Oxidative stress biomarkers of cadmium toxicity in mammalian systems and their distinct ameliorative strategy

Abstract

Cadmium is highly toxic heavy metal and a significant environmental pollutant. Cadmium can severely damage various organs and biochemical systems. It can induce severe, acute and especially chronic intoxications. The major target for acute cadmium toxicity is liver, kidney and lungs. Cadmium is a highly carcinogenic element causing preferentially prostate, lung and gastrointestinal cancers. Cadmium has a very high potential to induce ROS production. The toxicity by this metal ion induces oxidative stress in any organism by Fenton reaction which leads to alteration in the activities of certain antioxidant enzymes such as Cu- and Zn-Superoxide Dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT), glutathione reductase (GR) and glutathione-S-transferase (GST). Exposure to cadmium increases lipid peroxidation in mammalian systems. Plants which are rich in antioxidants such as flavonoids, alkaloids and other polyphenolic compounds have potential to be used against cadmium toxicity for removal of cadmium burden from system or for clinical recoveries of biochemical systems. Some plants and their phytochemicals have already shown their effect against cadmium toxicity in model organisms. This review presents an updated account of impact of cadmium exposure on different physiological and biochemical indices in mammalian systems. The article also includes the effects of various antidotes and certain plant based principles to protect from the adverse impact of cadmium exposure.

Keywords: oxidative stress, biomarkers, cadmium toxicity, antioxidant enzymes, antioxidants, phytochemicals, antidotes

Introduction

The heavy metals are generally characterized as the inorganic elements listed in d-orbital (transition elements) of modern periodic table with +2 oxidation state and low melting point. Cadmium (Cd), with atomic number 48 is soft and bluish-white in appearance. It is an important component of batteries, cadmium pigments and plating. It is also used as stabilizers for plastics, chemical stabilizers, metal coatings, alloys, barrier to control neutrons in nuclear reactions, television picture tubes and semiconductors as well as in molecular biology to block voltage-dependent calcium channels. Cadmium is highly toxic metal and plays an important role in industrial occupation. In present time, it is even more significant as environmental pollutant. Cadmium can severely damage various organs and biochemical systems of an organism and can induce severe acute and especially chronic intoxications. The major target for acute cadmium toxicity is liver, whereas severe nephrotoxicity has been observed in chronic cadmium poisoning. No any excretory mechanism is reported in humans for cadmium, as it accumulates in tissues of different organs. Any biological function of cadmium in mammals is not known. However, in marine diatoms it is reported to act as cofactor for few enzymes. This is the only known biological function of cadmium in a living system. Cadmium poisoning occurs through inhalation of cadmium fumes, intake of food, water and tobacco. In humans, the amount of cadmium deposition is very high in the kidney, liver, pancreas and lung. In kidney cortex, the half-life of cadmium is the main reason for long life of cadmium.1 Cadmium accumulates primarily in liver and kidney in humans.2 The long biological half-life (17–30 years) and almost no excretion of Cd facilitate continuous accumulation of it into the body systems. The bioaccumulation of Cd in mammalian systems may cause severe damage to nervous system, reproductive systems, gastrointestinal tract and mucous tissues and the occurrence of several ailments such as anaemia, osteoporosis, blood, brain, skin related diseases, malfunctioning of foetus which includes ability loss, club foot, exencephaly, microcephaly, non-hypertrophic emphysema, irreversible renal tubular injury, eosophilia, chronic rhinitis and microphthalmia. The local agricultural communities in Japan consuming Cd contaminated rice developed itai-itai disease and renal abnormalities, including proteinuria and Glucosuria.3 Cadmium is one of six substances banned by the European Union’s Restriction on Hazardous Substances (RoHS) directive because of its carcinogenic potential in humans. The International Agency for Research on Cancer of USA has classified Cd into the category of carcinogens.3

Though the exact mechanism of their pathogenicity is not known but there are various reports indicating that the exposure of this heavy metal or it’s accumulation in the body systems may induce generation of free radicals4 which leads to the production of oxidative stress.1,5,6 Cd may induce oxidative stress through the formation of ROS that results into the decrease in intracellular GSH content as it combines with thiol groups of enzymes involved in antioxidant mechanisms (SOD), catalase (CAT) and glutathione peroxidase (GPx) and exerts inhibitory effect on the level of their activities.7,8 Cd has been reported to form cadmium-selenium complexes in the active centre of GPx and shows the inhibition of enzyme activity. Complex III of the mitochondrial electronic transport chain has also been reported to be inhibited by Cd and increases production of ROS, damaging mitochondrial membrane. Cadmium can replace magnesium and...
calcinium in certain biological systems. Cd induced oxidative stress is involved in causing DNA damage/mutations and lipid peroxidation (LPO) and oxidation of proteins.

Another mechanism of Cd toxicity may be caused by zinc binding proteins. Zinc and cadmium contain the same common oxidation state (+2) and are almost the same in size. Due to their similarities, cadmium can replace zinc, magnesium and calcium in certain biological systems and iron and copper from various cytoplasmic and membrane proteins such as ferritin and apoferritin, thus increasing the pool of free metal ions in many biological systems. Cadmium can bind up to ten times more strongly than zinc in certain biological systems and is difficult to remove. The genotoxic potential of cadmium has also been studied and recognised as a clastogenic agent. Cadmium is known to cause its deleterious effect by deactivating DNA repair activity.

This article presents an updated account of impact of cadmium exposure on different physiological indices in general and the enzymes in particular in mammalian systems. The description also includes the effects of various antidotes and certain plant based principles to protect the exposed subjects from cadmium toxicity or to alleviate the adverse impact of cadmium.

**Entry of cadmium via different routes into the mammalian systems**

**Through food ingestion**

The cadmium absorption in human through gastrointestinal tract is about 5% of ingested amount of cadmium. This value depends on the exact consumed dose and nutritional content of food. The major route of cadmium deposition in human body is through food and drink. About 95% of cadmium is absorbed through this way. Several factors are responsible and can interfere with this amount, such as trace elements like zinc, copper, iron and calcium and vitamin D. Low intake of these entire elements can increase cadmium content. The presence of other polyvalent cations also influence cadmium uptake. Cadmium absorption in rat jejunum was suppressed by relatively higher concentration of polyvalent cations including Magnesium, Chromium, Nickel and Strontium. It is reported that high fibre diet can also elevate the cadmium uptake through gastrointestinal tract. The iron stock of a mammal is a very important parameter for cadmium uptake. The cadmium uptake is higher in people with low iron diet in comparison to people with balance iron stock. This is the main reason why the anaemic and habitual iron deficient people such as children and menstrual women show higher cadmium uptake. Low iron blood levels also promote the expression of DCT-1 gene. It is a metal ion transporter in the gastrointestinal tract, which plays an important role in divalent metal ion transport.

**Through inhalation**

The intoxication of cadmium through inhalation is mainly by cigarette smoking. The human lung exposed to tobacco smoke can absorb 40-60% of cadmium present in it. An average cigarette smoker has further intake of 30μg per day. The cadmium body burden in an average 50-year-old non-smoker is about 15mg. whereas this goes double in case of an average life long smoker which is about 30mg. Non-smokers generally have low cadmium blood levels; approximately 4-5 times lesser than a normal smokers. Many lung associated diseases are reported through cadmium inhalation. Cadmium-containing fumes exposed workers have been reported to develop acute respiratory distress syndromes (ARDS). The absorbed cadmium forms complex with cysteine-rich protein. This complex reaches to their target organs through blood circulation.

**Figure 1 Absorption of cadmium through different routes.**

**Through dermal contact**

Not much work has been done for dermal absorption of cadmium in recent years. The two main mechanisms involved in dermal absorption of cadmium are: binding of a free cadmium ion in the epidermal keratins with sulphhydryl radicals of cysteine or induction and association with metallothionein. Researchers also study the absorption of cadmium chloride from soil and contaminated water by human corpse skin in a diffusion cell model and have explained the cadmium penetration efficiency to be 12.7% and 8.8% from water and soil, respectively, by skin; whereas the plasma uptake of cadmium from water and soil has been reported to be 0.07% and 0.01%, respectively. According to one such study, cadmium chloride solution on dorsum (shaved skin) of rat showed high mitotic index with infrequent ulcerative changes, hyperkeratosis and acanthosis. They have also observed a significant increase in the level of cadmium concentration in liver, blood and kidney.
Effect of cadmium on parameters of oxidative stress biomarkers in mammalian systems

Circulatory system

Researchers have reported that cadmium influences oxidative status and antioxidant systems of organisms, which is independent of the route of exposure. However, its toxicity ratio varies with respect to the route of administration. The experiments were performed by treating organisms with different routes like orally through food and water, intra peritoneal, and inhalation. In all cases the results show imbalance in antioxidant system. The intra peritoneal doses of 1mg/kg and 2mg/kg body weight of cadmium chloride solution are sufficient to induce alteration in blood parameters. This may lead to absolute and relative changes in granulocytes in peripheral blood and leukocytosis. However, no changes were recorded in haematocrit value. Expression of catalase gene is also induced by cadmium.

The glutathione reductase (GR) activity is also significantly increased in serum of rodent treated with cadmium chloride, whereas glutathione peroxidase (GPs) activity is lowered in blood level. The acute cadmium exposure to the organisms has been shown to cause elevation in the levels of ALT, AST and Alkaline phosphatase. Cadmium also influences the protein content of organisms. Some researchers reported a significant decrease in total protein content, and concentrations of albumin and testosterone in serum.

Central nervous system

Cadmium has been shown to be very toxic for the central nervous system (CNS). It also affects the activity of certain enzymes and the level of neurotransmitters. The capability of cadmium as neurotoxin is well reported both in vivo and in vitro. Acetycholinesterase (AChE, EC 3.1.1.7) is a cholinergic esterase, that plays a very important role at neuromuscular junctions and cholinergic brain synapses, where it maintains the acetylcholine cycle. It is a membrane bound enzyme and inhibited by cadmium in a non-competitive manner indicating that cadmium is highly neurotoxic agent for mammals. These experiments were performed on rodents. They treated the rodents with cadmium by both in vitro and in vivo. The results of experiments explained the dose dependent differences in activities of enzymes. Pure AChE (electric eel AChE) is activated by low cadmium concentrations (0.1 mM). On the other hand, it was inhibited by higher Cadmium concentrations.

Cadmium metal ions compete with other metal ions for enzyme binding site and induce conformational changes. Brain AChE was found to be inactivated by the same high Cadmium concentrations and show dose dependent inhibition. Cadmium shows time dependent inhibition of AChE, which is also reported by other workers. The chronic cadmium administration in rat model causes significant decrease in glutathione content, superoxide dismutase (SOD) and glutathione S-transferase (GST) activity in rat brain. The Na–K ATPase is an enzyme involved in metabolic energy production and neural excitability. The role of Mg2+ ATPase in brain is to maintain high intracellular Mg2+ concentration. Changes in the level of Mg2+ also affect the protein synthesis and cell growth in brain. Brain Na–K ATPase was activated by cadmium low concentration and inhibited in higher concentrations. Mg2+ ATPase was not affected by in vitro low dose cadmium exposure, whereas it was activated by its higher concentrations. The total antioxidant status of brain was decreased by 25% in cadmium intoxication, indicating that these metals can induce oxidative stress. Biotransformation of xenobiotics is known to involve several oxidative enzymes such as Aldehyde Oxidase (AO), Xanthine Oxidase (XO) and Sulphite Oxidase (SO). These are soluble enzymes containing molybdenum and haem found in brain and other tissues.

Hepatotoxic effect of cadmium

Liver is the major site for biotransformation of toxic compounds. In case of cadmium administration, liver is the primary target for cadmium-acute toxicity. The antioxidant system of liver is highly influenced by cadmium. It disturbs the ratio of activities of alanine transaminase (ALT) and aspartate transaminase (AST), the markers of liver associated disorders. The cadmium induced alterations in the activities of ALT and AST reflect the impact on the metabolic rate of protein degradation. Cadmium has been observed to exert adverse impact on the activity of lactate dehydrogenase (LDH). It is presumed that reactive oxygen species (ROS) production by cadmium initiates series of reactions which may result in alterations of metabolic indices.

Some workers have reported that a single high dose of cadmium is more toxic in comparison to the same dose in several small doses given to mice by injection for long period. This treatment severely damages the liver of cadmium exposed animals. The pre-treatment of organisms with a small dose of cadmium induces metallothionein synthesis, which provides protection to acute liver toxicity. These results explained the association of cadmium with cystiene rich protein metallothionein, which protects liver by cadmium induced toxicity. By forming a complex with cadmium, metallothionein protects sensitive target enzymes and molecules in liver cells from being affected by cadmium ions. But at higher dose of cadmium administration the expression of mt-gene becomes much high, which causes easy transportation of cadmium in different tissues instead of protection.

Cadmium poisoning has been found to cause much variation in the expression levels of antioxidant enzymes and proteins. For example, osmotic stress protein OspH4, Oxidative stress protein A170, heat shock protein (HSPs), Heme oxygenase-1 (HO-1) and signal transduction regulatory protein MAP kinase activated protein kinase-2 was reported to be increased, while multidrug resistance genes expression were markedly decreased. The genes involved in cell growth arrest induced by DNA damage such as GADD45 and GADD153 and stress enzymes like phospholipase A2 and cytochrome P450 3A25 were also found to be increased. The expression of antioxidant enzymes such as catalase and Mn-SOD were suppressed, whereas the expression of Zn-SOD and Cu-SOD was not significant. Cadmium treatment has been found to reduce the expression of thiolaldehyde sulfurtransferase (rhodanese), microsomal UDP-glucuronosyltransferase, NADPH cytochrome P450 and their isozymes. The researchers have found that enhancement of heme oxygenase-1 (HO-1) may be as a general response to oxidative stress. They have observed that the level of HO-1 increases more than 15 fold in cadmium administration. Thus HO-1 is considered as one of the most sensitive biomarkers for acute cadmium toxicity.
Oxidative stress biomarkers of cadmium toxicity in mammalian systems and their distinct ameliorative strategy

Cadmium mediated modulation of respiratory system

The heavy metals are known to adversely influence the environmental health and hence pose risks to human’s quality of life. The heavy metals contamination in physical environment has been reported to induce asthma in humans, especially in children. The different sources to release cadmium in the environment have been presented in various review articles. Cadmium exposure causes induction of asthma or pulmonary emphysema mostly in the humans, who mostly do tobacco smoking. Although no concrete mechanism is known so far in the context of cadmium induced pathogenesis in the lungs or respiratory tract of humans, several workers have found it to be involved as a key player in the genesis of lung diseases of smokers and the effect was possibly through an imbalance in redox system of an exposed individual and also via modulation of functions of macrophages. The analysis of urine is considered to estimate the body burden of cadmium in smokers but it may not reflect the true value as cadmium also accumulates in various specific tissues. Asthma, an allergic disease, is known to be mediated via increased level of IgE sensitization due to heavy metals exposure. In one of the studies concerning this issue in Korean adults, it has been suggested that their exposure to cadmium had caused increase in the level of this heavy metal in their blood samples. Some workers have hypothesized that the presence of higher concentration of cadmium in the blood may be associated with onset and severity of asthma in the majority of Korean adults. Their epidemiological studies have indicated rise in the level of total / allergen-specific IgE in this condition.

Remediation strategy for cadmium toxicity

Through phytochemicals

Natural products are well known for their antioxidant properties. These natural compounds mainly exert their antioxidant action by metal chelating and free radical scavenging. Apple and their derivatives are already known for their nutritive value, as they are rich in antioxidants. These antioxidants include flavonoids (flavonols, quercetin, catechins), vitamins and phenolic acids (quercetin glycosides, epicatechin, procyanidins). Researchers have reported that apple derivatives are very useful against cadmium toxicity. Rat exposed to cadmium solutions show a high number of micronucleated cells in hepatocytes. The administration of apple juice has ameliorated the cadmium induced genotoxicity. The reasons behind this protection may be due to the presence of antioxidant activity of apple juice. Previous works have also shown that quercetin, a major content of apple, is very effective against oxidative DNA damage. These workers have demonstrated low level of catalase activity after apple juice administration in cadmium exposed rats. This reduction in catalase activity may be explained in terms of the antioxidative properties of polyphenols present in apples.
The elderberries are also having good nutritive value and their antioxidant content is also high. They are rich in polyphenolic compounds especially flavonols. These compounds provide antioxidant activity and protection against injurious effect of various toxins including heavy metals.86–90 Some workers have shown that elderberries have no effect on elevated cadmium concentration in kidney and bones of rat. But it improved the function of liver and kidney in cadmium intoxicated rat.91 The GR activity was lowered in the serum of rats treated with both elderberry and cadmium in comparison to cadmium treated rats. The workers displayed that the rats treated with cadmium alone exhibited lower GPx activity which was recovered after the administration of elderberry lyophilisate.

Rosemary (Rosmarinus officinalis) is well known for their therapeutic action against bronchial asthma, inflammatory diseases, cataract, hepatotoxicity, atherosclerosis, peptic ulcer and poor sperm quality.92 This therapeutic action of rosemary is due to presence of rosmarinic acid, a caffeic acid derivative. In other hand, the aqueous extract of rosemary also mitigates the cadmium chloride mediated hepatotoxicity. Rosemary also balances the antioxidant system of rodents. Studies in recent years have explained that rosemary can suppress the MDA level and stimulate synthesis of antioxidative enzymes such as CAT, GSH, and SOD.93,94 The antioxidant properties of some of the plants involved in treatment of cadmium induced toxicity are summarized in Table 1.95–107

Curcumin existing in two different chemical forms i.e. keto and enol is reported to act as a potential antioxidant in several studies in rodents and in vitro models. It has been shown that curcumin has the ability to protect the animal from cadmium induced nephrotoxicity, neurotoxicity98–102 and hepatotoxicity. It was also observed that curcumin prevents cadmium induced hepatotoxicity in rodents.103 Moreover, it also regulates the level of trace elements which are involved in cadmium poisoning such as Zn and Iron. According to several researchers, the combined dose of curcumin with metal ions or with vitamins is more effective in cadmium toxicity and it can prevent the organisms from oxidative damage. It can induce MT expression and balance the SOD activity.104,105 The keto-enol tautomers of curcumin are displayed in Figure 3.

Through antioxidants

Vitamins are metabolically active and provide protection against free radical stress induced by various toxic compounds. Pretreatment of vitamin E against cadmium administration results in the restoration of the normal hematological indices and reduction in the lipid peroxidation. The combined effects of vitamins have been found more effective against oxidative stress. It is reported that mixed supplementation of vitamin C and E reduces the ROS induced testicular damage. This synergistic effect of vitamins ameliorates normal testicular functions of cadmium exposed rats.106

Through metals ions as antidotes

By increasing the concentration of other useful metal ions in dietary supplement can reduce the cadmium body burden in rodents. It is well reported that zinc and magnesium supplementation reduces the cadmium deposition in tissues of rabbits; zinc being more effective in kidney as compared to magnesium.107 However, some workers have suggested that magnesium as a supplement in diet can reduce cadmium burden as it did not disturb any metal ion reservoir. On the other hand, Zn supplementation has been found to reduce the Mg concentration in blood by increasing its excretion. Magnesium provides high therapeutic range against heavy metal toxicity, and therefore further investigations are required to validate these results, especially against cadmium.111 Selenium also shows protective properties in cadmium toxicity. The major effect of selenium has been demonstrated on blood parameters. The administration of Se in cadmium toxicity significantly increases the counts of lymphocytes, erythrocytes (RBCs), platelets (PLTs) and the level of haemoglobin (Hb).114,115

Combination therapy

Combination therapy referred to the administration of two or more than two medications simultaneously to treat a single disease at the same time. The chelation therapy refers to the administration of two chelating agents that may immobilize or trap the toxic metals
from different tissues of mammalian systems.\textsuperscript{116–119} In such therapy, the co-administration of an amino acid, an essential metal,\textsuperscript{6,119} and/or dietary nutrients with the chelating agent, has been found to provide better recoveries.\textsuperscript{5,119} The co-administration of phytochemicals with chelating agents, dietary nutrients or essential metal may be useful in the alleviation of cadmium toxicities. In mammalian systems, the in-depth clinical studies with different combinations of chelating agents, dietary nutrients, essential metals in association with those of antioxidants are required to be done for the benefit with the least side effects. It is also important to find out the suitable dose and duration for the treatment to determine the optimal therapeutic index of drug(s) to be given in isolation or in different combinations in order to achieve optimum benefit.

\textbf{Table 1} Plants and their compounds used in the remediation of cadmium toxicity in mammalian systems

<table>
<thead>
<tr>
<th>Plant name</th>
<th>Family</th>
<th>Bioactive compounds</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apple</td>
<td>Rosaceae</td>
<td>Flavonols, quercetin and catechins</td>
<td>95,96</td>
</tr>
<tr>
<td>(\textit{Malus domestica})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elderberry</td>
<td>Adoxaceae</td>
<td>Anthocyanins, flavonoids, vitamin C and pectins</td>
<td>88,97</td>
</tr>
<tr>
<td>(\textit{Sambucus nigra})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fenugreek</td>
<td>Leguminosae</td>
<td>Polyphenolic flavonoids</td>
<td>98,99</td>
</tr>
<tr>
<td>(\textit{Trigonella foenum raecum})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Garlic</td>
<td>Amaryllidoceae</td>
<td>Allicin</td>
<td>100,101</td>
</tr>
<tr>
<td>(\textit{Allium sativum})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mimosa (\textit{Mimosa caesalpinifolia})</td>
<td>Mimosaceae</td>
<td>Mimosin, saponins, alkaloids and terpenoids</td>
<td>102</td>
</tr>
<tr>
<td>Oranges</td>
<td>Rutaceae</td>
<td>Naringenin</td>
<td>103</td>
</tr>
<tr>
<td>(\textit{Citrus sinensis})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosemary (\textit{Rosmarinus officinalis})</td>
<td>Lamiaceae</td>
<td>Rosmarinic acid, carnosic acid and carnosol</td>
<td>104,105</td>
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<tr>
<td>Turmeric</td>
<td>Zingiberaceae</td>
<td>Curcumin</td>
<td>106–108</td>
</tr>
<tr>
<td>(\textit{Curcuma anga})</td>
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</table>

\textbf{Conclusion}

Cadmium has a very high potential to induce oxidative stress via production of ROS and alterations in antioxidant systems. The toxicity caused by cadmium is mainly due to the formation of complexes with sulphhydryl group of several enzymes and proteins thereby causing perturbations in the three-dimensional conformations or by replacing the divalent metal ions from their catalytic pockets which are essentially required by concerned proteins/enzymes as cofactors for their optimal biological activity. In this situation, these biomolecules tend to lose their native conformations due to loss of non-covalent and weak interactions responsible for stabilising their structures, which lead to serious bearings on to their biological activities and finally the cellular health. Cadmium also chelates with proteins which utilise metal ions as a cofactor. Cadmium replaces other divalent metal ions and disrupts the conformation of proteins which leads to inactivation of associated biological function. All cells tend to make reductive environment. Since cadmium disturbs the normal redox potential in cells, it results into activation and production of hydrogen peroxides and free radicals, which are responsible for damage of key cellular ingredients such as protein, nucleic acid and lipids. Some plants and their phytochemicals already have been shown for their effects against cadmium toxicity in different model organisms. The oxidative stress could be ameliorated by different antioxidants, both herbal and synthetic. The amelioration by plant based principles is of great significance because they are highly cost effective and exert no side effects. In addition to them, the application of certain vitamins and chelating molecules is being tried with the expectation that they would make coordinate complexes with these heavy metals and help remove them thereby making the affected organs free from metal’s burden. Plant based natural compounds such as flavonoids, alkaloids and other polyphenolic compounds could be used against cadmium toxicity for removal or reduction of cadmium burden from various biological systems. Although the co-administration of antioxidants (natural, herbal, or synthetic) with other chelating agents may improve removal of this toxic metal from the biological systems, the in-depth clinical studies with newer chelating agents are required to assess their adverse effects.

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**Conflicts of interest**

The authors declare that they do not have any conflict of interests.

**References**


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