Chapter

Sources of Human Overexposure to Fluoride, Its Toxicities, and their Amelioration Using Natural Antioxidants

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Abstract

Fluoride (F) is released into the environment through a combination of natural and anthropogenic processes include the weathering from volcanoes, geothermal activity, and marine aerosols. Chronic fluoride exposure has been linked with amyriad of human diseases such as skeletal and dental fluorosis, diabetes, atherosclerosis, cardiovascular diseases, and hyperkeratosis. Since fluoride targets ubiquitous enzyme reactions, it affects nearly all organ systems in animals and humans. Apart from synthetic chemical chelators, studies have been carried out to explore natural antioxidants against F toxicity. Natural products contain substances that inhibit the theoxidation of substrate(s). Antioxidant molecules are thought to play a crucial role in counteracting free-radical-induced damage to macromolecules. In this book chapter literature survey of the different phytoremediation strategy is presented. The results show that natural antioxidants exhibit promising antidote against fluoride-induced toxicity in different mammal systems.

Keywords: amelioration, antioxidants, fluoride, natural products, overexposure, toxicity

1. Introduction

Trace elements such as Fluoride (F) are essential to animals and humans for normal health status. Fluorine is the ninth element on the periodic table. It has crustal abundance of 0.054%, which makes it the 24th most abundance element on the earth and most reactive member of the halogen family. It has an atomic weight of 18.9984. The physical and chemical properties of fluorine have been given in **Table 1**. Fluorine reacts with other elements to produce ionic compounds such as calcium fluoride (CaF), sodium fluoride (NaF), hydrogen fluoride (HF), aluminum fluoride (AlF), and many other compounds [1, 2]. In general, F-like elements causus only a source of local pollution [3]. The degree of toxicity, the scope of exploitation of the element, and its application and subsequent mobilization into the air, water, and soil are used to assess the environmental relevance of increased levels of these elements.

Physical properties	
Atomic number	9
Atomic mass	18.998403 $g.mol^{-1}$
Density	1.8×10^{-3} $g.cm^{-3}$ at 20°C
Melting point	−219.6°C
Boiling point	−188°C
van der Waals radius	0.135 nm
Ionic radius	0.136 nm (−1); 0.007 (+7)
Isotopes	2
Chemical properties	
Electronegativity according to Pauling	4
Electronic shell	[He] $2s^2 2p^5$
Energy of the first ionization	1680.6 $kJ.mol^{-1}$
Energy of second ionization	3134 $kJ.mol^{-1}$
Energy of third ionization	6050 $kJ\ mol^{-1}$
Standard potential	−2.87 V
Discovered by	Moissan in 1886

Table 1.
The physical and chemical properties of fluorine.

2. Source human overeexposure to fluoride

2.1 Air

Even though F is extensively distributed in the environment, only a small portion of overall human fluoride exposure is through the air [4, 5]. This is because the F concentrations in the air are relatively low in non-industrial locations, but they rise steeply among industrial places where phosphate fertilizers are produced or fluoride-containing coal is burnt. As a result, human exposure to fluoride from ambient air has been estimated to be only about 1–4 mg/day [6]. This is insignificant compared with other sources of human fluoride exposure [7, 8]. Nonetheless, F can enter the air from sea spray, and therefore, the immediate atmosphere might be expected more enriched near or within the coastal areas [9]. No data were found on fluoride levels in ambient air or residential soil.

2.2 Water

F is generally prevalent in many water supplies and drinking water sources around the world because they leach into groundwater from F-containing rocks and soils [10]. Because drinking water is fluoridated artificially in certain regions, this is often the major contributor to daily F consumption by humans in those areas. It is found that children who drink 1 L of water per day may consume up to 1.2 mg of fluoride per day [9]. WHO (World Health Organization)'s maximum permissible limit of F in drinking water is 1.5 mg/L and highest desirable limit is 1.0 mg/L.Estimation of

human lethal F shows a wide variation of values that range from 16 to 64 mg/kg in adults and from 3 to 16 mg/kg in children.

2.3 Toothpaste, mouthwash, and fluoride supplements

Over 80% of the toothpastes sold around the world are fluoridated, with fluoride concentrations ranging from 1 to 1.5 mg/g [11]. It is believed some fluorides are absorbed straight into the tooth enamel when a person brushes with fluoride toothpaste. Adults are estimated to ingest about 0.02–0.1 g of toothpaste per day; however, children may ingest 0.2–0.8 g per day [12]. Fluoride concentrations in mouthwashes range from 0.23 to 0.97 mg/gram [11]. Adults are likely to use and consume these more frequently than youngsters. On average, an adult person can swallow roughly 1.0 g of mouthwash every day, while a youngster would take about 0.5 g, according to the Office of Environmental Health Hazard Assessment (OEHHA).

2.4 Fluoride exposure from agricultural foodstuffs

Although raw foods contain some F, the greater portion of F exposure through the diet is as a result of F added to foods when they are cooked or processed with high F water. Nonetheless, among the foods that are highest in F include tea and ocean fish containing bones or bone meal. The consumption of tea in larger quantities can represent a potential F health risk because the tea plant (*Camellia sinensis*) is known to uptake high F levels from the soil and to accumulate them in the leaves, from where

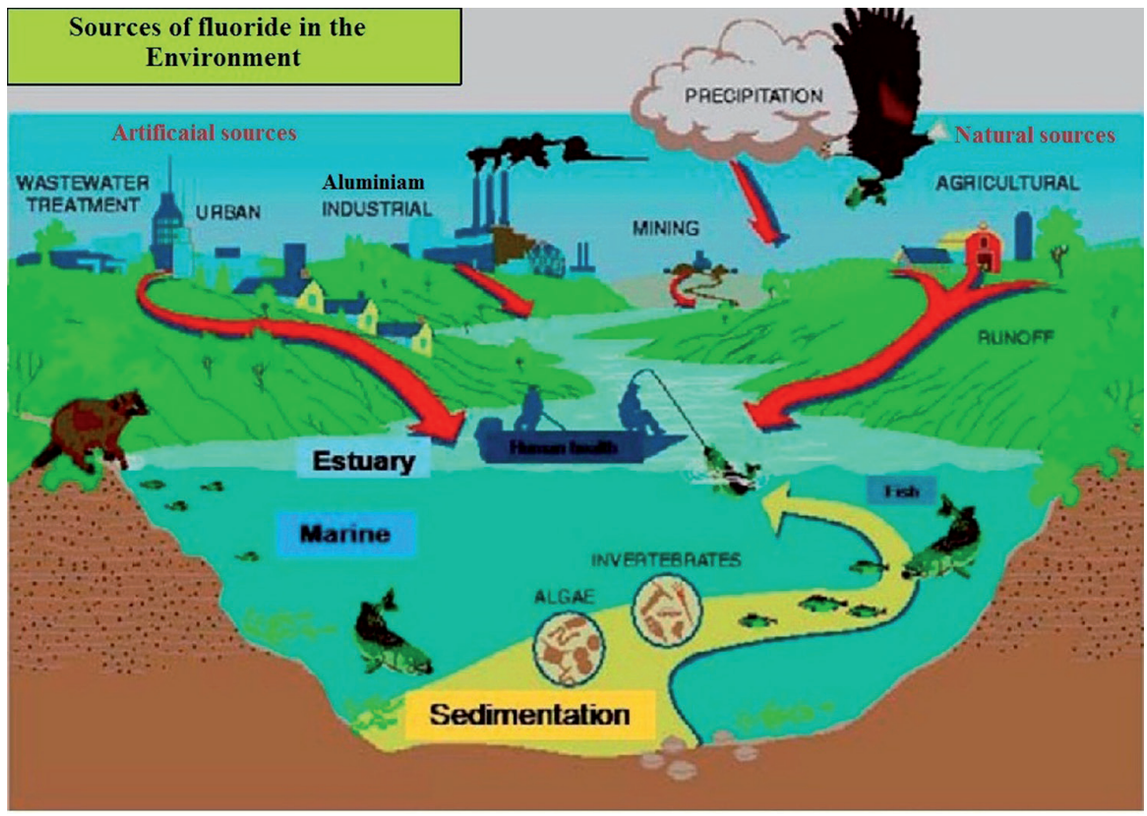

Figure 1.
Sources of fluoride and fluoride cycle in the environment.

it is easily released during the infusion of tea leaves during brewing. For communities with low F levels in foods, contribution in adults ranges from 0.3 to 1 mg/day.

2.5 Industrial source of fluoride pollution

Another major source of F pollution is the atmospheric or wastewater-based release from numerous industries that processor deal in steel, aluminum, copper, and nickel, phosphate ores, phosphatic fertilizers, glass, bricks, and other ceramics [4, 5]. The biggest industrial source of fluoride pollution into the environment is, however, the phosphate ore production and aluminum smelting. Fluoride dispersion, a pollution source, is also aided by the application of fluoride-containing insecticides and the combustion of coal and other fuel sources of geogenic origins. in the general environmental fluoride cycling between the surface waters, groundwater reserves, air, soils, and the biological components of the environment as a result of these activities is summarized in **Figure 1**.

3. Molecular mechanism of fluoride toxicity

F is redily absorbed by the stomach, lumen, and small intestine, and approximately 75–90% of ingested F is absorbed from the gastrointestinal tract. Fluoride

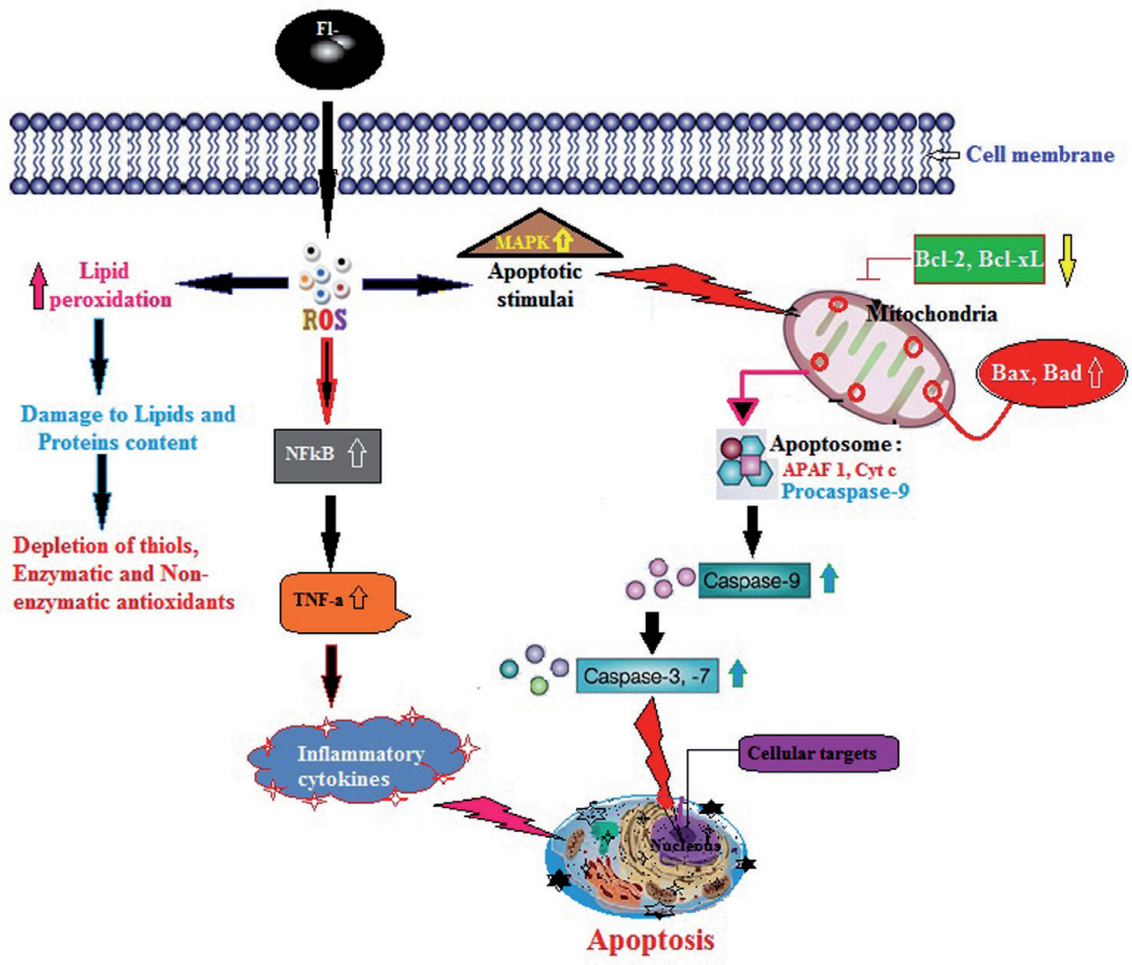

Figure 2.
Molecular mechanism of fluoride-induced toxicity.

transport through biological membranes occurs primarily through the non-ionic diffusion of hydrogen fluoride (HF). The small neutral molecule of HF penetrates cell membranes much faster than the dissociated fluoride ion, resulting in a more pronounced intracellular intake [13]. After ingestion, fluoride is rapidly and virtually absorbed into the blood stream. The ingested fluoride appears in the plasma within 30–60 min after uptake, and it is distributed from the plasma to all tissues and organs within 24 h. The element is taken up into all the tissues of the body, but it is retained and accumulated only in the teeth and other skeletal tissues resulting in dental and skeletal fluorosis when the elements water threshold levels of 1.5–20 mg/L are exceeded, respectively. In general, approximately 50% of absorbed F is retained by uptake in calcified tissues.

F is excreted primarily via urine. Urinary F clearance inceases with urine pH due to a decrease in the concentration of HF. The rate of F removal from plasma, which in healthy adults is approximately 75 mL/min, is approximately equal to the amount of the renal and calcified tissues clearances. For healthy young or middle-aged adults, only 50% of absorbed fluoride that is not assimilated into calcified tissues is excreted in the urine.

The intermediate interaction of fluoride with body systems between its absorption in the gut and its assimilation into skeletal tissue or renal clearance from the body results in a series of toxic effects to the body. These toxicities symptoms are generally referred to as non-skeletal fluorosis. It has been suggested that oxidative stress can be a possible mechanism through which fluoride induces damage to the various tissues. This F toxic mechanism can be summarized as in **Figure 2**.

4. Fluoride toxicity

4.1 Skeletal tissue toxicity

4.1.1 Dental fluorosis

Dental fluorosis is hypo-mineralization of teeth enamel that is characterized by greater surface and subsurface porosity than is found in normal enamel. It results from excess fluoride reaching the growing tooth during its developmental stages [14]. F has a greater affinity for developing enamel because tooth apatite crystals can bind and integrate fluoride ions into the crystal lattice [15]. Ameloblast epithelial cells are responsible for enamel development, and the life cycle of these cells has three stages, which comprise: secretory, transition, and maturation steps [16]. Tooth morphological studies [17] have shown that fluoride affects the secretory stage of the ameloblasts cells, which secrete the enamel proteins called enamelin, which mineralizes to form tooth enamel. When these stages are interfered with due to fluoride overexposure, the general mineralization of the enamel is compromised leading to dental fluorosis.

4.1.2 Skeletal fluorosis

Skeletal fluorosis is a painful crippling pathological condition, which can occur on long-term exposure to high dietary levels of fluoride exceeding 20 mg/L [18]. The mechanism of skeletal fluorosis suggests that fluoride ions are deposited in the bone by substituting hydroxyl groups in the carbonate apatite structure to produce

fluorohydroxyapatite, thus altering the mineral structure of the bone according to the equation below:

$$Ca_{10}(PO_4)OH + F \rightarrow Ca_{10}(PO_4)OH_6F$$

Because, F altered the mineralization of bone strength and finally causes week bone or soft bone called skeletal fluorosis (**Figure 3**).

4.2 Non-skeletal/physiological toxicity

4.2.1 Gastrointestinal effect

The dominant form in which F exists in solution is highly pH-dependent. At the normal pH of drinking water (pH = 7), fluoride occurs primarily as the free ion, F^-. In the stomach, the ingested fluoride combines with hydrogen ions from HCl to form largely molecular HF, depending on the pH in the stomach (2.4% HF at pH 5; 96% HF at pH 2). The stomach is among the first target organs for the adverse effects of fluoride. Among the soft tissues of the body, the propensity of gastric mucosa exposed to the highest concentrations of the HF is immense. HF easily crosses the gastric epithelium and is the major form in which fluoride is absorbed from the stomach. Several functional and structural changes might be associated with ingestion of fluorides such as increased mucus secretion, followed by patchy or widespread loss of the mucus layer, hyperemia, edema, and hemorrhage [19].

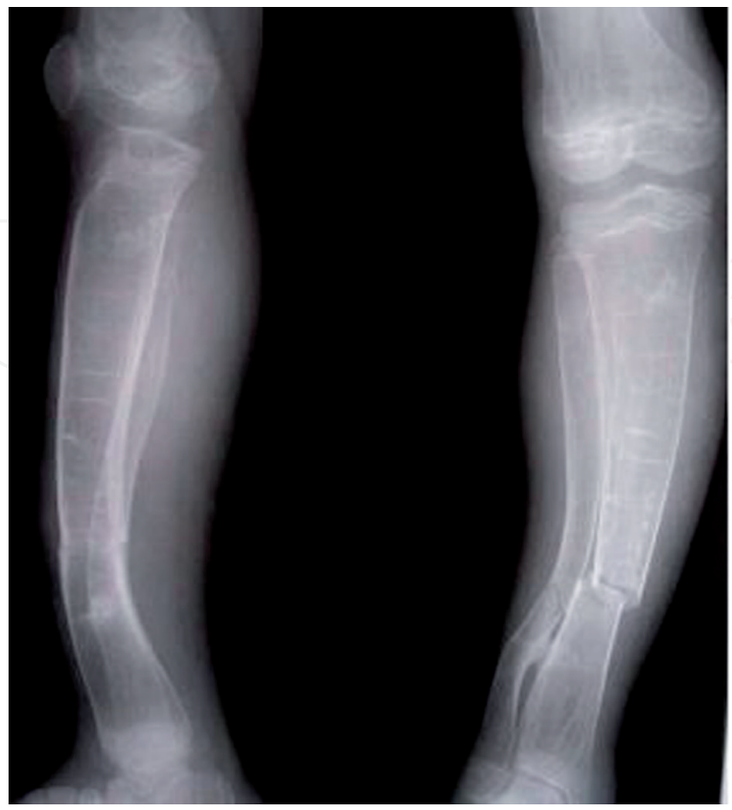

Figure 3.
Skeletal fluorosis shows brittle bone.

4.2.2 Hepatic effect

The liver is responsible for maintaining the body's metabolic homeostasis, and it has been considered as the key target organ for the toxic effects of fluoride [20]. Several mechanisms have been proposed to explain fluoride-induced hepatotoxicity. The important possible mechanism is the disturbance of prooxidant and antioxidant balances by the generation of reactive oxygen species (ROS). This decreases the activities of enzymatic antioxidants. Previous studies have shown fluoride induced abnormal function in the liver of rats, sheep, mice, etc. Especially, superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) were decreased with increased lipid peroxidation product, which cause damage to hepatocytes [21].

4.2.3 Kidney effect

The kidney is the potential site of acute fluoride toxicity because kidney cells are exposed to relatively high F concentrations [22]. Fluoride concentrations in the kidney show an increase in the gradient. Therefore, the kidney is thought to be one of the target organs for the adverse effects of fluoride because of the bioconcentration, metabolism, and kinetics excretion. F-induced ROS increases the excessive generation of nitric oxide, oxygen-free radicals, decreased CAT, SOD, glutathione (GSH), and increased lipid peroxidation, which may lead to severe damages in the nephron structure and functions and also biomacromolecules, such as proteins and nucleic acids [22, 23].

4.2.4 Respiratory effect

Fluoride exposure has been associated with asthmatic symptoms among workers in the aluminum industry [24]. However, only recently there is mounting evidence that ROS plays an important part in the complex physiological processes such as cell signaling and apoptosis. One of the organs commonly affected by ROS generation is the lungs. It is obvious that having a large surface that is constantly in contact with atmospheric oxygen and pollutants, the lungs are a site of major ROS production. The most fundamental adverse effect of fluorides in the respiratory system is the inhibition of Kreb's cycle enzymes in the lung by subsequent production of ROS. Furthermore, several studies have shown that the interaction of the lung immune system and oxidative stress might be associated with the development of several other pulmonary or respiratory diseases [25].

4.2.5 Reproductive effect

One of the toxicants that have harmful effects on the reproductive system is fluoride. The metabolism and morphology of spermatozoa were altered in the fluoride-exposed rats due to enhanced ROS/RNS-mediated lipid peroxidation. Long et al. [26] reported that fluoride significantly declined the weights of testes and cauda epididymis in rats. Sialic acid is an important constituent of mucopolysaccharides and sialomucoproteins, which are essential for the maturation of spermatozoa in epididymis and maintenance of the structural integrity of their membranes. However, fluoride overexposure can significantly altered the sialic acid [27]. Sharma et al. [28] have reported that female rats exposed to 6 ppm concentrations of sodium fluoride for 15 and 30 days revealed that the reproductive organ weights of the ovary, uterus,

and adrenal gland declined significantly due to the overproduction of reactive oxygen species with increased lipid peroxidation.

4.2.6 Cardiovascular effect

The heart is a muscular pumping organ, mainly involved in the purification and circulation of blood in the body. Heart failure results from a sudden reduction in coronary blood flow to a segment of the myocardium, which initiates severe cellular changes in the myocytes that, inevitably culminating in cell death and tissue necrosis. Sinha et al. [29] have shown that fluoride consumption causes ROS-mediated myocardium injuries and dysfunction. Also, Nabavi et al.[30] have reported that fluoride increases oxidative stress through abnormal biochemical parameters in the heart tissues of rats. Fluoride-induced oxidative stress plays an important role in the progression of a variety of cardiac disorders such as cardiac failure and ischemia [30]. Nicotinamide adenine dinucleotide phosphate-oxidase (NADPH oxidase) (Nox) is an important source of ROS in the vasculature and is activated by high levels of fluoride exposure. Fluoride can stimulate the Nox expression, and activity has implications in endothelial dysfunction and vascular disorders. It is possible that endothelial dysfunction in coronary heart disease could be related to the chronic inflammation that coexists with atherosclerosis [31].

4.2.7 Neurological effect

Fluoride is a powerful toxin of the central nervous system and adversely affects the brain functioning even at low doses [32]. It can induce neuron apoptosis and decreased cerebral functions, impaired memory and learning ability [33, 34]. F ions bind to antioxidants such as N-acetyl cysteine (NAC), glutathione (GSH), and other free-radical-defeating enzymes. This causes oxidative stress and eventually cell death [35]. The lack of a compensating antioxidant system combined with oxidative stress caused by increased free radicals plays a significant role in the onset of nerve cell membrane damage, particularly through enhanced lipid peroxidation. Several studies have reported the effects of fluoride in drinking water on cognitive capacities, and IQ reductions were observed at water-fluoride concentrations of about 1 mg/L and above [36].

5. Application of natural antioxidant against F toxicity in different organs

Studies have been carried out to explore natural antioxidants against toxic substances or elements [37, 38]. Antioxidant molecules are thought to play a crucial role in counteracting free-radical-induced damage to macromolecules [39]. There is a wide range of antioxidants that can counteract the condition of oxidative stress. It includes vitamins, phenolic compounds (flavonoids), and carotenoids. Minerals including selenium, zinc, manganese, magnesium, and copper also play a part in the body's hundreds of antioxidant functions. Aside from scavenging free radicals, natural antioxidants have been shown to influence the expression of several genes and signal regulatory pathways, potentially preventing cell death [40]. The natural antioxidants listed below were employed to alleviate F-induced oxidative stress-mediated damage in several organs in rats.

5.1 Hesperidin against F hepato toxicity

Recently, Caglayan et al. [41] reported that 600 ppm of fluoride administration induced the hepatotoxicity with severe damage in rats. However, hesperidins (HSP) 200 ppm administration to F group recovered completely from the F-induced toxicity in rats. The data showed the antioxidative potential of HSP on F-induced toxicity in liver tissue. Similarly, Küçükler et al. [42] also demonstrated the antioxidant property of HSP (100 mg/kg) in albino Wistar rats against F-induced hepatoxicity.

5.2 *Prunella vulgaris* against F nephrotoxicity

Natural antioxidants can help to conquer oxidative stress and free-radical-induced disorders. In an earlier study, epigallocatechingallate (EGCG) depicted ameliorative effects toward F nephrotoxicity in rats [43]. However, a recent study from Li et al., [44] observed that the oral administration of *P. vulgaris* (1.575 g crud drug) attenuated the fluoride-induced oxidative toxicity in rat kidneys. The hole plants were dried and powdered and extracted (Ethanol 80%, Distilled water 20%) the drug by using reflux extraction apparatus. This result indicates that natural antioxidants exhibit the attenuating efficacy over xenobiotics of the toxic element on different organs. After extraction of PV drug, it was passed through a series of HPLC (high-performance liquid chromatography), to identified the natural bioactive compounds followed by structural identification of natural bioactive compounds by using XRD.

5.3 Silymarin against F cardiotoxicity

Milk thistle extract has a centuries-old history of use in Indian folk medicine to treat a variety of illnesses including jaundice, gallstones, hemorrhage, bronchitis, or varicose veins. Its beneficial effects have been attributed to the antioxidant, anti-proliferative, and anti-inflammatory effects based on the regulation of specific signaling pathways. Nabavi et al. [45] reported that fluoride caused severe damage to the heart and brain tissue after administration. These effects are due to the alteration of enzymatic and non-enzymatic antioxidants with increased lipid peroxidation markers. This exploration shows that the Silymarin has the potential phytoremediation property against F-induced toxicity in rats.

5.4 Curcumin against F *in-vitro* toxicity

Curcumin longa is widely used as a food additive and was one of the bioactive natural products in phytoremediation therapy. In the traditional medicine of India, a cream of *Curcuma longa* called Ayurveda is used for the treatment of eye diseases, wounds, bites, burns, and various dermal diseases [46]. Fujiwara et al. [47] recently reported that the antioxidant efficacy of Curcumin in an in-vitro study against ameloblast LS8 cells treated with fluoride toxicity. In this study, Curcumin significantly attenuated the F toxicity on ameloblast LS8 cells due to the potent phytotherapeutic property of curcumin and its derivatives.

5.5 Quercetin against F neuro toxicity

Quercetin is one of the best-studied polyphenols found in onions, apples, berries, tea, and red wine. It prevents apoptosis, anticancer, anti-inflammatory, and cardiovascular

protective ability via its potent antioxidant properties [48]. Chouhan et al. [49] reported that Silymarin and Quercetin synergistically abrogated fluoride-induced oxidative toxic effect in rat liver and kidney via activation of phase I antioxidant enzymes such as SOD, CAT, GPx. Similarly, Nabavi et al. [50] reported that Quercetin showed preventive effect of fluoride toxicity in the brain due to the high concentration of antioxidant capacity of Quercetin to abrogates the Fl-induced ROS in different organs.

6. Conclusions

Taken together, F elements causing many illness by producing oxidative stress-mediated toxicity in different organs. However, the natural antioxidant from plant sources has rich chelating ability than synthetic chelators for many uncurable diseases. The supplementation of natural antioxidants mentioned in this book chapter could mitigate all kinds of organ toxicity elicited by F via modulation of oxidative damage, apoptosis in both in-vitro and in-vivo studies on different animals. This exploration also shed the lights on natural antioxidant therapy and future research in this fields.

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Conflict of interest

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