Peertechz

Life Sciences Group

Peertechz Journal of Environmental Science and Toxicology

DOI CC By

Vijay K Bharti*, Arup Giri and Krishna Kumar

Defence Institute of High Altitude Research (DIHAR), DRDO, Leh-Ladakh, Jammu & Kashmir, India

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

***Corresponding author:** Dr. Vijay K Bharti, Scientist - D, Defence Institute of High Altitude Research (DIHAR), DRDO, Ministry of Defence, Leh-Ladakh-194101, India, Tel: +91-9779618799; Fax: +91-172-2638500; E-mail: vijaykbharti@rediffmail.com

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

https://www.peertechz.com

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. Peertechz J Environ Sci Toxicol 2(1): 021-032.

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

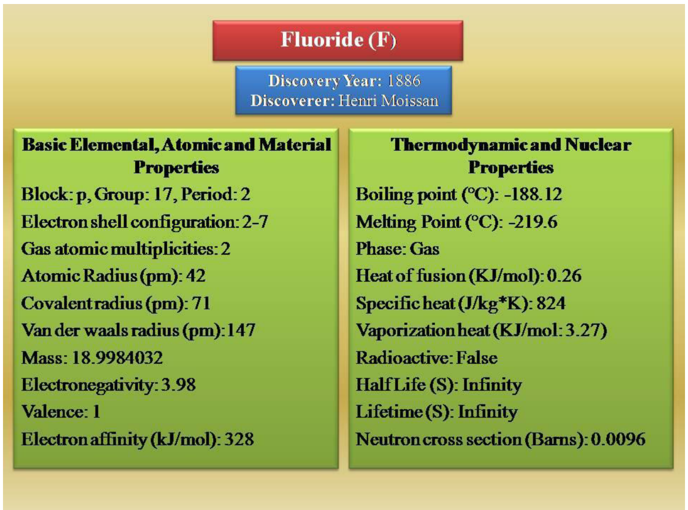

Figure 1: Basic properties of Fluoride [Source: 28].

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.

Citation: Bharti VK, Giri A, Kumar K (2017) Fluoride Sources, Toxicity and Its Amelioration: A Review. Peertechz J Environ Sci Toxicol 2(1): 021-032.

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, Ghanav	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^+

Citation: Bharti VK, Giri A, Kumar K (2017) Fluoride Sources, Toxicity and Its Amelioration: A Review. Peertechz J Environ Sci Toxicol 2(1): 021-032.

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]

Citation: Bharti VK, Giri A, Kumar K (2017) Fluoride Sources, Toxicity and Its Amelioration: A Review. Peertechz J Environ Sci Toxicol 2(1): 021-032.

	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.

Citation: Bharti VK, Giri A, Kumar K (2017) Fluoride Sources, Toxicity and Its Amelioration: A Review. Peertechz J Environ Sci Toxicol 2(1): 021-032.

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]

Citation: Bharti VK, Giri A, Kumar K (2017) Fluoride Sources, Toxicity and Its Amelioration: A Review. Peertechz J Environ Sci Toxicol 2(1): 021-032.

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]

References

1. Jentsch TJ, Stein V, Weinreich F, Zdebik AA (2002) Molecular structure and physiological function of chloride channels. Physiol Rev 82: 503–568. Link: https://goo.gl/28dJtp

2. Edwards JC, Kahl CR (2010) Chloride channels of intracellular membranes. FEBS Lett 584: 2102–2111. Link: https://goo.gl/CGDqTs

3. Zimmermann MB (2011) The role of iodine in human growth and development. Semin Cell Dev Biol 22: 645–652. Link: https://goo.gl/F5pIa0

4. Nabavi SM, Nabavi SF, Eslami S, Moghaddam AH (2012) In vivo protective effects of quercetin against sodium fluoride-induced oxidative stress in the hepatic tissue. Food Chem 132: 931–935. Link: https://goo.gl/IHEO8G

5. Jagtap S, Yenkie MK, Labhsetwar N, Rayalu S (2012) Fluoride in drinking water and defluoridation of water. Chem Rev 112: 2454–2466. Link: https://goo.gl/9fdnB3

6. Weinstein LH, Davison A (2004) Fluorides in the environment: effects on plants and animals. CABI Publishing, Cambridge. Link: https://goo.gl/bPwLXC

Citation: Bharti VK, Giri A, Kumar K (2017) Fluoride Sources, Toxicity and Its Amelioration: A Review. Peertechz J Environ Sci Toxicol 2(1): 021-032.

7. WHO (2006). World Health Organization, Fluoride in Drinking water, Fawell J, Bailey K, Chilton J, Dahi E, Fewtrell L, and Magara Y, Eds., IWA Publishing, Alliance House, 12 Caxton Street, London SW1H 0QS, UK, 41–75. Link: https://goo.gl/aIhF6h

8. WHO (2003). Background Document for Preparation of WHO Guidelines for Drinkingwater Quality. Fluoride in Drinking-water. Geneva: WHO. Link: https://goo.gl/4YSqwa

9. U.S. Environmental Protection Agency. (2003) Ground Water and Drinking Water. Drinking Water Contaminants (Online 2003). Link: https://goo.gl/8qPCS2

10. European Commission. (2011) "Critical review of any new evidence on the hazard profile, health effects, and human exposure to fluoride and the fluoridating agents of drinking water," Scientific Committee onHealth and Environmental Risks (SCHER). Link: https://goo.gl/fn283a

11. Planning Commission, India. (2007) Eleventh five-year plan approach paper. Rural watersupplyandsanitation. Link: https://goo.gl/VgUWJk

12. Franzaring J, Klumpp A, Fangmeier A (2007) Active Biomonitoring of Airborne Fluoride near an HF Producing Factory Using Standardized Grass Cultures. Atmos Environ 41: 4828- 4840. Link: https://goo.gl/GWku0c

13. Alves ES, Moura BB, Domingos M (2008) Structural Analysis of Tillandsia usneoides L. Exposed to Air Pollutants in São Paulo City-Brazil. Water Air Soil Pollu, 189: 61-68. Link: https://goo.gl/tZOEpo

14. Reddy MP, Kaur M (2008) Sodium fluoride induced growth and metabolic changes in Salicornia brachiata Roxb. Water Air Soil Pollut 188: 171-179. Link: https://goo.gl/TUhXeP

15. Lovelace CJ, Miller GW (1967) In vitro effects of fluoride on tricarboxylic acid cycle dehydrogenases and oxidative phosphorylation: Part I. J Histochem Cytochem 15: 195-201. Link: https://goo.gl/4pAqBe

16. Melchior NC, Melchior JB (1956) Inhibition of yeast hexokinase by fluoride ion. Sci 124: 402-403.

17. Lee C, Miller GW, Welkie GW (1965) The effects of hydrogen fluoride and wounding on respiratory enzymes in soybean leaves. Air Water Pollut Int J 10: 169-181.

18. Miller JE, Miller GW (1974) Effects of fluoride on mitochondrial activity in higher plants. Physiol Plant 32: 115–121. Link: https://goo.gl/sguKvD

19. Khandare AL, Kumar PU, Shankar HN. (2007) Effect of calcium deficiency induced by fluoride intoxication on lipid metabolism in rabbits. Fluoride 40: 184–189. Link: https://goo.gl/UWS01J

20. Coetzee PP, Coetzee LL, Puka R, Mubenga1 S (2003) Characterization of selected South African clays for defluoridation of natural waters. Water SA 29: 331–338. Link: https://goo.gl/GniZ6V

21. Dunipace AJ, Edward JB, Wilson ME (1998) Chronic fluoride exposure does not cause detrimental, extra skeletal effects in nutritionally deficient rats. J Nutr 128: 1392–1400. Link: https://goo.gl/N8G15g

22. Lohakare J, Pattanaik A, Khan SA (2010) Effect of long-term fluoride exposure on growth, nutrient utilization and fluoride kinetics of calves fed graded levels of dietary protein. Biol Trace Elem Res 138: 148–162. Link: https://goo.gl/lzBFk5

23. Heber D (2010) Pomegranate. Chapter 30. In Nutrition and Health: Bioactive Compounds and Cancer. Edited by J.A. Milner and D.F. Romagnolo. Humana Press, c/o Springer Science and Business Media LLC, New York 725-734. Link: https://goo.gl/QoGK92

24. Nabavi SF, Eslami SH, Moghaddam AH, Nabavi SM (2011) Protective effects of curcumin against fluoride-induced oxidative stress in the rat brain. Neurophysiol 43: 287-291. Link: https://goo.gl/VRqZVv

25. Nabavi SM, Nabavi SF, Eslami S, Moghaddam AH (2012) In vivo protective effects of quercetin against sodium fluoride-induced oxidative stress in the hepatic tissue. Food Chem 132: 931-935. Link: https://goo.gl/eQA1JV

26. Nabavi SF, Nabavi SM, Abolhasani F, Moghaddam AH, Eslami S (2012) Cytoprotective effects of curcumin on sodium fluoride induced intoxication in rat erythrocytes. Bull Environ Contam Toxicol 88: 486-490. Link: https://goo.gl/xxeyxK

27. Finger GC (1961) Fluorine Resources and Fluorine Utilization. Adv Fluorine Chem 2: 35-54.

28. Giri A, Bharti VK, Angmo K, Kalia S, Kumar B (2016) Fluoride versus Oxidative stress, Immune System and Apoptosis in Animals: a Review. Int J Bioass 5: 5163-5173. Link: https://goo.gl/1QiNES

29. Department of Health and Human Services. (1991) Report of the subcommittee on fluoride of the Committee to Coordinate Environmental Health and Related Programs, USPHS. Review of fluoride: benefits and risks. Public Health Service. Link: https://goo.gl/SF4MCG

30. Cengeloglu Y, Esengul K, Ersoz M (2002) Removal of Fluoride from aqueous Solution by Using red mud. Sep Pur Tech 28: 81-86. Link: https://goo.gl/Dn1unl

31. Susheela AK (1999) Fluorosis management programme in India. Curr Sci India 77: 1050–1256. Link: https://goo.gl/V4VjHH

32. Bombik E, Bombik A, Gorski K, Saba L, Bombik T, et al. (2011) Effect of Environmental Contamination by Fluoride compounds on selected horse tissues. Polish J Environ Stud 20: 37-43. Link: https://goo.gl/Ev5Ob6

33. Begum A (2012) Soil Profiles and Fluoride Adsorption in Intensely Cultivated Areas of Mysore District, Karnataka, India. Chem Sci Trans 1: 410-414. Link: https://goo.gl/d1YEIl

34. Blagojevic S, Jakovljevic M, Radulovic M (2002) Content of Fluorine in Soils In The Vicinity of Aluminium Plant in Podgorica. J Agricul Sci 47: 1-8. Link: https://goo.gl/pzHtdc

35. Ericson B, Hanrahan D, Kong V (2014) The world's worst pollution problems; the top ten of the toxic twenty. Link: https://goo.gl/4saMAJ

36. Li C, Gao X, Wang Y (2014) Hydrogeochemistry of high-fluoride groundwater at Yuncheng Basin, northern China. Sci Total Environ 508C: 155–165. Link: https://goo.gl/FA4STx

37. NRC (1960) The Fluorosis problem in livestock production. A report of the NRC committee on animal nutrition. Publication 824, National Research Council, Washington. Link: https://goo.gl/EFXplv

38. Radostits OM, Gay CC, Blood DC, Hinchcliff KW (2000) Veterinary Medicine, a textbook of the diseases of cattle, sheep, pigs, goats and horses, 9th edn. WB Saunders Company Ltd, London. Link: https://goo.gl/ixXkHL

39. Mascola JJ, Barth KM, McLaren JB (1974) Fluoride intake of cattle grazing fluoride-contaminated forage, as determined by esophageal-fistulated steers. J Anim Sci 38: 1298–1303. Link: https://goo.gl/xdgvvv

40. Araya O, Wittwer F, Villa A (1993) Evolution of fluoride concentration in cattle and grass following a volcanic eruption. Vet Hum Toxicol 35: 437–440. Link: https://goo.gl/IDlfgN

41. Bellomo S, Aiuppa A, D'Alessandro W, Parello F (2007) Environmental impact of magmatic fluorine emission in the Mt. Etna area. J Volcanol Geoth Res 165: 87–101. Link: https://goo.gl/vi0hp9

42. Thorarinsson S (1979) On the damage caused by volcanic eruptions with special reference to tephra and gases. In: Sheets PD, Grayson DK (eds) Volcanic activity and human ecology. Academic Press, New York, 125–159.

43. SEAN (1989) Lonquimay, continued tephra emission: cattle sickened by ash. Scientific Event Alert Network Bull, Smithsonian Institution 14: 2–3.

Citation: Bharti VK, Giri A, Kumar K (2017) Fluoride Sources, Toxicity and Its Amelioration: A Review. Peertechz J Environ Sci Toxicol 2(1): 021-032.

44. Armienta MA, de La Cruz-Reyna S, Cruz O, Ceniceros N, Aguayo A, et al. (2011) Fluoride in ash leachates: environmental implications at popocatepetl volcano, central Mexico. Nat Hazards Earth Syst Sci 11: 1949–1956. Link: https://goo.gl/Y2qCZr

45. Flueck WT, Smith-Flueck JA (2013) Severe dental fluorosis in juvenile deer linked to a recent volcanic eruption in Patagonia. J Wildlife Dis 49: 355–366. Link: https://goo.gl/oQO8DP

46. WHO (2002) World Health Organization, Geneva, Fluorides, Environmental Health Criteria, 227.

47. Paul ED, Gimba CE, Kagbu JA, Ndukwe GI, Okibe FG (2011) Spectrometric Determination of Fluoride in Water, Soil and Vegetables from the Precinct of River Basawa, Zaria, Nigeria. J Basic Appl Chem 1: 33-38. Link: https://goo.gl/c95FyM

48. WHO (2000) Fluorides. In: Chapter 6.5 Air quality guidelines, 2nd edn. WHO regional office for Europe, World Health Organization, Copenhagen.

49. Guijian L, Liugen Z, Duzgoren-Aydin NS, Lianfen G, Junhua L et al. (2007) Health effects of arsenic, fluorine, and selenium from indoor burning of Chinese coal. Rev Environ Contam Toxicol 189: 89–106. Link: https://goo.gl/Sf7JAD

50. Swarup D, Dwivedi SK (2002) Environmental pollution and effects of lead and fluoride on animal health. Indian Council of Agricultural Research, Pusa, New Delhi. Link: https://goo.gl/3d5B5B

51. Swarup D, Dey S, Patra RC, Dwivedi SK, Ali SL (2001) Clinico-epidemiological observation of industrial bovine fluorosis in India. Indian J Anim Sci 71: 1111–1115. Link: https://goo.gl/rPNGGc

52. Patra RC, Dwivedi SK, Bhardwaj B, Swarup D (2000) Industrial fluorosis in cattle and buffalo around Udaipur, India. Sci Total Environ 253: 145–150. Link: https://goo.gl/is32K0

53. Sahoo N, Singh PK, Ray SK, Bisoi PC, Mahapatra HK (2003) Fluorosis in sheep around an aluminium factory. Indian Vet J 80: 617–621. Link: https://goo.gl/zSW3gJ

54. Sahoo N, Ray SK (2004) Fluorosis in goats near an aluminium smelter plant in Orissa. Indian J Anim Sci 74: 48–50. Link: https://goo.gl/WPKkDk

55. Karram MH, Ibrahim TA (1992) Effect of industrial fluorosis on haemogram of camels. Fluoride 25: 23–36. Link: https://goo.gl/dh5oDh

56. Singh JL, Swarup D (1995) Clinical observations and diagnosis of fluorosis in dairy cows and buffaloes: case report. Agri Practice 16: 25–30.

57. Chinoy JN (1991) Effects of fluoride on physiology of animals and human beings. Indian J Environ Toxicol 1: 17-32.

58. Grobler SR, Dreyer AG, Blignaut RJ (2001) Drinking water in South Africa: Implications for fluoride supplementation. J South Afr Dent Assoc 56: 557–559. Link: https://goo.gl/7xnSHG

59. Mothusi B (1998) Psychological effects of dental fluorosis, Fluoride and Fluorosis, The Status of South African Research, Pilanesberg National Park, North West Province, 7, (1995): as cited in Muller WJ, Heath RGM, Villet MH, Finding the optimum: Fluoridation of potable water in South Africa. Water SA, 24: 1–27.

60. WHO (2005) World Health Organization, Geneva, Switzerland. Link: https://goo.gl/woF1q5

61. Apambire WB, Boyle DR, Michel FA (1997) Geochemistry, genesis, and health implications of fluoriferous ground waters in the upper regions of Ghana. Environ Geol 33: 13–24. Link: https://goo.gl/CeENsA

62. Kaimenyi TJ (2004) Oral health in Kenya. Int Dent J 54: 378–382. Link: https://goo.gl/VKAjUS

63. Nair KR, Manji F (1982) Endemic fluorosis in deciduous dentition—A study of 1276 children in typically high fluoride area (Kiambu) in Kenya. Odonto-Stomatologie Tropicale 4: 177–184. Link: https://goo.gl/GXKvU4

64. Nair KR, Manji F, Gitonga JN (1984) The occurrence and distribution of fluoride in groundwaters in Kenya. East Afr J Med 61: 503–512. Link: https://goo.gl/rhgcUL

65. Wongdem JG, Aderinokun GA, Sridhar MK, Selkur S (2000) Prevalence and distribution pattern of enamel fluorosis in Langtang town, Nigeria. Afr J Med Medical Sci 29: 243–246. Link: https://goo.gl/rWqVEw

66. Brouwer ID, Dirks OB, De-Bruin A, Hautvast JGAJ (1988) Unsuitability of World Health Organization guidelines for fluoride concentrations in drinking water in Senegal. Lancet 30: 223–225. Link: https://goo.gl/282Cqj

67. Mjengera H, Mkongo G (2003) Appropriate deflouridation technology for use in flourotic areas in Tanzania. Physics Chem Earth 28: 1097–1104. Link: https://goo.gl/sWTTM7

68. Rwenyonyi CM, Birkeland JM, Haugejorden O, Bjorvatn K (2000) Age as a determinant of severity of dental fluorosis in children residing in areas with 0.5 and 2.5 mg fluoride per liter in drinking water. Clin Oral Invest 4: 157–161. Link: https://goo.gl/fNLxny

69. Ibrahim YE, Affan AA, Bjorvatn K (1995) Prevalence of dental fluorosis in Sudanese children from two villages with respectively 0.25 mg/L and 2.56 mg/L F in the drinking water. Int J Paediatr Dent 5: 223–229. Link: https://goo.gl/3K3OQL

70. Smith DA, Harris HA, Kirk R (1953) Fluorosis in the Butana, Sudan. J Tropic Med Hyg 56: 57–58. Link: https://goo.gl/wd3zrZ

71. Al-Khateeb TL, Al-Marasafi AI, O'Mullane DM (1991) Caries prevalence and treatment need amongst children in an Arabian community. Commun. Dentistry Oral Epidemiol 19: 277–280. Link: https://goo.gl/lJVBxY

72. Akpata ES, Fakiha Z, Khan N (1997) Dental fluorosis in 12–15-year-old rural children exposed to fluorides from well drinking water in the Hail region of Saudi Arabia. Comm Dentistry Oral Epidemiol 25: 324–327. Link: https://goo.gl/OAmBxw

73. Health Canada (1993) Priority Substances List Assessment Report on Inorganic Fluorides, Canadian Environmental Protection Act, Minister of Supply and Services Canada, Canada Communication Group-Publishing, Ottawa, Canada K1A 0S9, 12–19. Link: https://goo.gl/llzi4a

74. Ismail AI, Messer JG (1996) The risk of fluorosis in students exposed to a higher than optimal concentration of fluoride in well water. J Public Health Dent 56: 22–27. Link: https://goo.gl/usvYm7

75. Paoloni JD, Fiorentino CE, Sequeira ME (2003) Fluoride contamination of aquifers in the southeast subhumid pampa, Argentina. Environ Toxicol 18: 317–320. Link: https://goo.gl/iIZosO

76. Cortes DF, Ellwood RP, O'Mullane DM, de Magalhaes Bastos JR (1996) Drinking water fluoride levels, dental fluorosis and caries experience in Brazil. J Public Health Dentistry 56: 226–228. Link: https://goo.gl/RqfSlb

77. Haimanot RT, Fekadu A, Bushra B (1987) Endemic fluorosis in the Ethiopian Rift Valley. Tropic Geogr Med 39: 209–217. Link: https://goo.gl/6NkJq2

78. Kloos H, Tekle-Haimanot R, Kloos H, Zein AH (1993) The Ecology of Health and Disease in Ethiopia, Westview Press, Boulder, CO, 445–541.

79. Diaz-Barriga F, Navarro-Quezada A, Grijalva MI, Grimaldo M, Loyola-Rodriguez JP et al. (1997) Endemic fluorosis in Mexico. Fluoride 30: 233–239.

80. Cohen D, Conrad MH (1998) 65,000 GPD fluoride removal membrane system in Lakeland, California, USA. Desalination 117: 19–35. Link: https://goo.gl/hOkasl

81. Reardon JE, Wang Y (2000) A limestone reactor for fluoride removal

from wastewaters. Environ Sci Technol 34: 3247–3253. Link: https://goo.gl/fKCdDk

82. Heikens A, Sumart S, vanBergen M, Widianarko B, Fokkert L et al. (2005) The impact of the hyperacid Ijen Crater Lake: Risks of excess fluoride to human health. Sci Tot Environ 346: 56–69. Link: https://goo.gl/GJhB3H

83. Queste A, Lacombe M, Hellmeier W, Hillermann F, Bortulussi B et al. (2001) High concentrations of fluoride and boron in drinking water wells in the Muenster region—Results of a preliminary investigation. Int J Environ Health 203: 221– 224. Link: https://goo.gl/iZknCh

84. Kim K, Jeong YG (2005) Factors influencing natural occurrence of fluoride-rich groundwaters: A case study in the southeastern part of the Korean Peninsula. Chemosphere 58: 1399–1408. Link: https://goo.gl/K2y2CJ

85. Bardsen A, Klock KS, Bjorvatn K (1999) Dental fluorosis among persons exposed to high- and low-fluoride drinking water in western Norway. Commun Dentistry Oral Epidemiol 27: 259–267. Link: https://goo.gl/21NdXZ

86. Czarnowski W, Wrzesniowska K, Krechniak J (1996) Fluoride in drinking water and human urine in Northern and Central Poland. Sci Total Environ 191: 177–184. Link: https://goo.gl/UyUi99

87. Hardisson A, Rodriguez MI, Burgos A, Flores LD, Gutierrez R et al. (2001) Fluoride levels in publically supplied and bottled drinking waters in the island of Tenerife. Spain. Bull Environ Contamin Toxicol 67: 163–170. Link: https://goo.gl/rF0qtH

88. Wang GQ, Huang YZ, Xiao BY, Qian XC, Yao H et al. (1997) Toxicity from water containing arsenic and fluoride in Xinjiang. Fluoride 30: 81–84. Link: https://goo.gl/dvIRx4

89. Azbar N, Turkman A (2000) Defluoridation in drinking waters. Water Science and Technology. 42: 403–407. Link: https://goo.gl/XQE0vb

90. Tsutsui A, Yagi M, Horowitz AM (2000) The prevalence of dental caries and fluorosis in Japanese communities with up to 1.4 ppm of naturally occurring fluoride. J Public Health Dentistry 60: 147–153. Link: https://goo.gl/KEdrCB

91. McGrady MG, Ellwood RP, Srisilapanan P, Korwanich N, Worthington HV et al. (2012) Dental fluorosis in populations from Chiang Mai, Thailand with different fluoride exposures – Paper1: assessing fluorosis risk, predictors of fluorosis and the potential role of food preparation. BMC Oral Health 12: 16. Link: https://goo.gl/rFfy3Q

92. Dissanayake CB (1996) Water quality and dental health in the Dry Zone of Sri Lanka. Environ Geochem Health 113: 131–140. Link: https://goo.gl/jOsSYw

93. Ayoob S, Gupta AK (2006) Fluoride in drinking water: a review on the status and stress effects. Crit Rev Environ Sci Technol 36: 433–487. Link: https://goo.gl/Wkh1Q6

94. Susheela AK (2003) A treatise on fluorosis, revised second edition, Fluorosis Research and Rural Development Foundation, New Delhi, India, 13–14. Link: https://goo.gl/OIDxVj

95. Jha SK, Nayak AK, Sharma YK (2010) Potential fluoride contamination in the drinking water of Marks Nagar, Unnao district, Uttar Pradesh, India. Environ Geochem Health 32: 217-226. Link: https://goo.gl/YKtBuC

96. Shah MT, Danishwar S (2003) Potential fluoride contamination in the drinking water of Naranji area, Northwest Frontier Province, Pakistan. Environ Geochem Health 25: 475–481. Link: https://goo.gl/AOX0v8

97. Choubisa SL (2012) Fluoride in drinking water and its toxicosis in tribals, Rajasthan, India. Proc Nat Acad Sci India Sect B Biol Sci 82: 325-330. Link: https://goo.gl/BTXpaO

98. Choubisa SL (2015) Industrial fluorosis in domestic goats (*Capra hircus*), Rajasthan, India. Fluoride 48: 105-112. Link: https://goo.gl/lhOKN6

99. Patel PD, Chinoy NJ (1998) Influence of fluoride on biological free radical reactions in ovary of mice and its reversal. Fluoride 31: S27.

100. Eraslan G, Kanbur M, Silici S (2007) Evaluation of propolis effects on some biochemical parameters in rats treated with sodium fluoride. Pest Biochem Physiol 88: 273–283. Link: https://goo.gl/SXqLRo

101. Bharti VK, Srivastava RS (2009) Fluoride-induced oxidative stress in rat's brain and its amelioration by buffalo (*Bubalus bubalis*) pineal proteins and melatonin. Biol Trace Elem Res 130: 131–140. Link: https://goo.gl/BvH6mX

102. Garcia-Montalvo EA, Reyes-Perez H, del Razo LM (2009) Fluoride exposure impairs glucose tolerance via decreased insulin expression and oxidative stress. Toxicol 263: 75–83. Link: https://goo.gl/J3vzdx

103. Zhang M, Wang AG, He WH (2007) Effects of fluoride on the expression of NCAM, oxidative stress, and apoptosis in primary cultured hippocampal neurons. Toxicol 236: 208–216. Link: https://goo.gl/VmfRKA

104. Ghosh J, Das J, Manna P (2008) Cytoprotective effect of arjunolic acid in response to sodium fluoride mediated oxidative stress and cell death via necrotic pathway. Toxicol in vitro 22: 1918–1926. Link: https://goo.gl/rnURqR

105. Morgan KT, Ni H, Brown HR (2002) Application of cDNA microarray technology to in vitro toxicology and the selection of genes for a real-time RT-PCR-based screen for oxidative stress in Hep-G2 cells. Toxicol Pathol 30: 435-451. Link: https://goo.gl/371SMA

106. Gao Q, Liu YJ, Guan ZZ (2008) Oxidative stress might be a mechanism connected with the decreased alpha 7 nicotinic receptor influenced by high-concentration of fluoride in SHSY5Y neuroblastoma cells. Toxicol In Vitro 22: 837-843. Link: https://goo.gl/qNC3zB

107. Sireli M, Bulbul A (2004) The effect of acute fluoride poisoning on nitric oxide and methemoglobin formation in the Guinea pig. Turk J Vet Anim Sci 28: 591–595. Link: https://goo.gl/JOeKTE

108. Izquierdo-Vega JA, Sanchez-Gutierrez M, del Razo LM (2008) Decreased in vitro fertility in male rats exposed to fluoride-induced oxidative stress damage and mitochondrial transmembrane potential loss. Toxicol Appl Pharmacol 230: 352–357. Link: https://goo.gl/vOX7PY

109. Flora SJ, Mittal M, Mishra D (2009) Co-exposure to arsenic and fluoride on oxidative stress, glutathione linked enzymes, biogenic amines and DNA damage in mouse brain. J Neurol Sci 285: 198–205. Link: https://goo.gl/V9DhQj

110. Shanthakumari D, Srinivasalu S, Subramanian S (2004) Effects of fluoride intoxication on lipidperoxidation and antioxidant status in experimental rats. Toxicol 204: 219–228. Link: https://goo.gl/nChBcL

111. Chouhan S, Lomash V, Flora SJS (2010) Fluoride-induced changes in haem biosynthesis pathway, neurological variables and tissue histopathology of rats. J Appl Toxicol 30: 63–73. Link: https://goo.gl/f94rRP

112. Aydin G, Cic E, Akdogan M, Gokalp O (2003) Histopathological and biochemical changes in lung tissues of rats following administration of fluoride over several generations. J Appl Toxicol 23: 437–446. Link: https://goo.gl/rtCTt3

113. Liu G, Chai C, Cui L (2003) Fluoride causing abnormally elevated serum nitric oxide levels in chicks. Environ Toxicol Pharmacol 13: 199–204. Link: https://goo.gl/9U8h3r

114. Hassan HA, Yousef MI (2009) Mitigating effects of antioxidant properties of black berry juice on sodium fluoride induced hepatotoxicity and oxidative stress in rats. Food Chem Toxicol 47: 2332–2337. Link: https://goo.gl/IibpcW

115. Zhan XA, Wang M, Xu ZR (2006) Effects of fluoride on hepatic antioxidant system and transcription of Cu/Zn SOD gene in young pigs. J Trace Elem Med Biol 20: 83–87. Link: https://goo.gl/0tquA8

116. Ghosh D, Das S, Maiti R, Jana D, Das U (2002) Testicular toxicity in sodium fluoride treated rats: association with oxidative stress. Reprod Toxicol 16: 385–390. Link: https://goo.gl/U0aMrL

117. Guo XY, Sun GF, Sun YC (2003) Oxidative stress from fluoride induced hepatotoxicity in rats. Fluoride 36: 25–29. Link: https://goo.gl/yVLwIU

118. Zhan XA, Xu ZR, Li JX (2005) Effects of fluorosis on lipid peroxidation and antioxidant systems in young pigs. Fluoride 38: 157–161. Link: https://goo.gl/rjuwIF

119. Mc-Cord JM, Keele BB, Fridovich I (1984) An enzyme based theory of obligate anaerobiosis, the physiological functions of superoxide dismutase. Proc Natl Acad Sci 68: 1024–1027. Link: https://goo.gl/PyLXOU

120. Guney M, Oral B, Demirin H (2007) Protective effects of vitamins C and E against endometrial damage and oxidative stress in fluoride intoxication. Clin Exp Pharmacol Physiol 34: 467–474. Link: https://goo.gl/sjbWZr

121. Mittal M, Flora SJS (2007) Vitamin E protects oxidative stress and essential metal imbalance during concomitant exposure to arsenic and fluoride in male mice. Drug Chem Toxicol 30: 263–281. Link: https://goo.gl/VSqhiW

122. Chouhan S, Flora SJS (2008) Effects of fluoride on the tissue oxidative stress and apoptosis in rats: biochemical assays supported by IR spectroscopy data. Toxicol 254: 61–67. Link: https://goo.gl/8AXH7T

123. Jhala DD, Chinoy NJ, Rao MV (2008) Mitigating effects of some antidotes on fluoride and arsenic induced free radical toxicity in mice ovary. Food Chem Toxicol 46: 1138–1142. Link: https://goo.gl/wXhFT8

124. Kanbur M, Eraslan G, Silici S (2009) Effects of sodium fluoride exposure on some biochemical parameters in mice: evaluation of the ameliorative effect of royal jelly applications on these parameters. Food Chem Toxicol 47: 1184–1189. Link: https://goo.gl/kp99Fl

125. Basha PM, Madhusudhan N (2010) Pre and post natal exposure of fluoride induced oxidative macromolecular alterations in developing central nervous system of rat and amelioration by antioxidants. Neurochem Res 35: 1017–1028. Link: https://goo.gl/r7ApN0

126. Chen T, Cui Y, Gong T (2009) Inhibition of splenocyte proliferation and spleen growth in young chickens fed high fluoride diets. Fluoride 4: 203-209. Link: https://goo.gl/1ntzY3

127. Shivarajashankara YM, Shivashankara AR, Gopalakrishna BP (2001) Oxidative stress in children with endemic skeletal fluorosis. Fluoride 34: 103–107. Link: https://goo.gl/3zlHEg

128. Xu B, Xu Z, Xia T (2011) Effects of the Fas/Fas-L pathway on fluoride-induced apoptosis in SH-SY5Y cells. Environ Toxicol 26: 86-92. Link: https://goo.gl/EWa7SM

129. Salgado-Bustamante M, Ortiz-Perez MD, Calderon-Aranda E (2010) Pattern of expression of apoptosis and inflammatory genes in humans exposed to arsenic and/or fluoride. Sci Total Environ 408: 760–767. Link: https://goo.gl/X9m6K5

130. Qiao J, Cui Z, Sun Y, Hu Q, Guan X (2014) Simultaneous removal of arsenate and fluoride from water by Al-Fe (hydr)oxides. Frontiers Environ Sci Eng 8: 169-179. Link: https://goo.gl/MnQCgQ

131. Chai L, Wang Y, Zhao N, Yang W, You X (2013) Sulfate-doped Fe_3O_4/Al_2O_3 nanoparticles as a novel adsorbent for fluoride removal from drinking water. Water Res 47: 4040-4049. Link: https://goo.gl/Zd3CKL

132. Mondal NK, Bhaumik R, Baur T, Das B, Roy P et al. (2012) Studies on Defluoridation of Water by Tea Ash: An Unconventional Biosorbent. Chem Sci Trans 1: 239-256. Link: https://goo.gl/36J8xV

133. Chakrabarty S, Patra PK (2013) Effect of sodium fluoride on seed germination, seedling growth and biochemistry of paddy (*Oryza sativa L.).* Asian J Exp Biol Sci 4: 540-544.

134. Thole B, Mtalo F, Masamba W, (2012) Effect of particle size on loading capacity and water quality in water defluoridation with 200°C calcined bauxite, gypsum, magnesite and their composite filter. Afri J Pure Appl Chem 6: 26-34. Link: https://goo.gl/9aJIPJ

135. Ghorai S, Pant KK (2005) Equilibrium, kinetics and breakthrough studies for adsorption of fluoride on activated alumina. Sep Purification Technol 42: 265– 271. Link: https://goo.gl/xTfLIc

136. Tripathy SS, Bersillon JL, Gopal K (2006) Removal of fluoride from drinking water by adsorption onto alum-impregnated activated alumina. Sep Purific Technol 50: 310–317. Link: https://goo.gl/a523Fm

137. Chauhan VS, Dwivedi PK, Iyengar L (2007) Investigations on activated alumina based domestic defluoridation units. J Hazardous Materials 139: 103–107. Link: https://goo.gl/ZRriyl

138. Hernandez-Montoya V, Elizalde-Gonzalez MP, Trejo-Vazquez R (2007) Screening of commercial sorbents for removal of fluoride in synthetic and groundwater. Environ Technol 28: 595–607. Link: https://goo.gl/HfqhqK

139. Daifullah AAM, Yakout SM, Elreefy SA (2007) Adsorption of fluoride in aqueous solutions using $KMnO_4$-modified activated carbon derived from steam pyrolysis of rice straw. J Hazardous Materials 147: 633–643. Link: https://goo.gl/yDCcbH

140. Kumar S, Gupta A, Yadav JP (2007) Fluoride removal by mixtures of activated carbon prepared from Neem (*Azadirachta indica*) and Kikar (*Acacia arabica*) leaves. Indian J Chem Technol 14: 355–361. Link: https://goo.gl/A7dkPD

141. Bashir MT, Salmiaton A, Nourouzi MM, Azni I, Harun R (2015) Fluoride removal by chemical modification of palm kernel shell-based adsorbent: a novel agricultural waste utilization approach. Asian J Microbiol Biotech Env Sci 17: 533-542. Link: https://goo.gl/w1I91L

142. Vardhan C, Karthikeyan J (2011) Removal of fluoride from water using low-cost materials. In: Fifteenth International Water Technology Conference. [Online] Alexandria, Egypt. Link: https://goo.gl/1ghK4y

143. Wartelle L, Marshall W (2006) Quaternized agricultural by-products as anion exchange resins. J Environ Manage 78: 157-162. Link: https://goo.gl/2s3mco

144. Shen F, Chen X, Ping G, Chen G (2003) Electrochemical removal of fluoride ions from industrial wastewater. Chem Eng Sci 58: 987– 993. Link: https://goo.gl/pV6s1u

145. Pinon-Miramontes M, Bautista-Margulis RG, Perez-Hernandez A (2003) Removal of arsenic and fluoride from drinking water with cake alum and a polymeric anionic flocculent. Fluoride 36: 122–128. Link: https://goo.gl/rjlp1o

146. Tahaikt M, Achary I, Menkouchi SMA, Amor Z, Taky M et al. (2006) Defluoridation of Moroccan groundwater by electrodialysis: continuous operation. Desalination 189: 215– 220. Link: https://goo.gl/Bc77Ae

147. Arora M, Maheshwari RC, Jain SK, Gupta A (2004) Use of membrane technology for potable water production. Desalination. 170: 105–112. Link: https://goo.gl/Azw8Qj

148. Hu K, Dickson JM (2006) Nanofiltration membrane performance on fluoride removal from water. Membrane Sci 279: 529–538. Link: https://goo.gl/t2QzrH

149. Qianhai Zuo, Xueming Chen, Wei Li, Guohua Chen (2008) Combined electrocoagulation and electroflotation for removal of fluoride from drinking water. J Hazardous Materials 159: 452–457. Link: https://goo.gl/BBSf7i

150. Hassan HA, Abdel-Aziz AF (2010) Evaluation of free radical-scavenging and anti-oxidant properties of blackberry against fluoride toxicity in rats. Food Chem Toxicol 48: 1999–2004. Link: https://goo.gl/pXybJx

151. Basha PM, Saumya SM (2013) Suppression of Mitochondrial Oxidative Phosphorylation and TCA Enzymes in Discrete Brain Regions of Mice Exposed to High Fluoride: Amelioration by *Panax ginseng* (Ginseng) and *Lagerstroemia speciosa* (Banaba) Extracts. Cell Mol Neurobiol 33: 453–464. Link: https://goo.gl/J7vuxH

152. Nabavi SF, Habtemariam S, Sureda A, Akbar HM, Daglia M, et al. (2013) In vivo protective effects of gallic acid isolated from peltiphyllum peltatum against sodium fluoride-induced oxidative stress in rat erythrocytes. Arh Hig Rada Toksikol 64: 553-559. Link: https://goo.gl/xBd4BC

153. Sinha M, Manna P, Sil PC (2008) Terminalia arjuna Protects Mouse Hearts Against Sodium Fluoride-Induced Oxidative Stress. J Med Food 11: 733–740. Link: https://goo.gl/8aU6DN

154. Vasant RA, Narasimhacharya AVRL (2012) Ameliorative effect of tamarind leaf on fluoride-induced metabolic alterations. Environ Health Prev Med 17: 484–493. Link: https://goo.gl/6koPxk

155. Chawla SL, Yadav R, Shah D, Rao MV (2008) Protective action of melatonin against fluoride induced hepatotoxicity in adult female mice. Fluoride 41: 44-51. Link: https://goo.gl/QqxdDn

156. Jain A, Mehta VK, Chittora R, Mahdi AA, Bhatnagar M (2015) Melatonin ameliorates fluoride induced neurotoxicity in young rats: an in vivo evidence. Asian J Pharm Clin Res 8: 164-167. Link: https://goo.gl/HJElEk

157. Bharti VK, Srivastava RS, Kumar H, Bag S, Majumdar AC, et al. (2014) Effects of melatonin and epiphyseal proteins on fluoride-induced adverse changes in antioxidant status of heart, liver, and kidney of rats. Adv Pharmacol Sci 2014:532969. Link: https://goo.gl/IESXbF

158. Bharti VK, Srivastava RS (2011) Effects of epiphyseal proteins and melatonin on the blood biochemical parameters of fluoride-intoxicated rats. Neurophysiol 42: 258-264. Link: https://goo.gl/5pgiO3

159. Rao MV, Chawla SL, Patel N (2009) Melatonin reduction of fluoride-induced nephrotoxicity in mice. Fluoride 42: 110–116. Link: https://goo.gl/BtLwwO

160. Bharti VK, Srivastava RS (2011) Effect of pineal proteins and melatonin on certain biochemical parameters of rats exposed to high-fluoride drinking water. Fluoride 44: 30–36. Link: https://goo.gl/kwE7ZU

161. Chawla SL, Rao MV (2012) Protective effect of melatonin against fluoride induced oxidative stress in the mouse ovary. Fluoride 45: 125–132. Link: https://goo.gl/7nWbhZ

162. Rao MV, Bhatt RN (2012) Melatonin protection against F-induced oxidative stress and testicular dysfunction in rats. Fluoride 45: 116-124. Link: https://goo.gl/NICNbv

163. Rao MV, Vyas DD, Meda RB, Chawla SL (2011) In vitro protective role of melatonin against hemolysis induced by sodium fluoride in human red blood cells. Fluoride 44: 77–82. Link: https://goo.gl/b5WUTb

164. Bharti VK, Srivastava RS, Anand AK, Kusum K (2012) Buffalo (*Bubalus bubalis*) epiphyseal proteins give protection from arsenic and fluoride-induced adverse changes in acetylcholinesterase activity in rats. J Biochem Mol Toxicol 26: 10-15. Link: https://goo.gl/Ofll3W

165. Bharti VK, Srivastava RS (2011) Effect of pineal proteins at different dose level on fluoride-induced changes in plasma biochemicals and blood antioxidants enzymes in rats. Biol Trace Elem Res141: 275-282. Link: https://goo.gl/8eDjlV

166. Mansour HH, Tawfik SS (2012) Efficacy of lycopene against fluoride toxicity in rats. Pharm Biol 50: 707–711. Link: https://goo.gl/z2hgHD

Citation: Bharti VK, Giri A, Kumar K (2017) Fluoride Sources, Toxicity and Its Amelioration: A Review. Peertechz J Environ Sci Toxicol 2(1): 021-032.