Protective Strategies Against Cadmium Chloride-Induced Hepatic Injury: Role of Antioxidants and Experimental Evidence

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***Abstract*—Cadmium chloride (CdCl) is among the most toxic heavy metals in the environment and is extremely harmful even in very small concentrations due to prolonged biological half-life and cumulative characteristics. Something important in cadmium contamination of environment has been rapid industrialization and mining, metal coating (electroplating), production of batteries, pigment synthesis, phosphate fertilizers and use of tobacco as these have been the major ways of introducing cadmium into the air land water, agricultural products, etc. Cadmium exposure leads to deposition mostly in liver and kidney tissues from where it slowly moves out and affects other target organs too. Since the liver has been described as one of the major organs of processing foreign compounds (xenobiotics), neutralizing the foreign body's toxins (detoxification), metabolizing nutrients and managing bodily metabolism, it is most targeted organ in cadmium toxicity. Oxygen free radicals are key in liver cell death (hepatocytelysis) by CdCl via mechanisms such as depletion of antioxidant reserves, generation of intracellular ROS (reactive oxygen species) inflammation DNA damage, peroxidaion in lipids, and apoptosis at the cell level. Experimental studies have been reporting high levels of hepatic enzymes in blood, extensive changes at the tissue level (histopathology), mitochondrial damage and liver fibrosis due to cadmium exposure. These changes are the result of an overall weakening of liver function by the cadmium and may lead ultimately to liver-related illnesses or even liver cancer. This paper reviews the present literature on the use of antioxidants to counteract cadmium-induced damage to the liver. Focus areas included the measurement of oxidative stress, the role of endogenous anti-oxidant defenses, the microscopic appearance of liver tissues before and after cadmium exposure, the molecular basis of hepatic protection, and the newest treatment possibilities of liver injury due to cadmium. The review also outlines the shortcomings of present research, translational barriers, and the future directions which will hopefully lead to new prevention and therapies for liver damage caused by cadmium.**

***Index Terms*—Cadmium chloride, Hepatotoxicity, Antioxidants, Oxidative stress, Reactive oxygen species, Liver injury, Phytochemicals, Experimental models, Inflammation, Mitochondrial dysfunction, Apoptosis, Therapeutic strategies**

I. Introduction

We are living in an era of rapid industrialization, urban expansion, agricultural intensification and increase in various human activities which result in a very serious pollution by heavy metals and the consequences with human health. One of the heavy metals to be toxic is cadmium (Cd) and it has been identified as a very dangerous environmental pollutant from its non-biodegradable character, easy bioaccumulation, and extremely toxic effects even at the low concentrations. While essential micro-nutrients like zinc, copper, and iron are key in physiology, there's no known physiological role of cadmium for living organisms. Prolonged exposure Still causes accumulation and dysfunction of various tissues and organs - In particular liver and kidneys. There are a number of chemical forms for cadmium. Among others, cadmium chloride (CdCl2) is widely used as an example of water-soluble toxic substance mainly due to its quick absorption and the reproducibility of the toxic effects[1-2]. A couple of examples of CdCl2 industrial use

are electrodeposition, color production, Ni-Cd batteries, and so on. The major factors which have contributed to environmental contamination by cadmium are inappropriate removal of industrial effluents from industries, mining operations, burning of fossil fuels, incineration of city waste, and the overuse of phosphate based fertilizers.Exposure of cadmium to humans mainly happens by the intake of contaminated foodstuffs through gastrointestinal tract and drinking water. Cigarette smoking may also lead to one type of human-body contact with cadmium. Also, inhalation is quite common in the workers who have occupational hazards. Pollution from the air and water, That means, may be also the sources of cadmium entering the human body. As a major means of cadmium exposure, the ingestion of contaminated dietary sources accounts for almost all general population's exposure to cadmium while occupational exposure is, on the contrary, more typical for the workers involved for example in mining, electrolyzing metals in solution, making batteries, working in welding, and pigment industry. It is well-known that the plant tobacco has the capacity to accumulate cadmium if it is grown in cadmium-contaminated fields which explains that smokers have Really higher cadmium content in blood and tissues compared to non-smokers. Killing cells or making them sick is among cadmium's main capabilities, a poison so potent that the smallest exposure in a very concentrated solution can cause death in the first few seconds[3-4].After absorption via the gut or pulmonary route, cadmium gets into the general circulation and mainly is deposited in the liver. There hepatocytic production of metallothionien continues which is a small-molecular-weight protein rich in cysteine that functions in binding the heavy metals. Metallothionein sequestration of the freely moving cadmium ions is known to provide some temporary relief from heavy metal toxicity. However, if the exposure has been long and the amount of heavy metal is large, it's quite impossible for even metallothionein to prevent the accumulation of cadmium. All in all. This means that the accumulation of intracellular cadmium would initiate the processes of oxidative stress, generation of inflammatory mediators, mitochondrial defects, loss of calcium homeostasis, disruption of the endoplasmic reticulum, the death of cells through programmed cell death (apoptosis), organ fibrosis, and interference of major biochemical events within the cell. Oxidative stress in general is a major step in the mechanism of cadmium toxicity for the liver. Cadmium indirectly results in reactive oxygen species (ROS) overproduction through various processes such as disturbance of mitochondrial electron transport chains, decreased activity of antioxidant enzymes, depletion of reduced glutathione, and the substitution of essential trace elements metalloenzymes. As a consequence, reactive oxygen species may be responsible for damaging the structural and functional integrity of the cellular components such that the liver cell gets more and more disturbed and injured[5].

During cadmium poisoning, various intracellular signaling pathways are activated like Nuclear factor - Kappa B (NF - B), Mitogen - Activated Protein Kinase (MAPK), Phosphatidylinositol- 3 - Kinase/ Protein Kinase B (PI3K/ Akt), Transforming Growth Factor - Beta (TGF -), c-Jun N-terminal Kinase (JNK), and Nuclear factor erythroid-2 related factor-2 (Nrf2). The activation of these different mechanisms leads to the generation of proinflammatory cytokines, cell death via apoptosis, accumulation of extracellular matrix, and fibrosis with the suppression of body's own antioxidative defense system. This set of molecular changes leads to serious damage of liver structure and functions.Better antioxidant therapies have been made possible because of recent developments in nanotechnology and targeted drug delivery. The formulations of nano-particles of herbal compounds and trace elements are characterized by higher availability, better targeting of tissues, and more effective therapy than are conventional forms. Combination of metal chelators with antioxidants has produced synergistic protective effects in several animal models[6].

This article has been compiled to provide updated information in a single place of antioxidant - mediated protective interventions against CdCl2-induced liver damage. Particular attention is paid to the animal models used, the oxidative stress markers, the native antioxidant systems, the histopathological changes, the molecular pathways of liver protection and the new treatment methods. Also, the challenges of existing research and the areas of future work, which will translate the findings from animal studies to human, are addressed here.

II. Experimental Models and Oxidative Stress Biomarkers

To reveal the cadmium chloride (CdCl) mechanism-induced hepatic toxicity, it is necessary to have experimental models that can replicate the pathological, biochemical, and molecular changes that occur in the human liver accurately. Animal models and in vitro cell culture systems are now considered a gold standard for cadmium toxicity studies, discovering biomarkers of early detection of injuries occurring in the liver, or testing and developing antioxidant therapy interventions. Data obtained from models can explain, the level at which toxic chemicals harm body is directly related to dose of the toxicity, signaling pathways on the molecular level of the toxicity, how the liver looks structurally when injured and even the preventive role that can be played by natural and man-made antioxidants[7-8].

2.1 Experimental Models for Cadmium-Induced Hepatic Injury

Animal models are still essential in toxicological research because they enable scientists to determine, on a holistic level, what changes happen in physiology, biochemistry, and histology after cadmium is introduced. Rodents like rats and mice have been the primary animals used in experiments because of their genetic closeness to humans, relatively short life cycle, ease of taking care of as lab animals, and consistent reactions when different poisons act on them[9].

2.1.1 Rodent Models

Albino Wistar rats and Sprague-Dawley rats are the most commonly used rodent models to investigate CdCl-induced hepatotoxicity. Administration of cadmium chloride is typically done via orally through drinking water, directly by a tube or syringe, or by injecting the substance below the surface of the abdomen or the skin. Experimental doses depend on study goals and generally range from low chronic exposure (1, Experiment period usually lasts from just a few days to a few months, which allows both acute and chronic toxic effects to be assessed[10-11].

In rodents, these findings are a consistent result of administering cadmium: liver enzymes activity is higher than normal, there are more free radicals in the liver, pro-inflammatory responses, liver cells are unable to produce energy (mitochondria function is impaired), there is cell injury to hepatocytes, and fibrotic tissue is formed. In addition, these models allow testing of the effects hepatoprotectors.

2.1.2 Mouse Models

In addition to being great animal models, they can also shed light on how cadmium toxicity is controlled at the genetic and molecular levels. With knockout and transgenic mice, it has become an easy task for researches to find out functions of genes that could regulate oxidative stress apoptosis inflammation, and metal metabolism through experiments.-12-13] Nrf2 knockout mice showed more sensitivity to cadmium's oxidative effects. This shows that antioxidant pathways are key in protecting the liver.Another illustration of this is Truth is mice without metallothionein genes accumulate more cadmium in their livers resulting in more severe liver damage. This further proves that metallothioneins help in heavy metal detoxification.

2.1.3 Cell Culture Models

The results obtained in the laboratory setting using isolated cells will give much more detailed and comprehensive picture of cellular molecular processes without the influence of a complex organism. Cultivation of human HepG2, primary hepatocytes and AML-12 mouse hepatocyte cell are the main approaches to study oxidative stress, inflammatory pathways, programmed cell death, apoptosis, and mitochondrial function caused by cadmium.Cultivation of cells under laboratory conditions will help to define the effect of the dose (low vs high) very precisely without much variation between different experiments[14]. The use of molecular inhibitors, gene silencing methods, and recombinant proteins makes it possible to investigate the effects of particular signaling pathways, like the p53 or the MAP kinase pathway on cell activity. Even though it is not possible to fully mimic human physiology by a single in vitro testing, these are among the best alternatives to the testing on animals which are necessary for the study of mechanisms of action of various liver protecting drugs.

2.1.4 Emerging Experimental Models

The latest developments in the area of biomedical research have led to the generation of three-dimensional liver organoids, precision-cut liver slices, a new kind of laboratory model called liver-on-chip which mimics human liver functions, etc. Compared with classic animal models, these techniques offer a closer representation of the human liver for structural and physiological microenvironment that allows for an enhanced evaluation of cadmium toxicity as well as therapeutic interventions. Ultimately, they could be a very attractive solution, as animal experiments are avoided and highly translational data about humans' liver diseaare provided[15-16].

2.2 Experimental Assessment of Hepatotoxicity

The determination of cadmium-induced hepatotoxicity needs the combination of various analytical methods including biochemical histopathological molecular, and ultrastructural aspects of analysis. Liver enzyme function tests in serum, activities of antioxidant enzymes, concentrations of inflammatory cytokines, biomarkers of oxidative stress, histological inspection, immunoassays of biotissues, ultrastructural (TEM) examination, and gene expression profiling work together to explain the picture of liver damage and toxic reaction as a full-spectrum disease. Evaluation of biomarkers of oxidative stress has become a very important method in particular as the damage by free radicals seems to have been the triggering event in most of the downstream changes seen in liver tissue of animals treated with Cd[17].Of the described methods, assessment of oxidative stress biomarkers has become Mainly important, as oxidative damage represents the initiating event responsible for nearly all other pathological changes occurring due to cadmium exposure.

2.3 Oxidative Stress Biomarkers

Oxidative stress occurs when the generation of reactive oxygen species (ROS) becomes greater than the cells' ability to neutralize them with antioxidants. One way Cadmium can cause a rise in ROS is by disturbing mitochondrial respiration, antioxidant enzyme inhibition, and glutathione depletion. As a result, various biochemical markers were found useful to assess oxidative injury in cadmium-induced poisoning experiments[18].

2.3.1 Reactive Oxygen Species (ROS)

Cadmium-induced oxidative stress begins with the generation of reactive oxygen species (ROS). The main ROS that are formed after CdCl2 exposure are the superoxide anion (O), hydrogen peroxide (HO), hydroxyl radicals (OH), and singlet oxygen. Higher concentrations of intracellular ROS can bring lipid per oxidation, protein oxidation, nucleic acid damage, and mitochondrial dysfunction[19].

2.3.2 Lipid Peroxidation

Lipid peroxidation among others is one of the consequences of oxidative stress which most researchers have studied. ROS molecules hit polyunsaturated fatty acids inside a cell membrane and then set off a cascade that eventually destroys a membrane and leads to a breakdown of cell functionalities.

Malondialdehyde (MDA)

Malondialdehyde is considered a primary tool for detecting lipid peroxidation by measuring the levels of MDA. High levels of hepatic and serum MDA due to cadmium intoxication, on the grounds of many studies, have been reported to result in marked hepatic damage due to the action of oxidative stress. Also, the results of many laboratory experiments show that a significant rise in levels of MDA was a good marker for liver damage on the histopathologic scale.

4-Hydroxynonenal (4-HNE)

4-Hydroxynonenal, a reactive aldehyde, is one of the major toxic products formed by lipid peroxidation. It has the ability to bind proteins, DNA, and phospholipids, which later leads to alteration of the normal functions of enzymes and the cell communication mechanisms. Elevation of 4-HNE in the liver is a hallmark of chronic oxidative damage[20].

2.3.3 Glutathione (GSH)

Reduced glutathione plays a major non-enzymatic part as a intracellular antioxidant that works by detoxifying reactive oxygen species (ROS) On one side, and maintaining redox balance on the other. This heavy metal binds very easily to sulfhydryl groups with such strength that it rapidly ties up glutathione leaving the cell unable to maintain its GSH reserves at a healthy level.Cadmium-induced depletion in glutathione levels in the liver is a characteristic change at the chemical level very commonly seen soon after exposure. Treatment of antioxidants has brought about the restoration of glutathione concentrations which is Because of this seen as a sign of effectiveness of hepatoprotection.

2.3.4 Superoxide Dismutase (SOD)

Superoxide dismutase, enzyme that catalyzes production of hydrogen peroxide from superoxide radicals, is the first line of enzymatic antioxidant defense. Cd is able to replace metal cofactors essential to the enzymatic activity like zinc and copper by its toxicity. That means SOD activity is diminished.Several studies performed in animals show that exposure to CdCl leads to remarkable decreases in liver superoxide dismutase activity. The recovery of SOD activity after taking antioxidants shows that cells are now more protected from the oxidative injury.

2.3.5 Catalase (CAT)

The hydrogen peroxide is broken down by catalase into water and molecular oxygen, thereby inhibiting the production of highly reactive hydroxyl radicals. The suppression of catalase caused by cadmium leads to a rise in the levels of hydrogen peroxide indoors and as a result it gets more oxidative stress.The suppression of catalase activity has been reported in numerous cadmium-induced liver toxicity animal models and has often been connected to high levels of lipid peroxidation..

2.3.6 Glutathione Peroxidase (GPx)

Glutathione peroxidase, a selenium-dependent enzyme, neutralizes hydrogen peroxide and lipid hydroperoxides by using reduced glutathione as the oxidizing agent. So, a deficiency in the level of this important trace mineral in the body may have serious consequences for GPx activity. Besides inhibiting the selenium-dependent GPx activity, cadmium may also affect its function by disturbing selenium metabolism in other ways.A diminished level of GPx activity leads to an increase in hydrogen peroxide and So, more oxidative damage occurs during exposure to cadmium[21].

2.3.7 Glutathione Reductase (GR) and Glutathione-S-Transferase (GST)

Glutathione reductase is mainly responsible for reducing glutathione and converting oxidized glutathione (GSSG) back to the reduced form. Conversely, glutathione-S-transferase performs detoxification by conjugating glutathione with various electrophilic toxic compounds.Cadmium is a heavy metal and when exposure occurs data shows it Really lowers the activities of both the enzymes leading to weaker detoxification capability and the body getting more damaged oxidatively.

2.3.8 Protein Oxidation Biomarkers

Oxidative stress changes the amino acid sequences of some proteins causing protein carbonyl derivatives which are used as stable biomarkers of oxidative damage. Higher levels of protein carbonyls show irreversible oxidation of structure proteins and enzymes.Advanced oxidation protein products (AOPPs) are other parameters that are routinely used to reflect cadmium-induced protein oxidative injury.

2.3.9 DNA Oxidative Damage

It is a fairly well established fact that oxidative modification of DNA really helps in the development of cadmium-induced mutagenesis and carcinogenesis. 8-Hydroxy2'-Deoxyguanosine (8-OHdG) has been considered as one of the main and common indicators of genotoxicity. This compound, when formed in DNA, is a sign of oxidation of the guanine bases and is an indication of DNA oxidation damage.Increase in the amount of liver 8-OHdG implies high DNA instability and deficient DNA repair after longterm cadmium exposure.

2.3.10 Nitric Oxide and Reactive Nitrogen Species

Cadmium-induced inflammation sets in motion the synthesis of inducible nitric oxide synthase (iNOS), leading to copious nitric oxide production. Nitric oxide then interacts with superoxide radicals to create peroxynitrite (ONOO)a very potent oxidant agent capable of causing protein, lipid and DNA breakdown.Detection of nitric oxide metabolites and iNOS activity is, That means, a good indication of oxidative and inflammatory processes[22].

2.4 Significance of Oxidative Stress Biomarkers

Estimation of oxidative stress biomarkers gives the researcher a good idea about the degree of cadmium-induced liver injury, and the extent of therapeutic interventions' benefits. The increase in ROS MDA 4-HNE, protein carbonyls, nitric oxide, and 8-OHdG, plus the decrease in GSH SOD CAT GPx GST, and GR activity, altogether indicate oxidative damage as a pivotal mechanism of CdCl-induced hepatotoxicity.

III. Antioxidant Defence System and Histopathological Findings

3.1 Antioxidant Defence System

Among various organ systems, the liver stands out as one with one of the most complex and well-balanced antioxidant defense mechanisms which are crucial for defending the liver cells or rather the hepatocytes against those reactive species called reactive oxygen species (ROS). These types of ROS are normally produced as part of the body's normal metabolism and also as a response to being introduced to or exposed to the environment's toxic substances. The main protective system of this type consists of a combination of enzymatic and non-enzymatic types of antioxidants, metal-binding proteins, as well as redox-regulated pathways of signaling which altogether safeguard the body from oxidative stresses by maintaining the balance of redox within the cells. Still, exposure to cadmium chloride (CdCl) can cause the disorganization and failure of these protective functions. This takes place when ROS production is enhanced, antioxidant substances are depleted endogenously, and the levels of antioxidants enzymes are being reduced[23]. The consequence of such a failure to manage is that oxidative stress takes on the role of the main reason of the liver cell injury, inflammation of the liver, functional decline of mitochondria, apoptosis or programmed cell death, and the condition called fibrosis where the tissue hardens and scarring sets in.

3.1.1 Enzymatic Antioxidant Defence

Superoxide Dismutase (SOD)

Superoxide dismutase is regarded as the body's primary enzymatic antioxidant defence system against excessive reactive oxygen species (ROS) which results in oxidative stress and This way damage to the tissues, cells and organs. This is so as Superoxide dismutase is the enzyme that converts the superoxide O radical into harmless water and hydrogen peroxide. In doing so, it inhibits the formation of one of the most aggressive radicals, the hydroxyl radical, which causes major damage in biological systems. The three types of SODs present in mammalian tissues are cytosolic Cu/Zn-SOD (SOD1), mitochondrial Mn-SOD (SOD2) and extracellular SOD (SOD3). Metals such as cadmium are not only capable of replacing essential metal cofactors (Cu and Zn) from the enzymes, but also cause the oxidation of the protein portion of the enzyme which would Quite a bit decrease the rate of reaction (the k cat) by the enzyme.Hundreds of experiments have found that giving CdCl results in significant lowering in SOD levels in the liver. It is now recognized that SOD activity can be taken as one of the biomarkers of hepatoprotective effect by showing that the level of antioxidants is increasing after the treatment with the anti-oxidants. In fact, this is considered very reliable.

Catalase (CAT)

Catalase is an antioxidant enzyme that contains haem and is mainly found in peroxisomes. It catalytically breaks down hydrogen peroxide to water and oxygen This way preventing the formation of highly reactive hydroxyl radicals by Fenton-type reactions.Cadmium exposure Really reduces catalase activity since enzyme proteins get oxidatively modified and the redox balance becomes disturbed. The decline in catalase activity results in hydrogen peroxide accumulating within a cell and this increases the oxidative damage

occurring to the lipids, proteins, and DNA.In reality the giving of some natural antioxidant substances - like curcumin quercetin vitamin E, selenium and silymarin - brings about the recovery of catalase activity and the alleviation of cadmium-induced oxidative damage in animals had been validated through a number of experimentations.

Glutathione Peroxidase (GPx)

Glutathione peroxidase enables the breakdown of hydrogen peroxide and different types of lipid hydroperoxides with reduced glutathione (GSH), acting as a substrate. In this case, selenium acts as a necessary helper (a cofactor), without which the activity of GPx cannot carry on at all.Cadmium can block the work of GPX because the toxic compound may replace selenium in the enzyme. Also, cadmium lowers glutathione level, causing an imbalance between oxidizing and reducing agents resulting in oxidative damage to the enzyme. As a consequence of this inhibition, GPx activity is Really lowered and the level of oxidative stress increases leading to an imbalance between reactive species and the organism's scavenger systems with lipid peroxidation being among the results. Eventually, this oxidative damage might cause progressive hepatic structural changes (degeneration).Administration of antioxidants is proven to restore GPx activity. This observation has been made in many experiments and emphasizes the crucial role of GPx in the protection of the liver.

Glutathione Reductase (GR)

This enzyme uses NADPH to reduce oxidized glutathione (GSSG) by donating electrons to it, generating reduced glutathione. Glutathion reductase plays an essential role in maintaining the level of glutathione within cells at an optimal point so that the antioxidant system does not get exhausted.It is a fact that the effect of cadmium on liver cells has been linked with the inactivation of glutathione reductase, the enzyme is essential in regeneration of glutathione.

Glutathione-S-Transferase (GST)

Glutathione-S-transferases are an enzyme family that plays a role in detoxification by catalysing the conjugation of glutathione with electrophilic toxic substances. This reaction results in facilitating removal of xenobiotics and lipid peroxidation byproducts.In general, exposure to cadmium is accompanied by a reduced GST activity. Detoxification processes are, as a result, impaired, and oxidative damage is more likely. So it comes as no surprise that the recovery from reduced GST activity is among the top reasons why an antioxidant-mediated hepatoprotection is sought.

3.1.2 Non-Enzymatic Antioxidant Defence

Reduced Glutathione (GSH)

Intra-cellularly reducing type glutathione is the major natural antioxidant agent which acts in coordination with various intracellular redox signaling pathways, In particular that involved in controlling liver function. GSH itself quenches harmful radicals, neutralizes dangerous electrophilic compounds, stabilizes thiol-redox state, reactivates antioxidant vitamins, and is involved in the multitude of metabolic processes.Cadmium preferentially interacts with sulfhydryl (-SH) groups and, upon binding, swiftly consumes large amounts of intracellular stores of glutathione. Scarcity of reducing type glutathione strongly impairs antioxidant protection and, as a consequence, the production of reactive oxygen species is greatly enhanced.Quite a few different laboratory setups have been employed to verify how antioxidant supplementation elevates the level of glutathione in liver cells and Much lessens toxic liver effects caused by heavy metal cadmium[24].

Metallothionein (MT)

Metallothioneins are heavy metal (such as cadmium, zinc and copper) binding proteins that have low molecular weight and high cysteine content. Such proteins are considered to play a significant part in the adaptive defense mechanisms at the beginning levels cadmium exposure.After cadmium reaches hepatocytes, metallothionein synthesis is increased very fast under the control of a metal-responsive transcription factor-1 (MTF-1). In beginning, MT limits toxicity by removing cadmium ions and decreasing their interaction with most cell proteins.Yet, long-term exposure ultimately leads metallothionein capacity to

exhaustion, causing an increase in the levels of free cadmium ions in intracellular which can initiate extremely harsh oxidative stress.

Vitamin C (Ascorbic Acid)
Vitamin C is a water-soluble compound of the group of antioxidants. It works directly by capturing reactive oxygen species as well as being a regenerator of oxidized vitamin E. Based on the experiments, research shows that supplementing with vitamin C can markedly reduce peroxidation of lipids and also enhance activities of antioxidant enzymes in a situation of cadmium intoxication.

Vitamin E (α-Tocopherol)
Vitamin E is the main lipid-soluble antioxidant that fights off lipid peroxidation of biological membranes by breaking down the free radical chain reactions in membrane phospholipids.Many animal studies show that giving subjects vitamin E leads to less production of malondialdehyde, better maintenance of membrane integrity, and more improvement in liver pathology following cadmium exposure.

3.1.3 Nrf2-Mediated Antioxidant Signalling

Cadmium-induced oxidative stress is prevented First and foremost by the natural Nrf2-Keap1 signaling pathway that protects the organism with the help of antioxidants. When cells encounter oxidants, Nrf2 is liberated from Keap1 complex and Nrf2 is shuttled into the nucleus where it binds to antioxidant response elements (AREs) that lead to the expression of defensive proteins (cytoprotective genes), including HO-1 NQO1 glutathione-S-transferase, superoxide dismutase, catalase, and glutathione peroxidase. Besides suppression of Nrf2 function by protracted cadmium exposure, some plant extracts (curcumin resveratrol quercetin, sulforaphane) through the activation of the same pathway, enhance the body's antioxidant response.

3.2 Histopathological Findings

The use of histopathological examination is not likely to be changed as it is still the best approach for assessingCdCl-induced hepatic injury. One reason is that histopathological changes almost invariably correlate with biochemical and molecular markers of liver malfunction. Cadmium toxicity at the cellular level in early stages mainly appears as in the form of cellular swelling, cellular granulation, hydropic and vacuolar degeneration, and various nuclear shape changes (irregular) - all pointing toward a cellular recovery which is possible at least on the surface. Prolonged exposure to the highly toxic metal cadmium leads to a breakdown of the microcirculation in the liver. This then leads to the sinuses being filled with excess blood, central and portal vein congestion, interstitial edema, and a decrease in the blood flow through the liver, which all in turn lead to a state of increased oxidative stress. From a cascade reaction, activation of Kupffer cells leads to the entry of neutrophils, macrophages, and lymphocytes into the liver tissue, which is concomitant with the expression of various inflammatory mediators like TNF-, IL-1, IL-6, COX-2, and NF-B.

3.3 Experimental Evidence Supporting Antioxidant-Mediated Hepatoprotection

A growing body of research has revealed that antioxidant treatment can Much improve liver damage caused by CdCl. Nature's bounty with various antioxidants like curcumin quercetin resveratrol, silymarin rutin hesperidin lycopene epigallocatechin gallate, vitamin C, vitamin E melatonin selenium zinc N-acetylcysteine, and coenzyme Q10 regularly increase antioxidant enzyme activities, reduce lipid peroxidation, control the release of pro-inflammatory molecules, maintain mitochondrial structure, limit programmed cell death, and reverse liver histopathology in laboratory rodents.The protective effects of these substances against liver damage operate via a series of intertwined mechanisms[25]. For instance, they trigger the Nrf2/ARE signaling which increases the production of antioxidant enzymes, hinder the NF-B and MAPK pathways that are responsible for inflammation and apoptosis, preserve glutathione levels which is an essential antioxidant, reinforce mitochondrial membranes, prevent apoptosis by caspases, and limit the deposition of collagen in the liver. In addition, liver samples of treated animals show a significant decrease in hepatocyte necrosis, congestion in the sinusoids, infiltration, and development of fibrosis relative to untreated cadmium-exposed controls.Merged together, these data are in favor of the idea that improving the

body's own defenses against oxidative stress should be considered as one of the key strategies to prevent or slow down cadmium chloride-induced. To move the field forward, upcoming studies are encouraged to work out efficient dose regimens, investigate synergistic effects of various antioxidant therapies, and confirm the efficacy of these treatments through clinical trials.

IV. Future Perspectives

Future research should emphasize the translation of the encouraging results from experiments to the development of effective, clinically relevant treatment options for cadmium-induced hepatotoxicity. There is a need for thorough, well-conceived, preclinical and clinical trials to determine the safety effectiveness pharmacokinetics, and optimal dosing of natural antioxidants as well as combination therapies. New developments that use nanotechnology-enabled drug delivery systems, targeted antioxidant compositions, gene therapy and the activation of cellular protective mechanisms like activation of Nrf2/ARE hold great promises towards improved treatment modalities. Also, the detection of early molecular markers, such as microRNAs, epigenetic modifications metabolomics proteomic markers could assist in identification of diseases in early stages and provide patients with personalized therapies. In addition, scientists should work on unraveling the potential of phytochemicals combined with the standard chelating drugs and the mechanisms of phytochemicals that are responsible for synergistic effects. It is equally important to conduct toxicity assessments over time as well as understanding the effects of environment and genetic factors on cadmium-induced diseases. An effective cross-disciplinary research collaboration including toxicology, molecular biology, pharmacology, and clinical medicine would be fundamental for creating and delivering efficient both preventive and therapeutic options for liver damage by cadmium.

V. Conclusion

Cadmium is a heavy metal toxic to human. Its chloride form causes hepatotoxicity due to the combined effects of various mechanisms of the liver injury like oxidative stress inflammation mitochondrial dysfunction, apoptosis, and liver tissue structure changes. The available literature clearly shows that cadmium causes depletion of endogenous antioxidant defences, resulting in increased production of reactive oxygen species, lipid peroxidation, production of inflammatory cytokines, and destruction of hepatocytes. Many natural and synthetic antioxidants like curcumin quercetin resveratrol silymarin vitamins C and E selenium zinc, melatonin, and N-acetylcysteine have displayed considerable hepatoprotective activities by enhancing the activities of antioxidant enzymes, regulating Nrf2 signaling, suppressing inflammatory pathways, and maintaining liver histology. It must be noted though that while these results are quite positive, most supporting evidence comes from studies carried out on animals, That means, there is definitely a need for translational and clinical trials. Antioxidant based treatment options are considered as a viable method for preventing cadmium caused liver injury and may even help in coming up with interventions that can manage heavy metal poisoning and related liver disorders.

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