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Mitigating Fluoride, Lead, Arsenic and Cadmium Toxicities in Laboratory Animals and Ruminants through Natural Products

Abdellatif Rahim [1,2], Fatma Aydogmus-Öztürk [3], Cansel Cakir [4], Abdelkhalid Essamadi [2] and Bouchra El Amiri [*,1]

[1]*Animal Production Unit, Regional Center Agricultural Research of Settat, National Institute for Agricultural Research (INRA), Avenue Ennasr, P.O. Box 415 Rabat Principal, 10090 Rabat, Morocco*

[2]*Hassan First University of Settat, Faculty of Sciences and Techniques, Laboratory of Biochemistry, Neurosciences, Natural Ressources and Environment,P.O. Box 577, 26000 Settat, Morocco*

[3]*Köycegiz Vocational School, Mugla Sitki Kocman University, 48121 Mugla, Türkiye*

[4]*Deparment of Chemistry, Faculty of Science, Mugla Sitki Kocman University, 48121 Mugla, Türkiye*

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Abstract: Environmental pollutants are considered a serious health problem for humans and animals mainly in ruminants for several regions of the world. Previously, many studies have investigated the mechanisms of toxicity of these pollutants on laboratory animals. Afterward, other studies have demonstrated that exposure to environmental pollutants may cause several adverse effects on the ruminant organs, influencing their performance and leading to socio-economic problems for breeders. Fluoride, lead, arsenic, and cadmium are the most common poisonings in ruminants, they can cause several irreversible toxic effects in many organs depending on the mode of action. The adverse effects of fluoride, lead, arsenic, and cadmium toxicities in laboratory animals and ruminants have been clearly summarized in this review. In addition, several results on protective or ameliorative effects by means of natural products against these toxicities have been illustrated.

Keywords: Environmental pollutants; laboratory animals; ruminants; toxicity; mitigation; natural products.

1. Introduction

Livestock occupies a prominent place in several regions of the world. About 1.3 billion habitats worldwide live in developing countries where their livelihood depends directly or indirectly on livestock [1]. It plays an important socio-economic and cultural role in the well-being of rural households, such as food supply, source of income, asset saving, source of employment, soil fertility, livelihoods, transport, agricultural traction, agricultural diversification, and sustainable agricultural production [2]. Ruminants including cattle, sheep, and goats are the domestic animals that dominate global livestock

[*] Corresponding author: E-Mail : bouchraelamiri@hotmail.com; Phone:+212523729300/07; Fax: +212523729306/ +212523720927

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production [3] due to their adaptability to various climatic conditions [4]. However, in several regions, ruminants are continuously exposed to environmental poisonings which are harmful at specific doses [5]. Besides, it was highlighted that the most toxic environmental poisonings for ruminants are fluoride, lead, arsenic, and cadmium [6]. Furthermore, the ingestion and/or inhalation of these toxic elements can cause several adverse effects on the animal body, influencing its performance, and resulting in socio-economic problems. Moreover, these pollutants lead to irreversible toxic effects [7, 8]. Accordingly, to facilitate the understanding of the toxicity mechanisms of these poisonings and to highlight preventive solutions, several studies have been performed first on laboratory animals and then on ruminants.

To prevent the effects of all environmental pollutants cited above, several synthetic metal chelators also have been reported with encouraging degrees of success [9]. However, these synthetic chelators have toxic effects [10, 8]. Recently, research have been directed towards the use of natural biomolecules originating from medicinal plants, rich in natural minerals which can chelate these environmental pollutants, and contain a wide range of antioxidants that can reduce the oxidative stress [7, 8]. This review focuses on investigating the sources, the harmful effects, and the mechanisms of fluoride, lead, arsenic, and cadmium toxicities in both laboratory animals and ruminants. In addition, this review addresses the dietary strategies pursued to prevent the toxic effects of these elements, and the results obtained by the previous studies are illustrated to provide more information to specialist readers.

2. Sources of Environmental Pollutants

Environmental pollutants are widely distributed [11] and are produced by natural factors including geological degradation of bedrock materials, volcanic eruptions, salt spray, forest fires, rock weathering, biogenic sources, and wind-blown soil particles [12]. These latter are also produced by anthropogenic inputs that cause disturbances and acceleration of the natural geochemical cycle [13]. More precisely, the intensive and non-optimal use of agrochemical fertilizers, pesticides, wastewater irrigation, supplements of sewage sludge, higher atmospheric deposition by industrial units, and the combustion of fossil fuels have led to a high level of inorganic pollutants in the air and soil [14]. Compared to natural sources, anthropogenic sources are generally considered to be the major causes of increasing environmental pollutants [15]. They have the potential to contaminate both soils, the surface water and the air. Soil pollution by environmental pollutants is a critical global environmental problem [16]. In addition, the presence of environmental pollutants in soils can contaminate many crops and plant species [14]. Therefore, their consumption poses risks to the health of humans and animals [17]. On the other hand, drinking water is of the essential need for human and animal survival. However, anthropogenic inputs can contaminate it with excess environmental pollutants. In addition, industrialization and urbanization are considered as a significant contributors to the increase in the level of water contamination by environmental pollutants [12]. Environmental pollutants are transported by runoff from industries, municipalities, and urban areas. Most of them eventually accumulated in the soil and sediment of water bodies [18] and are also released into the atmosphere [19] through the emission of industrial gas combustions, mining, automobile exhaust, dust, etc. The atmosphere accumulates these pollutants [20] and then transmit them to ground through precipitation [21] or contaminate the soil and water subsequently entering into the food chain of animals [19, 13].

3. Toxicity of Environmental Pollutants on Laboratory Animals and Ruminants

Chronic exposure to environmental pollutants by humans and animals, either through inhalation or through consumption of contaminated plants and water, can result in toxic effects. Fluoride, lead, arsenic, and cadmium, are the most popular pollutants for humans and animals [6]. Table 1 and 2 summarize the main clinical signs of these pollutants in laboratory animals and ruminants respectively, and causes adverse effects on different organs such as liver, kidneys, hard tissues, reproductive organs as well as growth and biochemical parameters.

Table 1. Toxic effects of fluoride, lead, arsenic and cadmium on laboratory animals

Element	Effects	References
Fluoride	Impaired tooth enamel development and the presence of white chalk-like incisors with broken tips in rats and mice	[28, 29]
	Reproductive system and fertility in mice and rabbits	[34, 35, 133]
	Altered liver function in mice	[23]
	Oxidative stress and disturbance in liver and kidney functions in rabbits, mice and rats	[134, 135]
	Heart troubles in rabbits	[136]
Lead	Reproduction and oxidative stress in rats	[57]
	Oxidative stress in rats and mice	[58]
	Hepatic and renal toxicities in rats	[55, 137]
	Systolic blood pressure and bone mineral density in rats	[56]
	Weight gain and risk of obesity in rats	[138]
Arsenic	Carcinogenesis in rats and mice	[69]
	Liver damage and fibrogenesis oxidative stress in mice	[73]
	Exacerbates atherosclerotic lesion formation and inflammation in mice	[139]
	Oxidative stress and hepatorenal toxicity in rats and mice	[140],
	Reduced plasma levels of testosterone and gonadotropin in male mice and rats	[84, 141]
	Fetal malformations in female mice and rats	[72, 142]
Cadmium	Carcinogenesis in rats and mice	[92, 93, 143]
	Increased uterine wet weight, promoted growth and development of the mammary glands in female rats	[94]
	Reproduction disturbance	[96, 98]
	Pathological testicular alterations, and liver and kidney damage in rats	[99]
	Increased lipid peroxidation in liver and kidney tissues in rats	[100]

3.1. Fluoride

Fluoride is the 13th most abundant halogen in nature and in the world [22]. It has many physiological roles for animals [23] but it may lead to toxic effects in critical doses. Among domestic animals, ruminants have less fluoride tolerance than simple-stomach animals [24]. Fluoride enters the ruminants body by several routes, including inhalation, consumption of contaminated water, or plants growing in contaminated soil leading to fluorosis [8]. More precisely, its bioaccumulation in teeth and bones may cause several injurious effects in the form of dental and skeletal fluorosis [24, 25]. Moreover, increasing the duration of exposure to fluoride has been shown to produce adverse effects in other tissues, leading to oxidative stress, DNA damage, apoptosis, and necrosis [26].

3.1.1. Effects of Fluoride on Laboratory Animals

Rabbits, rats, and mice are all very sensitive to fluoride toxicity [27]. For this reason, these species are widely used in experimental studies to analyze the fluoride toxicity [24]. Oral administration of sodium fluoride altered the development of tooth enamel and revealed chalk-like white incisors with broken tips in rats and mice [28, 29]. On the other hand, chronic fluoride intoxication has caused bone

damage, osteosclerosis, osteomalacia, and osteoporosis in rats [30, 31]. Moreover, several studies reported that

Table 2. Toxic effects of fluoride, lead, arsenic and cadmium on ruminants

Element	Effects	References
Fluoride	Skeletal fluorosis in buffaloes, cattle, camels, goats, and sheep.	[37]
	Dental and skeletal fluorosis in sheep.	[144]
	Mandibular lesions in sheep.	[145]
	Alteration of some serum, kidney and liver biochemical parameters in cattle.	[38]
	Increase in fluoride milk yield in goats.	[146]
	Disturbance of Cu, Ca, Mg, Mn, P, and Zn levels in sheep bones.	[41]
	Adverse effects on the antioxidant system of kidneys, liver and muscles in sheep.	[40]
	Liver disturbances and nephropathy in sheep.	[36]
Lead	Increase of concentrations lead in blood and tissues in cattle.	[65]
	Severe depression, paresis of hypoglossal nerve, ataxia, muscle twitching in cattle.	[147]
	Convulsion in cattle.	[62]
	Decrease in triiodtironine (T3) and thyroxine (T4) concentration, increase in estradiol plasma concentration in cattle.	[46]
	Paralysis of hindlimbs, lameness, osteoporosis, abortion and transient infertility in sheep.	[147]
	Nephrosis, osteoporosis, and fractures in lambs.	[60]
	Moderate excitation, ataxia, weight loss and pale mucous membranes in cattle.	[63]
Arsenic	Weakness, congestive mucous membranes, emaciation and several ulcers in different parts of the skin in ruminants.	[75]
	Weight loss, weakness, languor, ill-thrift, dry and alopecic coat that readily comes off, focal skin lesions, congested mucous membranes and stomatitis in sheep.	[56]
	Buccal erosion, stomatitis, cutaneous ulcers and serous atrophy of fat deposits were observed in ewes.	[75]
	Abnormal growth in wool, and biochemical, hematological and histopathological disturbances in sheep.	[76]
	Hepatotoxicity in goats and sheep.	[148, 149]
	Severe clinical signs of toxicity and toxico-pathological changes in goats.	[150]
	Weight loss, changes in heart and respiratory rhythms, hair loss on the flanks, and keratosis of the nose and mouth in goats.	[151]
	Presence of leukopenia, anemia and an increased rate of erythrocyte fragility in goats.	[152]
	Disruption of some biochemical parameters in cattle.	[78]
Cadmium	Meat quality affected in goats.	[102]
	Decrease in the levels of zinc and copper in sheep and cattle.	[103]
	Cadmium toxicity associated with copper deficiency in cattle.	[51]

fluoride results in liver and kidney function disturbances associated with oxidative stress in rabbits, mice, and rats [32, 33]. Furthermore, chronic fluoride intoxication caused a significant decrease in the

weight of the testes, epididymis, and ventral prostate. It also negatively influenced sperm quality parameters and fertility rate in mice [34, 35]. Fluoride also affected blood and genetic parameters in rats and mice [23].

3.1.2. Effects of Fluoride on Ruminants

Several studies in many endemic areas reported the harmful effects of fluoride on ruminants such as cattle, sheep, goats, camels, and buffaloes [36, 37, 24]. In endemic areas of India, about 31.2% of mature animals and 10.7% of immature animals such as buffaloes, cattle, camels, goats, and sheep, showed signs of skeletal fluorosis like periosteal exostoses, intermittent lameness, and tendon stiffness in the legs [37]. Moreover, dental and skeletal fluorosis have been highlighted in this species in many other endemic areas such as Morocco, Turkey, and other countries [36, 38, 39, 40, 41, 42]. On the other hand, many studies reported the negative effects of fluorosis in soft tissue, genetic parameters, teratogenic effects, apoptosis, genotoxic effects, reproductive organs, and growth in ruminants [5, 43, 44].

3.2. Lead

Lead is a common heavy metal found in low concentrations in the Earth's crust [45], it has many biological properties in ruminants' bodies however it is highly toxic when it exceeded the recommended dose [46]. It is accumulated in the environment naturally and by anthropogenic activities [47, 48]. Lead toxicity has been reported in several countries around the world such as Nigeria, Mexico, India, China, France, and United States [49]. Exposure to lead in industrial regions induces several clinic pathological changes through toxicity occurring in the kidney and endocrine systems. Moreover, a high level of lead in ruminants resulted in reproductive failure [50]. The cattle are poisoned more frequently, followed by sheep and goats [51, 48]. Additionally, the bioaccumulation (a blood concentration ≥ 0.20 µg of Pb/mL) of this metal in meat and milk of some ruminants can be considered as a major risk for human public health [48, 52, 51].

3.2.1. Effects of Lead on Laboratory Animals

The researchers have reported various lead-induced toxic effects on laboratory animals [53]. The research on lead poisoning focuses primarily on its toxic effects on the kidneys, liver [54, 55], heart [56], and reproductive organs [50, 57]. In addition, the relationship between the toxicity of lead and the generation of oxidative stress [58, 59] has also been reported.

3.2.2. Effects of Lead on Ruminants

Toxicological studies reported several clinical symptoms in cattle, sheep, and goats [48]. The clinical signs generally presented in poisoned cattle are ill-thrift, emaciation, muscle wastage and developmental abnormalities in fetuses [60], opaque hair, thickening of phalange epiphyses, and moderate anemia [51]. Moreover, other studies have observed that lead poisoned cattle present severe depression, paresis of the hypoglossal nerve, ataxia, muscle twitching [61], convulsion, coma, respiratory failure, and death [62]. Swarup et al. [46] have reported a decrease in triiodothyronine (T3) and thyroxine (T4) concentration, and an increase in estradiol plasma concentration in some ruminants. On the other hand, lead poisoned sheep presented paralysis of hindlimbs, lameness, osteoporosis, abortion and transient infertility [61], nephrosis, osteoporosis, and fractures [60]. Whereas, goats presented moderate excitation, ataxia, weight loss, and pale mucous membranes [63].

3.3. Arsenic

Arsenic is a carcinogenic metalloid found ubiquitously in the form of organic and inorganic pollutants in water, soil, and air arising from natural and anthropogenic sources [64]. It is the 20th most abundant element on earth. According to the National Academy of Sciences Committee on Medical and

Biological Effects of Environmental Pollutants, the average of arsenic content in the earth's crust is 2.5 mg/kg with a concentration in soil ranging from 0.1 to 50 mg/kg [65]. In addition, the World Health Organization has recommended that the maximum allowable concentration of arsenic in drinking water is 10 μg/L. However, its concentration in some countries such as Bangladesh, China, India, Mexico, Argentina, Chile, the United States, and Brazil has been found in the range of 50-3200 μg/L [66]. Furthermore, arsenic is readily soluble in groundwater due to pH, redox conditions, temperature, and dissolution composition [67]. Accordingly, the exposition of this metal can lead to severe clinical manifestations [68].

3.3.1. Effects of Arsenic on Laboratory Animals

Since arsenic is a toxic agent, significant efforts have been made in recent decades to test its various toxic effects using animal models, especially rodents (rats and mice). Several studies reported that chronic exposure to arsenic induces carcinogenesis in rats and mice [69, 70]. Additionally, a large number of experimental toxicological studies on both sexes of rats and mice have shown remarkable toxic effects of arsenic on reproduction[71, 72]. Similarly, a study reported that chronic arsenic exposure resulted in the fatty liver with serum aminotransferase and alanine aminotransferase levels followed by hepatic fibrosis in mice [73]. Histological and hematological disturbances have been observed in the same species [74].

3.3.2. Effects of Arsenic on Ruminants

Many species including sheep, goats, and cattle have been documented to be susceptible to arsenic poisonings [5]. Due to the high level of arsenic contamination in a village located in northwestern Iran, sheep showed various clinical signs such as weakness, atrophy, and inappropriate integument. In the same study, microscopic observations revealed hyperemia in the kidneys and heavy parasite infestation of the abomasum wall [75]. In another study, biochemical, hematological, and histopathological disturbances were observed in the same species, after with the administration of 6.6 mg/kg of body weight of sodium arsenite mixed with water for 133 days [76]. Moreover, the effect of chronic arsenic poisoning in sheep was investigated in another study [61]. It revealed that this metal causes weight loss, weakness, languor, dry coat and alopecia, focal skin lesions, congested mucous membranes, and stomatitis. On the other hand, Selby et al. [77] reported that cattle showed signs of arsenic poisoning, such as severe irritation of the digestive tract. It also reported that cattle are more sensitive to arsenic poisoning than other animals [77, 35]. In the Ghentugachi village of Nadia district, West Bengal, India, the high level of arsenic in the drinking water showed arsenic concentration was above the permissible limit, cattle exhibited decreased superoxide dismutase and catalase activities, decreased erythrocyte level and plasma nitrite level, increased rate of lipid peroxidation, protein carbonyl, and blood arsenic level in cattle, compared to those raised in free areas [78].

3.4. Cadmium

Cadmium is a non-essential heavy metal [79], which can induce toxic effects in many animals. It is considered to be one of the most toxic elements in the environment, with a wide range of organ toxicity and a long elimination half-life [80]. Anthropogenic sources, resulting in contamination of forage, feed, and water, are sources of cadmium exposure in farmed ruminants in many regions [81]. Moreover, some geographic areas are also associated with high natural concentrations of cadmium such as Ireland [82, 83], Poland, Germany Sardinia [84]. Long-term chronic exposure to cadmium has been associated with anemia, anosmia, and cardiovascular disease [85]. In affected areas, chronic ingestion or inhalation of cadmium can result in several adverse effects in ruminants, mainly in the liver and kidneys [86, 87]. Furthermore, this metal can affect growth rate [88] and reproduction [89]. Chronic ingestion of 2-5 mg/kg body weight per day for one year produced subclinical effects [90]. For that, Wilkinson et al. [91] proposed that the livers and kidneys of adult ruminants reared in contaminated areas for more than one grazing season be removed from the human food chain to reduce the risk of cadmium intake by the human population.

3.4.1. Effects of Cadmium on Laboratory Animals

Several experimental studies reported that cadmium results in carcinogenesis of various organs mainly kidney, lung, liver, and prostate cancer [92, 93]. In another study, exposure to cadmium increased uterine wet weight, promoted growth, and development of the mammary glands, and induced hormone-regulated genes in female rats [94]. Other toxic effects of cadmium on reproduction have been reported by Zhu et al. [95] such as damaged seminiferous tubules [96], production of reactive oxygen species, a decrease of spermatogonia number, and a decrease in sperm motility and count [97, 98]. On the other hand, it showed pathological testicular alterations, and liver and kidney damage after chronic exposure to cadmium in rats [99]. Moreover, other studies reported that the administration of cadmium inhibited superoxide dismutase (SOD) activity, increased endogenous levels of lipid peroxides, and increased lipid peroxidation in liver and kidney tissues in rats [100].

3.4.2. Effects of Cadmium on Ruminants

A study reported that cadmium poisoned sheep results in a significant reduction in humoral immunity [101]. Moreover, high levels of cadmium have been recorded in the liver, kidneys and muscles of goats grazing on areas highly contaminated with cadmium in Nsukka-Nigeria, this also affected their meat quality [102]. On the sewage treatment field of Marrakech-Morocco, the high level of cadmium found in the muscles, liver, kidneys, and bones of sheep and cattle has led to a disruption of the normal metabolism of trace elements, and decreasing the levels of zinc and copper [103].

4. Mechanisms of Environmental Pollutants Toxicity

After their ingestion and distribution through food or water into the body of animals, the environmental poisons exert their effects by different pathways, according to their chemical activities, biological features, and cellular targets [15, 104]. The toxicity mechanisms of environmental pollutants toxicity are not yet clear. While some studies claim that these pollutants induce their toxicity in biological systems by binding the sulfhydryl groups and generating reactive oxygen species [104]. More precisely, these pollutants are acidified in the body and oxidized to their various oxidative states. Hence, they can readily bind to biological molecules such as cations, proteins, and enzymes to form stable and strong bonds [105]. For instance, as fluoride is highly electronegative with a strong affinity towards electropositive elements, it binds with calcium, reducing their absorption and causing dental fluorosis and skeletal fluorosis [7]. Moreover, fluoride has been reported to bind to other divalent cations and inhibit many enzymes involved in the pentose phosphate pathway, antioxidant defense system, and myosin-ATPase activity [8, 106]. On the other hand, arsenic, cadmium, and lead can bind to the thiol (-SH) groups of certain enzymes and proteins, and modify their cysteine residues. In addition, they can bind to lipids and nucleic acids altering several biological activities in animals [104, 107]. Arsenic, lead, and cadmium metal ions have the ability to substitute the divalent cations such as Ca^{2+}, Mg^{2+}, Fe^{2+} and monovalent cations such as Na^{+} and K^{+}, and causes significant changes in various biological processes such as cell adhesion, intra-, and intercellular signaling, protein folding, maturation, apoptosis, ion transport, enzyme regulation and neurotransmitter release [53, 108, 109].

5. Prevention Dietary Strategies Against Environmental Pollutants

To prevent or reduce toxicity from environmental pollutants, several preclinical and clinical studies have tested heavy metals supplementation as chelating agents to promote pollutants excretion, or synthetic antioxidants to correct the oxidative stress generated. However, these therapeutic strategies are themselves reported to have a number of different safety and efficacy concerns. Hence, several recent studies have been directed towards medicinal plants (Table 3 and 4) as natural sources of biomolecules, such as essential metals and antioxidants, which can simultaneously exercise the two therapeutic strategies, chelation and free radical scavenging [110].

Table 3. Selected studies natural products having ameliorative effects against fluoride, lead, arsenic and cadmium toxicities in laboratory animals

Element	Natural product	Effects	References
Fluoride	*Spirulina platensis*	Ameliorates behavioral changes, neuronal damage, and thyroid dysfunction in rats	[117]
	Emblica officinalis	Protective effect against hyperlipidemia and oxidative stress in rats	[153]
	Tamarindus indicia	Increase in urinary excretion and decrease in retention of fluoride in bones rats	[154]
Lead	*Lycopersicon esculentum*	Prevention of oxidative stress in blood plasma and kidney in rats	[155]
	Camellia sinensis	Alleviates the oxidative stress in the liver, and regulates hepatic metabolism in rats	[156]
	Camellia sinensis	Reduces lead levels and improves renal functions in rats	[157]
	Allium sativum and *Zingiber officinale*	Reduces blood lead levels, and regulates the hepatic and testicular cytoarchitecture in rats	[158]
Arsenic	*Withania somnifera*	Maintains the cellular integrity of testicular cells and improves sperm quality parameters in rats	[126]
	Ipomea aquatica	Amelioration of antioxidant parameters in liver, kidney, heart, brain and testis in mice	[127]
	Tamarindus indica	Regulation of serum hepatic and oxidative stress markers in rats	[128]
	Triticum aestivum	Attenuates arsenic-induced oxidative stress, normalizes body weight, organ weight, hematological profiles, serum biochemical profile and modulates liver and kidney biochemical parameters in rats	[159]
	Moringa oleifera	Reduces the elevation of serum triglycerides, glucose, urea, alkaline phosphatase, aspartate aminotransferase and alanine aminotransferase activities in mice	[132]
Cadmium	Glycine max	Ameliorates cardiac, and aorta oxidative stress in rats	[122]
	Sesamum indicum	Reduces serum levels, and cardiac biochemical parameters in rats	[123]
	Satureja hortensis	Prevents the cadmium induced lesions in hepatic functions in rats	[161]
	Withania somnifera	Reduces oxidative stress in testis in rats	[162]
	Royal jelly	Attenuates cadmium induced nephrotoxicity in mice	[129]
	Terminalia chebula	Decreases serum uric acid, urea, creatinine and total protein levels, and regulates serum lipid profiles and liver biomarkers in rats	[130]

Moreover, these natural resources provide a great variety of other nutrients, such as protein, and secondary metabolites, which have been reported to have beneficial effects against environmental pollutants [111]. Firstly, several preclinical studies on the protective effects of natural products against

these pollutants were carried out on laboratory animals. Then, other studies addressed some ruminants with encouraging levels of success. Because of their low cost, availability, and low or no side effects even at high doses [24], several preclinical studies have tested herbal medicine such as *Tamarindus indicia* [112, 113], *Terminalia arjuna* [114], *Mangifera indica* [115], *Curcuma longa* [116], *Spirulina platensis* [117] and *Aloe vera* [118]. These natural products revealed encouraging results against environmental pollutants toxicities.

Table 4. Studies on the effects of natural products against fluoride, lead and arsenic toxicities in ruminants

Element	Natural product	Effects	References
Fluoride	*Tamarindus indicia*	Reduce in serum fluoride and urinary hydroxyproline concentrations, increase in serum calcium level in cattle.	[119]
	Tamarindus indicia	Increase in calcium level and serum alkaline phosphatase activity, decrease in serum hydroxyproline level in cattle.	[7]
	Plants rich in vitamins C and D	Reduces dental and bone damage in sheep.	[163]
Lead	*Allium sativum*	Reduces serum lead concentration and increases urine lead concentration in goats.	[121]
	Allium sativum	Reduces blood, kidney, bone and ovary lead levels in sheep.	[120]
Arsenic	*Curcuma Longa* and *Passiflora foetida*	Reduce the absorption of arsenic from the body, restore normal liver and kidney function, protect against oxidative stress and prevent DNA damage in sheep.	[116]
	Curcuma longa and *Zingiber officinale*	Remove arsenic from the body and protect against potential damage in calve.	[132]
	Curcuma longa and *Amaranthus spinosus*	Remove arsenic from the body and protect against DNA fragmentation in cattle.	[131]

5.1. Fluoride Toxicity Prevention

Tamarindus indica contains has a wide range of antioxidants (L-ascorbic acid, alpha-tocopherol, carotenes), essential minerals, proteins, sugars, phytosterols, and triterpenes [113]. Additionally, its beneficial ameliorative effects against fluorosis in laboratory animals was reported [112, 113]. Recent studies have tested its effects in fluorotic cattle [7, 119]. Gupta et al. [119] reported that the supplementation of fluorotic cattle with 100 g of dried powder of *Tamarindus indica* fruit pulp for 90 days, resulted in a significant increase in serum calcium and alkaline phosphatase levels, and a decrease in urinary hydroxyproline compared to fluorotic cattle not supplemented [119]. Furthermore, it was shown that chronic fluoride intoxication caused a significant decrease in plasma copper, zinc and iron concentration in cattle, while these parameters were increased in fluoridated cattle supplemented with dried powder of *Tamarindus indica* fruit pulp [7].

5.2. Lead toxicity Prevention

To prevent lead poisoning several dietary strategies have been tested in the laboratory animals, like *Allium sativum*, *Lycopersicon esculentum*, *Camellia sinensis*, and *Zingiber officinale*, and it was concluded that intake of diets rich in natural products may be helpful in preventing lead poisoning [111]. Furthermore, the ameliorative effect of *Allium sativum* against this intoxication has been evaluated in small ruminants, and it has been reported that this plant reduced kidney, bone, and ovary lead contents in sheep [120]. Additionally, it reduced bones, lungs, heart, liver, kidneys and skeletal muscles lead levels in goats [121].

5.3. Arsenic and Cadmium Toxicity Prevention

A large number of researches confirmed the beneficial effect of *Glycine max* [122], *Sesamum indicum* [123], *Satureja hortensis* [124] *Withania somnifera* [125, 126], *Ipomea aquatica* [127], *Tamarindus indica* [128], Royal jelly [129], and *Terminalia chebula* [130] on arsenic and cadmium toxicities reduction. Concerning the effects of natural products on arsenic toxicity in ruminants, it was reported that *Curcuma longa*, *Zingiber officinale*, and *Amaranthus spinosus* have eliminated the absorption of arsenic from the bovine body and protected against DNA fragmentation in these species [131, 132]. In a recent study, *Curcuma longa* powder and *Paederia foetida* powder were effectively able to remove arsenic from the body of arsenicosis induced by sodium arsenite in sheep. These two plants also helped to protect against arsenic damage, restored normal liver and kidney function, protected against oxidative stress, and prevented DNA damage [116]. In addition, the improving effects of *Curcuma longa* powder were better than those of *Paederia foetida* powder [116]. Contrastingly, until now there are no studies carried out on the evaluation of the ameliorative effects of natural plants on cadmium toxicity in ruminants.

6. Conclusion

This study has highlighted the importance of using natural products in the prevention and reduction of the toxic effects of fluoride, lead, arsenic, and cadmium in laboratory animals as well as in ruminants. Plant species (*Tamarindus indicia* and *Allium sativum*) have been reported as promising new approaches to prevent of these poisonings. Other less-researched natural products may offer promising starting points for future studies, such as *Spirulina platensis* as a rich source of protein, minerals, and antioxidants. We expect that this review will stimulate further research, especially in endemic countries. On the other hand, we suggest more toxicity studies of these natural products in ruminants to prevent their indiscriminate use. In addition, it is absolutely necessary to raise public awareness of the importance of these precious resources in the treatment of these toxicities in ruminants. Finally, studies must also be oriented towards the integration of these natural products in the diet intended for endemic regions to facilitate their uses and applications.

ORCID
Abdellatif Rahim: 0000-0001-5832-1710
Fatma Aydogmus-Öztürk: 0000-0001-6070-7452
Cansel Cakir: 0000-0002-6175-9008
Abdelkhalid Essamadi: 0000-0003-4537-1684
Bouchra El Amiri: 0000-0003-3443-5988

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