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Fluoride Contamination, Toxicity and its Potential Therapeutic Agents

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Abstract

Fluoride is the thirteenth most abundant element in the earth's crust. It is highly electronegative and distributed ubiquitously in nature. During weathering of rocks and soil, fluoride can leach out and dissolve in the groundwater. Both plants and animals are exposed to several compounds of fluoride through contaminated soil and water. Fluoride contamination in groundwater is a major global concern as groundwater is frequently used for drinking in various parts of the world, especially in developing countries. Fluoride compounds have been reported to impose acute and chronic health hazards. Millions of global populations are suffering from dental and skeletal fluorosis due to high fluoride intake through drinking water. In green vegetation, fluoride accumulation causes necrosis in the tip and marginal portions of leaves. Diverse detrimental effects of fluoride on health have insisted researchers globally to identify compounds having protective potential against fluoride toxicity. Several plant extracts, vitamins, polyphenols, melatonin, hypophyseal proteins, and lycopene have been demonstrated to enhance the antioxidant status and subvert fluoride-induced health hazards in model organisms. However, more studies are required to forward conclusive opinions in terms of the real-life efficacy of these antioxidants against fluoride toxicity.

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1. Introduction

Being strongly electronegative, fluoride is the 13th most abundant element in the earth's crust. It is widely distributed in nature. Hydrogen and fluorine are easily conjugated to produce Hydrogen Fluoride (HF). HF is a physiologically active compound that undergoes gastrointestinal and intracellular absorption. Fluoride is prevalent inside the majority of calcified tissues because of its strong affinity for calcium ions. Fluoride is known to induce new bone formation. Hence, it is clinically used to treat osteoporosis. Further, fluoride has a cariostatic effect as it is readily absorbed in enamel and forms fluorhydroxyapatite. Fluorhydroxyapatite is less acid soluble than hydroxyapatite[1]. Therefore, it aids in reducing tooth decay because of acid secretion by plaque-forming bacteria[2]. Fluoride helps in the mineralization of enamel and therefore helps to maintain healthy tooth structure. Fluoride is also a well-known G-protein activator requiring a trace amount of Al_3^+ or Be_2^+. These ions are essential for the fluoride-induced activation of heterotrimeric GTP-binding proteins and signal transduction. AlFx can limit the G protein's GTPase function because it resembles γ-phosphate at its transition state in a Gα protein. Hence, fluoride can modulate various biochemical reactions in the body.

Fluoride uptake through the gastro-intestinal tract is much higher in absence of dietary calcium and some other cations. Calcium and other cations can bind with fluoride to form insoluble compounds that are difficult to be absorbed within the body. If absorbed, fluorides are typically eliminated from the body through renal filtration. Renal excretion of fluoride compounds depends on the pH of the tubular fluid. In healthy young and middle-aged adults, approximately 50% of fluoride compounds are retained by calcified tissues. Surprisingly, this scenario is different in children where approximately 80% can be retained by calcified tissues due to higher uptake of fluoride by developing bones and teeth[3].

Excessive fluoride intake triggers toxicological consequences. Fluoride toxicity is manifested through various actions. Fluoride when coming in contact with moisture forms hydrofluoric acid which has a corrosive effect. Fluoride drops the blood calcium level and hence the availability of calcium, which is necessary for the optimum neural function is reduced. Therefore, the nervous system is affected[4]. Fluorides have an inhibitory action on various intracellular enzymes and hence cell death may result due to fluoride intoxication. Fluoride also disrupts the electrolyte balance which can impede cardiac function[5].

This review discusses the basic biochemistry of fluoride compounds in terms of their global distribution, potential physiological roles, and toxicological implications in animals and plants. The first half of this literature is centred on the chemical nature, global distribution, sources of contamination, and basic physiological effects of fluoride compounds. The second half of this paper emphasizes the route of fluoride absorption, their toxicological impacts on various physiological systems of animals along with molecular mechanisms, and adverse effects on plants. The final section of the present article provides a concise glimpse of agents having the pharmaceutical potential to lower fluoride-induced health hazards in a living system.

2. Chemical Nature of Fluoride

Fluoride is a mono-atomic anion (F^-). It binds with Sodium or Hydrogen ions to form salts which are white in colour. Fluoride salts are bitter in taste and usually odourless. Fluoride is a weak base and hence it does not easily dissolve in solution but unfortunately higher concentrations of fluorides can be corrosive and detrimental to skin surface. Numerous salts having fluoride as one of the major constituents are available. Typically, a fluoride anion is surrounded by four or six cations. Fluoride when treated with strong acid, it produces hydrogen fluoride and metal salts. Fluoride upon oxidation can generate fluorine. Inorganic fluorides are soluble in water and aqueous solution exist in F^- and bifluoride ions (HF^-).

3. Global Distribution of Fluoride Contamination in Groundwater

Fluoride contamination in groundwater shows spatial and temporal variations. Almost every continent of the earth is affected by groundwater fluoride contamination. India, China, Ethiopia, Kenya, and Argentina are mostly affected by fluoride contamination. South Asia can be considered the epicentre of fluoride contamination in groundwater[6]. Countries of South Asia such as India, Pakistan, and Sri Lanka have high fluoride content in groundwater. Approximately, 75% of groundwater samples in the East Punjab area of Pakistan exceed WHO standards[7]. In the

case of Sri Lanka, mainly the eastern and southern parts of the country are mostly affected. In East Asia, China is the most affected country. Groundwater in areas of low rainfall and high temperature is highly fluoride-contaminated[6]. In the African continent, the rift valley extending through Jordan valley, Sudan, Ethiopia, Uganda, Kenya, and Tanzania shows a high level of fluoride contamination in groundwater. European countries show fluoride levels within the permissible range. Up to 8.8 mg/L of fluoride has been reported from private wells in Germany[8]. Razo *et al.*,[9] has reported fluoride concentration in a range of 0.5-3.7 mg/L in the groundwater of Northern Mexico. In South America, Argentina is the most affected country. Smedley *et al.*,[10] investigated fluoride contamination in the La Pampa area of Argentina. They reported fluoride concentration in the range of 2.9-25.7 mg/L in the shallow aquifer (9–10 mbgl). In the USA, fluoride in groundwater ranges between 0.2 to 3.58 mg/L in Ohio[11].

In India, high fluoride in groundwater has been reported in all states[12]. The fluoride contamination in groundwater is widespread, intense, and alarming. Endemic fluorosis is prevalent in India since 1937[13]. The effect of fluoride contamination in India is most profound in the state of Rajasthan[14]. Andhra Pradesh and Telangana are the second most affected states in India after Rajasthan[9]. In 1991, groundwater in 13 states of India including West Bengal, was reported to contain fluoride concentration greater than 1.5 mg/L[15]. By 1999, the number went up to 17 states, including West Bengal (UNICEF). Das and Nag[16] documented that, there is a high fluoride level in groundwater in the Birbhum district of West Bengal.

4. Other Sources of Fluoride Contamination

People are exposed to fluorides through numerous sources. Exposure mainly occurs through milk, fluoridated drinking water, beverages, and food supplements. Unintentional exposure to fluorides is due to contact with pesticides, fluoride-contaminated soil, environmental pollution, drugs, gels, and varnishes. Major sources of fluoride intake by humans include milk derivates, fish, chicken, water, and several fluoride-containing oral products like toothpaste, mouthwash etc. Intake of fluoride is dependent upon several factors like extent/frequency of consumption and diversity of products available. The ingestion of fluoridated toothpaste in children younger than 6 years of age has also been strongly associated with increased fluoride intake.

5. Absorption of Fluoride within the Body

The absorption rate of fluoride depends upon the vehicle with which it is consumed. When fluoride compounds are taken with the liquid in which the compound is soluble, the absorption is almost complete across the gastrointestinal tract. When fluoride compounds are taken with liquids rich in calcium such as milk, fluoride forms insoluble adducts which are difficult to absorb. The absorption and bioavailability of fluoride compounds from toothpaste where sodium fluoride or monofluorophosphate has been used is maximum[17]. Besides, co-ingestion of fluoride and caffeine or some other methylxanthines also increases the bioavailability of fluoride.

6. Beneficial Impacts of Fluoride

Dental cavities may be gifted by acid solutions coming in contact with enamel from varieties of sources. It solubilizes hydroapatite, the chief component of enamel, and damages dental shape and strength. Fluoride from saliva and other sources may be taken through the enamel and form fluorhydroxyapatite which is less soluble in acid and therefore less prone to decay. This helps to maintain a healthy internal as well as external architecture of the teeth. Fluoride also inhibits some bacterial enzymes, therefore, limiting metabolism as well as acid secretion by plaque-forming bacteria. Hence, these activities of fluoride may reduce the demineralization of teeth and promote the remineralization of enamel.

7. Toxicity of Fluoride

Besides the beneficial impacts of fluorides, detrimental effects are also reported when ingested in excess amounts. Due to the consumption of high fluoride-containing groundwater (>1.5 mg/L), 260 million population around the world[18] and 62 million population in India[6] are suffering from fluorosis. As per the recommendation of The American Dental Association, fluoride intake of more than 120mg at one time is toxic to human health. American Association of Poison Control Centers suggested that approximately 68% of all fluoride intoxication is due to fluoride dentifrice ingestion, 17% due to fluoride-containing mouth rinses,

and 15% due to other fluoride-containing supplements[19]. 80% or more cases of fluoride intoxication are reported in children below 6 years of age[20]. Over-ingestion in children through dental supplements is the main reason behind fluoride toxicity. Some of the common symptoms of acute fluoride toxicity include abdominal cramps, nausea, and vomiting. Muscle tetany may also result as a response to a drop in blood calcium levels. Hypocalcaemia, hyperkalemia, convulsions, and cardiac arrhythmias may also be the additional outcome of excessive fluoride intake. In addition, it has been reported that chronic fluoride exposure is toxic for the diabetic patient because it inhibits glycolysis and increases blood sugar levels[21].

7.1 Effects on Dental Health

Dental fluorosis is a condition in which hypomineralization of enamel takes place as a result of excessive exposure to fluoride during tooth formation[22]. Dental Fluorosis necessitates an excessive amount of fluoride during a critical period of enamel formation[23]. The Year of susceptibility to fluorosis is the first two years of life[24]. In communities where water fluoridation programs are carried out, approximately 1 ppm concentration of fluoride is sufficient to generate early symptoms of fluorosis. At approximately 10 ppm concentration, the porosity of enamel is increased and large pieces of enamel are fractured after the eruption. Fluoride concentration in extracellular fluid that surrounds the enamel also acts as a key regulator of fluorosis development[25]. Evidence suggests that the impact of fluoride on enamel is determined by both concentration and time of exposure[26]. Epidemiological studies have claimed that additional factors may be responsible for the development and severity of dental fluorosis. A relationship exists between high altitude and the severity of dental fluorosis even if people are exposed to optimum levels of fluorides. Physiological health and malnutrition of individuals are also responsible for increased fluorosis development. Interestingly, drugs responsible for acid-base imbalance within body fluids have been reported to increase risk of dental fluorosis in human beings[27].

7.2 Skeletal Fluorosis

Exposure to fluoride more than the recommended levels may cause skeletal fluorosis. Skeletal fluorosis is characterized by increased deposition of fluoride in the bone matrix resulting in higher bone mass and density[28]. Initial symptoms of skeletal fluorosis include pain and stiffness of joints resulting in difficulty in mobility. Primary symptoms may appear with a fluoride dose greater than 4 mg/l. Advance-stage skeletal fluorosis is manifested with symptoms of osteoporosis and arthritis, compression of the spinal cord, and calcification of ligaments. Muscle weakness and fatigue are also reported[29]. Abnormal bone outgrowths are seen in the case of skeletal fluorosis. Crippling skeletal fluorosis is rare and it leads to remarkable immobilization of joints. The problem usually occurs at a fluoride dose greater than 10 mg/L[30]. The amount of water intake, quality of drinking water, kidney diseases, and intake frequency of a calcium-rich diet determine the severity of skeletal fluorosis in human beings[31].

7.3 Effect on Gastrointestinal Tract

Ingested fluoride primarily affects the gastrointestinal environment. Acute fluoride exposure may promote gastrointestinal disturbance or even the death of organisms[32]. Fluoride can stimulate the secretion of HCl and simultaneously reacts with the acid to form Hydrofluoric acid. Hydrofluoric acid acts as a corrosive agent for intestinal epithelium[33]. Intake of drinking water with a fluoride concentration of 3.8 ppm or more can produce dysplastic symptoms. Adverse effects of fluoride compounds on the intestinal tract are more common in people having hypersensitivity to the compound[31]. Moreover, fluoride intoxication induces chronic atrophic gastritis. Other microscopic alterations viz. scanty microvilli, surface abrasions, and desquamated epithelium are also associated with fluoride exposure. Notably, fluoride could act as a possible aetiological factor in non-ulcer dyspepsia.

7.4 Effects on Excretory System

Approximately 50-60% Fluoride containing compounds go through the renal system for its elimination through urine. Therefore, the renal system is on the verge to get affected by fluoride intoxication. Exposure to higher concentrations of fluoride could contribute to renal damage that culminates in chronic kidney disease. When the fluoride content in drinking water is 8 ppm or higher, it severely affects renal tubules. Morphological alterations in kidneys like swelling, loss of renal epithelia, glomerular atrophy, and fibrosis are likely to result following fluoride intoxication[29,34]. Malfunction of renal tubules may lead to increased serum creatinine and serum nitrogen contents

in the urine[29]. Moreover, inhibition of tubular reabsorption leads to alteration in urinary ion excretion by the nephrons thereby disrupting collagen biosynthesis in the body, and causing damage to the kidneys and other organs. Fluoride ions could also block the catalytic function of kidney enzymes, affecting the overall functioning of enzyme pathways and renal physiology.

7.5 Effects on Central Nervous System of Fetus and Children

Fluoride can cross the blood-brain barrier and affect the development of the brain and neural circuits in a developing fetus. These compounds can lower the levels of neurotransmitters and receptors in neural junctions[29]. Children exposed to fluoride counter difficulties in gaining learning and intellectual skills. Visuospatial capabilities and hence IQ scores of children are affected by exposure to higher doses of fluoride[31]. Neurological symptoms in patients with occupational fluorosis have been detected which suggests the involvement of nervous system anomaly and includes several biological impacts[35]. At molecular levels, fluoride compounds alter the concentration of non-enzymatic Advanced Glycation End Products (AGEs), the metabolism of neurotransmitters (influencing mainly glutamatergic neurotransmission), and the energy metabolism of neurons by the impaired glucose transporter- GLUT1. These changes at the molecular level can fuel abnormal cell differentiation and the activation of apoptosis. Apoptosis is induced by changes in the expression of Neural Cell Adhesion Molecules (NCAM), Glial Fibrillary Acidic Protein (GFAP), Brain-Derived Neurotrophic Factor (BDNF), and MAP kinases. All these changes ultimately lead to substantial damage to various components of the brain, impaired cognition, reduced learning ability, memory dysfunction, and behavioural problems.

7.6 Effects on Immune System

Some recent studies have demonstrated the immunotoxic potential of fluoride in model organisms. Mouse phagocytes treated with NaF showed impaired phagocytosis in an NF-kβ dependent manner[36]. NaF exposure suppresses immunity in silk worms[37]. In another study, exposure to fluoride (50-75 mg/L) triggers the generation of Reactive Oxygen Species (ROS) and reactive nitrogen species in mouse macrophage[38]. Therefore, fluorides may lower immunological reactions against viral, bacterial, and protozoan infections in human beings. Notably, fluoride compounds can impart a significant reduction in percentages of $CD3^+$, $CD3^+CD4^+$, and $CD3^+CD8^+$ T lymphocytes in the peripheral blood. In addition, exposure to fluoride can down-regulate optimum levels of serum T helper type 1 (Th1) cytokines including interleukin (IL)-2, interferon (IFN)-γ, tumour necrosis factor (TNF), and Th2 cytokines including IL-4, IL-6, IL-10, and Th17 cytokine (IL-17A) contents. All these factors are key to cellular and humoral immunity and therefore contamination with fluoride could subvert immune reactions against a variety of microbial pathogens. This can increase susceptibility to a variety of diseases.

7.7 Effect on Fertility

Studies suggest that fluoride adversely affects human reproductive health and may lead to male and female infertility which creates a growing concern in the scientific community. According to the US database, increasing fluoride concentration in male and female individuals is associated with a reduced fertility rate[39]. The adverse effects of NaF on model organisms are evident in recent studies. Sub-lethal concentrations of NaF trigger apoptosis in ovaries followed by disruption in the normal ovarian architecture of fruit flies, *Drosophila melanogaster*[40,41]. In the same study, NaF-induced oxidative stress and DNA damage have been in the developing oocytes of adult flies. Moreover, the fecundity of exposed females was adversely affected. Kumar *et al.*,[42] documented a decrease in sperm count and altered histological structure of testes in rabbits fed with NaF. A fluoride treatment in male Wistar rats causes a decrease in the weight of the testes, epididymis, and ventral prostate leading to reproductive impairment[43]. Moreover, fluoride intoxication can be detrimental to spermatogenesis and linked hormones in adult males[44]. Fluoride also blocks the calcium signalling cascade involved in sperm hyperactivation and fertilization[45]. Therefore, studies on animal models suggest the adverse effects of fluoride contamination on reproductive physiology.

7.8 Effects on Intracellular Environment

Studies have claimed that fluoride may modulate the intracellular environment and cellular metabolism within the organisms[46]. Fluoride alters intrinsic anti-oxidant enzyme activities resulting in ROS production. Consequently, higher ROS level causes DNA damage

and cell death[47]. Fluoride like HF and NaF damage the mitochondrial membrane and release cytochrome C, therefore, promoting caspase-dependent cell death[48]. Fluoride can also open the Permeability Transition pore (PT pore) and destroy membrane stability[49]. Fluoride-induced ROS production can up-regulate Uncoupling Protein 2 (UCP-2). UCP-2 can negatively affect membrane potential and ATP generation within the mitochondrial chamber[50]. Therefore, it may be suggested that fluoride-induced attenuation in ATP generation, interferes with mature ameloblasts to reabsorb enamel matrix proteins necessary for the solidification of enamel. Hence, this may result in dental fluorosis. Fluoride-induced oxidative stress also acts as a mediator of Endoplasmic Reticulum Stress (ERS). Oxidative stress can hike the accumulation of unfolded and misfolded proteins within the ER and trigger Unfolded Protein Response (UPR)[51]. UPR maintains the homeostatic balance between ERR and normal ER function. In case this homeostatic balance is disrupted, apoptotic pathways are triggered[52]. Moreover, ROS can fuel the production of inflammasome that up-regulates proinflammatory cytokines[53]. Glucose regulatory protein 78 (GRP-78) harboured within the ER, binds with Inositol-Requiring Enzyme 1 (IRE-1) under normal conditions. In presence of ERS, IRE-1 is released from GRP-78 and acts as a chaperone to repair misfolded proteins[54]. Whenever the duration of ERS is prolonged, the IRE-1 pathway activates pro-apoptotic factors such as C/EBP homologous protein (CHOP) to induce apoptosis in fluoride-exposed cells (Figure 1).

8. Molecular Mechanism of Fluoride Toxicity in Animals

Several experiments have indicated the deleterious effects of fluoride and other substances in model organisms[47,55–64]. In recent studies, it has been shown that fluoride has adverse effects on cellular systems even at low doses. Published studies have claimed that fluoride can increase oxidative stress which modulates intracellular homeostasis like increased lipid peroxidation and protein carbonyl content[40]. Altered homeostasis affects gene expression and also triggers apoptosis in vital tissues. Fluoride in an aqueous medium is converted into HF due to its high electronegativity and up to about 40% of ingested fluoride is absorbed from the stomach as HF in an acidic medium[65].

Fluoride moves across biological membranes in the form of HF. It has been proved that the permeability coefficient of HF is similar to the water and hence, it can easily diffuse faster through biological membranes than the dissociated fluoride ion. This phenomenon increases intracellular fluoride concentration[65]. Hydrogen fluoride (HF) has a higher ability to cross the biological membranes via facilitated diffusion than fluoride[66] and approximately 45% of ingested fluoride is absorbed through the intestine. After cellular uptake, fluoride affects cellular respiration by inhibiting enzymes of glycolysis and the Krebs cycle[67]. It also disrupts ATP generation and inhibits cytochrome C production[67], which in turn causes metabolic arrest. It has been reported that inhibition of cyt C production leads

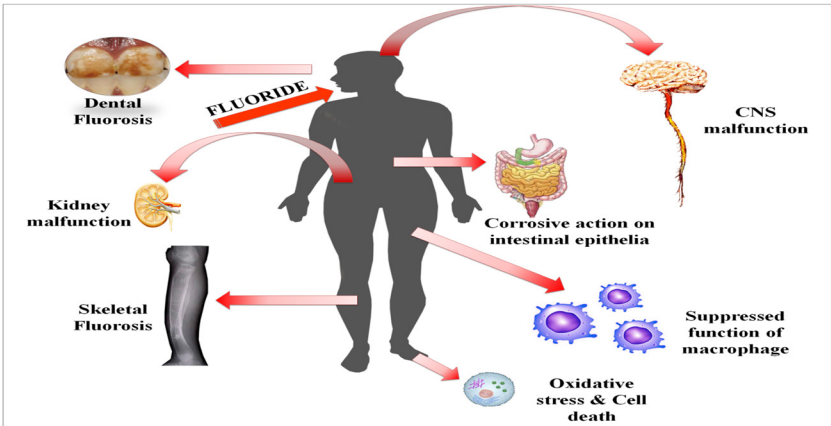


Figure 1. Detrimental effects of fluoride exposure on human health. Fluoride intoxication exerts several health hazards in human beings. It causes dental and skeletal fluorosis. In addition, fluoride-induced oxidative stress can be detrimental to renal, intestinal and CNS functions.

to intracellular induction and activation of Nitric Oxide (NO) and NO blocks cellular respiration.

Mitochondria are the major site for the generation of ROS. Several *in vivo* and *in vitro* studies have demonstrated that fluoride can disrupt the intracellular antioxidant system by hampering the activity of antioxidant enzymes such as catalase, superoxide dismutase and glutathione peroxidase[47]. Higher ROS level due to fluoride exposure increases membrane lipid peroxidation and protein carbonyl content, which disrupts cellular homeostasis and finally contributes to cellular demise.

Cell apoptosis includes the combined action of delicate signalling molecules. Studies have proved that fluoride alters signalling cascades[67], and promotes DNA damage. Furthermore, fluoride also modulates the intracellular calcium homeostasis[67] which causes altered cellular signalling.

Additionally, fluoride is also related to epigenetic alterations. It has been reported that fluoride-induced epigenetic changes enhance skeletal and dental fluorosis. Studies proved that alteration in DNA methylation after fluoride treatment results in skeletal fluorosis. Daiwile *et al.*,[68] reported that fluoride treatment causes methylation of promoters of genes that lead to skeletal fluorosis.

Another response of fluoride, demonstrated by what is known as paradoxical dose response has been reported in the case of fluoride intoxication[69]. A paradoxical dose response is a condition where a decrease in response with an increase in concentrations is observed. A stimulatory or beneficial effect of a sub-inhibitory concentration of a toxic substance is also known as hormesis. The molecular mechanism of fluoride toxicity has been illustrated in Figure 2.

9. Effects on Vegetation

Plants absorb fluorides from soil and groundwater[70]. The general baseline of fluoride content in the plant is < 10 mg/Kg but the concentration may vary depending on the plant species. In the case of *Trifolium repens*, fluoride uptake does not usually exceed 30 mg/Kg. Fluoride uptake in *Lolium multiflorium* is about 50 mg/Kg[70]. Some plants are highly sensitive to fluoride exposure. According to studies[72,73],

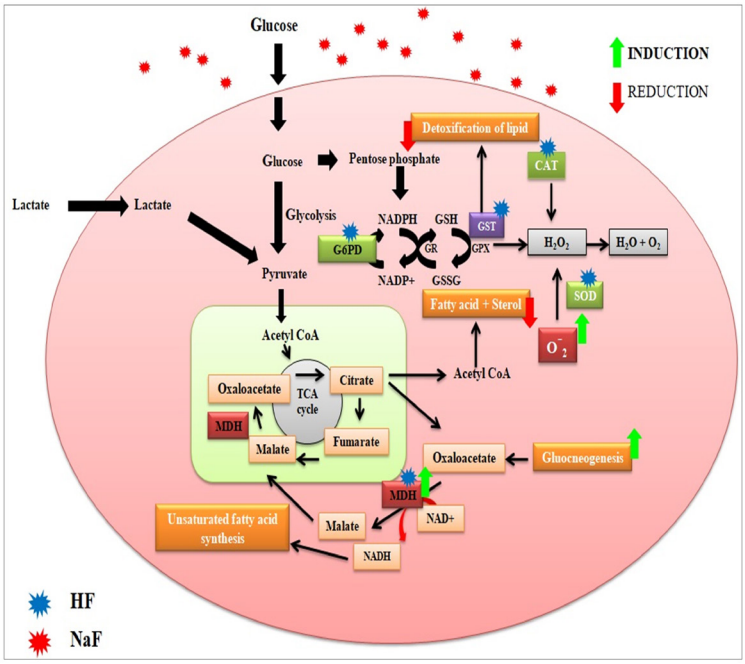


Figure 2. Molecular mechanism of fluoride toxicity. Fluoride in the form of NaF and HF affects the various biochemical pathways at sub-cellular moiety. Fluoride alters the concentration of Malate Dehydrogenase (MDH) and Glucose-6-Phosphate Dehydrogenase (G6PD) that are linked to TCA cycle. Moreover, fluoride alters endogenous antioxidant molecules and generates free radicals that impart oxidative damage to various macromolecules like proteins and lipids. All these effects modulate sub-cellular pathways to alter the overall physiology of an organism.

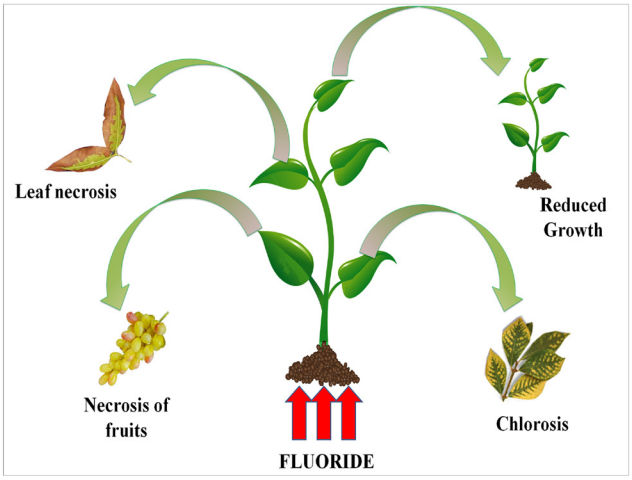


Figure 3. Multiple adverse effects of fluoride exposure on vegetation.

exposure to fluoride can reduce plant growth and promote chlorosis, leaf necrosis, and leaf tip burning. Fluoride is an accumulative poison for plants. It undergoes accumulation in the leaves through a transpiration pool and causes marginal and tip necrosis which may spread towards the interior of the leaf. Fruits like apricot, blueberry, grapes, and plums are affected by fluoride exposure. The effects of fluoride toxicity on vegetation are shown in Figure 3.

10. Potential Therapeutic Agents of Fluoride Toxicity

Some food products and synthetic chemicals may be taken into account to minimize fluoride intoxication. Generally, milk is better at minimizing fluoride-related adversities as it contains calcium that binds with fluorides to form insoluble adducts and therefore decreases their absorption into the serum. Other compounds like Calcium gluconate and Calcium lactate are also effective. Synthetic compounds like Al-Fe oxides, Sulfate doped Fe_3O_4/Al_2O_3 nanoparticles, waste tea ash and neem charcoal are very good adsorbents of fluoride[74,75]. Besides, activated aluminium, bone char, and activated carbon have been proven to have adsorbent activity for fluoride[76,77].

Several plant-based natural products have been tested to ameliorate fluoride toxicity in model animals. Pre-oral administration of blackberry juice in adult male Wister albino rats can enhance *in vivo* antioxidant activity to reduce the damaging effects of fluorides. Ethanol extract of bark of *Terminalia arjuna* increases heart SOD, GPx, GSH and CAT in NaF-exposed male Swiss albino mice to fight against fluoride toxicity[78]. Oral administration of *Tamarindus indica* leaf powder minimizes NaF-induced oxidative stress in colony-bred male albino mice[79]. Other agents like melatonin, epiphyseal (pineal) proteins and lycopene protect model organisms from the toxic effects of fluoride in experimental organisms. Intra-peritoneal and oral administration of melatonin (10 mg/kg body weight) in mice and rats can lower ROS generation by boosting the up-regulation of antioxidant enzymes[80]. In another study[81], a significant reduction in fluoride-induced hemolysis has been reported in human red blood cells treated with NaF. Pre-oral administration of epiphyseal proteins to fluoride-treated female Wistar rats has reduced peroxidation levels in cardiac, hepatic and renal tissues. Simultaneous up-regulation in CAT, SOD, GPx, GR, and GSH was noticed[82]. Intraperitoneal administration of epiphyseal proteins can significantly reduce plasma fluoride content in adult female wister rats[80]. Lycopene enhances antioxidant activity in luoride-treated male albino rats[83] to get better protection from fluoride-induced health hazards. microorganisms secrete high-affinity anion-binding compounds called ionophores that can conjugate with anionic forms of compounds to form an anion-ionophore complex. This complex can be absorbed back into the organism for metabolic processes. Therefore, these microorganisms can provide opportunities to remove fluoride from soil or groundwater. Studies around the globe have investigated the role of selected microorganisms specifically bacterial strains in the micro-remediation of fluoride content. Fluoride-resistant bacterial strains such as Acinetobacter RH5 and *Pseudomonas aeruginosa* are known to possess defluoridation capability of 25.7% and 22.1% respectively[84,85]. The bacterial strain *Bacillus flexus* NM25 is known to reduce fluoride content by up to 67.45% from contaminated soil[86]. Mukherjee *et al.,*[87] in their study documented that; *Providencia vermicola* (KX926492) can remove fluoride contents in groundwater by up to 82%. This finding insisted they conclude that *Providencia vermicola* (KX926492) could be a potent microorganism in removal of fluoride from contaminated ground water of both rural and urban areas. In another study[87], *Acinetobacter sp.* RH5 was examined to assess its ability in reducing fluoride concentration in water. The authors reported that the bacterial strain can achieve maximum fluoride removal of 25.7 % from the culture media at 30 °C temperature and pH 7 following 8 days of incubation. Sharma *et al.,*[88]

in their study concluded that the defluoridation capacity of *Paenibacillus sp.* is remarkable and could also be used for commercial applications.

11. Conclusion

Fluoride though has beneficial advantages on teeth and bone development, but it has several health hazards on plants and animals. It promotes dental and skeletal fluorosis in human beings. Fluoride has also been reported to suppress the immune system, and affect the kidneys, liver and gastrointestinal tract. Water fluoridation programs should use fluoride not higher than the recommended amount. Plant extracts, synthetic agents as well as microorganisms have emerged as ameliorative agents against fluoride toxicity. Detailed investigations are still needed to ensure their applicability to human beings.

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