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ANNALS OF
Environmental Science and Toxicology

ISSN: 2641-2969 DOI: https://dx.doi.org/10.17352/aest

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Dates: Received: 30 December, 2016; **Accepted:** 17 January, 2017; **Published:** 21 January, 2017

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Keywords: Ameliorative measures; Fluoride toxicity; Human Health; Oxidative stress

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Review Article

Fluoride Sources, Toxicity and Its Amelioration: A Review

Abstract

In recent scenario, fluorosis is now going to be a severe problem throughout the globe due to toxic effects of fluoride (F) on both plants and animals. F presents in the halogenated group of the periodic table and has the characteristics of electronegativity. Natural geological sources and increased industrialization have contributed greatly to the increasing incidence of fluoride-induced human and animal health issues. In animals and human beings, it exerts adverse effects mainly through the attenuation of antioxidant defense mechanism and chelation of enzymatic cofactors. Thereafter, it causes metabolic disorders through interacting with various cellular processes such as gene expression, cell cycle, metabolism, ion transport, hormonal secretion, endocytosis, apoptosis, necrosis, and oxidative stress. These effects lead to dental mottling, skeletal dysfunctions including crippling deformities, osteoporosis, and other vital organs dysfunction. It was found that, water is the main source of fluoride intake to plants and animals, which further may go into food chain of human beings through consumption of high fluoride content plant and animal origin food. Several preventive and control measures have been developed to ameliorate the fluoride toxicity, like application of synthetic chemicals, plants bioactive molecules, and plant products like fruit pulp, seed mixture, and plant buckle products. Therefore, this article presents up-to-date information on the fluoride sources, toxicity and different amelioration measures to reduce fluoride level directly from water as well as application of different natural/synthetic products/molecules to ameliorate the toxic effects of fluoride in *in-vivo* models.

Introduction

In the halides group of the periodic table, fluoride (F) has great importancy due to its smallest size and most electro negativity. Although the mechanisms of F in biological forms are remains unclear but it has the unique chemical and biochemical properties for the size and reactivity [1-3]. It is ubiquitously present in soil, water, plants and air. In the animal body, F makes its presence through water and food. But, some of the recent studies indicate that, most of the F comes from pharmaceutical drugs (20%) and through agrochemicals (30-40%) [4,5]. The variability and presence of fluoride depends upon the location. It was found that F is present in the soil within the range of 10-1000 parts per million (ppm). However, in water it ranges from 0.5 to 2000 ppm. This incident depends upon the sources of water [6,7]. According to World Health Organization (WHO), F exposure to animals above the 1.5 ppm, set at chronic fluoride toxicity. Through water exposure, this type of toxicity is going to endemic in most of the countries across the world [8]. In USA, the normal level of F in drinking water is 4 mg/L [9]. But, in the European country, it is 0.8 ppm [10]. In India, most of the states are showing the greater level of F in drinking water [11]. Fluoride exerts its effects on plants also [12]. It attenuates all the cells and tissues, impaired the stomatal conductance. Simultaneously, it acts as the metabolic and reproductive inhibitor, impaired photosynthesis and respiration pathways. Ultimately, F caused even to plants death [13-18]. In animals, fluoride intoxication causing skeletal impairment, called as skeletal fluorosis. Recently, high fluoride intake has been associated with dental cancer and tumors of other organs. First clinical symptoms appeared like reduced in food intake and loss of body weight gain. After attenuating the antioxidant defence mechanism, F also affect to the gastrointestinal tract, brain, muscle etc.. [19-22]. To ameliorate these effects, several types of synthetic chemicals, herbal drugs, plant bioactive molecule, and plant natural products have been incorporated in the medicinal documentary. For example, melatonin, pineal proteins (epiphyseal proteins), quercetin, curcumin, ascorbic acid, lipoic acid, flavonoids, polyphenols have been found great role against the F toxicity [23-26]. The present review critically discusses on the fluoride sources, worldwide levels and its toxic effects on plants and animals. Furthermore, the article discusses the recent ameliorative steps developed through synthetic chemicals, plant bioactive molecules, and plant natural products.

Citation: Bharti VK, Giri A, Kumar K (2017) Fluoride Sources, Toxicity and Its Amelioration: A Review. Ann Environ Sci Toxicol 2(1): 021-032.
DOI: https://dx.doi.org/10.17352/aest.000009

Biochemistry of fluoride

In the halides group of the periodic tables (group VII), among all other molecules, fluoride has the great importancy due to it's smallest size and most electro negativity. Although, the mechanisms of F in biological forms are remains unclear but it has the unique chemical and biochemical properties for the size and reactivity [1-3]. It is 13th most abundant element and distributed widely throughout the earth in soil, water, and food. F, a pale yellow colored gas, has atomic number 9 and atomic weight of 18.9984 at standard temperature and pressure [27]. The brief about the F, have been mentioned in the Figure 1 [28]. It has the tendency to exist in the Free State as diatomic molecules. Due to electromotivity characteristics, these can react with less electromotive elements or chemical groups. Fluoride compounds are formed when the element fluoride combines with other chemical elements. It does not occur in a free state in nature [28]. Fluoride however has many unique chemical properties. These properties had a great impact on the special biochemical physiological effects. For these reason, F can affect the metabolism and mechanisms of action within the living system [29]. In addition to the chemical properties and isotopic nature of fluorine has had an important impact on our understanding of the metabolism, toxicity, and therapeutic effects of fluoride. 19-F is one of the isotopes of F and occurs naturally. This isotope has the extremely short half-life.

Sources of fluoride

Natural and anthropogenic sources are the two main ways through which F entered in the environment [30].

Natural sources

Soil: The normal total fluoride content of soil ranges from 150-400 mg/kg. F level in the clay soil is 1000 mg/kg [31]. F contamination to soil is because of the utilization of phosphorus fertilizers which have total 1-1.5% fluorine [32]. Contaminated soil with F, show it's toxicity after the inhalation of soil contaminants which have vapourized or through the contaminated ground water after the F leaching from the soil [33-35].

Water: Water containing the F concentration up to 1.0 mg/L is safe. Whereas, the F levels in between 1.1 and 2.5 mg/L are marginally contaminated. However, above 2.6 mg/L F level is determined as the highly contaminated [31]. It was found that the level of F in ground water is higher than the surface water as the F percolates from the soil to ground water through leaching process. There are several factors which are responsible for the presence of F in natural ground water from the soil. Among them, geological factors, consistency of the soil, nature of rocks, pH and temperature of the soil, chelating action of other elements, depth of wells, leakage of shallow groundwater, and chemical and physical characteristics of water [36]. Water is an important source of F exposure to human beings and animals.

Forage, grasses and grains: At the vicinity of industrialized area, it was found that forages and grasses contain the higher level of F than the other area. Some studies also found that, grasses and forages has the higher level of F than the industrialized area. It is due to the fluoride rich dust, ash, raining factors for which plants could be affected far from the industry. Plants contamination depends upon several factors like the amount of F released in to the atmosphere, distance between the F source and contaminated area, type of vegetation, height of plants, atmospheric condition, and seasons etc. [37-39]. It has been established the relationship between the F level in soil and plants of F will be increased by 3 ppm for each 100 ppm increase in soil F up to the 2200 ppm [39].

Volcanic activities: Due to volcanic eruption, animals and plants kingdom have been affected throughout the globe (Table 1). Volcanic ash contains high level of F and contaminations of F to the geochemical cycle are frequent. From the volcanic eruption, F has been released in the form of hydrogen fluoride. Erupted F may covered several places and stay for many years. After decaying and leaching, F caused severe casualty to domestic and wild animals [6,40,41].

Anthropogenic sources

Anthropogenic fluoride contamination happens by human activities like industrialization, motorization, fluoride

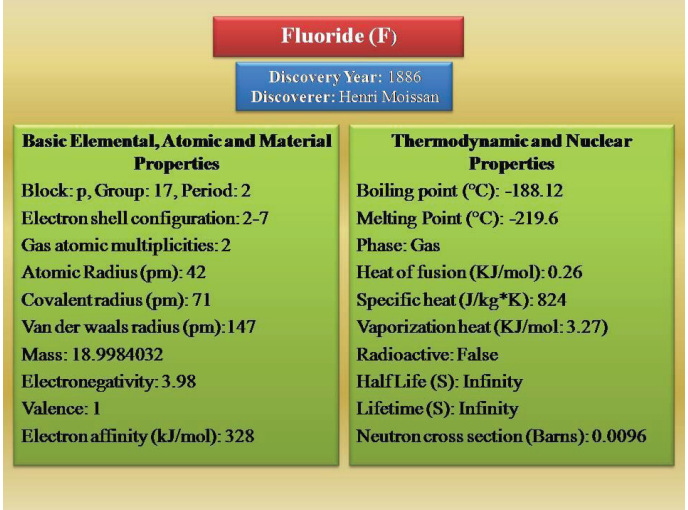

Figure 1: Basic properties of Fluoride [Source: 28].

Table 1: Volcanic eruption leads to increase in Fluoride exposure.

Sl. No.	Country	Casulty	References
01	Hekla volcano, Iceland	F concentration was 350–4300 µg/g.	[42]
02	Lonquimay volcano, Chile	Affected more than 10,000 farm animals. Death occurred of more than 4000 livestock animals.	[43]
03	Ruapehu volcano, Mexico	Livestock and wild animals dead.	[44]
04	Puyehue–Cordon Caulle volcano, Argentina	Severe fluorotic dental lesions were observed in died wild red deer.	[45]
05	Hekla volcano, Iceland	Livestock and wild animals died.	[44]

*Sl. No.-serial number.

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containing pesticides, fluoridation of drinking water supplies, dental products, refrigerants, and fire extinguishers [46,47]. F contamination due to airborne sources also occurred. The mean F concentration in normal areas (unpolluted/non-industrialized) is generally less than 0.1 µg/m³. The levels may be slightly higher in the vicinity of industries, but should not exceed 2–3 µg/m³ [6]. In many countries, coal burning for household purposes was documented as the main source of F causing endemic fluorosis [48,49]. Industrial release fluoride-rich fumes and effluents into the environment also caused casualty in livestock sector like cattle, buffaloes, sheep, goats, camels etc. [50-55]. There are several reports documenting mineral mixture supplements as a major source of fluoride toxicity in livestock [56]. Moreover, incorporation of modern creation and utilization of chemicals in different sectors like hydrogen fluoride (HF), calcium fluoride (CaF), sodium fluoride (NaF), fluorosilicic corrosive (H SiF), sodium hexafluorosilicate (Na SiF), sulfur hexafluoride (SF), and phosphate manures are the main sources of fluoride.

Global scenario of fluoride levels

Around the globe, twenty three nations are belongs to the critical region regarding the fluoride level. Among them India is also present. Billions of people are affected due to fluoride exposure. In India, twenty million people are severely affected by fluorosis and 40 million people are exposed to risk of endemic fluorosis [57]. Level of fluoride in drinking water throughout the globe has been tabulated in the Table 2.

Fluoride toxicity

In Animals: Chronic exposure to F induces an array of deleterious impacts in livestock animals, experimental animals, as well as humans also [6,97,98]. First symptoms of chronic F toxicity in animals are reduced feed intake and body weight gain (BWG) loss [19,22]. Prolonged exposure to F causes fluorosis, leading to a progressive degenerative disease, dental mottling and several types of skeletal dysfunctions [4]. Main mechanism of these deformities, after exposure of F is mainly the generation of different types of ROS production (Table 3). Experimental evidence (Tables 4,5) has indicated that exposure to fluoride results in oxidative stress both in vitro and in vivo in soft tissues such as liver, kidney, brain, lungs etc. Fluoride inhibits the activities of antioxidant enzymes like superoxide dismutase, glutathione peroxidase and catalase and reduces levels of glutathione. Glutathione reduction leads to overproduction of reactive oxygen species at the mitochondrial level, resulting in damage of cellular components. Besides, production of excessive reactive oxygen species results in oxidation of macromolecules, membrane phospholipid breakdown, lipid peroxidation, mitochondrial membrane depolarization and apoptosis (Tables 4,5). Neurodegeneration also occurred due to the F exposure. Several studies indicated that hippocampus of rat brain can lead to the degenerate due to the imbalance between oxidant– antioxidant balance. F crossed the blood brain barrier (BBB) easily and induces neural cell degeneration [24,99-101]. All the effects of fluoride are summarized in the Tables 4,5.

Amelioration of fluoride toxicity

Table 2: Fluoride level in drinking water sources throughout the globe.

Sl. No.	Country Name	Fluoride level	References
01	Pilanesberg and Western Bushveld, South Africa	30 mg/L	[20]
02	Sanddrif, Kuboes and Leeu Gamka, South Africa	30 mg/L	[58,59]
03	Ivory coast, Africa	Above permissible limit	[60]
04	Bongo, Ghana	0.11-4.6 mg/L	[61]
05	Lakes Elmentaita and Nukuru, Kenya	2–20 mg/L	[62-64]
06	Tibiri, Nigeria	4.7–6.6 mg/L	[65]
07	Senegal	4.6-7.4 mg/L	[66]
08	Tanzania	8.0-12.7 mg/L	[67]
09	Rift Valley, Uganda	0.5-2.5 mg/L	[68]
10	Abu Deleig and Jebel Gaili, Sudan	0.65–3.2 mg/L	[69,70]
11	Hail, Saudi Arabia	2.8 mg/L	[71]
12	Mecca, Saudi Arabia	2.5 mg/L	[72]
13	Middle and eastern part of Turkey	13.7 mg/L	[46]
14	Alberta, Canada	4.3 mg/L	[46,73,74]
15	Saskatchew, Canada	2.3 mg/L	[73]
16	Quebec, Canada	2.5 mg/L	[73]
17	Rigolet, Canada	0.1–3.8 mg/L	[73]
18	Coronel Dorrego, Argentina	0.9–18.2 mg/L	[75]
19	Olho D'Agua, Brazil	2–3 mg/L	[76]
20	Wonji-Shoa sugar estates, Ethiopia	1.5–177 mg/L	[77,78]
21	Hermosillo and Abasolo, Mexico	1.5 to 2.8 mg/L	[79]
22	Illinois, USA	1.06-4.07 mg/L	[80]
23	Texas, USA	0.3-4.3 mg/L	[81]
24	Czech republic	>3 mg/L	[82]
25	Munster, Germany	8.8 mg/L	[83]
26	Pohang and Gyeongju, Korea	>5 mg/L	[84]
27	Hordaland, Norway	0.02–9.48 mg/L	[85]
28	Northern and Central Poland	>3 mg/L	[86]
29	Tenerife, Spain	2.50-4.59 mg/L	[87]
30	Kuitan, Chaina	21.5 mg/L	[7,88]
31	Finland	>3 mg/L	[89]
32	Japan	1.4 mg/L	[90]
33	Indonesia	0.1–4.2 mg/L	[7]
34	Thailand	>0.9 ppm	[91]
35	North Central Province, Sri Lanka	10 mg/L	[92]
35	India	0.5-69.7 mg/L	[7,93-95]
37	Pakistan	8–13.52 mg/L	[96]

Table 3: Summary of reactive oxygen and nitrogen species [Source: 28]

Reactive Oxygen Species				Reactive Nitrogen Species			
Free Radicals		**Other Substances**		**Free Radicals**		**Other Substances**	
Superoxide anion radical	$O_2^{\cdot -}$	Hydrogen peroxide	H_2O_2	Nitric oxide radical	$NO^{\cdot}$	Peroxy nitrite	$ONOO^-$
Hydroxyl radical	$HO^{\cdot}$	Hypochlorous acid	HOCl	Nitric dioxide radical	$NO_2^{\cdot}$	Nitrites	NO_2^-
Alkoxyl radical	$RO^{\cdot}$	Ozone	O_3			Nitrates	NO_3^-
Peroxyl radical	$ROO^{\cdot}$	Singlet oxygen	$^1O_2$			Nitrosyl	NO^+

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Table 4: Modulation of different oxidative biomarkers during hepatic oxidative damages occurs on high exposure of fluoride.

Type of the study	Model & Dosage	End point*	References
In-vitro (Animal cells)	Mouse pancreatic beta-cells (ßTC-6) at 1.35 and 2.5mM for 12 h	↑Generation of O_2^-, ↓activity of SOD, ↓Δψ m	[102]
	Primary rat hippocampal neurons at 20, 40, and 80 mg/l, equivalent to 1.05, 2.1 and 4.2mM for 24 h	↑Generation of ROS, ↓level of GSH, ↓activities of GSH-Px, and SOD, ↑lipid peroxidation	[103]
	Murine hepatocytes at 100mM for 1 h	↑Generation of ROS, ↓level of GSH, ↓GSH:GSSG ratio, ↓activities of SOD, and catalase, ↑lipid peroxidation, and oxidation of proteins	[104]
In-vitro (Human Cells)	Hepatocellular carcinoma (HepG2) cells at 3mM for 6 and 24 h	↑GSH/GSSG ratio, ↑gene expression of Mn-SOD	[105]
	Neuroblastoma (SH-SY5Y) cells exposed at 0.05–5mM for 24 h	↑Lipid peroxidation, and ↑protein oxidation	[106]
In vivo (Animals)	Male albino guinea pigs exposed at 250mg NaF/kg subcutaneously and sacrificed 8 h later	↑Generation of NO in blood	[107]
	Male Wistar rats exposed at 5mg/kg body mass/day, orally for 8 weeks	↑Generation O_2^-, ↓activity of SOD, ↓Δψm, ↑lipid peroxidation in spermatozoa	[108]
	Male Swiss mice exposed at 50 mg/L in drinking water for 10 weeks	↑Generation of ROS, ↑lipid peroxidation, ↓activities of SOD, and catalase, ↑activities of GST, and GSH-Px, ↑ratio GSH:GSSG in brain	[109]
	Albino rats exposed at 100 mg/L in drinking water for 4 months	↑Level of ascorbic acid ↓ level of uric acid in plasma ↑Lipid peroxidation, ↑level of GSH, ↑activity of GSH–Px, ↓activity of SOD in erythrocytes ↑Lipid peroxidation, ↑activities of GSH-Px, and GST, ↑GSH in brain and liver	[109]
	Male albino Wistar rats exposed at 1, 10, 50, and 100 mg/L in drinking water for 12 weeks	↑Generation ROS, changes in levels of GSH in blood, ↑generation ROS in liver, kidney, and brain	[110]
	Second generation of Male Albino adult Wistar rats exposed at 10, 50, and 100 mg/L in drinking water for 180 days	↑Lipid peroxidation, ↓activities of SOD, catalase, and GSH-Px in lung	[111]
	Chicks exposed by diet to 100, 250, or 400 mg F/kg for 50 days	↑Generation of NO, ↑lipid peroxidation, ↓activities of SOD, catalase, and GSH-Px in serum	[112]
	Male albino rats exposed at 10.3 mg NaF/kg body weight/day, orally for 5 weeks	↑Lipid peroxidation, ↑generation NO, ↓activities of SOD, and catalase, ↓Total antioxidant capacity, and ↓level of GSH in liver	[113]
	Pig exposed to food supplemented with 250 mg F/kg for 50 days	↓Expression of gen Cu/Zn SOD in liver	[114]
	Male rats exposed at 20 mg/kg/day for 29 days by oral gavage	↑Level of conjugated dienes in the testis, epididymis, and epididymal sperm pellet. ↓activities of GDH-Px, and catalase in the sperm	[115]
	Male Wistar rats exposed at 50 and 100 mg/L in drinking water during 4 months	↓Activity of CuZn-SOD in pancreas	[116]
	Male and female Wistar rats exposed at 50, 100, and 150 mg/L in drinking water during 3 months	↑Lipid peroxidation, ↓activities of SOD, and GSH-Px in liver	[116]
	Barrows exposed at 250 and 400 mg/kg (from NaF) in their diets for 50 days	↑Generation of NO, ↑lipid peroxidation, ↓activities of GSH–Px, and SOD in serum ↑Lipid peroxidation, ↓activities of GSH-Px, and SOD in thyroid, liver, and kidney	[117]
	Male Swiss mice exposed at 5 mg/kg body mass/day, orally for 8 weeks	↑ROS in erythrocytes, ↓level of GSH in blood, ↓activities of SOD, catalase, and GSH-Px, ↑lipid peroxidation, in kidney and liver	[118]
	Female rats exposed at 100 mg/L in drinking water for 60 days	↑Lipid peroxidation, ↓activities of SOD, catalase, and GSH-Px in endometrium	[119]

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	Swiss albino male mice exposed at 50 mg/L in drinking water for 3 weeks	↑Generation of ROS, ↓GSH level, ↓activity of SOD in βλοοδ, ↑activity of catalase in liver	[120]
	Male albino rats exposed at 10, 50 and 100 mg/L in drinking water for 10 weeks	↑Generation ROS in blood, liver, kidney, and brain ↓GSH/GSSG ratio in liver, kidney, and brain	[121]
	Female Albino mice exposed 5 mg/kg body weight/day, orally for 30 days	↓Activities of SOD, catalase, and GSH–Px, ↓level of GSH, ↓total, dehydro and reduced ascorbic acid, ↑lipid peroxidation in ovary	[122]
	Male Balb/c mice exposed at 200 mg/L, in drinking water for 7 days	↓Activities of SOD, GSH-Px, and catalase, ↑lipid peroxidation, in erythrocytes, and liver	[123]
	Female Wistar rats exposed at 150 mg/L in drinking water for 28 days	↓Level of GSH, ↓activities of SOD, GPx, catalase and, glutathione reductase, ↑lipid peroxidation in brain	[101]
	Wistar albino pups placentally and lactationally exposed from mother rats at 50, and 150 mg/L in drinking water	↑Lipid peroxidation, ↑protein oxidation in developing central nervous system	[124]
In-vivo (Human Cells)	Residents from China-endemic area (mean urine concentration of 2mgF/L)	↓Activities of SOD, catalase, and GSH-Px ↑Lipid peroxidation, in serum	[125]
	Children with skeletal fluorosis from Indian-endemic area (mean water concentration of 5.53mgF/L)	↑Level of ascorbic acid, ↓level of uric acid in plasma ↑Lipid peroxidation, ↓GSH, ↓activities of SOD and GSH–Px in erythrocytes	[126]

*Arrows refer to increases (↑) or decreases (↓) regulation [Source: 28].

Table 5: Regulation of apoptotic and cytokines related gene expression by fluoride exposure [Source: 28].

Type of the study	Model & Dosages	End point	References
In vitro (Human cells)	Neuroblastoma (SH-SY5Y) cells at 40, and 80 mg/L, equivalent to 2.1, and 4.2mM for 24 h	↑Apoptosis molecules Fas, Fas-L, and caspases 3 and 8.	[127]
In vivo (Humans)	Peripheral blood mononuclear cells from Mexican individuals drinking water with levels of 1.9–4.02mgF/L	↓Inflammatory Chemokines (CCL1, CCL18, CCL19), ↓cytokines (IL-11; IL-2), ↓pro- and anti-inflammatory molecules (LTA, TNF-a, TGF-a, TGF-b1,and TGF-b3), ↓Apoptosis molecules (TNF-a, FasL, CD30L, 4-IBBL, TANK, TRAIL, DR3, Casp-2, Casp6, CIDE-A and CIDE-B), ↑survivine	[128]

Arrows refer to increases (↑) or decreases (↓) genes regulation.

Recently, various studies have been conducted in various fields like development of different techniques to reduce the fluoride level from the water sources directly, use plant metabolites on the experimental animals, and use of different chemical/molecule (melatonin, pineal protein, quercetin etc.). In case of different techniques, several natural and chemical adsorbents such as red soil, charcoal, brick, Waste tea ash, fly-ash, serpentine, alum, Activated carbon, Al-Fe (hydr) oxides, sulfate-doped Fe_3O_4/Al_2O_3 nanoparticles, aluminum salts etc have been used (Table 6). On the other hand, use of leaves, seeds, fruit pulps, plant juices of *Azadirachta indica*, *Ficus religiosa*, *Acacia catechu*, *Peltiphyllum peltatum* and tamarind seeds etc. are also using to reduce the toxic effects of fluoride and summarized in the Table 7. Additionally, some synthetic chemical molecules like melatonin, pineal protein, lycopene, and quercetin, etc. also have the great role to reduce the fluoride induced toxicity. All are summarized in the Table 8.

Conclusions

Through this review, it is summarized that having the electronegativity, fluoride is ubiquitously present in the environments. In some countries it is within the range, whereas most of the countries which have been reviewed showed more than the permissible level as per guideline recommended by WHO. Among different sources, water is the important source of fluoride exposure. Hence, water purification techniques should be developed for safe and economic method for portable water. High fluoride exposure affects human beings and animals health through oxidative stress, immune suppression, apoptosis, and affecting nutrient utilization. Hence, ameliorative measures are important to prevent their endemicity and disease progress. Meanwhile, plant bioactive molecules, several synthetic molecules, and pineal gland secretions have shown protective effect against fluoride toxicity. However, more extensive studies are required for wide application of these molecules as therapeutics agents.

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Table 6: Available technologies for removal of fluoride in water.

Sl. No.	Technique for water defluoridation	Component Used	References
01	Adsorption	Al-Fe (hydr)oxides	[129]
02	Adsorption	Sulfate-doped Fe_3O_4/Al_2O_3 nanoparticles	[130]
03	Adsorption	Waste tea ash	[131]
04	Adsorption	Neem charcoal	[132]
05	Adsorption	Calcined bauxite, gypsum, magnesite and their composite filter	[133]
06	Adsorption	Activated alumina	[134-136]
07	Adsorption	Bone char	[67,137]
08	Adsorption	Activated carbon	[138,119]
09	Adsorption	Palm kernel shell-based adsorbent	[140]
10	Adsorption	Rice husk and activated charcoal	[141]
11	Anion Exchange	Leaf biomass	[142]
12	Electrochemical method	-	[143]
13	Coagulation	Aluminum salts	[144]
14	electro- dialysis	-	[145]
15	Reverse osmosis	-	[146]
16	Nanofiltration	-	[147]
17	Membrane processes	-	[148]

Table 7: Experimental studies on plant based natural products in amelioration of fluoride toxicity.

Sl. No.	Species of experimental animals	Fluoride dose and route of administration	Duration of study	Dose and route plants	Effect on studied parameters	References
01.	Adult male Wistar albino rats	10.3 mg/kg bw/day; Oral	35 days	Black berry juice, 1.6 g/kg bw administered perorally	↑Glutathione level, total anti-oxidant capacity and superoxide dismutase activity	[149]
02.	Adult albino mice	600 ppm NaF; Oral	45 days	Ginseng Extract, 50, 150, and 250 mg/kg bodyweight/day, administered perorally	↑ of TCA enzymes (ICDH, SDH, and aconitase) were noted in brain regions	[150]
03.	Adult albino mice	600 ppm NaF; Oral	45 days	Banaba Extract, 50, 150, and 250 mg/kg bodyweight/day, administered perorally	↑ of TCA enzymes (ICDH, Succinate dehydrogenase (SDH), and aconitase) were noted in brain regions	[151]
04.	Adult female albino mice	1030.675 mg m^3; Oral	14 day	Gallic acid of *Peltiphyllum peltatum*.10-20 mg/kg bw/day, i.p.	↑Succinate dehydrogenase (SDH), Catalase and superoxide dismutase enzyme activities and glutathione levels	[152]
06.	Male Swiss albino mice	NaF at a dose of 600 ppm; Oral	14 days	Ethanol extract of the bark of *Terminalia arjuna*. 50 mg/kg of body weight, administered perorally	↑Heart SOD, ↑GPx, ↑GR, ↑GSH, ↑ CAT ↓SGOT, ↓ ALP	[153]
07.	Colony-bred male albino rats	NaF at a dose of 100 ppm; administered perorally	30 days	*Tamarindus indica* leaf powder, 2.5 to 10 g% of feed administered through diet	↓Plasma glucose, ↓Lipid levels, ↓Lipid peroxidation, ↑Hepatic glycogen content, ↑Hexokinase activity, ↑ Cholesterol excretion, imrovement in antioxidant profiles of both hepatic and renal tissues	[154]

Table 8: Experimental studies supporting protective effect of melatonin, epiphyseal (pineal) proteins, quercetin, and lycopene in amelioration of fluoride toxicity.

Sr. No.	Species of experimental animals	Melatonin dose and route of administration	Duration of study	Dose and route of fluoride exposure	Effect on studied parameters	References
			Melatonin			
01.	Adult female albino mice	10 mg/kg bw/day; i.p.	30 days	10 mg/kg bw/day, administered perorally	↑Liver ALP, ACP, SDH, SGOT, SGPT, liver weight, body weight, Liver protein content	[155]
02.	Young Wistar rats	10 mg/kg bw/day; administered perorally	60 days	NaF 4 mg/kg bw/day; administered perorally	↓TBARS and ROS in brain tissues , ↑ GSH and GPx brain tissue, attenuation of NaF induced rise in brain levels of TNF-α	[156]
03.	Adult female Wistar rats	10 mg/kg bw/day; i.p.	28 days	150 ppm in drinking water, administered perorally	↓MDA (LPO) levels in cardiac, hepatic, and renal tissues, ↑CAT, ↑SOD, ↑GPx, and ↑GR activities and ↑GSH	[157]

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04.	Adult female Wistar rats	10 mg/kg, bw/day; i.p.	28 days	150 ppm in drinking water, administered perorally	↓ [Na^+], [K^+], and ALP levels, ↑plasma glucose.	[158]
05.	Adult female albino mice	10 mg/kg bw/day; i.p.	30 day	10 mg NaF/kg bw/day, administered perorally	↑Succinate dehydrogenase (SDH), ↑ protein and creatinine levels, ↑Acid phosphatase (ACP) and ↑ alkaline phosphatase (ALP), ↓ Lipid peroxidation (LPO) and Glutathione (GSH)	[159]
06.	Adult female Wistar rats	10 mg/kg bw/day; i.p.	28 days	150 ppm in drinking water, administered perorally	↑plasma glucose, ↓Plasma creatinine, ↓urea, ↓BUN, ↓cholesterol, ↓K^+, ↓Na+ ,↓ SGPT, ↓SGOT, ↓ ALP plasma ↓Na^+, ↓ALP, and ↓cholesterol	[160]
07.	Adult female Swiss-strain albino mice	10 mg/kg bw/day; i.p.	30 days	10 mg/kg bw/day, administered perorally	Lowered the level of lipid peroxides and enhanced the antioxidant status.	[161]
08.	Adult female Wistar rats	10 mg/kg bw/day; i.p.	28 days	150 mg/L administered perorally	↓Brain MDA , ↑SOD, ↑GPx, ↑GR, ↑GSH, ↑ CAT	[101]
09.	Mature male Wistar rats	10 mg/kg bw/day; i.p.	60 days	5 and 10 mg NaF/kg bw, administered perorally	↑Lipid peroxidation (LPO), ↑glutathione peroxidase (GPx), ↑glutathione (GSH), ↑total ascorbic acid (TAA), ↑glutathione-S-transferase (GST), ↑glutathione reductase (GR), ↑superoxide dismutase (SOD), and ↑catalase (CAT) in the testiculare cells	[162]
10.	Human red blood cells (Male)	5 µg/mL and 10 µg/mL	4 hr at 37°C	50–500 µg NaF/mL in a final normal saline volume of 4.0 mL	Significant reduction in F-induced hemolysis with maximum amelioration occurring at 10 µg/mL	[163]
Epiphyseal (pineal) proteins						
01.	Adult female Wistar rats	100 µg/kg bw/day; i.p.	28 days	150 ppm administered perorally	↓MDA (LPO) levels in cardiac, hepatic, and renal tissues, ↑CAT, ↑SOD, ↑GPx, ↑GR and ↑GSH	[156]
02.	Adult female Wistar rats	100 µg/kg bw/day; i.p.	28 days	150 ppm, administered perorally	Plasma reduction of [Na^+], [K^+], and ALP levels, increases in the plasma glucose	[157]
03.	Adult female Wistar rats	100 µg/kg bw/day; i.p.	28 days	150 ppm administered perorally	↑Plasma glucose, ↑Plasma creatinine, ↑urea, ↑BUN, ↑cholesterol, ↑K^+, and ↑Na^+ ,↓SGPT, ↓SGOT, ↓ALP, ↑Plasma Na^+, ↑ALP, and ↑cholesterol	[159]
04.	Adult female Wistar rats	100 µg/kg bw/day; i.p.	28 days	150 mg/L administered perorally	↓Brain MDA,↑SOD, ↑GPx, ↑GR, ↑GSH, ↑CAT	[101]
05.	Adult female Wistar rats	100 µg/kg bw/day; i.p.	14 days	150 ppm, administered perorally	↑AChE activity in plasma, RBCs, heart, and brain.	[164]
06.	Adult female Wistar rats	50, 100, and 200 µg/kg bw/day; i.p.	21 days	150 ppm, administered perorally	↓ Plasma F, lipid peroxidation (LPO), ↓alkaline phosphatase (ALP), ↑plasma and RBCs acetyl cholinesterase (AChE) activity. ↓Plasma and RBCs LPO Red blood cells (RBCs). ↑RBCs GSH, CAT, GR, and GPx level.	[165]
Quercetin						
01.	Male Wistar rats	NaF at a dose of 600 ppm; administered perorally	14 days	Quercetin 10 to 20 mg/kg; i.p.	↓Kidney Glutathione (GSH), ↓LPO, ↓ Superoxide dismutase (SOD), ↓ catalase activity	[4]
Lycopene						
01.	Adult male albino rats	NaF 10.3 mg/kg body weight/day, administered perorally	35 days	Lycopene (10 mg/kg body weight/day), administered perorally	↑Glutathione level, total anti-oxidant capacity and superoxide dismutase activity	[166]

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DOI: https://dx.doi.org/10.17352/aest.000009