REVIEW ARTICLE

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Cadmium Toxicity: Mechanisms of Oxidative Stress, Inflammation, and Organ Damage

Yomna A. Farahat*, Asmaa Radwan, Reem M. Hazem, Norhan M. El-Sayed

Department of Pharmacology and Toxicology, Faculty of Pharmacy, Suez Canal University, Ismailia, Egypt

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*Corresponding Author:

Tel: +201022907337

E-mail address:

yomna_abdelaziz@pharm.suez.edu.eg

Abstract

Cadmium (Cd) is present in the environment in substantial quantities as a consequence of human activities, including the incineration of metal ores, the use of fossil fuels, and the burning of waste. Cd is a persistent heavy metal that does not degrade into less toxic forms and is excreted inefficiently from the body, leading to its bioaccumulation. Exposure to Cd can cause itai-itai disease and multiple organ dysfunction, including the lungs, testes, prostate, cardiovascular system, skeletal system, nervous system, and immune system. However, the primary sites of Cd accumulation are the liver, lungs, kidneys, and bones. At the cellular level, Cd induces toxicity through several mechanisms. One of the major pathways is the induction of oxidative stress, characterized by the excessive generation of reactive oxygen species (ROS) that overwhelm the cell's antioxidant defense systems. This oxidative imbalance damages vital cellular components such as lipids, proteins, and DNA, leading to functional impairment and structural instability. In addition, Cd triggers inflammatory responses by activating pro-inflammatory signaling pathways and promoting cytokine production, contributing to chronic tissue inflammation and further exacerbating cellular injury. These disturbances disrupt cellular homeostasis and shift the balance toward cell death over survival, ultimately resulting in tissue and organ damage. This review aims to discuss the complex cellular events underlying Cd toxicity and their implications for human health.

Keywords: Toxicity; Oxidative stress; Inflammation; Apoptosis.

1. Introduction

Cadmium (Cd) is a heavy metal that serves no physiological purpose and is frequently regarded as a toxin **(Sinicropi et al., 2010)**. Volcanic activity, the gradual erosion and abrasion of rocks and soil, and forest fires contribute to the elevated concentrations of Cd in the environment. Additionally, anthropogenic sources of Cd originate from copper and nickel smelting and refining, fossil fuel burning, and the application of phosphate fertilizers. Zinc, lead, and copper mining operations facilitate the release of this metal into the atmosphere, leading to soil contamination **(Genchi et al., 2020)**.

Cadmium is also involved in the industry of daily products, including batteries, pigments, PVC stabilizers, metal coatings, alloys, television screens, lasers, water pipes and cosmetics **(Bernhoft, 2013)**. Moreover, smoking cigarettes is a significant source of Cd exposure. Smokers

usually have body Cd levels that are more than twice those of nonsmokers **(Wróblewski et al., 2024)**. In fact, blood samples from smokers have shown Cd concentrations that are 4–5 times higher than those found in nonsmokers, indicating a strong link between smoking and Cd accumulation **(Munisamy et al., 2021)**.

In Egypt, water contamination with Cd represents a major route of exposure, multiple studies were conducted to evaluate Nile River content of Cd and it was found that Cairo, Giza, Helwan, Beni Suef, Sohag, Qena, and Samalut have high levels of Cd in their water, with values above the recommended limits **(El-Saadani et al., 2022)**. Furthermore, water tests taken from Wadi EL-Rayan Lakes have Cd concentrations above the maximum allowable limit advised by Egyptian environmental law **(Bakr et al., 2023)**.

2. Cadmium Pharmacokinetics

The primary method of absorption following exposure to airborne particulate Cd in industrial settings is inhalation, which is a crucial pathway for tobacco users. The small intestine shows a lesser extent of absorption, with men and women absorbing approximately 5% and 10% of Cd from the gastrointestinal tract, respectively **(Nordberg & Nordberg, 2022)**.

According to the particle size, only 5–10% of the consumed Cd is absorbed. Persons with iron, calcium, or zinc deficiencies have higher intestinal absorption **(Bernhoft, 2013)**. Once in the body, Cd is transported into the bloodstream via alpha-2-macroglobulin and albumin and is then accumulated in kidneys and liver. It is also concentrated in the pancreas, spleen, heart, lung, and testis. Cd is excreted from the body slowly via the kidneys, saliva, urine, and milk during lactation **(Tinkov et al., 2018)**.

Cadmium has a half-life around 25 to 30 years and accumulates in both plants and mammals. This long half-life allows Cd to accumulate in the human body throughout the lifetime, so its unique cumulative nature helps it to deposit in liver and kidney making them the most targeted organs **(Bernhoft, 2013)**. Brain, nervous system, immunity, cardiovascular system and gastrointestinal system are all affected by Cd exposure **(Niture et al., 2021)**.

3. Cadmium Toxicity

Cadmium doesn’t break down into less hazardous forms and is excreted poorly. The liver, kidneys, lungs, testes, prostate, heart, skeletal system, neurological system, and immune system are the primary organs affected by Cd toxicity. Moreover, the primary reservoirs for Cd are the liver, lungs, bones, and kidneys **(Das & Al-Naemi, 2019)**.

Consequently, itai-itai illness, osteomalacia, osteoporosis, bone fractures, significantly compromised renal function, emphysema, anosmia, chronic rhinitis, hepatic and cardiovascular disorders, testicular dysfunction, and cancer are linked to Cd poisoning **(Moroni Gonzalez et al., 2023)**. Furthermore, Cd can induce chronic rhinitis, eosinophilia, anemia and non-hypertrophic emphysema **(Valko et al., 2005)**. Cd has been linked to the development of cancer and has been classified as a type I carcinogen by the International Agency for Cancer Research. This is in addition to its direct cytotoxic effects, which could cause an apoptotic or necrotic event **(Arroyo et al., 2012)**.

4. Cadmium mechanisms of toxicity

4.1. Oxidative stress

Pathology of Cd intoxication is strongly associated with oxidative stress, which is considered the key regulator of other subsequent pathways. The phenomenon of oxidative stress arises from an imbalance between reactive oxygen species (ROS) production and the body's ability to detoxify them. ROS, including superoxide radicals, hydrogen peroxide, hydroxyl radicals, and singlet oxygen, are generated during biological processes like immune response, apoptosis, and differentiation. While normally maintained at low levels by antioxidants such as nuclear factor erythroid 2-related factor 2 (Nrf2), superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), and vitamins (E, C, and A), excessive ROS can contribute to diseases like cancer, atherosclerosis, and cardiovascular disorders by overwhelming the body's defense mechanisms **(Das & Al-Naemi, 2019)**.

Although Cd is a redox stable metal that cannot directly produce ROS, it can increase their production by indirect processes such as glutathione depletion, kupffer cell activation, inflammation, and iron's role in the Fenton

reactions **(Das & Al-Naemi, 2019)**. One mechanism of ROS production is Cd-induced mitochondrial dysfunction, where Cd impairs the electron transport chain, particularly Complexes I and III. This disruption leads to electron leakage and the generation of superoxide radicals **(Branca et al., 2020)**.

As shown in **Figure 1**, depletion of defensive mechanisms including antioxidant enzymes such as SOD, CAT and GSH is another pathway of Cd to accumulate ROS. Since Cd has a strong affinity to thiol groups, GSH, the primary thiol antioxidant, is thought to be the first line of defense against Cd poisoning **(Das & Al-Naemi, 2019)**. GSH depletion is recognized as a major mechanism of Cd-induced oxidative stress and toxicity **(Delalande et al., 2010)**.

Additionally, Cd raises the concentration of free iron, by replacing it within different proteins, which in turn raises the quantity of free redox-active metals in cells. Free iron can enter Fenton reaction and subsequently Haber-Weiss reaction leading to further ROS production **(Cuypers et al., 2010)**.

Exposure to Cd suppresses Nrf2 expression, a transcription factor that regulates the redox system and is responsible for antioxidation against oxidative stress, thereby diminishing its protective function **(Choudhury et al., 2021)**. Normally Nrf2 is esponsible for antioxidation as it increases transcription of cytoprotective genes such as heme oxygenase-1 (HO-1), which provides protection against ROS. However, in the case of Cd toxicity, the inhibition of Nrf2, along with the suppression of antioxidant defenses, leaves the cell vulnerable and unprotected **(Habtemariam, 2019)**.

Oxidative stress induced by Cd eventually disrupts cellular components as ROS has high affinity towards almost all macromolecules as proteins, DNA, and lipids especially polyunsaturated fatty acids producing lipid peroxidation end products, responsible for membrane bilayer destruction **(Branca et al., 2020)**.

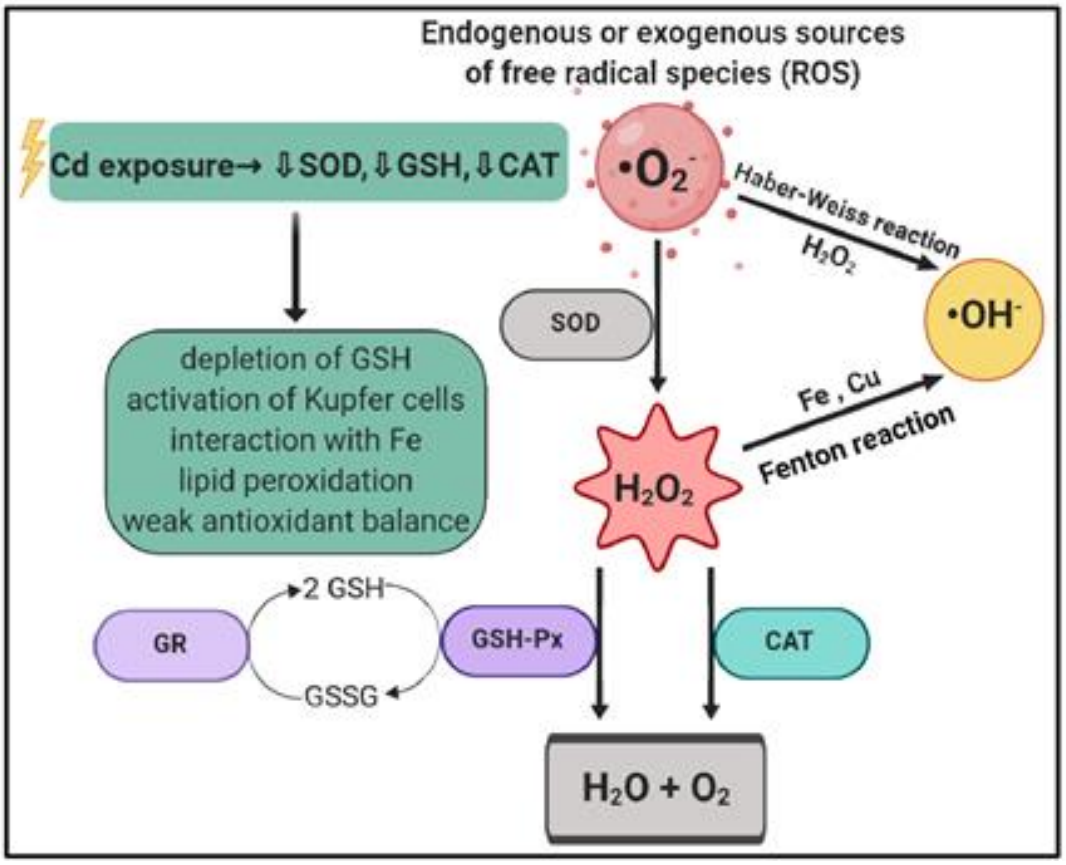

Figure 1. Cd-induced oxidative stress **(Das & Al-Naemi, 2019)**. Cd: Cadmium, SOD: Superoxide dismutase, GSSG: Glutathione disulfide, GSH: reduced Glutathione, CAT: Catalase, ROS: Reactive oxygen species, GSH-Px: Glutathione peroxidase.

4.2. Inflammation

Exposure to Cd can trigger both acute and chronic inflammatory responses. Cd injury initially leads to acute inflammation, and if unresolved, it progresses to chronic inflammation, each characterized by distinct cytokine cascades **(Das & Al-Naemi, 2019)**.

Micromolar doses of Cd stimulate various signaling pathways, notably the nuclear factor kappa-light chain-enhancer of activated B cells (NF-κB), mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase/Akt (PI3K/Akt) leading to the overexpression of inflammatory mediators. Moreover, Cd-induced ROS production promotes mitochondrial damage, diminishes antioxidant enzyme activity, triggers the oxidative stress response, and activates endoplasmic reticulum (ER) stress pathways, thereby exerting a proinflammatory effect on immune cells **(Hossein-Khannazer et al.; Wang et al., 2021)**.

A study investigating the Cd effect on the gall bladder revealed that ROS-induced inflammation caused by Cd-exposure were closely associated with activation of the Akt/ERK signaling pathway which subsequently induces inflammation as evidenced by a significant upregulation in expression of cyclooxygenase (COX-2), NF-κB and its subsequent inflammatory mediators **(Sharma et al., 2020)**.

Another important player in Cd-induced inflammatory response is NF-κB as higher expression of this transcription factor can initiate a cytokine cascade including IL-1β, TNF-α, IL-6 and IL-8 as well as adhesion molecules and chemokines **(Das & Al-Naemi, 2019)**. In case of Cd toxicity NF-κB can be activated through toll like receptor (TLR-4) MYD88 pathway, TNF-α activation or accumulated ROS **(Guo et al., 2024)**.

The interplay between inflammation and oxidative stress are bidirectional as Cd-induced ROS triggers NF-κB activation while inflammation can increase ROS production and inhibit Nrf2 expression. The interplay between oxidative stress and inflammation is illustrated in **Figure 2 (Das & Al-Naemi, 2019)**.

4.3. Genotoxic effect

Cadmium can affect many cellular activities causing cell cycle progression, disrupt cell proliferation and differentiation, and apoptosis. Cd affects DNA synthesis and repair leading to genomic instability and tumorigenesis, proto-oncogene activation, dysregulated gene expression and altered DNA methylation **(Bertin & Averbeck, 2006; Joseph, 2009)**.

DNA damage induced by Cd includes insertion/deletion loops, single base mismatch, single strand breaks and double-strand breaks **(Aimola et al., 2012)**. Cd exposure is positively correlated with elevated DNA damage, as evidenced by an increased incidence of mono- and binucleated cells, sister chromatid exchanges, chromosomal abnormalities, and oxidative DNA damage **(Nagaraju et al., 2022)**.

Prior studies indicated that Cd exposure may lead to genomic mutations. It has been reported that Cd induces hypermutability by inhibiting mismatch repair mechanisms. These studies clearly demonstrate that exposure to Cd has the potential to potentiate mutation and genomic instability, which may contribute to the onset of cancer **(Lützen et al., 2004)**.

4.4. Autophagy

Autophagy is a cellular process of destroying abnormal or damaged cell components such as proteins, nucleic acids, lipids or aged organelles by lysosomal degradation under stressful conditions like infection, cancer, nutrient deprivation, oxidative stress, etc. to maintain homeostasis or cell survival **(Niture et al., 2021)**.

It was reported that Cd exposure was associated with high LC3, Atg5 and Beclin-1 levels indicating high autophagosome formation with impaired lysosomal fusion **(Liu et al., 2016b)**. Presence of high ROS and elevated Ca^{2+} associated with Cd insult interrupts normal autophagy by inhibiting autophagosome fusion with lysosome resulting in overactive yet defective autophagy directing the cell to apoptosis **(Arab et al., 2023)**. On the other hand, Cd was reported to suppress autophagosome production with decreased LC3 levels indicating autophagy suppression **(Rosales-Cruz et al., 2018)**. In either case, Cd exposure impairs autophagy by disrupting autophagosome formation or by causing their accumulation due to defective fusion with lysosomes.

Additionally, exposure to high doses of Cd causes lysosomal acidification hence blocks autophagosome-lysosomal fusion that increases

chances of developing liver toxicity and HCC **(Niture et al., 2021)**.

A study investigating Cd effect on autophagy in neuronal cells reported that Cd exposure was associated with a significant increase in LC3 and p62 indicating high autophagosome formation with impaired autophagic flux. This was attributed to Cd activation of Akt/ERK pathway as Cd insult phosphorylated Akt which subsequently increased mTOR, a negative regulator of autophagy, eventually reducing ULK-1. Importantly, Akt phosphorylation activated BECN-1 which plays a key role in Cd-induced autophagosome-dependent neuronal apoptosis as shown in **Figure 3 (Zhang et al., 2019)**.

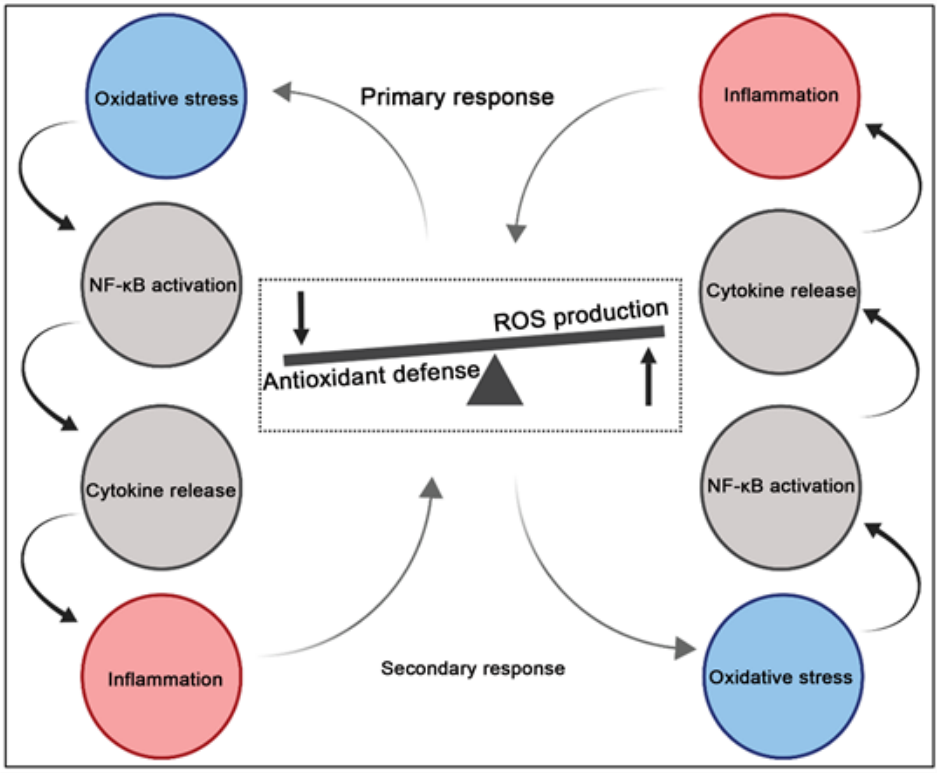

Figure 2. Oxidative stress and inflammation interconnection **(Das & Al-Naemi, 2019)**. ROS: reactive oxygen species NF-κB: nuclear factor kappa-light chain-enhancer of activated B cells.

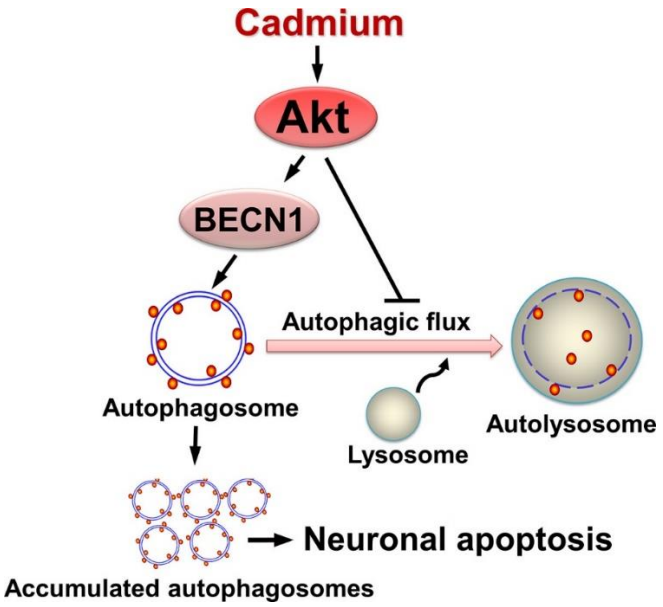

Figure 3. Cd impairs autophagy by inhibiting autophagosome-lysosome fusion **(Zhang et al., 2019)**.

Cadmium increases intracellular Ca levels by acting on ER via Phospholipase C (PLC) producing IP3 from phosphatidylinositol 4,5-bisphosphate (PLC-IP3) pathway and this Ca elevation results in activation of both p38 MAPK and JNK drive cells to apoptosis rather than cell survival. Moreover, Cd induced p38 activation contributes to autophagic flux inhibition that aggravated Cd induced apoptosis **(Gu et al., 2018)**.

Furthermore, Cd interferes with the 5' adenosine monophosphate-activated protein kinase (AMPK)/mTOR pathway, a critical regulatory axis of autophagy. AMPK serves as a positive regulator of autophagy, whereas mTOR functions as a negative regulator. In addition to its role in autophagy, AMPK contributes to the maintenance of redox homeostasis by upregulating key antioxidant enzymes such as SOD and CAT, thereby mitigating ROS-induced oxidative stress **(Zhao et al., 2017)**.

4.5. Apoptosis

Apoptosis is the type of cellular destruction, which is programmed and intended, it is used to get rid of unwanted, infected or cancerous cells that are dangerous to remain in the body. Cd toxicity can trigger apoptosis by both mitochondrial caspase-dependent and caspase-independent pathways. It can also occur by minor pathways that include Ca, ER stress and ROS **(Liu et al., 2013; Liu et al., 2016a)**.

Mitochondria, the cell organelle known for energy production, plays an important role in apoptosis as it is considered the main source of ROS which are byproducts of mitochondrial respiration. Cd can cause ROS accumulation in mitochondrial membrane that leads to lipid peroxidation and outer mitochondrial membrane rupture which results in pro-apoptotic proteins release triggering different types of cell death **(Yi et al., 2022)**.

The main regulator of mitochondrial-mediated apoptosis is B-cell lymphoma protein-2 (Bcl-2) which is a family of proteins responsible for apoptosis switch by controlling the mitochondrial outer membrane permeabilization. Bcl-2 family members have different effects on apoptosis as BH3 (the Bcl-2 homology 3)-only proteins send signals to start apoptosis, Bcl-2 itself can act as anti-apoptotic while BAK (Bcl-2 antagonist/killer) and BAX (Bcl-2-associated X protein) proteins act as pro-apoptotic effector proteins **(Czabotar et al., 2014)**.

In case of Cd exposure, a significant inhibition of antiapoptotic Bcl-2 and an elevation of proapoptotic BAK/BAX are reported **(Mahdavi et al., 2017)**. BH3-only proteins increase in concentration until they reach the apoptotic threshold, which results in the oligomerization of BAK and BAX. These proteins permeabilize the outer mitochondrial membrane, facilitating the release of cytochrome c into the cytosol, where it subsequently activates caspase-9 through its interaction with apoptotic peptidase activating factor-1 (Apaf-1) then caspase-9 activates the effector caspase **(Czabotar et al., 2014)**.

Normally, cytochrome C is bound to anionic phospholipid cardiolipin which is present mainly in inner mitochondrial membrane hence in normal case cytochrome C is unable to exit the outer mitochondrial membrane **(Tuominen et al., 2002)**. Cd exposure disrupts mitochondrial membrane integrity creating BAX pores which subsequently allows cytochrome C to reach cytoplasm **(Lee et al., 2005)**. Once cytochrome C gets to cytoplasm it initiates the caspase cascade which begins with the initiator caspases, caspase-9 in intrinsic pathway and caspaes-8 in extrinsic pathway, and ends with executioner caspase-3 **(Zhang et al., 2017)**.

Cadmium-induced proapoptotic proteins include apoptosis-inducing factor (AIF) and second mitochondrial activator of caspase (Smac) **(Liu et al., 2016a)**. Once AIF is out of mitochondria, it reaches the nucleus to bind to DNA and this bond leads to activation of caspase-independent chromatin condensation and DNA fragmentation by downstream nucleases **(Kim & Soh, 2009)**.

Another pathway involved in Cd-induced apoptosis shown in figure 5 is the Ca related pathway. It's well known that Ca is an important signaling ion in the cell stored mainly in the ER and any increase in Ca leads to alteration in cell function. When Cd enters into a cell it causes ER stress by activating a G-protein coupled receptor (GPCR) on ER membrane followed by (PLC-IP3) activation and release Ca into the cytosol leading to caspase-3 activation and apoptosis **(Fujiwara et al., 2012)**.

5. Conclusion

Cadmium is a toxic heavy metal with widespread use in various industrial applications. Cd exposure poses serious health risks and has been associated

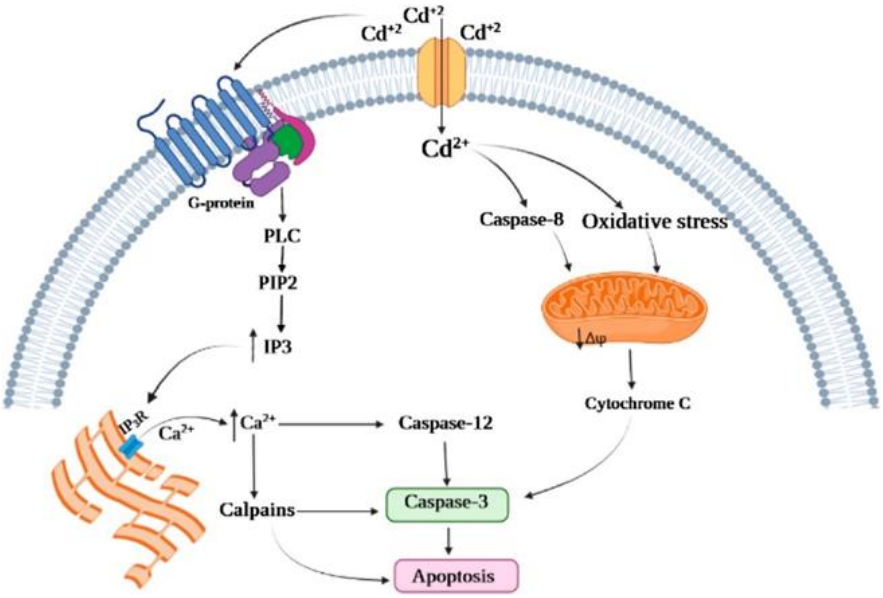

Figure 4. Mechanism of apoptosis induction by Cd intoxication **(Mirkamali et al., 2022)**. Cd: Cadmium, Ca: Calcium, PLC: Phospholipase, PIP2: Phosphatidylinositol 4,5-bisphosphate, IP3: inositol 1,4,5-trisphosphate, IP3R: Inositol-1,4,5-trisphosphate receptor.

with multiple pathological manifestations and organ-specific toxicities. Cd toxicity involves several interrelated cellular and molecular pathways such as excessive Ca and ROS production, depletion of antioxidants, suppression of the AMPK/mTOR pathway, inhibition of autophagy, activation of MAPK pathway, and direct stimulation of apoptotic factors.

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