organisms at higher concentrations because binding affinity of CO to hemoglobin when compared to oxygen.so,it was considered to be lethal earlier. In recent days, evidences from extensive research on biological activity has been proved that the release of CO from prodrug CO-releasing molecules (CO-RMs) have significant role in various pharmacological activities when administered in controlled pattern into the cellular systems than direct administration of CO. Based upon the covalent bond formation between CO and metal carbonyl complexes (MCCs) many CORMs are produced such as CORM-1, CORM-2, CORM-3, ALF492, CORM-A1 and ALF186. Inversely, degradation of CORMs generate a metal residue (i-CORMs) which lead to toxicity in the body,Inorder to minimize this effect new CORMats such as micellization, nanoparticles, nanosheet and nanodiamond have been developed. Now a days, inhaled CO (iCO) and hybrid carbon monoxide-releasing molecules (HYCOs) are also used in the therapy of CO. CORM can control the release of CO to a target site, this potential of CO-releasing molecules (CO-RMs) can be useful to formulate CO-based pharmaceuticals This article highlights characteristics of CO-releasing molecules (CO-RMs) and various mechanisms intricated in the therapy of CO when administered in the form of CO-RMs.

Index Terms – Cytotoxicity, Carbonmonoxide releasing molecules (CO-RM), Therapy, Target sites.

I. INTRODUCTION

Above -190°C CO lacks COLOR, odor and taste. Due to its characteristic property to cause toxicity in humans at higher levels CO is reputed as ''silent killer''. Endogenously CO is produced by oxidation of heme catalyzed by constitutive (HO-2 and HO-3) and inducible (HO-1) isoforms of heme oxygenase. In liver and spleen ,Isoforms HO-1is found abundantly as an element . Isoforms HO-1is stimulated by free heme molecules and leads to degradation of heme . constitutively expressed HO-2, is found significantly in vasculature and testes.CO has 220 times higher affinity to hemoglobin than oxygen, thereby leads to formation of carboxyhemoglobin.Thus,reduces circulation of oxygen in the body.CO regulate cyclic guanosine 3′,5′-monophosphate (cGMP) by activating guanylate cyclase . By both cGMP-dependent and independent processes ,CO involued in signaling pathways by modulating p38 mitogen-activated protein kinase as well as CO directly activates calcium-dependent potassium channels and by phosphatidylinositol 3-kinase/Akt pathway induces protein kinase B (Akt) phosphorylation.cGMP will act as secondary messanger and regulate surfeit cellular function signals, such as vasodilation and platelet aggregation inhibition. Reaseach has been done on the non-cGMP pathway because CO as signaling molecule triggers largeconductance voltage-gated K+ channels, which are known as BK (big potassium) channels..Through the non-cGMP pathway and leads to hyperpolarization of the membrane and the ion cardiac L-type Ca2+channel carry CO cardioprotective properties.CO can be generated fastly whenever it is necessary.CO as gas transmitter can enter and pass out of cells without receptor mediation and effectively regulate cellular fuctions. In minimal concentrations, carbon monoxide has many positive effects on inflammatory disorders, vasorelaxation,tumor growth, bacterial infections, cardiovascular diseases,organ transplantations cellular reactive oxygen species (ROS) generation. Research based on signaling pathways of CO are still in progess

CO gas alone don't have potential to capitalize these effects. On the other hand, there is risk of toxicity when administered as a gas.CO therapy also lack target specificity because of random diffusion. Moreover, hemoglobin ranges of patient will largely interfere with the pharmacological effects of CO inhalation. Due to higher affinity between CO and hemoglobin, low doses of CO that can be released in a controlled pattern at predetermined target site and time and maintain the values of COHb in circulation to baseline values (≤5% COHb).Therefore, carbon monoxide-releasing molecules (CO-RMs) have been proposed as a specific technology to circumvent the problems faced by CO toxicity.CO-RMs are essentially prodrugs which are formulated to liberate CO under specific conditions at target site. From past few years,several molecules of CORM was identified,they includes many types of organometallic complexes (M = Cobalt, Iron, Cr, Molybdenum, tungsten), silacarboxylates, oxalates, xanthene-9-

carboxylic acid (XCA). To classify bioactive CO carriers, CO-releasing molecules' (CO-RMs) was named. Motterlini first identified CORM1(Mn2(CO)10) ,CORM2and proposed that they can be used as pharmaceutical agents. Later, CORMs, like the water-soluble [Ru(CO)3Cl(glycinate)] (CORM-3) and CORM-L1, were synthesized .A CORM has two parts: a CORM sphere and a drug sphere. CORM sphere controls the number of CO molecules that can be released, stimulates mechanism necessary for CO release and the kinetics of CO release. Drug sphere regulate the partition ratio between the various body fluids. By thermal activation /hydrolysis all of these molecules liberate CO .Controlled and specific CO delivery will be achieved internal trigger/ external trigger (photo excitation). CORM-1 and CORM-L1 are known as Photo Corms release CO from CORMs by photochemical activation at different light wavelengths. Other triggers include degradation by enzymes ET-CORMs (enzyme triggered-CORM) and oxidation.

Of all the Corms, most therapeutic studies are on CORM-2 and water-soluble CORM-3. In a heart attack mouse model, CORM-3 prolongs the survival rate in organ transplantation by reducing cardiac muscle damage and infarct size. Other properties of CORMs include arthritis, vasodilatory properties bacterial infection or neuroinflammation, reduce platelet aggregation and ant apoptotic effect.CORMs have therapeutic benefits in diabetes and Alzheimer's disease.

Through functionalized nanoparticles or polymers, target control can be achieved by tissue accumulation. Target control can be exerted by two mechanisms:(a) "active" decoration, or(b) by enhanced permeability and retention (EPR) effect. In tumors newly formed blood vessels have high permeability.So,holes sizes rises to 50nm(normal tissue has pore size 5–8 nm).These increased pore size allow polymers, nanoparticles to pass through them. The lymphatic system fails to remove them. This leads to liberation of CO at target site.

II. DISCOVERY AND DEVELOPMENT OF CO-RMS:

In late 1990s, crucial role of HO-1/CO pathway in curing many diseases was identified. This lead to development of CO carrier.CO binds with transition metals to form metal carbonyl compounds. The early findings shows that, under suitable conditions, Mn2CO10 (manganese decacarbonyl) and Ru(CO)3Cl2 dimer [tricarbonyldichlororutheium(II)] were able to liberate CO and have therapeutic effects as vasodilatation and hypotension. This lead to the research to develop convinced a new class of compounds (CORMs) for delivering predetermined amount of CO in tissues and organs. All these carbonyls had some issues. As [Mn2(CO)10] (CORM-1) and [Fe(CO)5] are hydrophobic and liberate CO by photolysis.[Ru2(CO)6Cl4] (CORM-2) is also hydrophobic in nature, by using as a solution in DMSO and in myoglobin at 0.9 CO/mol of [Ru2(CO)6Cl4], CO can be liberated . CORM 2 was popular in biological activity because of low toxicity and it can be used as vasodilator. The CORM-3, which is a relatively stable in water but appropriately liberates CO in the presence of myoglobin.In CORM3 don't have carboxylic group is transformed into CO by hydrolysis. In Invitro CORM-3 don't change the potentiality of porcine aortic endothelial cells. Ruthenium metal, have antihypertensive and vasodialtion effects. On the other hand CORM-A1 have mild vasorelaxation and hypotension properties. CORM1 liberation of CO is through endothelium-independent pathway by activation of guanylate cyclase and potassium channel. Around 2012 CORM-401(manganese-carbonyl CO complex).CORM-401 has $t_{1/2}$ of 13 -14 min and liberates 3 moles of CO per one mole of CORM-401 in a phosphate buffer.

Hybrid CORMs was developed by Wilson et al. HYCO-1 is a unsymmetric compound that have one [Co2(CO)6] moiety. HYCO-2 carries two bimetallic fragments and is symmetric. Unlike the other CORMs, Hybrid(HYCO-1 & HYCO-2) CORMs are based on irreversible oxidation of cobalt. Manganese based HYCOs are HYCO-3, HYCO-7 and HYCO-13 and HYCO-6 and HYCO-are based on Ru.

For intracellular delivery of CO through esterase-mediated hydrolysis enzyme-triggered CORMs (ET-CORMs) were developed. These molecules are Acyl-oxydiene-Fe(CO)3 complexes. Example: iron carbonyl complex (Cyclohexadienone-Fe(CO)3).

ALF492, ALF795, and B12-ReCORM-2 are other new CORMs which have increased solubility, determined CO-release rates and target specificity. In ALF492,RuCl2-thiogalactopyranoside(CO)3],Ru is binded to a galactose-derived ligand.ALF794[Mo (CNCMe2CO2H)3(CO)3] is molybdenum-based CORM. The rhenium(II) conjugate, B12-ReCORM-2,metal moiety bounded to the axial cyano group of the vitamin. Adjusting and accuracy of CO-release rates in CORMs are required, this release depend on the temperature, oxygen, light conditions and assay solution.In recent days,CO release compounds are classified according activation. They are solvent-triggered CORMs, enzyme-triggered CORMs (ET-CORMs),thermal triggered CORMs, oxidation-triggered CORMs, pH-triggered CORMs, photoCORMs etc.

In Solvent-Triggered CORMs, CO is liberated within a solvent by activating solvent induced ligand exchange with the solvent or solutes, examples are CORM2 and CORM3.Photo-CORMs are complexes liberates CO when exposed to light at an accurate wavelength but remains stable in absence of light. Enzyme-triggered systems (ET-CORMs) liberates CO to an appropriate stimulus, they are tissue/cell specific in nature. For example, the η4 -acyloxybutadiene-Fe(CO)3 .This complex is stimulated by an esterase. This esterase targets ester group and releases CO. For rhenium II-based CORMs CO liberation is pH dependent. The CO is released faster at low pH value from the metal complexes.

The stimulation and kinetics of CO liberation, the solubility in aqueous medium, and their metal residues play pivotal roles in CORM design. Romao and co-workers introduced a model of a metal carbonyl complex (MCC).This model includes three various components: (A) a metal core(intrinsic properties),(B) a coordination sphere with CO and subordinate ligands (thermodynamic and kinetic stability)(C) a drug sphere(pharmacological parameters).

There are numerous opportunities for chemists in the development of CO-RM as diverse pharmacological agent.

III.THERAPEUTIC USE OF CO AND CORMS

By administrating 3.0mg per kg per hr dosing(single one hour dose/daily for 10days),blood level of COHb were raised up to 12% in a recurrent and predictable manner ,and no evidences of adverse events of gas over placebo were seen in first single, blind, randomized, placebo controlled phase I trial.

However ,CO is known to have both physiologically and therapeutic activity. But duration of exposure, dose concentration and dose timing should be determined properly. The challenges of administration of a gaseous pharmaceutical have lead to identify many novel molecules, which can deliver CO parenterally or orally.

INFLAMMATION: The anti-inflammatory properties of CO and CORMs have been correlated to many animal models, recommending feasible therapeutic application for inflammatory diseases. These anti-inflammatory properties are by the involvement of signaling pathways of mitogen-activated protein kinase (MAPK) & c-Jun N-terminal kinase (JNK) pathways along with activator protein 1 (AP-1).Moreover, key role is played by the mitochondria respiratory chain23 for the effect. For example, beneficial effects of CO is seen in a mouse model of experimental cerebral malaria (ECM).When Plasmodium infected the brain,an inflammatory cascade was detected in the neighbouring tissue. If CO was inhaled for 3 days after the plasmodium infection, edema in mouse brain was significantly prevented as well as increase in survival rate was also observed. In rheumatoid arthritis and osteoarthritis CO & it's carriers have promising results. By administration of CORMS, decline in leukocyte sequestration and inflammation can be observed in thermal injury of mice. In mice models,cecal ligation and puncture (CLP) were done to induce sepsis, CO-RM3 and CORM2 decreased inflammation by inhibiting the production of nuclear factor κB (NF-κB)and prolonged survival rate of mice as well as livery injury was minimized after CLP.In the same way, a pretreatment in lipopolysaccharide (LPS) induced acute lung injury pig, 250 ppm of CO prevented lung derangement and improved many acute pathological changes by endotoxin.CO and its carriers also shows potential therapeutic activity by minimizing inflammation in intestinal muscalaris of mice in Postoperative ileus.CORM-A1 improves pathological symptoms of Experimental autoimmune encephalomyelitis(EAE).After EAE, Induction of HO-1 by cobalt protoporphyrin IX (CoPPIX) administration reverses paralysis.

CO and CORMs tends to have good therapeutic activity in sickle-cell anemia, asthma and airway hyper-responsiveness, carrageenan-induced mesenteric inflammation and diabetes which was proved by many animal models.

ORGAN TRANSPLANTATION AND PRESERVATION

In the medical field, CO has been evaluated and has achieved significant progress in organ transplantation system. For example transplantation of Lung in rats and mice administration of 250 ppm of CO inhibit chronic rejection, Ischemia-reperfusion injury (***IRI***) and cell death and acts as organ protector. Inhaled CO is said to have promising results on the heart, lung, kidney, liver and pancreatic islet. A phase II trial (ClinicalTrials.gov identifier: NCT00531856) is currently underway on intraoperatively deliver of CO (3mg per kg for 1 hour) to improve organ function after transplant. Restoration of renal blood flow (RBF) and enhanced renal function indexes such as the glomerular filtration rate (GFR) & creatinine clearance rate (CCR) was seen by delivering accurate dose of CORM-3 (50 & 100 μM) in Kidney transplantation of pigs and rabbits and rats . Interestingly, this effect was blocked via the GC-cGMP pathway . According to Nakao et al. in a renal graft model, Cytochrome P450 (CYP450) plays an important role in Ischemia-reperfusion injury IRI along with CO and stabilized by CO.CO also have ability to decrease the ischaemia–reperfusion and bring normality in functioning of kidney. In the same way, non-heart -beating donor kidney in pigs, less concentrations of CORM3 improves a loss in renal blood and urine flow.

CARDIOVASCULAR DISEASE:

In research it is revealed that, aortic transplantation in mice, which are HO1 deficient leads to mortality within 4 days due to severe arterial thrombosis. In contrast, when they are treated with CORM2, there is increase in rate of survival (62.9% survival at >56 days) and therapy with CORM2 shows rapid decrease in platelet aggregation in the graft. In a coronary artery occlusion model of mice, administration of CORM3 intravenous infusion as well as exposure to CO leads to inconsiderable sized myocardial infarct and further study using isolated rat hearts shows a significant decrease in the occurrence of reperfusion-induced ventricular fibrillation (VF) as well as tachycardia (VT).This result is due to interaction of CORMs with potassium channels. Another cigarette smoke rat model, also explained the antioxidant role of HO-1.

In vascular diseases HO-1/CO/CORMs seize the hyper proliferation of vascular smooth muscle cells in rats, which reduce intimal hyperplasia and facilitated re-endothelialization by mobilization and recruitment of progenitor cells in bone marrow. In rodent models with induced pulmonary hypertension, administration of inhaled CO brings back right ventricular along with pulmonary arterial pressure to near normal. These protective action is due to cGMP dependent pathway, BK channel, ion cardiac L-type Ca2+channel. In a latest experimental study by Suliman et al.,61 embryonic stem (ES) cell differentiation and maturation into cardiomyocytes can be achieved by modification of HO-1/CO and usage of CORM5 (B12-ReCORM-2) .This interaction increases mitochondrial biogenesis.

OBESITY AFFECTED BY CORMS:

Chances of diabetes, heart disease, inflammation are associated with chronic obesity. Due to endoplasmic reticulum (ER) stress, obesity is caused.Leptin regulates intake of food and weight of the body. Zheng et al. Studied effect of CORM's on obesity and

suggested that CO may prevent leptin resistance during ER stress. ER stress in human cells will be caused by Thapsigargin/tunicamycin,they mimizes leptin mediated STAT3 phosphorylation, which causes ER stress induced leptin resistance. Treatment of these cells with CORM-2,inhibited the STAT3 phosphorylation and mediated the protein kinase R-like ER kinase phosphorylation and factor-2 initiation of eukaryotic translation during ER stress. In vivo testing, CO exposure animals showed declined in the body weight even they fed with high fat rich diet. So, it is proved that CO does have a role in treating obesity.

NEUROPROTECTION AND NEURONAL DIFFERENTIATION

A study by Verma et al. [91] revealed that CO gas may also function as a neurotransmitter. They found high ranges of heme oxygenase in the brain. Moreover, degradation of heme by heme oxygenase produces biliverdin and liberates CO. It was identified that as CO being a weak activator of guanylyl cyclase (GC) produces relaxation in smooth muscle and effectively inhibit platelet aggregation. In the research done by Piantadosi et al., awaken rats were treated with high levels of CO i.e 2500 ppm for one hour. Due to this exposure significant damage was noted in the cerebral cortex than compared to the basal ganglia and cerebellum. However, gradual improvement was sees in the performance of the CO-treated rats and normalized after one month of the exposure. But exposure to high levels of CO led to accumulation of interstitial glutamate, which led to high levels of hydroxyl radical formation. In addition,these effects led to the opinion that CO shows toxic effects in the brain. In a simulation of ischemic stroke to neuronal cells CORM ALF186 can stop nerve cell apoptosis.Lin et al. reported that, in rat brain astrocytes CORM-3 sequentially triggers a c-Src/Pyk2/PKCα/Erk1/2 pathway produce induction of HO-1 and after inhibit interleukin-1β-mediated neuroinflammation.

EFFECT OF CORMS IN THE LUNGS

Abid et al.[74] studied beneficial effects of CO on reverse pulmonary hypertension (PH). Treatment of hypoxia induced mice with CORM-3 cures PH ventricular hypertrophy and distal pulmonary artery muscularization.CORM-3 treatment also reversed PH in smooth muscle promoter 22 serotonin transporter mice by decreasing Ki67. Furthermore, CORM-3 increased p21 mRNA and protein levels in lungs.

. Abid et al.have performed an experiment on beneficial effects of CO on reverse pulmonary hypertension (PH), a complication that occurs as a result of certain diseases. CORM-3 exposure was seen to prevent PH ventricular hypertrophy and distal pulmonary artery muscularization in hypoxiainduced mice. CORM-3 treatment also reversed PH in smooth muscle promoter 22 serotonin transporter mice by decreasing Ki67. Furthermore, CORM-3 increased p21 mRNA and protein levels in lungs. Taken together, the data suggested that through its modulation of p21, CORM-3 may serve as an effective treatment for PH. However, when CORMs were tested under the influence of hypoxic pulmonary vasoconstriction (HPV) using an in vitro model, it was observed that the CORMs did not significantly diminish HPV. Furthermore, CORM administration did not result in the inhibition of CYP, a cytochrome that regulates HPV. When higher concentrations of CORMs were used, irreversible pulmonary vasoconstriction resulted. However, inhaled CO led to a decrease in HPV and CYP. +us, using CORMs for the purpose of treating hypoxic pulmonary vasoconstriction is not particularly effective. Nevertheless, it is possible that the application of CORMs in vivo may lead to different results, and they may even have inhibitory effects on HPV.

MICROBIAL INFECTION:

CO and it's carriers, CORM 3, have potential activity against many microorganisms including Staphylococcus aureus(Gram-positive) and Escherichia coli(Gram-negative bacteria).CO kills bacteria by inhibiting adenosine triphosphate (ATP) and hinders respiration.Moreover,By Phagocytosis CO will acts as bactericide against Escherichia coli through Toll-like receptor 4 (TLR4). First visible-light-activated CORM,tryptophan-derived manganese-containing complex(Trypto-CORM) have bactericidal activity against Escherichia coli.This Trypto-CORM,have least toxic profile against cell and liberates CO and tryptophan in the presence of visible light (1.401 mol of CO at 465 nm, and 2.1 mol at 400 nm) .E. coli cells when treated with ALF 062 liberates huge Mo (155 g g1) and this Mo accumulates inside the E. coli cells, where it liberates CO to the cellular targets.

OCULAR SYSTEM

At Low concentrations of CO can treat various ocular conditions, for example, glaucoma .Moreover,Stagni et al. have concluded that CORM-3 can lower intraocular pressure in rabbits. A markable range of decrease in intraocular pressure was reported after 30 min of CORM-3 treatment for up to 24 hours.A maximum therapeutic effect was observed 6 hours after CORM-3 treatment and maximum drop in pressure of 12 mm Hg was noted.Further,therapy with 0.01% and 0.1% CORM-3 solutions resulted in intraocular pressure(IOP) drops of 3 and 7 mm Hg, respectively.No effect was observed with the administration of inactive form,iCORM-3.

CORMS AS PEPTIDES

Schatzschneider et al. were the first to covalently binds photoactive CORM-L1 fragment $[Mn(CO)3(tris(pyrazolyl)methane)]^+$ using Pd-catalyzed Sonogashira cross-coupling and copper-catalyzed azide–alkyne 1,3-dipolar cycloaddition to amino acids and peptides. These CORM conjugates resulted in target specific in the treatment of cancer. For example, the CO-releasing peptide compound which have the five amino-acid sequence Thr-Phe-Ser-Asp-Leu (Fig. 2), which have properties of the tumor suppressor protein

p53. This peptide conjugate { Mn(CO)3(tpm)} releases 1.71 mol CO per mol Mn (as observed in myoglobin assay of phosphate-buffered solution). IR vibration bands are observed at 2048 and 1941 cm^{-1} , which represents CORM-L1 moiety.

CORMS AS POLYMERS:

Nanosized polymer conjugate were first synthesized by Hubbell et al.For the slow diffusion of CO to the target site, polymeric micelles with conjugated CORM-3 were formulated. This micelles were designed from a troblock copolymer poly(n-butylacrylamide), (PEG-bl-OrnRu-bl-nBu) of poly(ethylene glycol) and poly[Ru(CO)3Cl (ornithinate acryl amide)].In this micelles have diameter of 30–40 nm. This micelles were stable in water & serum, liberates CO slower than CORM-3 itself .CORM-3 liberated 0.124 mol CO per mol CORM over a period of two hours but from the micelles in the same duration only 0.05 mol CO per mol CORM was released. These micelles have huge loading capacity as evident from myoglobin assay. Another advantage is size of the micelle can be controlled and so it will be easy to formulate.This micelles due to hydrophilic PEG toxicity will be reduced.

CORMS AS NANOPARTICLES

Silicium dioxide nanoparticles was studied by Schatzschneider,they are obtained by the attachment of PhotoCORM-L1 via a copper-catalyzed azide–alkyne 1,3-dipolar cycloaddition. The major advantages of this nanoparticles were the ease in synthesis, controllable size distribution, and biocompatibility. In a recent study revealed that an organic photo-CORM191 loaded with electro spun poly(ε-caprolactone) scaffolds could serve as a nontoxic, biocompatible CORM, that liberates CO when exposed to visible light(470 nm).This CORM used for tissue-engineering of small-diameter vascular grafts.

CORM AS DENDRIMERS AND MOFS

Metallodendritic photo CORM which was synthesized by Smith et al. have the property to act as drug carrier. This photo corm can accumulate by enhanced permeability and retention (EPR) effect in tumor tissue. On the basis of photoactive CORM fragments, the CORM-dendrimers liberated are between 8 and 15. CO ligands per dendrimer molecule (that is two CO ligands per CORM unit.

CORM TOXICITY

Endogenous CO production from heme catabolism producing 1% of CO-Hb.CO in low doses is considered safe. on the other hand, Higher dose of CO exposure is considered to be toxic. 15–20% CO-Hb may cause mild symptoms, for example headache and nausea, but fatal effects can be seen at levels >20% and death can occur when the levels are greater than 60%.

Due to the toxic effects of CO, CORMs have been designed to provide increased CO concentrations for the treatment without producing toxic CO-Hb levels. CORM-2 and CORM-3 which generates CO-Hb levels lower than the acceptable limits of FDA (12–14.5%). However, regarding the cytotoxicity of CORMs persist after CO release. According to Seixas et al. CORM-2 and CORM-3 have reported that they induced hem agglutination and were hemolytic in nature. CORM-2 can disturb vitamin D3 metabolism in mice and can produce eryptosis in erythrocytes, which leads to anemia and it has reported marked cellular toxicity by decreasing cell viability, mitochondrial enzyme activity and causing cell death in cardiomyocytes. Moreover, therapeutic windows for CORM-2 appears to be narrow in respect to cardio protection and CORM-2 and -3 produces ROS. Ruthenium-based CORMs ,chromium-CORMS, molybdenum-CORMS, and tungsten-containing CORMs causes severe damage of liver and kidney. When mice are exposure for a longer duration to CORM-2 cause lymphocyte accumulation .

Motterlini et al. have reported that by increasing the water solubility and controlling the rate of CO release of several iron-containing CORMs (CORM-307,) can assist in limiting potential harmful side-effects [129]. Development of compounds that release CO in specific tissue is another approach being considered to reduce unwanted toxicity. Such compounds include Photo Corms which release CO only when irradiated with light enzyme triggered-CORMs which are activated intracellular, for example, by esterase activity and CORMs covalently attached to carriers such as nanoparticles, micelles, or dendrimers Others have opted to circumvent possible metal-based toxicity by developing transition metal-free CORMs such as CORM-A1 [135]. +e continued work in this area and rational design of CORMs, particularly with careful consideration of the “drug sphere” of these molecules, are vital to the development of safe and therapeutically useful CORMs.

Pharmacological action	DOSE	Activity of CORM'S
Wound healing in mice	Not tested	CO-RM2 at 8mg per kg, intravenously attenuates leukocyte infiltration and kidney injury
Rheumatoid arthritis in mice	Not tested	CO-RM3 administered once a day from days 22 to 31 reduced joint inflammation and erosion in CIA
Renal vascular resistance and acute renal failure in rabbits and rats	20 ppm for 30 days or 1 h per day prevents CAN	CO-RM3 to perfused kidneys improves renal microcirculation; CO-RMA1 improves renal haemodynamics; intrarenal CO-RM1 increases GFR; CO-RM2 dilates afferent arterioles
Myocardial infarction in mice; cardiac IRI in rats	250–1,000 ppm after injury prevents infarct mass induced by left anterior descending artery ligation	CO-RM3 reduced injury from myocardial infarction
Angioplasty trauma in rodents and pigs; vascular access graft hyperplasia in pigs	250 ppm for 1h before injury prevents stenosis and enhances re-endothelialization	CO-RMA1 administered 1 h before injury enhances re-endothelialization
Cardiac graft rejection in mice and rats; mouse to rat xenografts	250–400 ppm for 5–6 days prevents rejection	CO-RM3 prolongs graft survival 20 ppm prolongs survival
Lung allograft rejection in rats and mice; IRI in rats and mice	Not tested	250 ppm prevents chronic rejection, IRI and apoptosis
Aortic allograft rejection in mice and rats	250–400 ppm prevents transplant vascular stenosis	CO-RM2 prolongs aortic graft survival
Kidney and liver preservation in rats; kidney IRI in rats; hindlimb ischaemia-induced liver failure in rats; CAN in rats; delayed graft function in swine	Saturated preservation solution prevents IRI; 250 ppm prevents injury following hindlimb ischaemia; 20 ppm prevents and acts therapeutically in CAN; saturated blood improves liver function after transplant; 3 mg per kg improves renal function after treatment	CO-RM3 (50 μM) in preservation solution improves liver and kidney function after transplant Saturated preservation solution prevents IRI
CD1 athymic mice xenotransplanted with pancreatic cancer cells	500 ppm for 24 h inhibited tumor proliferation and microvascular density of xenotransplanted tumors	CORM2 treatment (5 mg/kg per day) for 3 days inhibited tumor proliferation and microvascular density of xenotransplanted tumors.

Table 1: THERAPEUTIC ACTIVITY OF CO-RM'S

CONCLUSION:

In near future development of metal-based CORMs is on its way we see more advanced and well-targeted corm molecules. In this view,we can select the proper CORM for the therapeutic activity, based on CO-releasing profile and pharmacokinetic behaviour. Overall, appropriate designing and synthesis of novel corm molecules could reduces drug load for patients.

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