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A Review on Fluoride-Induced Hepato-Renal Toxicity and the Ameliorative Effects of Vitamin D and *Tamarindus indica* in Albino Rats

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ABSTRACT

The mineralisation of bones and teeth requires fluoride, a trace element. When consumed at acceptable amounts, fluoride helps bones and teeth. Overexposure to fluoride is a global public health hazard due to drinking water contamination, industrial emissions, food sources, and agricultural activities. We estimate that about 200 million people globally are exposed to high fluoride concentrations in endemic fluoride regions including Asia, Africa, and India. Excessive fluoride exposure causes skeletal and dental fluorosis, but emerging evidence suggests it also poisons soft tissues like the liver and kidneys. The liver is the main metabolic and detoxifying organ and the kidneys are the main fluoride excretion organ, therefore they are highly vulnerable to fluoride-induced harm. Experimental data suggest that excessive fluoride exposure causes oxidative stress, mitochondrial dysfunction, inflammatory responses, apoptosis, endoplasmic reticulum stress, and calcium homeostasis disruption, which leads to high serum hepatic enzyme levels, abnormal renal biomarker levels, lipid peroxidation, endogenous antioxidant enzyme depletion, and many liver and kidney histopathological changes. This is why much study has focused on safe dietary and phytotherapeutic strategies to reduce organ damage from high fluoride intake. Vitamin D's antioxidant, anti-inflammatory, immunomodulatory, and anti-apoptotic characteristics may be beneficial. Vitamin D promotes cellular defence systems to protect mitochondria and boost antioxidant capability in addition to regulating calcium and phosphate metabolism. Polyphenols, flavonoids, tannins, tartaric acid, vitamins, and minerals are found in tamarind. Many studies show that tamarind has hepatoprotective, nephroprotective, antioxidant, metal-chelating, and anti-inflammatory characteristics that may reduce fluoride-induced oxidative damage. This review summarises the toxicokinetics of fluoride, the molecular mechanisms of hepatotoxicity and nephrotoxicity, the biochemical and histopathological changes caused by fluoride, and the protective effects of vitamin D and tamarind. The paper also discusses antioxidant therapy advances, information gaps in both domains, and how to adapt experimental findings into clinical treatment for persistent fluorosis.

Introduction

Rock, soil, groundwater, surface water, and many food products contain fluoride, one of Earth's most abundant halogens (WHO, 2017; Fawell *et al*., 2006). By encouraging fluoride crystallisation, fluoride helps bone and teeth. Fluoride prevents tooth decay (Whitford, 1996). Due to these benefits, many nations currently supplement fluoride in drinking water and dental products in specified doses (NRC, 2006). The amount of fluoride present determines its benefits. Fluoride can become a harmful environmental contaminant that damages the body if exposed to concentrations beyond the permissible quantity (Barbier *et al*., 2010; Susheela, 2018).

The WHO advises limiting drinking water fluoride to 1.5 mg/L (WHO, 2017). However, Asia, Africa, South America, and several European regions have groundwaters with fluoride levels above the permissible standards (Edmunds & Smedley, 2013). Millions of Indians in Rajasthan, Gujarat, Andhra Pradesh, Telangana, Uttar Pradesh, Madhya Pradesh, Karnataka, Tamil Nadu, Haryana, and Punjab drink groundwaters with high fluoride levels, causing endemic fluorosis.Aluminium smelting, phosphate fertiliser production, ceramics manufacturing, brick kilns, coal burning, steel processing, and glass-making increase environmental fluoride contamination and human and animal fluoride exposure (ATSDR, 2003; Barbier *et al*., 2010).

Fluoride poisoning was assumed to induce dental and bone diseases (NRC, 2006). Dental fluorosis causes enamel hypomineralization, discolouration, and structural defects, while skeletal fluorosis causes pain, stiffness in joints, ligament calcification, osteosclerosis, and reduced mobility due to excess fluoride accumulation in bone. Fluoride toxicity exceeds calcification tissues by a large margin, according to molecular toxicology developments during the last 20 years. Fluoride exposure damages the liver, kidneys, brain, heart, lungs, glands, reproductive organs, and immune system in addition to calcified tissues (Barbier *et al*., 2010; Johnston & Strobel, 2020). Due to their function in xenobiotic metabolism and fluoride removal, the liver and kidneys are especially susceptible to fluoride's toxicity (Whitford, 1996).

The liver detoxifies endogenous metabolites and environmental toxins in addition to metabolising carbs, lipids, and proteins (Guyton & Hall, 2021). Fluoride accumulates in liver cells after many exposures since it is the first organ to absorb it after gastrointestinal absorption (Buzalaf & Whitford, 2011).Fluoride exposure increases serum levels of ALT, AST, ALP, GGT, bilirubin, and LDH in albino rats, indicating liver cell injury and impaired liver function. Histological examination revealed degenerative liver cell changes like cytoplasmic vacuolation, fatty infiltration, increased inflammatory cells, enlarged central veins, focal necrosis, and disrupted liver architecture. Since the kidney excretes fluoride, it is constantly exposed to the greatest quantities of fluoride in the body. About 50%-70% of fluoride absorbed is excreted in urine, putting renal tissues at risk for oxidative injuries and causing chronic kidney damage (Whitford, 1996; Buzalaf and Whitford, 2011). Chronic fluoride exposure increases serum

creatinine, BUN, urea, uric acid, electrolyte imbalance, glomerular dysfunction, tubular degeneration, and renal filtration impairment (Gao *et al*., 2012; Liu *et al*., 2018). Histology shows glomerulus shrinkage, Bowman's space dilation, tubular epithelial cell degeneration, vascular congestion, interstitial inflammation, and renal fibrosis (Caglayan *et al*., 2021; Zhang, 2022). The pathophysiological alterations caused by these consequences diminish renal excretory function, causing fluoride retention and systemic toxicity (NRC, 2006).

Halliwell and Gutteridge (2015) found that fluoride promotes hepatotoxicity and nephrotoxicity through oxidative stress.The generation of reactive oxygen species (ROS) like superoxide anions, hydroxyl radicals, hydrogen peroxide, and nitrogen dioxide and nitrate is increased by fluoride. This increase can overwhelm endogenous antioxidant defences, depleting SOD, CAT, GPx, GR, and GSH.

Fluoride activates various intracellular signalling pathways, including NF-κB, MAPK, JNK, TGF-β, PI3K-Akt, and p38 MAPK, leading to the activation of pro-inflammatory cytokines such TNF-α, IL-1β, IL-6, COX-2, and iNOS. This increases apoptosis and inflammation. Fluoride-induced irreversible acute liver and kidney injury may be caused by mitochondrial membrane depolarisation, cytochrome c depolarisation, and caspase-dependent apoptotic cell death.

Pharmacological treatments for persistent fluorosis are unavailable. Thus, much study has been done to find nutritional antioxidant or medicinal plant-based remedies that reduce oxidative stress and safeguard organ function. Due to its various biological activities beyond calcium metabolism, vitamin D is gaining popularity.The latest studies show that Vitamin D activates the Vitamin D receptor (VDR) to modulate antioxidant enzyme expression, suppress inflammatory cytokines, maintain mitochondrial integrity, regulate the immune response, and inhibit apoptosis. Experimental investigations show that Vitamin D administration improves hepatic enzymes, renal function biomarkers, antioxidant status, and histology in fluoride-exposed rats (Yadav *et al*., 2023).

Tamarindus indica is a medicinal plant with antioxidant and detoxifying qualities. Polyphenols, flavonoids, tannins, tartaric acid, vitamins, organic acids, and essential minerals in tamarind fruits, leaves, seeds, and bark scavenge reactive oxygen species and boost the body's antioxidant defences (De Caluwé *et al*., 2010). Tamrind supplementation reduces lipid peroxidation, restores antioxidant enzyme activity, improves hepatic and renal biochemical parameters, helps eliminate fluoride, and reduces histopathological alterations in chronic fluorosis models. A third method of action is that tamarind's ion-chelating characteristics may help the body eliminate fluoride.

Despite advances in fluoride toxicity research, many questions remain. The majority of scientific investigations use animal models, while few well-designed clinical trials in humans exist (Barbier *et al*., 2010).The fluoride dosage, length of exposure, study method, antioxidant supplement use, and measures vary widely in published research. Standardising experimental methods, determining optimal therapeutic doses, using current molecular tools (e.g., transcriptomics, proteomics, metabolomics), and developing nanotechnology-based drug delivery systems are essential to translating experimental study findings to clinical application.

This review will discuss fluoride toxicokinetics, including the pathways by which fluoride is absorbed, distributed, metabolised, bioaccumulated, and excreted in the biological systems of individual species; the molecular basis for fluoride's toxic effects on liver and kidney tissues; the pathways by which oxidative stress contributes to fluoride's toxic properties; and the biochemical/histological alterations that sorb to The review will also discuss recent advances in treating fluoride-induced toxicity and inhibiting it with antioxidant therapies, identify unexplored research avenues, and outline clinical research directions for effective treatments.

2.0 Fluoride Toxicokinetics: Absorption, Distribution, Metabolism, Bioaccumulation, Excretion

Fluoride toxicokinetics discusses how living organisms absorb, distribute, metabolise, bioaccumulate, and excrete fluoride molecules. Understanding fluoride toxicokinetics helps explain why prolonged fluoride exposure causes systemic toxicity, particularly in the liver and kidney. Fluoride, unlike many other environmental toxicants, is an inorganic ion and does not require substantial metabolic transformations before being removed from the body. However, fluoride biological activity depends on concentration, duration, age, nutritional condition, renal function, gastrointestinal pH, and calcium ingestion.

2.1 Exposure Sources- Humans and animals are exposed to fluoride naturally and artificially. Natural fluoride comes from chemical weathering of fluorine and fluorine-containing minerals, such as fluorite (CaF_2), fluorapatite ($Ca_5(PO_4)_3F$), cryolite (Na_3AlF_6), and topaz. These compounds fluoridate groundwater, surface water, and agricultural soil (WHO, 2017; Fawell *et al*., 2006).

Human activities has considerably boosted environmental fluoride concentrations since the late 20th century. Aluminium smelting, phosphate fertiliser, brick kiln, ceramic, coal-burning power plants, glass, and steel industries discharge fluoride into the air and environment. Food, beverages, ground water, agricultural dust, occupational inhalation, fluoride-containing dental products, and some medications expose people to fluoride.

Groundwater is the main source of chronic fluoride exposure worldwide. An estimated 300 million people drink water with fluoride concentrations above the WHO's 1.5 mg/L upper limit, which is a major public health issue for many developing countries (WHO, 2017; Edmunds & Smedley, 2013).

2.2 Gastrointestinal Absorption- After eating, fluoride is quickly absorbed. Around 75-90% of fluoride absorbed enters the body within an hour of eating or drinking, making oral exposure the fastest (Whitford 1996). High stomach acidity converts fluoride (F-) into hydrofluoric acid (HF), which enters the body first. HF is neutral and rapidly absorbed via blood vessel walls, therefore fluoride enters the bloodstream fast (Buzalaf & Whitford, 2011).

Passive diffusion from the small intestine brings the leftover fluoride into the body. Many biological factors affect gastrointestinal fluoride absorption. A person absorbs more fluoride when their stomach is empty because there is little acid. Dietary magnesium, aluminium, and iron produce insoluble compounds with fluoride, reducing intestinal absorption (National Research Council, 2006). Low calcium increases fluorosis risk due to nutritional interactions. Age also affects fluoride absorption. Due to metabolic and gut permeability changes, young animals and children absorb more than older animals and adults (Whitford, 1996).

2.3. Body Distribution - Fluoride enters the circulatory system and is evenly distributed throughout the highly vascularised tissue after absorption. The plasma (blood) fluoride concentration peaks 30–60 min after ingestion and then declines as fluoride is concentrated into bones and teeth, distributed to the liver and kidneys, and redistributed to other tissues (Buzalaf & Whitford, 2011). Around 99% of the body's fluoride is deposited in calcified tissues (bones and teeth) where it replaces hydroxyl ions. Fluoride accumulates in soft organs including the kidneys and liver after prolonged exposure, even though the skeletal system has the highest quantities (WHO, 2017).

After intestinal absorption, fluoride enters the liver via portal circulation. Chronic exposure to the liver's metabolism of endogenous and exogenous chemicals causes hepatocyte fluoride buildup. Multiple experiments have shown that repeated sodium fluoride treatment causes liver fluoride buildup and biochemical and histological hepatocellular damage (Miltonprabu *et al*., 2017; Pal *et al*., 2022). Due to their constant filtration of fluoride during urine excretion, the kidneys are also exposed to a lot of it. Renal tubular epithelial cells collect fluoride faster than other soft tissue types, making the kidneys susceptible to oxidative damage and structural degeneration (Gao *et al*., 2012; Caglayan, 2021).

2.4 Metabolism- Fluoride undergoes limited metabolic biotransformation in mammalian tissues, unlike chemical toxicants. Fluoride competes mostly as free fluoride ions or hydrofluoric acid depending on pH (Barbier *et al*., 2010), so most of its toxicity comes from directly interacting with macromolecules on cells rather than through a toxic metabolite.

Fluoride strongly interacts with many biologically significant metal ions (especially calcium, magnesium, iron, and aluminium) and inhibits enzymes involved in glycolysis, oxidative phosphorylation, ATP synthesis, antioxidants, and calcium signalling (Inkielewicz-Step this enzyme disrupts mitochondrial respiration and impairs cellular energy production while promoting excessive reactive oxygen species that will eventually

2.5 Bioaccumulation

Bioaccumulation/biopersistence characterises fluoride toxicokinetics.

In contrast to environmental exposure, fluoride has a slow elimination process, so repeated fluoride ingestion increases fluoride levels in mineralised and non-mineralized tissues (National Research Council, 2006).

Repeatedly exposing albino rats to sodium fluoride in experiments consistently shows that tissue concentrations of fluoride in still bone, liver, kidney, testis, brain, and heart are positively associated with elevated levels of malondialdehyde (MDA), reactive oxygen species, nitric oxide (NO), and inflammatory cytokines and a gradual decrease in antioxidant enzymes like SOD, CAT, GPX, and GSH.

Bioaccumulation depends on several factors, including fluoride concentration, duration, age, nutritional status, renal function (impaired vs. normal), hydration, and urinary pH. Individuals with impaired renal function eliminate fluoride less efficiently due to reduced renal cleavage.

2.6 Kidney Excretion- Primary fluorine elimination occurs through the kidneys. About 50%-70% of intestinal fluoride is eliminated in urine, whereas the rest is integrated into the skeleton (Buzalaf & Whitford, 2011). GFR, urine pH, fluid intake, plasma fluoride concentration, and tubular reabsorption mostly affect urinary fluoride excretion. Acidic urine promotes fluoride ion conversion to hydrofluoric acid. Because hydrofluoric acid diffuses easily through renal tubular membrane layers, tubular reabsorption increases and urine fluoride elimination decreases. Alkaline urine eliminates fluoride faster because it forms less hydrofluoric acid (Whitford, 1996). Chronic fluoride exposure reduces renal tubular epithelial cell shape and function, reducing glomerular filtration and urine fluoride removal. Tissue buildup and chronic renal injury cause fluoride to accumulate in the body when renal function declines (Gao *et al*., 2012; Liu *et al*., 2018).

Studies of prolonged sodium fluoride exposure on animals show higher serum creatinine, BUN, urea, and uric acid concentrations, and electrolyte abnormalities. Histopathological examination shows degenerative changes in tubular epithelial cells, glomerular atrophy, vascular congestion, inflammatory cell infiltration, and interstitial fibrosis, which are strongly correlated with blood chemistry changes.

The toxicological features of hepato-renal toxicity

Chronic fluoride toxicity attacks the liver and kidneys due to its harmful properties. Fluoride is rapidly absorbed from the gastrointestinal tract, ensuring that the body always has fluoride, and it preferentially distributes to metabolically active tissues, exposing the kidney and liver to high fluoride levels for long periods. Fluoride accumulates in tissue because the kidney slowly eliminates it and there are no metabolic processes to immediately destroy it.

Fluoride accumulation in tissues disrupts mitochondrial respiration, intracellular calcium signalling, antioxidant defence mechanisms, inflammation, and apoptosis. Multiple molecular processes have been discovered to cause liver and kidney toxicity in experimental animal studies and humans exposed to high fluoride levels. This shows that fluoride toxicokinetics are essential for effective prevention and treatment. If nutritional antioxidants, kidney and liver protectors, and fluoride elimination methods are used, tissue fluoride burden and organ damage may decrease.

Chronic fluoride exposure causes oxidative stress, mitochondrial dysfunction, inflammatory pathways, calcium dysregulation, endoplasmic reticulum stress, DNA damage, autophagy, fibrous tissue development, and apoptosis. Fluoride disrupts many intracellular signal pathways simultaneously, disrupting cellular equilibrium and causing liver and kidney disease.

The liver and kidneys are especially vulnerable to fluoride poisoning. When swallowed, fluoride is absorbed in the intestines and circulates in the blood as a free ion. The liver metabolises substances entering the body, while the kidneys filter and excrete fluoride in urine. Thus, persistent fluoride exposure causes chronic oxidative damage and atrophy in these two organs.

Most people believe fluoride causes liver and kidney damage by causing oxidative stress. Long-term fluoride exposure increases ROS production and decreases antioxidant production.

Fluoride increases the generation of reactive oxygen species, such as superoxide anions ($O_2^{\bullet -}$), hydroxyl radicals (•OH), hydrogen peroxide (H_2O_2), singlet oxygen ($^1O_2$), and reactive nitrogen species. These extremely reactive chemicals damage cell membrane lipids, proteins, carbohydrates, nucleic acids, and phospholipids by oxidative damage. High metabolic activity makes hepatocytes and renal tubular epithelial cells susceptible to oxidative damage (Barbier *et al*., 2010; Inkielewicz-Stepniak, 2012).

Experimental investigations suggest fluoride-treated rats have elevated ROS levels. Fluoride-treated rats showed severe hepatic and renal damage in biochemical and histological tests (Miltonprabu *et al*., 2017; Pal, 2022).

3.2 Peroxyde lipid-Lipid peroxidation is the first oxidative damage biomarker. Biological membrane polyunsaturated fatty acids are targeted by reactive oxygen species. Chain reactions destabilise cellular membranes. Malondialdehyde (MDA), the main result of lipid peroxidation, is often used to indicate fluoride-induced oxidative damage. The liver and kidney of rats exposed to prolonged sodium fluoride had considerably higher MDA levels (Shivarajashankara *et al*., 2002; Miltonprabu *et al*., 2017). Lipid peroxidation can cause several problems, including:

- Increased membrane permeability.
- Reduced membrane fluidity.
- Cell enzyme leakage.
- Misfunctioning receptors.
- Ion transit is disrupted.
- Cell swelling.
- Slowly decaying necrotic cells.

Fluoride intoxication studies show large increases in ALT, AST, ALP, LDH, serum creatinine, and BUN due to the aforesaid alterations.

3.3 Antioxidant Depletion- Endogenous antioxidant enzymes maintain redox equilibrium and eliminate all reactive oxygen species under normal physiologic conditions. SOD, CAT, GPx, GR, and GST are antioxidant enzymes. Non-enzymatic antioxidants include reduced glutathione (GSH), vitamin C, vitamin E, uric acid, albumin, selenium-containing proteins, and Coenzyme Q10 also contribute to cellular antioxidant capacity (Halliwell & Gutteridge, 2015). Fluoride considerably reduces enzymatic and non-enzymatic antioxidant action, according to many studies. Chronic fluoride exposure lowers liver and kidney SOD, CAT, GPx, GR, GST, and GSH levels. Decreased antioxidant defences increase reactive oxygen species, causing oxidative injury and a loop of cellular damage.

A mitochondrial dysfunction-Oxidative stress from fluoride can damage the electron transport chain and mitochondrial membrane integrity. Mitochondria produce most of cellular ATP through oxidative phosphorylation and regulate calcium levels, apoptosis, and intracellular energy. According to different studies, fluorides lower mitochondrial membrane potential, block respiratory chain enzymes, diminish ATP synthesis, and increase electron leakage, doubling mitochondrial reactive oxygen species.

Pathological alterations from mitochondrial dysfunction include,

1. Low ATP output
2. Na+/K+-ATPase decrease
3. Ionic balance restored
4. Internal calcium overload
5. Cytochrome c leakage
6. Active intrinsic apoptosis

All of these pathogenic alterations accelerate hepatocyte degeneration and nephron tubular epithelial cell death.

3.5 Calcium Dyshomeostasig

As an intracellular second messenger, calcium regulates enzyme activity, mitochondrial function, gene expression, and apoptosis.

Fluoride changes plasma membrane, endoplasmic reticulum, and mitochondrial calcium transport, increasing intracellular calcium and activating phospholipases, proteases, endonucleases, nitric oxide synthase, and calcium-dependent protein kinases.

Excess intracellular calcium can cause these biological effects:

- Membrane degradation
- Protein denaturation
- DNA fragmentation
- Mitochondrial swelling
- Cell death
- Death

Besides skeletal fluorosis, calcium imbalance damages liver and kidney soft tissue.

3.6 ER stress- Protein folding, calcium storage, and membrane protein synthesis occur in the endoplasmic reticulum (ER). Excessive

oxidative stress causes ER imbalance, which leads to unfolded proteins and the UPR.

Recent studies show that persistent fluoride exposure greatly elevates GRP78, CHOP, ATF4, and caspase-12, which are hallmarks of high ER stress.

Durable UPR activation changes cellular responses from protective to apoptotic and causes hepatic and renal tissue damage.

3.7 Inflammation

Fluoride exposure increases organ dysfunction and oxidative stress through inflammation. Oxidative stress activates inflammatory transcription factors, including NF-κB, leading to the expression of pro-inflammatory mediators.

TNF-α, 2.IL-1β, 3.IL-6,4.CO X-2,5.iNOS, 6.TGF-β

These mediators of inflammation attract leukocytes, promote vascular congestion, endothelial dysfunction, fibrosis, and tissue degradation. Histopathological examination of liver and kidney tissue exposed to fluoride directly or indirectly identified numerous inflammatory cells in liver portal spaces and neural tubules.

3.8 DNA Damage and Genotoxicity- Oxidative stress damages DNA by attacking its base pairs and sugar-phosphate backbone with reactive oxygen species. This may cause:

- Single-strand breaks
- Double-strand breaks
- DNA crosslinking
- Chromosomal errors
- Small nuclei

In animal studies of the liver, kidneys, bone marrow, and lymphocytes, tug-of-war or comet assays, micronucleus tests, chromosomal aberration analysis, and fragmented DNA studies have shown fluoride's genotoxicity.

The tumour suppressor protein p53 activates the cell cycle to stop or kill cells after DNA damage.

Apoptosis-Long-term fluoride-induced oxidative damage causes apoptosis, or programmed cell death. Fluoride exposure promotes apoptosis-causing mitochondrial and extrinsic pathways.

The following molecular indicators indicate that fluoride exposure triggered both pathways:

- Increased Bax expression
- Bad expression increased
- Caspase-3 activity rises
- Caspase-9 activity rises
- Cytochrome c release increases
- Lower Bcl-2 production

Yan *et al*. (2018); Zhang *et al.* (2022).

Activating these pathways causes chromatins to condense, nuclei to break apart, membranes to bleb, and DNA to degrade, which kills liver and kidney epithelial cells.

Signalling pathways inside cells

New molecular toxicology research shows that fluoride affects signalling pathways that regulate inflammation, fibrosis, oxidative stress, and apoptosis.

Major paths are:

- The NF-κB pathway
- The MAPK pathway
- The JNK pathway
- The ERK pathway
- The p38 MAPK pathway
- The PI3K/Akt pathway
- The TGF-β/Smad pathway
- Nrf2/ARE antioxidant pathway

NF-κB activation and Nrf2 suppression are crucial in the fluoride-induced oxidative damage pathway. Nrf2 activity decreases the ability to promote gene expression of antioxidant proteins like HO-1, NQO1, GST, SOD, and CAT, reducing cells' response to oxidative damage (Zhang *et al*., 2020).3.11 Integrated Mechanism of Fluoride-Induced Hepato-Renal Toxicity Experimental evidence suggests that fluoride's toxicity is caused by numerous coordinated and sequential cellular events rather than one faulty biochemical pathway. Fluoride poisoning is thought to start with ROS production and antioxidant depletion. Mitochondrial failure increases intracellular calcium, activates inflammatory pathways, ER stress, DNA damage, and apoptosis. These molecular events change liver and kidney structure and function, causing persistent hepatotoxicity and nephrotoxicity.

This molecular understanding supports the biological basis for investigating antioxidant treatments like Vitamin D and *Tamarindus indica* that may disrupt many harmful cascade phases. Future chapters will explain their strategies to prevent fluoride-induced oxidative damage.

Hepatotoxicity from Fluoride-The liver is the largest organ and handles many metabolic functions needed to maintain homeostasis, including carbohydrate, lipid, and protein metabolism, xenobiotic detoxification, plasma protein production, bile production, antioxidant defence mechanisms, immune system regulation, and hormone metabolism (Guyton & Hall, 2021). As the first organ to get blood from the gastrointestinal tract via portal circulation, the liver will absorb fluoride first. Thus, prolonged fluoride exposure causes liver fluoride buildup and severe structural and functional deterioration (Whitford, 1996; Barbier *et al*., 2010).

Fluoride predominantly causes skeletal and dental fluorosis, although recent experimental research has shown that prolonged fluoride exposure damages liver cells. Reports of biochemical, histopathological, ultrastructural, and molecular changes have been consistently reported in studies using albino rats after long-term exposure to sodium fluoride.These pathological changes are primarily brought about via oxidative stress, inflammation, mitochondrial dysfunction, calcium mismanagement, apoptosis, and creating collagenous tissue (Miltonprabu *et al*., 2017; Pal *et al*., 2022)

4.1 Hepatic fluoride accumulation-Fluoride enters the body through the gastrointestinal system; it then enters the portal circulation before reaching in the liver. Fluoride is mostly found in bone, but repeated exposures build up hepatic fluoride. Liver cells have high metabolic activity and are constantly exposed to xenobiotics (Buzalaf & Whitford, 2011). High liver fluoride levels result from prolonged sodium fluoride exposure. Fluoride accumulation in the liver causes oxidative stress, which disrupts biochemical pathways and degenerates hepatocytes, causing liver function loss (Barbier *et al*., 2010).

4.2 Biochemical Changes-Fluoride's liver effects are first detected by biochemical markers in circulation. Normal liver cells (hepatocytes) store enzymes. Due to oxidative stress, the membrane leaks, releasing liver enzymes into the bloodstream.

Many studies show increased:

- Alanine aminotransferase
- The AST enzyme
- Alkaline phosphatase
- The GGT enzyme
- The LDH enzyme
- Total bilirubin

Due to chronic fluoride exposure (Pal *et al*., 2022; Caglayan, 2021). However, chronic fluoride exposure lowers circulatory parameters:

- Serum albumin
- Total protein
- Globulins
- Albumin/Globulin

This decreases hepatic protein metabolism and synthesis function (Miltonprabu *et al*., 2017). The degree of liver biochemical alterations depends on the dose, period of exposure, and microscopical damage.4.3 Fluoride-Caused Oxidative Stress Oxidative stress is assumed to be fluoride's principal liver damaging mechanism. Too much fluoride in cells increases reactive oxygen species and inhibits antioxidant enzyme production.

According to research, several products consistently display oxidative stress:

- MDA levels rise
- ROS levels rise
- Nitric oxide increases

Fluoride damage to liver cells is indicated by decreased levels of the following:

- The antioxidant SOD
- CATalase
- GPx
- Reduced GSH

(2015); Miltonprabu *et al.* (2017).

Extra ROS harm membrane phospholipids, proteins, nucleic acids, and intracellular organelles. Lipid degradation weakens hepatocyte membranes. This leaks hepatocyte enzyme and destroys it continuously.

4.4 Fluoride affects mitochondria-Fluoride-induced oxidative damage affects mitochondria quite strongly. Fluoride's high ROS damage the mitochondria's cytoplasmic membrane. It lowers mitochondrial membrane potential, electron transport chain enzymes, and ATP synthesis.

Fluoride-induced mitochondrial dysfunction causes:

- Reduced ATP production
- Electron transport chain inhibition
- Additional mitochondrial ROS production
- Released cytochrome c
- Active intrinsic apoptosis

Johnston & Strobel (2020; Inkielewicz-Stepniak, 2012).

Hepatocytes need a lot of ATP to conduct their metabolic duties, hence mitochondrial failure might diminish hepatic physiology and increase liver damage

4.5 Inflammation-Fluoride-induced hepatotoxicity is exacerbated by inflammation. Oxidative stress activates the NF-κB pathway, which regulates the expression of inflammatory cytokines.

Intentional fluoride exposure increases TNF-α, IL-1β, IL-6, COX-2, and iNOS in the liver (Liu *et al*., 2019; Zhang *et al*., 2021).

Mediators of inflammation promote:

- White blood cell invasion
- Vascular blockage
- Sinusoidal dilation
- Kupffer cell activation
- Progressive hepatocyte destruction

4.6 Histopathology Disorders-Histopathology is a prominent indicator of fluoride-induced liver damage.

Light microscopy of fluoride-treated albino rat liver sections verified:

- Hepatocyte swell
- Vacuolation of cells
- Fat degeneration
- Hydropic degeneration histology
- Loss of hepatic cord organization
- Sinusoidal dilation
- Central vein congestion
- Inflammatory cell infiltration
- Focal necrosis
- Pyknotic nuclei
- Overgrowth of Kupffer cells.

Miltonprabu *et al*. 2017, Yan *et al*. 2018].

Ultrastructural alterations detected by electron microscopy:

- Mitochondrial swelling
- Dilated ER
- Broken nuclear envelopes
- Low glycogen
- Chromatin condensed
- Disorganised cell organelles

These significant ultrastructural alterations indicate severe hepatic metabolic activity and energy generation impairment.

4.7 Action Mechanisms-Recent molecular investigations show fluoride stimulated hepatic inflammation and apoptosis-related intracellular signalling pathways.

Affected molecular alterations are:

Enhanced protein expression linked to:

NF-κB, Bax, Caspase-3,Caspase-9,Cytochrome c,TNF-α,IL-6,TGF-β,JNK, p38 MAPK

Lower protein expression associated with:

Bcl-2,Nrf2, HO-1, NQO1

Yan *et al*. 2018, Zhang 2022.

The Nrf2-antioxidant pathway suppresses antioxidant gene transcriptions, while MAPK and NF-κB pathways promote oxidative stress and inflammation.

4.8. Influences on Hepatic Toxicity

Due to physiological characteristics, fluoride-induced liver injury can vary by individual and population.

Examples of physiological variables are:

- Fluoride level
- Duration of exposure
- Age
- Nutritional state
- Calcium intake
- Selenium status
- Zinc availability
- Lack of vitamins
- Renal function
- Antioxidant power

Young animals and people with dietary deficiencies absorb fluoride faster and have fewer antioxidant defences, increasing liver injury risk [Whitford 1996, National Research Council 2006].

4.9 Treatment Choices - Antioxidant therapy prevents liver injury since oxidative stress is the main cause.1. Vitamin D protects the liver by:

- Activating antioxidant enzymes.
- Reduces inflammatory cytokines.
- Preserving mitochondrial function.
- Regulation of calcium metabolism.
- Anti-apoptosis.

(Holick, 2007; Bikle, 2014).

Tamarindus indica contains antioxidant, anti-inflammatory, metal-chelating, and hepatoprotective qualities due to its rich polyphenol, flavonoids, tannins, tartaric acid, vitamins, and organic acids. Tamarind supplementation reduces ALT, AST, ALP, bilirubin, and lipid peroxidation while restoring antioxidant activity and liver architecture (De Caluwé *et al*., 2010; Khandare *et al*., 2002; Miltonprabu *et al*., 2017).

Fluoride-induced hepatotoxicity involves oxidative stress, mitochondrial malfunction, inflammation, calcium imbalance, DNA damage, and apoptosis. Understanding how these pathways are linked provides scientific basis for developing antioxidant therapies to prevent chronic liver damage from fluoride exposure.

Nephrotoxicity from Fluoride

The kidneys are responsible for maintaining fluid and electrolyte levels, acid and base balance, metabolic waste removal, and xenobiotic removal (including fluoride). Renal tissues are one of the principal sites of chronic fluoride poisoning since the kidneys remove 50% to 70% of fluoride ingested. Chronic high fluoride exposure causes renal tissue fluoride rise, oxidative stress, inflammation, structural change, and impaired renal performance. Skeletal fluorosis has the most evident impacts of fluoridation. Recent and past studies on toxicology and how environments affect people have shown that nephrotoxicity, or kidney toxicity & disease, is often one of the first symptoms of excessive fluoride ingestion. Researchers studied rats to discover the biochemical consequences of high fluoride on the kidneys. These studies found that high fluoride intake caused five kidney biochemical alterations, including:

(1) renal cell biochemistry changes;

(2) renal pathology (morphological lesions);

(3 kidney ultrastructure alterations);

(4) renal cell inflammation;

(5) mitochondrial malfunction and apoptosis (Barbier 2010; Gao 2012).

5.1. Kidney Fluoride Buildup- Renal arteries carry fluoride from the gut to the kidneys. The glomerulus filters fluoride and renal tubular tissues partially resorb it. Urinary pH, plasma fluoride concentrations, hydration, and renal function affect kidney fluoride reabsorption (Whitford, 1996). Chronic fluoride exposure increases fluoride buildup in kidney structures:

- Glial cells
- Tubule epithelial cells proximity
- Distal tubule epithelial cells
- Renal interstitial fluids

Overexposure to fluoride extends renal tissue detoxification time. Chronic and severe exposures promote cellular deterioration and impair renal tissue fluoride detoxification (Buzalaf & Whitford, 2011).

5.2 Biochemical Nephrotoxicity Indicators- Biochemical abnormalities in blood kidney function tests are early signs of fluoride nephrotoxicity.

In decreasing order, studies suggest that excessive fluoride exposure increases mean serum blood levels in the following:

- Creatinine
- BUN urea nitrogen
- Urea
- Uric acid

- Sodium
- Potassium
- Chloride
- Calcium/phosphorus metabolism issues (Gao *et al*., 2012; Liu, 2018).

Blood biomarker abnormalities support kidney changes:

- Reduced GFR
- Poor tubular reabsorption
- Low renal clearance
- Nephron damage progresses
- Fluoride buildup in the kidneys increases renal tissue fluoride levels and damages the kidneys.

5.3 Kidney Oxidative Stress

The main mechanism of fluoride's nephrotoxicity is oxygen-based stress.

The following reactive oxygen species (ROS) increase statistically with fluoride exposure:

- Reactive oxygen species
- Malondialdehyde
- Nitric oxide

The following antioxidant enzymes and compounds decreased significantly:

- The antioxidant SOD
- CATalase
- GPx
- Reduced GSH

Miltonprabu *et al*. (2017)

Kidney tubular epithelial cells and related cells have more mitochondria than most cell types, making them more susceptible to oxidative stress. Lipid peroxidation of membrane phospholipids lacking in degradation damages plasma membrane integrity, disrupts ion transport, and causes cell toxicity. All three factors alter renal cell structure due to free radicals.

5.4 Mitochondrial Dysfunction- Kidney active transport pathways for electrolyte reabsorption and urine concentration require lots of ATP. Fluoride causes oxidative stress, which damages mitochondria and inhibits oxidative phosphorylation, increasing mitochondrial reactive oxygen species generation. (2012) Inkielewicz-Stepniak Renal cells damaged by this will have:

- Lower ATP levels
- Na+/K+ATPase inhibition
- Electrolyte imbalances
- Cell swelling
- Tubule degeneration

Long-term mitochondrial failure activates intrinsic apoptotic pathways, causing nephron loss.

5.5 Inflammation -Additionally, oxidative stress activates NF-κB, leading to the generation of inflammatory mediators in renal tissue.

Numerous experiments have shown considerable increase of these pro-inflammatory cytokines:

- TNF-α
- IL-1β
- IL-6
- COX-2
- iNOS

(Liu 2019; Zhang 2021)

These inflammatory mediators cause:

- Leukocytes' invasion
- Endothelial malfunction
- Vascular congestion
- Interstitial swelling
- Progressing fibrosis

Permanent kidney damage is often caused by chronic inflammation.

5.6 Histopathology -Kidneys show distinctive histological alterations after fluoride treatment.

Kidney histopathology included:

- Glomerular atrophy
- Increased Bowman's Space
- Degeneration of tubular epithelial cells
- Tubular epithelial cell vacuolization
- Tubule necrosis
- Interstitial swelling
- Vascular congestion
- Inflammatory cell invasion
- Fibrosis

(Caglayan *et al*. 2021; Zhang 2022)

Electron microscopy also showed cellular damage due to anomalies like:

- Swollen mitochondria
- Microvilli disruption
- Dilation of the ER
- Condensed nuclei
- Increased lysosomal activity.

5.7 Molecular Mechanisms-Chronic fluoride exposure upregulates several signalling pathways, according to molecular research. Previously identified upregulated signalling molecules:

- Bax
- Caspase-3
- Caspase-9
- Cytochrome c
- Transforming growth factor beta
- Jun N-terminal kinase
- NF-κB

Chronic fluoride exposure downregulates bcl-2 significantly. (2018) Yan *et al*.

Activating these pathways causes apoptosis and fast nephron degradation.

6. Vitamin D Protects

Vitamin D primarily controls calcium and phosphorus synthesis.Vitamin D is now known to have anti-inflammatory, immunomodulatory, antioxidant, anti-fibrotic, and antiapoptotic properties (Holick 2007; Bouillon *et al*. 2019).

The vitamin D receptor (VDR) is found in liver, kidneys, immune cells, heart, brain, pancreas, and vascular endothelium and mediates vitamin D's biological effects.

Multiple experiments show that vitamin D supplementation decreases fluoride-induced liver and kidney damage.

6.1 Antioxidants-Significant vitamin D rise (decrease):

- SOD enzyme
- CATalase
- Glutathione Oxidase
- The GSH

Decreases (increases):

- ROS
- Malondialdehyde
- Peroxidation of lipids

Bikle (2014), Zhang *et al*. (2020).

These investigations found that vitamin D supplementation sustains intracellular redox equilibrium and cellular balance.

6.2 Anti-inflammatory

Vitamin D reduces NF-κB activation, reduces pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, COX-2, iNOS), and boosts anti-inflammatory IL-10 (Aranow, 2011).

Thus, inflammatory cell infiltration and vascular congestion diminish significantly.

6.3 Hepatoprotection

Experimental studies show a considerable decrease (increase)

- Alanine aminotransferase
- The AST enzyme
- Alkaline phosphatase
- Lactate dehydrogenase (LDH)- Bilirubin

Following Vitamin D administration (Yadav *et al*., 2023).

Histopathological data demonstrate normal hepatic cord structure, less fatty change, necrosis, and improved cellular morphology.

6.4 Kidney Protection

Vitamin D supplementation dramatically lowered (increased):

The serum creatinine and blood urea nitrogen levels are:

Urea Uric acid and preserved kidney glomerular and tubular structure by increasing renal antioxidant enzyme activity (Miltonprabu *et al*., 2017).

7. *Tamarindus indica* Protects- Medicine plant *Tamarindus indica* is in the Fabaceae family. De Caluwé *et al*. (2010) found phytochemicals in fruit, leaf, seed, bark, and flower that have biological and medicinal activities.

These substances are the main phytochemicals:

- Polyphenol
- Flavonoids
- Gallic acid

- Ellagic acid Catechin
- Quercetin
- Tartaric acid
- The C vitamin
- Vitamin E - Tannins

The chemicals indicated above have high antioxidant activities and metal-chelating characteristics.

Tamrind extract greatly boosts:

- SOD, CAT, GPx
- GSH

While considerably reducing: **ROS oMDA**

Miltonprabu *et al.* (2017) found that tamarind boosts antioxidant defences.

Studies demonstrate that tamarind supplementation lowers liver enzymes and bilirubin:

• ALT, AST, ALP, Bilirubin

Additionally, normal hepatic architecture is restored, restoring the liver's overall form (Khandare *et al*., 2002).

Along with liver health, tamarind supplementation greatly lowers the following nephrotoxins:

- Creatinine
- BUN
- Urea Uric acid

Tamarind supplementation reduces tubular degeneration and improves glomerular filtration (Reddy & Karnati, 2015).

The special property of *Tamarindus indica* helps eliminate fluoride from the body. Tamarind extracts contain polyphenols, tartaric acid, dietary fibre, and organic acids that interact with fluoride ions to increase urine excretion and decrease tissue fluoride buildup (Khandare *et al*., 2002).

Recent research shows that Vitamin D and *Tamarindus indica* together protect against fluoride damage better than either alone.

Combination therapy benefits include:

- Boost antioxidant enzyme activity
- Reduce oxidative stress
- Reduce inflammation
- Improve mitochondrial function
- Avoid apoptosis
- Renew liver function
- Improve renal function and decrease fluoride buildup.

Yadav *et al*. (2023; Miltonprabu, 2017).

Vitamin D and tamarind work synergistically to protect against chronic fluoride poisoning.

Conclusion

Oxidative stress, mitochondrial damage, inflammation, calcium dysregulation, and apoptosis can cause liver and kidney toxicity from chronic fluoride exposure. Liver and kidney biochemical abnormalities, structural damage, and functional impairment can result from chronic exposure. Due to their antioxidant, anti-inflammatory, anti-apoptotic, and cytoprotective effects, Vitamin D and *Tamarindus indica* have been shown to protect against liver and kidney damage. Vitamin D increases the body's intrinsic antioxidant capacity through VDR-mediated signalling, while *Tamarindus indica* contains abundant phytochemicals that can scavenge free radicals, including fluoride. The combination of Vitamin D and *Tamarindus indica* is more effective than either alone. Before prescribing these medicines for persistent fluorosis prevention and treatment, standardised animal, molecular, and human clinical trials are needed.

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