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FLUORIDE AND ITS INTERACTION WITH HUMAN LIFE - A REVIEW

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ABSTRACT

The objective of this comprehensive review is to update the impact of Sodium Fluoride on human system and other life on the earth. Sodium Fluoride is a source of Fluoride ion used in miscellaneous applications includes health, insecticidal and metallurgical. Fluoride is often referred as ***"double edged sword"*** because in small doses it acts as an essential trace element and on excessive exposure it causes harmful effects.It is a known fact that Fluoride prevents dental caries through dual-mode of action; inhibits demineralization and enhances the remineralisation of dental hard tissues.The ionic Fluoride in saliva, enamel and dentin shifts the equilibrium of demineralization-remineralisation toward remineralisation. Fluoride acts as a catalyst for the uptake of calcium and phosphate ions and results in a greater efficiency in demineralising the areas of enamel and dentin that have been affected by acidic attack**.** On the other hand, excess levels show negative impact on different systems in humans. When Fluoride concentration exceeds permissible levels it shows impact on plants, animals, microorganisms and different enzymes involved in metabolic processes. It affects flora growth by the inhibition of *Enolase* and other metabolic enzymes.Enolase plays a key role in glycolysis, an energy (ATP) synthesis source for the flora and decreases production of ATP. Improper ATP synthesis directs the impact on further molecular mechanisms leading to death of organism. The antibacterial action of Fluoride on the organism is due to acidification of bacterial cytoplasm.

KEYWORDS: Sodium Fluoride,Dental fluorosis, Skeletal fluorosis, Enolase.

1. INTRODUCTION

Fluorine is an electronegative trace element of halogen family occurring naturally in earth's crust and enters surface and ground water through natural and anthropogenic sources. Fluorine occurs both in organic and inorganic forms. Organic forms are methyl Fluoride, acetyl Fluoride and inorganic forms are sodium Fluoride, hydrogen Fluoride, fluorosilicic acid, sulphur hexaFluoride and beryllium Fluoride.Most abundant form of fluorine is sodium Fluoride.

1.1 Sodium Fluoride

Sodium Fluoride is signified as a nutritional supplement for the prevention of dental caries in children of areas with inadequate Fluoride concentration in the drinking water. In optimally fluoridated communities, the prevalence of dental caries can be reduced by administrating sodium Fluoride at a rate of 2.2mg/day.[1] Fluoride binds to calcium ions in hydroxyapatite of exterior tooth enamel and helps preventing deterioration of tooth enamel by remineralisation process. This agent also inhibits acid production by commensal oral bacteria.[2]

2. SOURCES OF FLUORIDE - Common sources of Fluoride include: [3] Air, Food, Soil and Water.

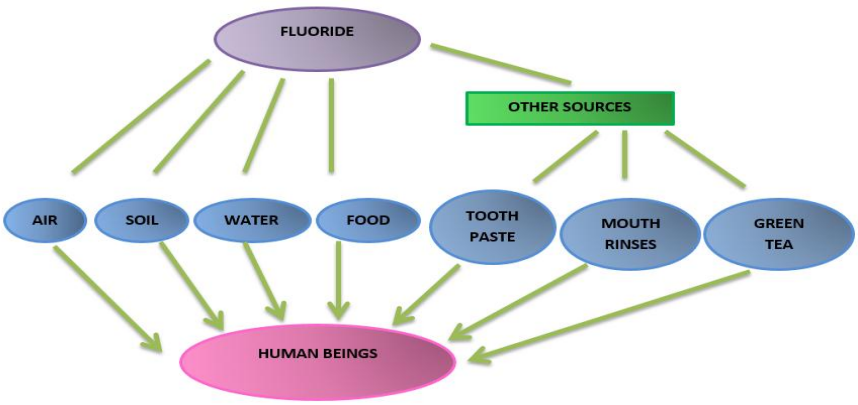

Figure 1: Sources of Fluoride.

2.1Air

Fluoride enters the atmosphere in gaseous and other particulate forms from a variety of natural and anthropogenic sources include volcanic eruptions and combustion of Fluoride containing coal. Airborne Fluoride concentrations are high in areas close to emission sources and industrial zones.[4] Distribution and deposition of airborne Fluoride depends on factors such as level of emission.[5]

2.2 Food

Almost all the food materials comprise minute concentrations of Fluoride. The Fluoride level in most of the fruits, vegetables, meats are very low.[6] Natural vegetation contains Fluoride, which is absorbed from sources like soil and water.[7]Sardines, canned salmon are the fish that contain Fluoride. Fluoride used in some pesticides, have high levels of Fluoride particularly grape products, dried fruit, dried beans, cocoa powder, and walnuts.

2.3 Water

Fluoride is naturally found in rocks and soil. Water passes through the earth and absorbs the naturally occurring Fluoride; as a result Fluoride is found in all natural waters to some extent. The content of Fluoride varies by region; dry regions generally have higher Fluoride levels than regions with high rainfalls.[8] It can be extremely high in ground water depending on the type of rocks and minerals of the region. Based on acidity, pH and hardness of the water inorganic Fluoride compounds dissolve into Fluoride ions.[9]

2.4 Soil

Fluoride is a common element of most types of soil, with concentrations ranging from 20 to 1000 µg/g.**[10]**Clay, organic carbon and pH of soil are primarily responsible for the retention of Fluoride in soils.**[11]** In general, Fluoride present in the soil is resistant to leaching which helps as soluble content to terrestrial animals and plants. In places with no natural phosphate deposits in the soil, Fluoride combines with aluminium and forms Aluminium Fluoride complexes, research have been done to know the toxicity of these compounds.[12]Aluminium is the abundant metal with highest affinity for Fluoride.Excess Fluoride concentration in soils can be removed by calcite, reaction of Fluoride with calcite results in the precipitation of fluorite.[13] Anthropogenic processes that release Fluoride to air, water and soil are.

✓ Phosphate fertilizer production	✓ Chemicals production
✓ Aluminium production	✓ Steel and oil production
✓ Coal burning	

2.4 Other sources of Fluoride

2.4.1 Tooth paste

Tooth paste is significant in maintaining oral health, as it helps in the removal of plaque and debris. Tooth paste helps in preventing the accumulation of microorganisms. In modern life, tooth pastes are used by individuals on a daily basis and hence can be a source of various therapeutic agents including Fluoride. Tooth paste is a major source of Fluoride in

communities with low fluoridated drinking water. Fluoride is added to tooth paste mostly as sodium Fluoride, during exceptional cases sodium fluoromonophosphate, amine Fluoride and stannous Fluoride are added as Fluoride sources.[14]

2.4.2 Mouth rinses

Fluoride mouth rinses have been used extensively for the prevention of dental caries. Fluoride in rinses incorporates into enamel coating of teeth and protects people from acids produced by the bacterial plaque. Mouth rinses are used on daily, weekly and fortnightly basis.[15]

2.4.3 Green tea

Green tea contains Fluoride. The Fluoride in green tea is double the concentration found in black tea. Green tea is obtained by the infusion of leaves from "*Camellia sinensis"* plant.*"* *Camellia sinensis"*retains Fluoride from soil, air and is the only plant with more content of Fluoride. Tea composition includes flavonoids, caffeine, Fluoride and theanine.[16] Green tea usually made from older leaves which contain low level of anti-oxidant and high Fluoride level. The average Fluoride concentration of infusions from decaffeinated tea were found to be 3.19 ppm and ranged from 1.01 to 5.20.[17]Drinking high amount of green tea causes bone pain, muscle pain, joint pain, calcification of ligaments, bone spurs, fused vertebrae and difficulty in moving joints. Fluoride concentration in green tea causes Alzheimer's disease.[16] Fluoride in green tea combines with aluminium to form aluminium Fluoride, aluminium further combines with oxygen and forms aluminium oxide or Alumina. Formation of Alumina is a major cause of Alzheimer's disease.[16]

2.4.4 Fluoride drugs

Fluoride drugs are prescribed to the people with Fluoride deficiency. There are many Fluoride drugs in use for different applications in different countries. Some of them include.

Luride, Ludent, ACT (Johnson & Johnson, United States), Bifluorid (Sodium Fluoride and Calcium Fluoride, Voco, Denmark; Voco, France), Bifluorid 12 (Sodium Fluoride and Calcium Fluoride, Meda, Sweden), Buclorhex (Sodium Fluoride and Chlorhexidine, Sertex, Argentina), Butler F 0.1% (Sunstar, Japan), Butler Fluodent Foam A 2% (Sunstar, Japan), Butler Fluodent Foam N (Sunstar, Japan), Caristop (Maver,Chile), CaristopDiario (Maver, Chile), Colgate Dry Mouth Relief (Colgate Oral Pharmaceuticals, United States), Dentasep-F (Sodium Fluoride and Chlorhexidine, Stedman, India).

3. PROPERTIES OF SODIUM FLUORIDE

Table 1. Properties of sodium Fluoride.

Chemical composition	A simple ionic compound made of the sodium (Na^+) cation and Fluoride (F^-) anion.
Appearance	White crystals or powder
Occurrence	Occurs in nature as the rare mineral villiaumite
Odour	Odourless
Solubility	Soluble in water and insoluble in alcohol
Taste	Salty
Combustion	Non-combustible and corrosive to aluminium
Symmetry	Cubic or Tetragonal crystals
Density	2.78 g/cm³
Moisture	NaF is a hygroscopic solid and, absorbs moisture from air.
Boiling point	Approximately 1700˚C at 760.0 mm Hg
Melting point	993˚C
Molar mass	41.99 g/mol
Decomposition	Stable under normal conditions. When heated to high temperatures, it decomposes with the release of toxic and corrosive fumes of hydrogen Fluoride (HF). Decomposition emits toxic fumes of hydrogen Fluoride and disodium oxide.

Symmetry of sodium Fluoride

Sodium ions Na^+ and fluorine ions F^- have almost the same ionic radius. Both have small polarizabilities. Stoichiometric clusters Na_NF_N are known to adopt, when possible, "cuboidal" geometries which resemble fragments of the parent rock salt structure material NaF.

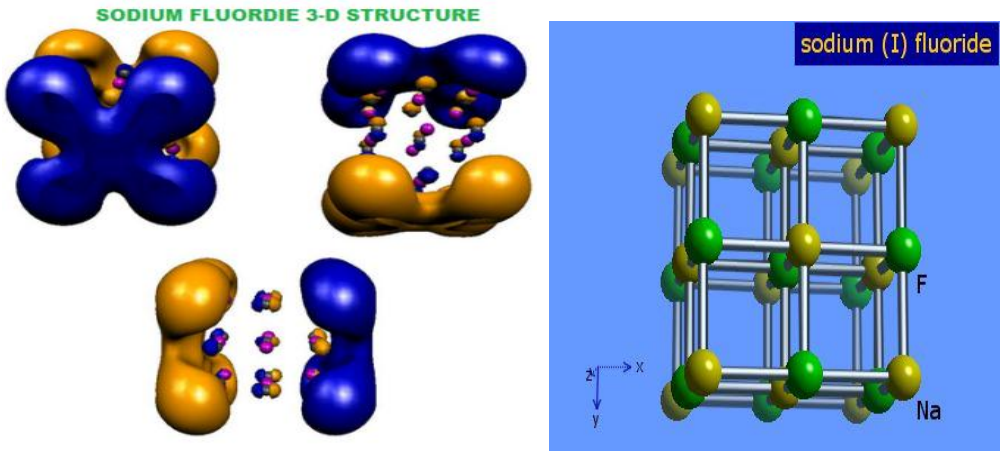

Figure-2: Symmetry of sodium Fluoride

3.1 Classification of Fluoride

Based on the mode of application, Fluoride is categorized into two types: Systemic and Topical.

3.1.1 Systemic Fluoride

Systemic Fluoride is taken into body through water, supplements, foods and beverages. Once systemic Fluoride is absorbed in gastrointestinal tract, blood distributes Fluoride throughout the body. Systemic Fluoride is also found in saliva and provides a topical application for protecting teeth.

3.1.2 Topical Fluoride

Topical Fluoride is taken into body through oral hygiene products such as toothpastes, mouth rinses, foams, gels and varnishes which contain a safe and effective concentration of Fluoride. These are rinsed from the mouth without swallowing. Topical Fluorides such as foams, gels or varnishes are applied during a cleaning treatment.

4. INTAKE, ABSORPTION, DISTRIBUTION AND EXCRETION OF FLUORIDE

4.1 Intake

The Fluoride concentration in drinking water is a representative of daily Fluoride intake. Fluoridated water will be used in the manufacturing of foods, beverages, soft drinks, tea and juices etc. Hence all the products are used as sources of Fluoride. Milk is another daily intake of Fluoride to the people.[18]

Table 2: Fluoride dietary intake at various stages of human being[19]

Stage	Age	Fluoride dietary intake (mg/day)
Infant	0-6 months	0.01
	7-12 months	0.5
Children	1-3 years	0.7
	4-8 years	1.0
	9-13 years	2.0
Adolescents and adults	Male age 14-18 years	3.0
	Male over 18 years	4.0
	Female over 14 years	3.0
Pregnancy females	14 through 18 years	3.0
	19 through years	3.0
Lactation females	14 through 18 years	3.0
	19 through years	3.0

4.2 Absorption and distribution of Fluoride

Fluoride absorption is extremely diverse. Fluoride enters the body and absorbs quickly in the gastrointestinal tract without enzymatic action.[20] More soluble compounds such as sodium Fluoride (NaF) and hydrogen Fluoride would absorb fastly, calcium Fluoride (CaF2) and

magnesium Fluoride (MgF2) are less soluble and absorbed slowly. Once absorbed, Fluoride is rapidly distributed throughout the body via the blood. The short term plasma half-life is normally in the range of 3 to 10 hours. Peak plasma Fluoride levels are typically seen within 30–60 minutes after ingestion.[20] The rate of Fluoride absorption in gastrointestinal tract is directly proportional to the acidity of the intake. However, other factors also influence the rate of absorption Eg: Solubility. Once Fluoride distributes to plasma, it is rapidly deposited in the Skeleton. Fluoride skeletal uptake is modified by factors such as bone modelling, remodelling and age. The amount of Fluoride deposited in the skeleton is inversely proportional to the age of individual.[20]

4.3 Excretion of Fluoride

The excretion of Fluoride is unpredictable, 37 to 48% of Fluoride is usually retained.

Various routes of Fluoride excretion include:

Table 3: Excretory routes of sodium Fluoride.

Modes of Excretion		
Excretion routes	Major	Kidney
	Minor	Tears, Milk, Sweat and expiration etc.

In human beings, excretion mainly occurs through kidney. Renal clearance depends on pH, diet with high proportion of vegetable and fruit intake lead to urinary pH on the alkaline side whereas protein rich diet lead to acidification of the urine.[20] During a person's growth stage, excretion of Fluoride through kidneys is more and begins to decline with increase in age. Fluoride excretion is slow in people with kidney impairment. Fluoride enters into renal tubules at the glomeruli, some amount will be reabsorbed and remaining will be excreted through urine.

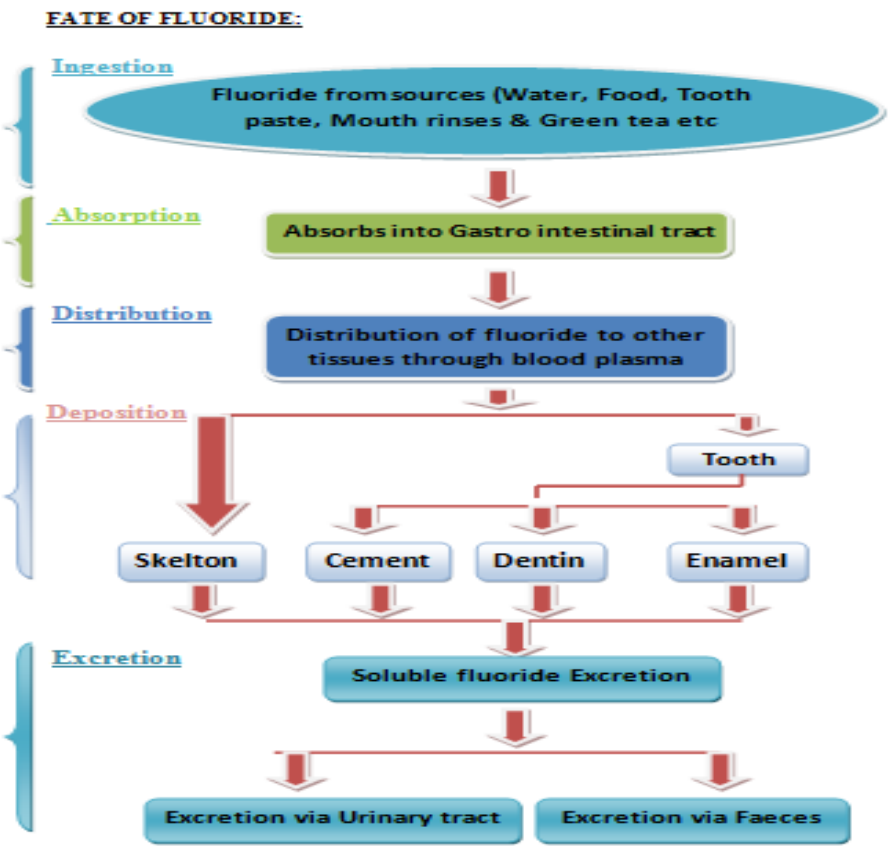

Figure 3: Fate of Fluoride in the human being.

5. POSITIVE EFFECTS OF FLUORIDE

5.1 Role of Fluoride in Dental health

Fluoride is considered as effective means of reducing dental caries. Historically, people consuming fluoridated drinking water had a lower prevalence of dental diseases than people consuming non fluoridated drinking water. Fluoride is said to improve lattice stability and renders the enamel less soluble to acid demineralization. Incorporation of Fluoride into enamel as partially fluoridated hydroxyapatite is essential for its action. However Fluoride action is part of cariostatic activity and the continual presence of Fluoride in the saliva is critical to its mechanism of action.[21] Fluoride inhibits the demineralization and promotes the remineralisation activity at the surface of the teeth.

The controlled fluoridation of community drinking water to an optimum level is one of the most effective means of delivering Fluoride to large numbers of individuals. Fluoride supplements are available in the form of tablets, liquid drops. Use of fluoridated mouth rinses has significant importance among health care programmes particularly children. Solutions, gels and varnishes are also sources of Fluoride applied frequently over the courses.

Prevention of dental caries is one of the strong antimicrobial effects of Fluoride. It is well established that Fluoride can inhibit the growth of bacteria. After bacterial exposure to Fluoride, studies (atomic force microscopy) revealed that bacterial species exhibited lower adhesion forces. Fluoride makes bacteria less able to stick to teeth; decay-causing microorganisms are more easily washed away by saliva or brushing.

6. NEGATIVE EFFECTS OF SODIUM FLUORIDE

Table 4. Negative effects of sodium Fluoride.

Common negative effects with excess Fluoride exposure	
Dental fluorosis	Skeletal fluorosis
Arthritis	Bone fracture
Thyroid	Immune system malfunctioning
Hypersensitivity	Impact on brain
Impact on IQ	Diabetes
Renal diseases	Impact on male fertility

6.1 Fluorosis

Fluorosis diseases are caused due to exposures of excess Fluoride. A daily intake of around 10-20 mg/day for adults and as low as 3-8 mg/day for children has been found to be harmful.[22] Excess Fluoride affects many processes in the body, firstly body requirement for calcium increases. People such as pregnancy and lactation women, growing children and adults beyond the age of 40, prone to calcium deficiency diseases. Secondly, iron absorption is reduced which is important to all of us especially for pregnant women who faces anaemia, under-weight and unhealthy children at birth. There are two main types of fluorosis, namely

- **Dental fluorosis**
- **Skeletal fluorosis**

- **Dental fluorosis**

Dental fluorosis (also termed as mottled enamel) is hypo mineralization of tooth enamel caused by excessive Fluoride during enamel formation. It appears as a visual change in enamel causing degrees of intrinsic tooth discoloration. The severity depends on the dose, duration and age of the individual during exposure. In the mildest form, faint white lines or specks whereas in severe form white mottled patches, brown discoloration, brittle, pitted and rough enamel are characterized.Infants consuming fluoridated water are at an increased risk for developing dental fluorosis.[23] The critical period of risk to dental fluorosis is between 1 and 4 years of age. Sometimes this risk continues up to 8 years of age till permanent tooth establishes.[24]In enamel, excess Fluoride ions alter the enzymatic digestion rate of matrix

proteins. Fluoride alters the action of protease by decreasing the availability of free calcium ions in the mineralization environment. This results in the formation of enamel with less mineralization. Hypo mineralized enamel comprises altered optical properties and appears to be opaque and lustreless than the normal enamel. Pits, bands and enamel loss are seen in severe fluorosis as a result of damage to enamel after erupting into the mouth.

- **Skeletal fluorosis**

Skeletal fluorosis is one of the earliest clinical symptoms of Fluoride toxicity in children of age up to six years. During this age, fluorosis is observed due to the intake of high levels of Fluoride in the tooth development stage. Skeletal fluorosis is said to be a clinical manifestation of Fluoride toxicity in the first six years of life. Ingested Fluoride incorporated into the bones, may affect the structural or mechanical properties of bone.[25]Accumulation of Fluoride in the bones over a period of time results in skeletal fluorosis and its early symptoms comprise stiffness and pain in the joints.[26] This disease is associated with osteosclerosis, calcification of tendons and ligaments, and bone deformities. Skeletal fluorosis further symptoms include tingling sensation in the fingers and toes, nervousness and depression. Neurological manifestations like paralysis of the limbs, vertigo, spasticity and impaired mental acuity are observed in the complex stages of fluorosis.

6.2 Arthritis

Joints pain and stiffness are common symptoms. Arthritic symptoms are advanced forms of excessive Fluoride intake. Fluoride-induced joint pains can occur in the absence of skeletal fluorosis. Reduction in daily Fluoride intake for a period of several weeks or months eliminates the symptoms of arthritis without any medical treatment.

6.3 Bone fracture

Excessive dose of Fluoride shows impact on bone tissue. People with kidney disease have an impaired ability to excrete Fluoride; they accumulate higher levels of Fluoride in their bone tissue than healthy individuals.[27] Individuals in fluoridated areas with kidney disease have vulnerability to Fluoride and suffer from fragile bones as a result of fluoridated water intake. Excess Fluoride intake increased the rate of fractures and causes other side effects including gastric distress, joint pain etc. Dialysis patients in fluoridated areas accumulate more levels of Fluoride in their bone, which results osteomalacia.

6.4 Thyroid and other endocrine glands

Thyroid gland maintains body's metabolic rate and plays a crucial role in the human health. Thyroid disruption shows many negative effects on the body, as all metabolically active cells require thyroid hormone for proper functioning. Fluoride is being supplemented to reduce tooth decay and also used as a drug to reduce hyperthyroidism. Higher intake levels of Fluoride in drinking water contribute hypothyroidism, in which thyroid gland fails to produce sufficient quantity of hormones tri iodothyronine (T3) and thyroxine (T4).[28] When T3 and T4 levels are begin to fall, the pituitary gland secretes excess production of "Thyroid Stimulating Hormone" (TSH) to produce more T3 and T4, which are required by all metabolically active cells, their absence trigger a range of ill effects including fatigue, muscle pain, joint pain, depression, weight gain, menstrual disturbances, impaired fertility, impaired memory and inability to concentrate.

Fluoride is an endocrine disruptor that alters normal function and shows negative impact on these glands.

- ✓ Thyroid gland
- ✓ Parathyroid glands
- ✓ Pineal gland
- ✓ Adrenal gland
- ✓ Pancreatic gland
- ✓ Pituitary gland

Thyroid hormones interact with all other hormones, including cortisol, insulin, and sex hormones like progesterone and testosterone. Cells need thyro hormones to function normally; a dysfunctional thyroid shows severe impact on the health.

6.4.1Iodine role in thyroid

Iodine is the basic building block of T3 and T4 hormones, and sufficient iodine intake is essential for proper functioning of the thyroid gland. If iodine intake is inadequate during infancy, it leads to iodine deficiency disorders (IDD) in which muscle, heart, liver, kidney, brain are affected. [29]In hypothyroidism, TSH level is elevated and T3 and T4 hormones will be less than the normal range. Although subclinical hypothyroidism is insignificant, it is considered a "clinically important disorder."[30]

6.4.2 Fluoride role in Goitre

Fluoride plays a role in Goitre development, which results in the enlargement of thyroid gland and produces visual swelling in the neck. The main cause of goitre is iodine deficiency, hypothyroidism and goitrogens.

6.5 Immune system malfunctioning

Excess Fluoride level in milli molar range shows number of effects on immune cells including polymorph nuclear leukocytes, lymphocytes, neutrophils and macrophages. If macrophage function is impaired; the invasion and destruction of foreign cells will be ceased.[31]

Fluoride can fatally damage cells in the spleen, the "largest peripheral lymphatic organ". Treatment with sodium Fluoride has shown lymphocyte apoptosis, the programmed death of cells in the lymphatic system.[32]In the immune compromised individuals like HIV, transplanted and bone-marrow-replaced people the immunologic effects of Fluoride are at greater risk.[33]

Damage to immune system fails to recognise body proteins and initiates autoimmune diseases. Autoimmune diseases include:

- ✓ Rheumatoid arthritis,
- ✓ Systemic lupus erythematosis,
- ✓ Asthma,
- ✓ Systemic Sclerosis
- ✓ Hashimoto's Disease
- ✓ Grave’s disease

Thyroid antibodies cause Hashimoto thyroiditis results in hypothyroid disease. This disease results in the damage of muscles, tendons, ligaments and bones followed by rheumatoid illness, osteoporosis and deformation of bones.

6.6 Hypersensitivity

Some persons are hypersensitive to Fluoride. Hypersensitive reactions are caused due to both topical Fluorides and systemic Fluorides. In hypersensitive individuals, Fluoride occasionally causes skin eruptions such as atopic dermatitis, perioral dermatitis, stomatitis, eczema or urticaria. Allergy includes skin rashes, mouth lesions, headache, weakness, joint

pain, gastric distress, and fatigue and vision problems. These symptoms usually disappear rapidly after discontinuation of the Fluoride.[34]

6.7 Fluoride impact on brain

Transportation of Fluoride takes place through active transport mechanism like other halogens and ionic substances. Fluoride enters the brain when blood barrier fails to exclude from nervous tissues. Fluoride accumulation occurs in the critical regions of brain, especially hippocampus. Levels of Fluoride in the brain portion inclines with an increase in the drinking water Fluoride levels.The prolonged ingestion may cause significant damage to the nervous system.[35] The effects of Fluoride on brain include reduction in nicotinic acetylcholine receptors, damage to hippocampus, damage to purkinje cells, exacerbation of lesions induced by iodine deficiency, impaired antioxidant defence systems, increased uptake of aluminium and accumulation of Fluoride in pineal gland.A study in "The Lancet" (medical journal) recommended that Fluoride be classified as a developmental neurotoxin along with lead, mercury, arsenic, Poly Chlorinated Biphenyls and toluene.[36]

6.7.1 Impact of Fluoride on brain cell structure

Fluoride is toxic to brain. Chronic Fluoride intoxication cause malfunctions in the brain cell architecture. Passage of the Fluoride through placenta of mother and its accumulation in the brain of foetus shows adverse impact on brain development. Brain with fluorosis impacts reduction in the mean volume of neurons. The chronic administration of Fluoride as Sodium Fluoride or Aluminium Fluoride in drinking water results distinct morphological changes in the brain. Fluoride toxicity also results in abnormal alterations of the cerebro vasculature.

6.7.2 Alzheimer's disease

Alumina is the compound of aluminium, found in the brains of Alzheimer's disease. Fluoride effect leads to the formation of beta-amyloid plaques. Generally, a barrier exists between the body and the brain that stops metals reaching the brain. Studies showed the relationship between Fluoride and aluminium in escaping this barrier. Aluminium does not enter the brain naturally. Fluoride combines with aluminium to form aluminium Fluoride, which is absorbed by the body then it combines with oxygen to form aluminium oxide or alumina.[37]

6.7.3 Fluoride impact on IQ

Fluoride shows impact on cognitivity and behavioural issues in adults and children respectively. Chronic exposure to increased levels of Fluoride results in decreased memory

and also learning ability.[38] Fluoride enhances absorption of manganese and reduces IQ in children. A study by Harvard university meta-analysis stated that children in high fluoridated areas have low IQ.[39] Fluoride shows more impact on children especially in developing brains leading to brain damage. Fluoride accumulates in pineal gland in brain, and inhibits melatonin production. 10% of excess Fluoride in water shows immunosuppressive effects and cause neurotoxicity leading to impact on the memory and learning. Hippocampus is the central processor of the brain. Increase in Fluoride levels results in hippocampal damage leading to hyperactivity and cognitive deficits.

6.8 Diabetes

Diabetes mellitus is a life-threatening disease in which the body fails to regulate proper blood sugar levels. Chronic Fluoride ingestion leads to Diabetes, which inhibits insulin secretion leading to an increase in blood glucose levels and impairs glucose tolerance resulting in hyperglycaemia (elevated blood sugar). Fluoride is mainly excreted by kidney, kidney malfunction can prevent Fluoride excretion, thus increasing body burden of Fluoride.[33] People with diabetes mellitus drink more water than normal and were found to have reduced renal clearance of Fluoride.[40] Drinking fluoridated water not only increases plasma glucose and lipid profile levels, but also elevates hepatic and renal lipid peroxidation.[41]

6.9 Impact of Fluoride on renal system

Kidney is responsible for the excretion of Fluoride. It is exposed to Fluoride five times higher than the other organs. Hence renal system is at a higher risk of Fluoride toxicity than other tissues of the body. Fluoride in both acute and chronic doses affects the kidney. Structural damage occurs to the renal cortex.[42] People with impaired kidney function are unable to excrete efficiently and retain Fluoride, even at normal recommended limit.[43]It has been known that people with renal failure are at high risk of developing skeletal fluorosis. In such people elevated plasma Fluoride levels and accumulation of Fluoride in the skeleton is increased.[44] Long-term ingestion of Fluoride in drinking water at 4 mg/L contributes to the formation of renal calculi (kidney stones). Over the years, even at below 1.2 mg/L Fluoride concentrations increases the risk for kidney stones.

6.10 Male fertility

Male infertility is responsible for about 50% of the fertility problems. Infertility in male results in reduced sperm count, abnormal sperm quality and altered levels of sex hormones.

Studies have been done to show Fluoride impact on oxidative stress and melatonin and reproductive system.[45]

Fluoride impacts the male reproductive system through below factors.

- ✓ Decrease in testosterone levels
- ✓ Reduced sperm motility
- ✓ Altered sperm morphology
- ✓ Reduced sperm quantity
- ✓ Increased oxidative stress
- ✓ Reduced capacity to breed.[46][47][48][49][50][51]

Blood Fluoride levels of 0.2 to 0.26 ppm Fluoride for an eight week period causes oxidative stress, reductions in sperm motility and reduced fertility.

6.11 Apoptosis

Apoptosis is a phenomenon that includes the regulation of signalling proteins via gene expression. Apoptotic signalling is the expression and regulation of pro and anti-apoptotic genes. Fluoride induces apoptosis by oxidative stress and induced lipid peroxidation resulting mitochondrial dysfunction and activation of downstream pathways. Studies have been shown that sodium fluoride increased apoptosis of lymphocytes in mice spleen, mediated by Endoplasmic Reticulum stress.[52]

7. EFFECT OF FLUORIDE ON DIFFERENT ENZYMES

The main toxic effect of Fluoride in cell is its interaction with enzymes. Fluoride acts as an enzyme inhibitor. In some cases it stimulates enzyme activity. The mechanism depends on the type of enzyme affected.[53] Fluoride inhibits many enzymes that contain iron, calcium and magnesium;these enzymes are involved in energy production in cells. Fluoride inhibits several enzymes, both in vivo and in vitro at mill molar concentrations, including phosphatases.[54] Fluoride combines with heme group of peroxidase, catalase and cytochrome oxidase and inhibits these activities.

7.1On Peroxidase

Peroxidase catalyses reduction of H_2O_2 and oxidation of thiocyanate (SCN^-), to form hypothiocyanite, ($OSCN^-$). Fluoride is a potent inhibitor of this enzyme in acid environments.

7.2 On Pseudo catalase

Pseudo catalase is a Mn^{2+} containing enzyme, inhibited by Fluoride over a wide range of pH. In acidified environments, inhibition occurs with Fluoride levels below 1.0 mM.

7.3 On Catalase

Fluoride binds to catalase enzyme in a pH-sensitive approach and leads to the inhibition of enzyme. Inhibition of catalase enzyme compromises the bacterial cell in acid environments resulting oxidative damage. At low pH Fluoride binds to catalase enzyme and inhibits it.

7.4 On urease

Fluoride is inhibitor of urease enzyme. Inhibition of ureases is similar to that of enolase inhibition. Inhibition of urease by Fluoride is 'Pseudo non-competitive'. Fluoride binds to the activated complex forming a urease–substrate–Fluoride complex or a urease–product–Fluoride complex. Enzyme inhibition is pH-sensitive and enhanced in acidic environments.

7.5 On F-ATPases

Fluoride inhibits F-ATPases of microorganisms. Inhibition of enzyme depends on the trace amounts of aluminium. Fluoride exerts impact on F-ATPase through increased Trans membrane proton Permeability and dissipation of pH across the membrane.

7.6 On Antioxidant enzymes

Fluoride inhibits antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase. Fluoride alters glutathione levels resulting in the production of Reactive Oxygen Species [ROS] at mitochondrial level leading to the damage of cellular components. Excessive production of ROS leads to attack on membrane phospholipids, membrane damage, mitochondrial membrane depolarization and apoptosis.

8. FLUORIDE IMPACT ON ANIMALS

Animals normally ingest minor quantities of Fluoride from their diet. An increased ingestion of Fluoride is harmful to animals and grazing animals are affected by the consumption of excess Fluoride vegetation. Cattle species is the commonly affected and symptoms of excess Fluoride ingestion include lesions in the developing dentition, skeletal lesions and lameness. Studies have been shown that Fluoride impact on pancreatic digestive enzyme activities in young pigs[55] and also accumulation of Fluoride on brain enzymes in mice.[56]

8.1 Dental lesions in cattle

In cattle, tooth development is vulnerable to Fluoride. Abnormalities in dentition are the signs of chronic Fluoride toxicity. Strength of incisors and molar teeth are diminished.

8.2 Osseous lesions in animals

Ingestion of excess Fluoride for prolonged period of time results in the development of exostotic lesions, thickening and changing in shape of certain bones. Excess fluoridation triggers mineralization of the tendons during attachment to leg bones.

8.3 Systemic effects on cattle

Fluoride toxicity symptoms include appetite impairment, weight loss, cachexia and diminished milk production. Fluoride exposure also impacts food intake and digestibility of the cattle, physiological processes of milk secretion and productive ability.

8.4 Behavioural disruption in rats

Fluoride affects nervous system of the rats. Effect on behaviour varies with the time of Fluoride exposure during CNS development. Suppression of spontaneous motor activity indicates the action of Fluoride on motor dysfunction.

9. FLUORIDE IMPACT ON PLANTS

Fluoride derivatives from various industries contaminate water, air and soil. The Fluoride in the soil is mostly insoluble and less available to plants. However, high soil Fluoride concentrations can increase Fluoride levels in the soil and plant uptakes via root. Most Fluorides enter plant tissues through stomata as gases and accumulate in leaves. Small amounts of airborne particulate Fluoride can enter through epidermis and cuticle of the plant. Plants irrigated with water containing Fluoride develop Fluoride toxicity. Signs of fluorosis in plants include necrotic regions at the tips and margins of leaves which turn yellow or brown and sometimes become dry and brittle, slowed growth. In plants, excess Fluoride affects enzymes involved in respiration, photosynthesis, Nucleotide and Nucleic acid synthesis, metabolism of carbohydrates, amino acids and proteins.

10. FLUORIDE IMPACT ON MICROORGANISMS

Fluoride shows antibacterial activity especially on cariogenic bacteria and other bacteria. It inhibits carbohydrate metabolism in bacteria i.e., Glycolysis, process by which cariogenic bacteria metabolize sugars to produce acid.[57] [58] [59] Fluoride is known to impact cellular

respiration of micro flora by inhibiting metabolic enzymes like *Enolase,ATPase* which are key enzymes in glycolytic catabolism and energy generation. Inhibition of glycolysis and ATP synthesis results lack of ATP for further subsequent metabolic and molecular processes.

10.1ROLE OF FLUORIDE ON GLYCOLYSIS AND ATP SYNTHESIS[60]

Fluoride ions can show inhibitory effect on enzymes of the glycolytic pathway and the Krebs cycle by binding to functional amino acid groups surrounding the active centre of an enzyme. Na+/K+-*ATPases* are also inhibited, which leads to ATP depletion and a disturbance in cell membrane potential.[53] Therefore, Fluoride inhibits cellular respiration and also decreases the production of ATP. Fluoride interferes with the breakdown of glucose to pyruvic acid by inhibiting *Enolase*, a mediator enzyme in the pathway. The decreased outputof Phosphoenol pyruvate (PEP) in the presence of Fluoride, in turn, results in the inhibition of sugar transport via the PEP phosphotransferase system (PTS). This cause a reduction in the synthesis of lactic acid and in the metabolic activity of the cariogenic bacteria.[61]Sodium Fluoride inhibits *Enolase* enzyme in the glycolytic pathway, and has no effect on the enzymes that act early in the glycolytic pathway. [62]Fluoride is transported as Hydrogen Fluoride into the bacterial cell, where it dissociates into H^+ and F^-. This process leads to an accumulation of Fluoride inside the cell and acidification of the cytoplasm. The acidification of the cytoplasm can inhibit the glucose transport into the cell.[63] Thus, Fluoride has the dual action of dissipating proton gradients and preventing their generation through its action on H^+/ATPase. The collapse of trans membrane proton gradient, reduces the ability of cells to transport solutes via mechanisms involving proton motive force.

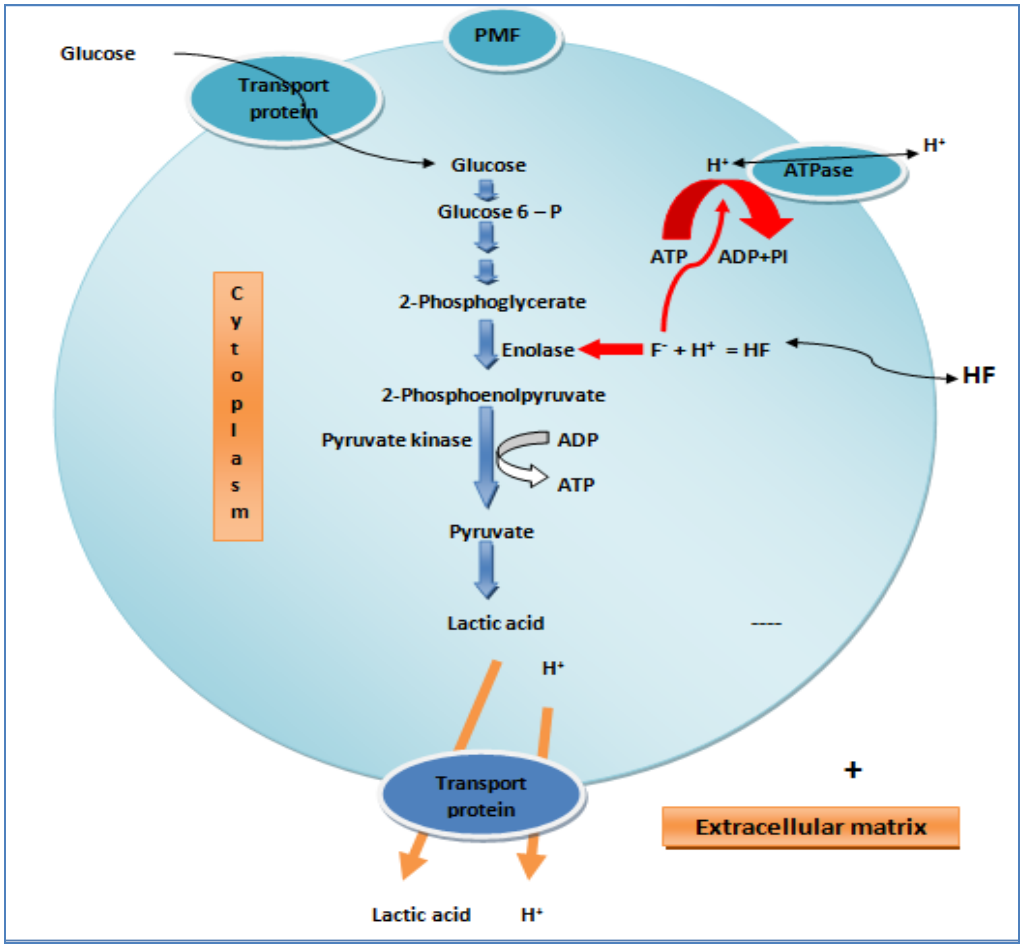

Figure- 4: Fluoride Action Sites on Enzymes in Glycolysis (*Enolase, ATPase*)

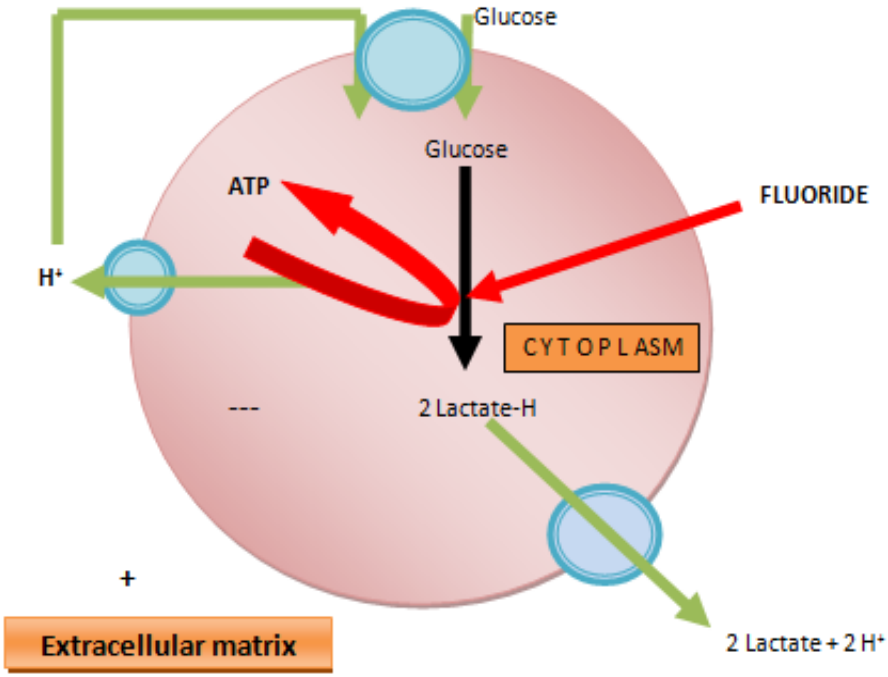

Figure 5: Fluoride Impact on Glycolysis.

11. CONCLUSION

Studies on Sodium Fluoride provide evidence that it shows impact on human system, animal, plant and bacteria. In bacteria it acts on enzymes like *Enolase* and *ATPase* etc., which plays crucial role in cellular respiration and decreases the production of ATP, inhibition of glycolysis and ATP synthesis results in lack of ATP for further subsequent metabolic and molecular processes. Further we are interested to continue on Protein profiles of the Probiotic Microorganisms against to Fluoride toxicity.

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