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REVIEW

Fluoride-Induced Mitochondrial Dysfunction and Approaches for Its Intervention

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Abstract

Fluoride is present everywhere in nature. The primary way that individuals are exposed to fluoride is by drinking water. It's interesting to note that while low fluoride levels are good for bone and tooth growth, prolonged fluoride exposure is bad for human health. Additionally, preclinical studies link oxidative stress, inflammation, and programmed cell death to fluoride toxicity. Moreover, mitochondria play a crucial role in the production of reactive oxygen species (ROS). On the other hand, little is known about fluoride's impact on mitophagy, biogenesis, and mitochondrial dynamics. These actions control the growth, composition, and organisation of mitochondria, and the purification of mitochondrial DNA helps to inhibit the production of reactive oxygen species and the release of cytochrome c, which enables cells to survive the effects of fluoride poisoning. In this review, we discuss the different pathways involved in mitochondrial toxicity and dysfunction induced by fluoride. For therapeutic approaches, we discussed different phytochemical and pharmacological agents which reduce the toxicity of fluoride via maintained by imbalanced cellular processes, mitochondrial dynamics, and scavenging the ROS.

Keyword Fluorosis · Mitochondrial dynamics · ROS · Apoptosis · Antioxidant

Introduction

Fluoride is an essential component for the development and growth that are typical for animals; however, an excessive amount of fluoride can cause the body of the animal to become damaged. Dental fluorosis [1], hypertension [2], skeletal fluorosis [3], reproductive disorders [4], and dementia [5] have been identified as the usual manifestations of fluorosis, and a huge number of studies indicate [1]. Fluoride exists in large quantities in our environment in a variety of various forms, and it's having ability to damage the health and natural environment. Fluorosis has been spotted in a significant number of people all over the world. The fluorine pollution in soil is a major cause for concern all over the world, but especially in China because it is having a bigger detrimental effect on human health as well as the ecological environment [6]. Over 260 million people worldwide have fluorosis, according to studies on the condition's prevalence in 20 different countries, which is brought on by exposure to a variety of fluorine sources [7]. Fluoride can be found in various food and beverages, such as fish, milk, and brick tea, as well as in water, toothpaste, and mouthwashes [8].

Fluoride is most commonly consumed by humans through drinking water, which can be contaminated by rocks and fluoride-containing minerals in the groundwater. For humans, this is only the major origin of fluoride element [3]. The levels of fluoride that are acceptable in consumable water are set by various organisations which have been shown in Table 1 [9].

Following consumption, around 75–90% of the soluble fluoride is rapidly absorbed, making its way into the bloodstream and making a contribution to the plasma fluoride levels [10]. Fluoride creates insoluble complexes with cations like calcium (Ca2+) and magnesium (Mg2+) which are then removed from the body through faeces, because of its

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Table 1 Acceptable fluoride concentration in drinking water

Name of organization	Desirable limit (mg/L)
Indian Council of Medical Research	1.00
The Committee on Public Health Engineering Manual and Code of Practice, Government of India	1.00
Bureau of Indian Standards	0.6–1.2
US Public health standard	0.80
Indian Statistical Institute	1.50
World Health Organization (International Standards for Drinking Water)	0.50

instability and high binding affinities. The absorption distribution of fluoride in different body parts has been shown in Fig. 1.

A significant amount of fluoride that is dispersed throughout the body bond with Ca2+ in the body's hard tissues [11], where it takes the place of hydroxyl ions in the enamel that is naturally present (hydroxyapatite). When an individual consumes an excessive amount of fluoride, their digestive system is largely affected. This may cause nausea, nausea or vomiting, abdominal cramp, and diarrhoea [12]. Fluorosis, also known as fluoride poisoning, is caused by prolonged exposure to fluoride (more than 1.5 mg/L). This condition is frequently connected with the progressive degradation of bones and teeth. In

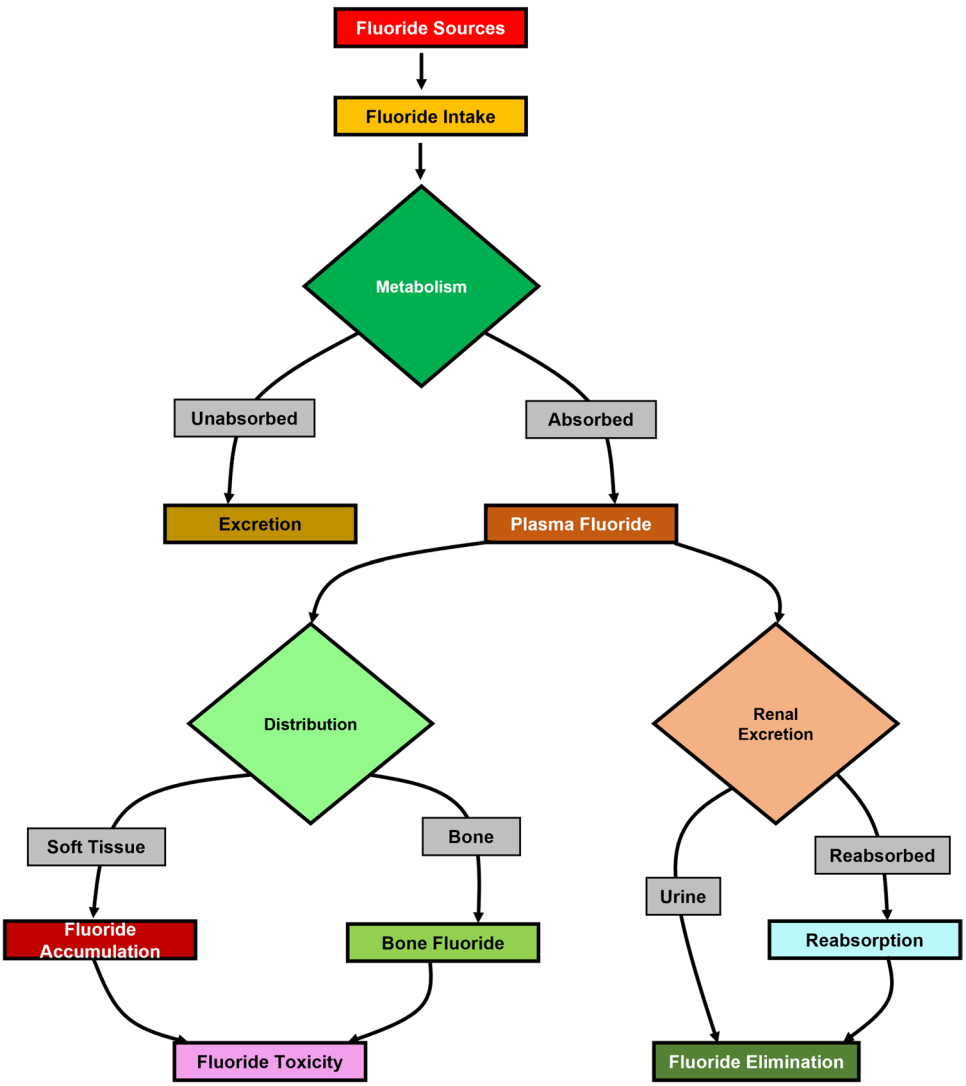

Fig. 1 Every ecosystem has the element fluoride (F), which is present in the soil, groundwater, vegetation, and animals. Diet and accidental ingestion of fluoride via dental products (toothpaste and mouth wash) are the two most important contributors to an individual's fluoride intake. Eighty to ninety percent of the ingested F is absorbed by passive diffusion from the gastrointestinal system. Then get into the plasma accumulated in different part of body via excrete out the different route.

addition, there is evidence that fluoride poisoning can have a negative impact on soft tissues, including the lungs [13, 14], liver [15, 16], heart [17, 18], kidney [19], spleen [20], and brain [21–23], which has been shown in Fig. 1. Both the placenta and the blood-brain barrier (BBB) can be penetrated by fluoride in the form of non-ionic hydrogen fluoride (HF) [24, 25]. It is believed that children's BBB are undeveloped or underdeveloped, making them more susceptible to poisons like fluoride [26, 27]. Fluoride transport over the BBB has negative impact on neuron metabolism, enzyme, neurotransmitters, and oxidation homeostasis, which eventually results in impaired mental status [28, 29]. Fluoride has a high level of chemical and biological activity, which is related to its toxicity. Fluoride readily and quickly crosses biological membranes when the pH of nearby bodily fluid compartments changes, most frequently by passively non-ionic diffusion in the form of HF [30]. Depending on the kind of cell, the concentration, and the length of exposure, fluoride can have different effects on cellular metabolism and physiology (Fig. 2) [31]. For example, fluoride micromolar concentrations in tooth and bone tissues create potentially advantageous effects by stimulating cell division and development, but fluoride millimolar dosages decrease cell multiplication and cause programed cell death. Various literatures have been revealed that higher exposure of fluoride levels results in cell death by apoptosis in ameloblasts [32–34], odontoblasts [35], and osteoblasts [36–38]. Fluoride has a number of detrimental consequences, such as inflammatory responses, cell contractile responses, suppression of cell growth and cell cycle arrest, and DNA oxidative stress [31]. Apoptosis is a sophisticated and tightly controlled event that is essential for the elimination of unneeded or damaged cells as well as for a number of regular physiological events such as cell multiplication and proliferation, tissue homeostasis, and ageing [39–41]. Studies show that high fluoride ingestion causes cell dysplasia and reduces cell proliferation and differentiation. Fluoride alters the mitochondrial morphology of cells and prevents the mechanism of the respiratory chain complex, leading to drop in adenosine tri phosphate and an elevation in ROS (Fig. 2). In this review, we have explained how fluoride accumulation occurs in body and pathways involved in fluorosis via a different source, which cause mitochondrial dysfunction and responsible to raise the level of ROS. In this review, we discuss the different mechanisms involved in mitochondrial dysfunction via fluorosis. How fluoride acts on the different metabolic activities of mitochondria alters the energy production. In this review, we discuss therapeutic approaches for fluoride toxicity and different antioxidant, phytochemical, and pharmacological modulators which act on the different targets and neutralised the toxicity of fluoride.

Different Apoptotic Pathways Involved In Mitochondrial Disturbance via Fluorosis And There Therapeutic Intervention

In Energy Metabolic Pathway

Different energy metabolic pathways are used by immune system cells to create intermediates that enable cellular growth and proliferation as well as provide ATP to support cellular functions and survival [42, 43]. These bioenergetic requirements are principally satisfied by three metabolic processes that are interconnected: glycolysis, the tricarboxylic acid cycle, and OXPHOS. Glycolysis takes place in the cytoplasm, which is in contrast to the mitochondria, which are the exclusive locations for the OXPHOS and TCA cycles. Glucose is the first taken in from the outside environment by glucose transporters, where it is then phosphorylated by hexokinases to G6P. G6P is converted into pyruvate during the glycolytic pathway, converting NAD+ to NADH and producing two molecules of ATP in the process. G6P can also take part in the PPP, which is a byproduct of glycolysis that produces the reducing equivalents of NADPH that are necessary for the NOX-controlled microbicidal pathways and the riboses that are necessary for the synthesis of nucleotides. G6P can participate in both of these processes. During conditions of normoxia, the pyruvate that is created as a byproduct of glycolysis is converted into acetyl-CoA. This acetyl-CoA is then oxidised as part of the TCA cycle events, which leads in the formation of NADH and FADH2. These molecules are responsible for the transmission of electrons to the ETC so that OXPHOS can be fuelled and for the more efficient production of 30–36 molecules of ATP for each molecule of glucose. Fluoride prevents the transfer of nutrients, cell respiration, and glycolysis by inhibiting metalloproteins [44–46]. Long-term exposure to fluoride causes metabolic disturbance, production of stress signals, inhibition of transmembrane proteins, aberrant mitochondria, and electrolyte imbalance at the molecular level [47–49]. Chronic exposure of fluoride causes damage in mitochondria permanently and leads in an aberrant respiratory chain. This is mostly because anaerobic glycolysis produces less ATP (ATP ADP+AMP+H+), which releases protons and causes intracellular acidification and oxidative stress [44, 46, 50].

Role of fluoride in SIRT1

Sirtuins are NAD+-dependent class III deacetylases, human homologues of the yeast gene sir2, which stands for silent information regulator-2 [51–53]. The acetyl groups removing from cellular protein, such as histones and transcription regulators, by sirtuins, which controls the post-translational biological functions of the protein substrates [54], is how sirtuins exert their influence. There are seven different

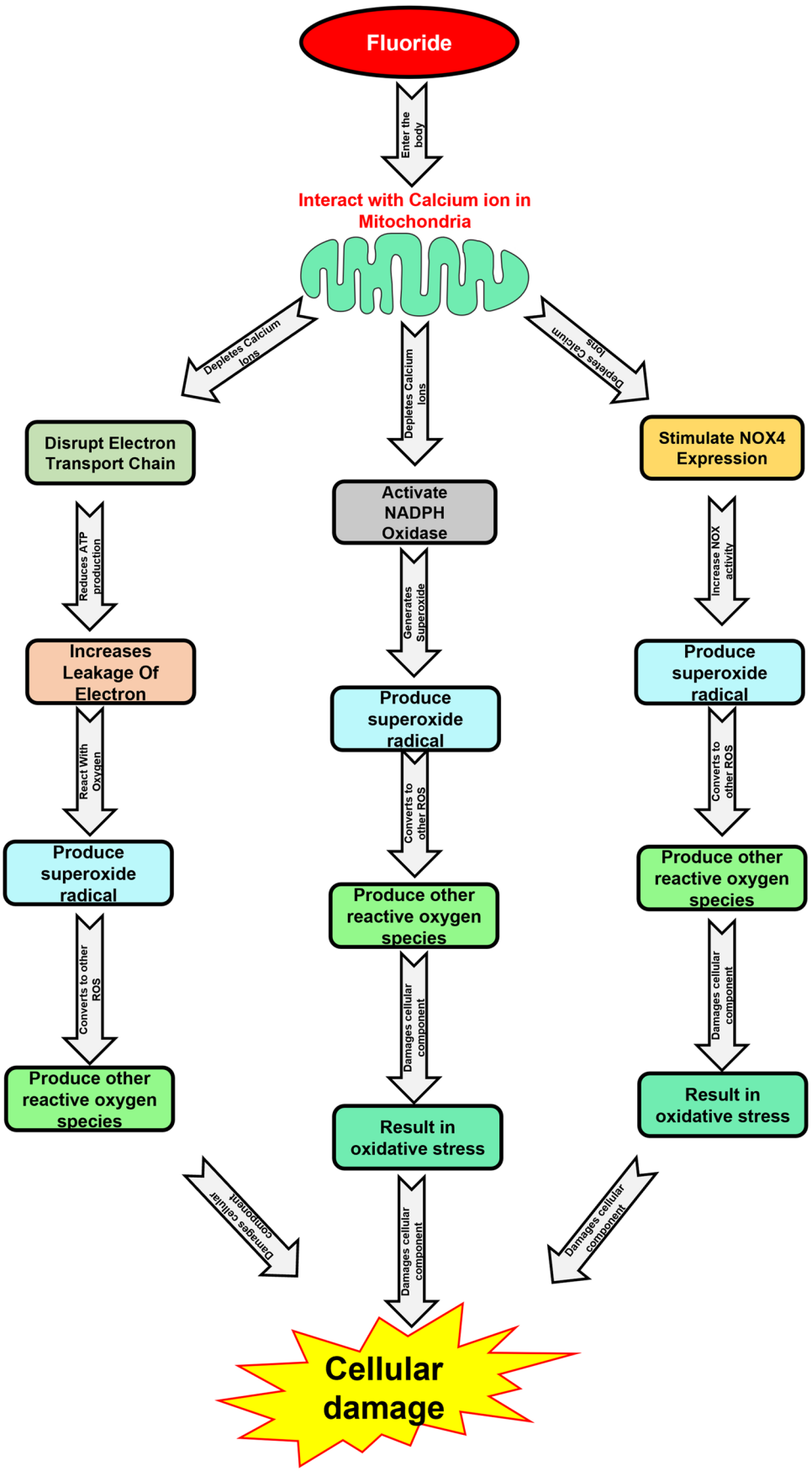

Fig. 2 Schematic representation of environmental fluoride from different source can easily crass the biological membrane and bound with intracellular calcium to form insoluble fluoride and accumulated in intracellular environment and damage the mitochondria, disturb the ETC which cause oxidant and antioxidant imbalance, and increase the level ROS.

proteins that make up the sirtuin family in mammals (SIRT1 to SIRT7) [55]. SIRT1 is related to the Sir2 gene that is found in *Saccharomyces cerevisiae* [34, 56], and SIRT1 itself is regulated posttranscriptionally by the process of phosphorylation [57–59]. cyclinB/Cdk1 is responsible for phosphorylating residues Thr530 and Ser540 [58], whereas c-Jun N-terminal kinase 1 (JNK1) is responsible for phosphorylating residues Ser27, Ser47, and Thr530 [59]. In comparison to its version that has not been phosphorylated, phosphorylated SIRT1 (p-SIRT) functions as an active deacetylase [58]. SIRT1 helps the cell resist the stress induced by oxidative stress, caloric restriction (CR), and endoplasmic reticulum (ER) stress [60–63] by deacetylating target substrates such as FOXOs, PGC-1, and p53. SIRT1 is in responsible for controlling cellular activities involved in maintaining homeostasis and responding to stress; it is clear that SIRT1 is favourable to the continued existence of cells. During times of cell stress, SIRT1 is responsible for regulating autophagy [64, 65]. Macroautophagy, or autophagy as it is more widely known, is an intracellular catabolic process that is phylogenetically conserved and allows the breakdown of cytoplasmic content [66–68], such as defective proteins and organelles. Autophagy is often referred to as the term "autophagy." It has been discovered that sirtuins mostly have an anti-apoptotic property. In the traumatic brain damage mouse model, SIRT1 activation downregulates the pro-apoptotic protein Bax and upregulates the anti-apoptotic protein Bcl-2, which is consistent with decreased neuronal death [69]. By increasing autophagy during oocyte ageing, SIRT2 inhibition exacerbated cell apoptosis and supported the anti-apoptotic function of SIRT2 [70]. SIRT3 was discovered to inhibit COX-1 deacetylation-induced cell death in response to oxidative stress, which could be beneficial in preventing cerebral ischemia/reperfusion injury [71]. Additionally, pancreatic cell apoptosis and dysfunction brought on by the injection of too much palmitate and glucose were reduced by overexpression of SIRT5 [72]. In vitro exposure of podocytes to high glucose levels resulted in SIRT6 suppressing Notch signalling in a way dependent upon deacetylation activity, as demonstrated by [73]. Additionally, SIRT7 increased cardiomyocytes' resistance to apoptosis, possibly through deacetylating p53 [74]. Sirtuins may play pro-apoptotic roles in some situations, despite the fact that numerous research have focused on their anti-apoptotic functions. For instance, SIRT5 can increase tumour cell death by acting as a tumour suppressor through its desuccinylase activity [75]. IDH1 mutation-induced R-2-hydroxyglutarate (R-2HG) accumulation results in mitochondrial hypersuccinylation, which promotes carcinogenesis and apoptosis resistance. However, desuccinylase SIRT5 overexpression can reverse these effects. The varied enzymatic activities of sirtuins and their numerous downstream targets may help to explain these seemingly contradicting actions of sirtuins in controlling cellular death. Therefore, more research is required to demonstrate the sirtuins' complex functions in apoptosis.

Fluoride was found to activate SIRT1 and autophagy, which are adaptive reaction that prevent cells from cell stress [76]. Many studies confirmed that fluoride has this effect. SIRT1 is controlled by a number of different variables in response to cellular stress [77]. SIRT1 expression can be boosted, for instance, by transcription factors such as peroxisome proliferator-activated receptors (PPARs) [78, 79] and cAMP response element binding (CREB) [80].

For therapeutic approach, since SIRT1 is known to regulate crucial metabolic pathways and has been linked to both oncogenic and chemotherapeutic processes, its activation may be advantageous in the fight against metabolic disorders. In recent years, scientists who were interested in finding SIRT1 modulators were able to find new small molecules that target SIRT1 activity. Many studies have shown that different natural phytochemicals, like resveratrol, fisetin, curcumin, quercetin, and berberine, are natural non-polyphenolic substances which are good for your health [81]. Natural polyphenols are possible ways to prevent and treat oxidative stress diseases. They are present in many plants and fruits. Long-term consumption is linked to health benefits and reduced the toxicity of fluoride (Fig. 3).

Reactive oxygen species pathway

Reactive oxygen species are formed when O^2-derived free radicals such as hydroxyl radicals ($HO^{\bullet}$), peroxyl ($RO2^{\bullet}$), superoxide anions ($O^{2\bullet}$), and alkoxyl ($RO^{\bullet}$) as well as O^2-derived non-radical species like hydrogen peroxide (H_2O_2) combine (ROS)[82]. A significant intracellular generator of ROS is the mitochondrion. According to research, 1–2% of the mitochondrial O^2 used is diverted to production of ROS, particularly at complex I and complex III of the mitochondrial membrane [83, 84]. This is thought to vary on the tissue and species [83, 84]. In the presence of metallic ions, manganese antioxidant enzyme transforms mitochondrial $O2^{\bullet}$ to H_2O_2 and produces highly reactive $HO^{\bullet}$, damaging cellular components, phospholipid, and DNA. Approximately 10 putative ROS-generating mechanisms in mitochondria have been found thus far [85]. Krebs cycle enzyme complexes, including pyruvate dehydrogenase and -ketoglutarate dehydrogenase (-KGDH), have been mentioned as important mitochondrial superoxide anion radical and H_2O_2 sources among these [86]. It is important to note that higher levels of nicotinamide adenine dinucleotide (NADH) are connected with higher levels of H_2O_2 synthesis by mitochondria -KGDH. This increased oxidant strain results in more ROS generation from mitochondrial complex I, which accelerates the death of cells [87]. Other mitochondrial ROS generators include p66Shc

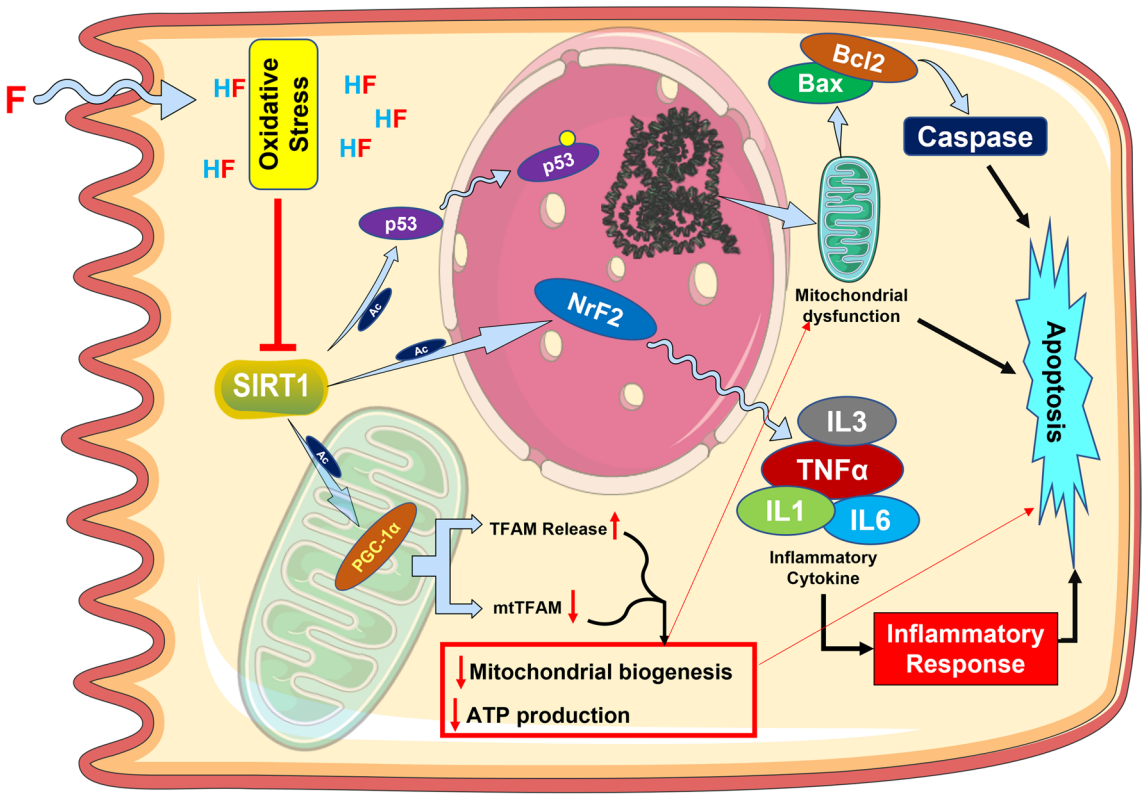

Fig. 3 A representation in schematic form of the apoptosis caused by fluoride and mediated by the SIRT1-p53 pathway. Fluoride is responsible for the formation of intracellular ROS, which in turn activates the cytosolic SIRT1. It is able to attach to deacetylated p53 and prevent the protein from moving into the nucleus. The deacetylation of p53 causes it to go into the OMM, where it then releases the pro-apoptotic proteins BCL2 and BAX. When BAX is activated, this process causes cytochrome c (Cyt C) to be released from the mitochondria into the cytoplasm. Fluoride is transported into the mitochondria from the cytoplasm, where it then induces an increase in the ROS concentration of the mitochondria. The increases in ROS both cause acetylation of SOD2 and decrease the expression of the sirt-1 protein in mitochondria. The decrease in mitochondrial sirt-1 leads to an increase in acetylation of PGC1, which in turn causes mitochondria to become dysfunctional. Apoptosis is commonly caused by mitochondria that are not functioning properly. The structural integrity of mitochondria is preserved, its translocation is facilitated, and its transcriptional activity is carried out as a result of resveratrol's activation of the AMPK pathway. In addition, active AMPK is responsible for the phosphorylation of PGC-1, which allows the protein to enter the nucleus and be deacetylated by SIRT1. After that, PGC-1 will support Nrf2, which will result in a rise in the expression of antioxidative genes, which will eventually lead to a reduction in oxidative stress. Resveratrol triggers the activation of AMPK, which in turn promotes SIRT1, which in turn inhibits MAPK signalling pathways, which ultimately leads to autophagy.

[88], the outer membrane enzyme monoamine oxidase [85], the modified membrane potential of the mitochondria [89], and the pH of the matrix [90]. Due to their role as significant ROS producers, mitochondria are frequently exposed to high levels of ROS, which can have harmful effects such oxidative DNA damage [91, 92]. The mechanism by which mitochondrial DNA damage drives apoptotic signals is not fully understood and should be a promising path for further research. Elevated O2• and HO• linked to mtDNA damage cause apoptosis (Fig. 4) [93]. Peroxisomes are known to be sources of cytosolic H_2O_2 under physiological conditions; however, the removal of peroxisomal H_2O_2 is compartmentalised due to the structural arrangement of peroxisomes. During this time, H_2O_2 that has been catalysed by urate oxidase is being transferred into the cytoplasm by means of crystalloid core tubules [94], and the H_2O_2 that is produced in the matrix is removed by catalase. NADPH oxidase-derived ROS at the cellular membranes signal cells. Endoplasmic reticular (ER) some protein, such as cytochrome P450, are causes the large levels generation of cellular hydroxyl radicals and oxygen radicals, all of which contribute to the promotion of peroxidation, calcium metabolism, mitochondrial dysfunction, and cell death [95, 96]. ROS, which are connected to the development and spread of cancer, are the cause of nearly all types of nuclear damage [97] as well as base alterations, strand breakage, genomic cross-linking, and peptides; ROS damages proteins. However, the potential of ROS to trigger apoptotic, which are a major technique in the treatment of cancer [98–100], presents a conundrum in the context of biological systems, ROS interrupt the electron transport chain, open the permeability transition pore (PTP), damage the mitochondrial membrane, and release Cyt c. Together with

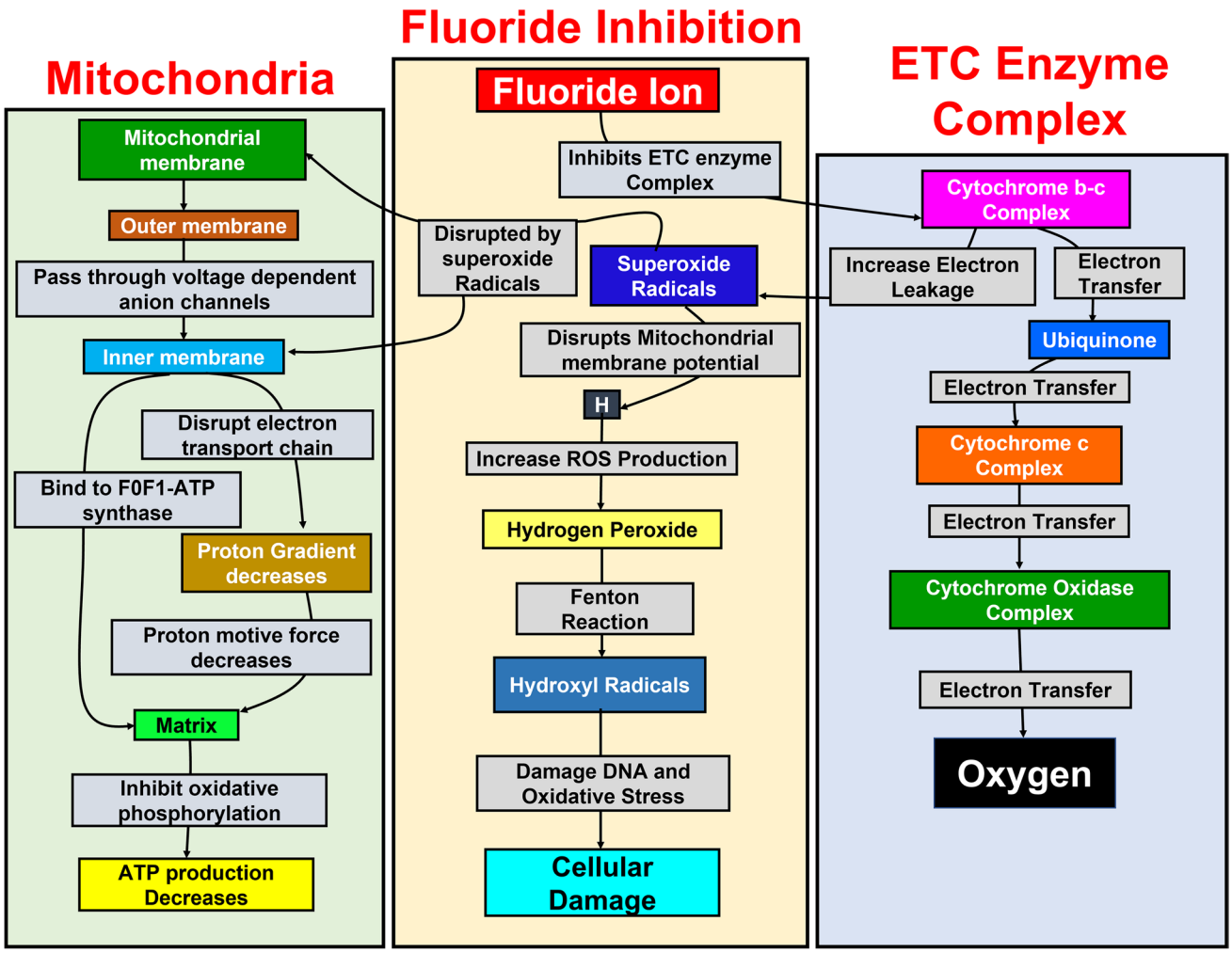

Fig. 4 The electron transport chain is responsible for the release of ROS. Complexes I and III of the mitochondrial matrix are responsible for the release of reactive oxygen species (ROS). Complex III is responsible for the release of reactive oxygen species into the intermembrane gap. UQ, ubiquinone; Cyt C, cytochrome c

Apaf-1 and procaspase-9, cyt-c generates "apoptosomes" in the cytoplasm, which stimulate caspase-9, which stimulates caspase-3, leading to protein breakage and apoptotic cell death [101–104]. In point of fact, one of them is hydrogen peroxide (H_2O_2), which is both a direct inducer of apoptosis and a major ROS that ranks among the most significant ROS (Fig. 4) [105]. The ability of antioxidant phytochemicals to reduce the formation of reactive oxygen species (ROS) by scavenging free radicals [51–54, 106–108] and inhibiting pro-apoptotic signals [55–59, 109–112] is what is thought to be responsible for the protective effect that antioxidant phytochemicals have against diseases that are related to oxidative stress.

Fluoride-induced oxidative damage and apoptosis through use of natural and synthesised phytochemicals that neutralise ROS-mediated harm in Body. Different phytochemical likes gallic acid, *Panax ginseng*, blackberry, *Tamarindus indica*, curcumin, silymarin, lycopene, quercetin, *Terminalia arjuna*, thymoquinone, epigallocatechin gallate, and proanthocyanidin. Other ingredients include epigallocatechin gallate, thymoquinone, and proanthocyanidin. Others phytochemicals such as aloe vera [26, 61, 62, 113, 114], *Ocimum sanctum* [62], fisetin [60, 113], genistein, and pomegranate [63, 115] are showing antioxidant property and neutralise the toxicity of fluoride.

Effected the autophagy and apoptosis mechanism

Elevated ROS levels are a result of the cellular process known as autophagy, which involves the destruction of proteins and organelles. Autophagy regulation by ROS has been researched extensively [116–118]. Autophagy has a variety of outcomes, including as pathogen removal, infection prevention, and the death of defective cellular organelles in individual cells. These effects suggest that ROS may have

the ability to function as a signalling target in autophagy-related survival [119–121]. Recently, the focus of study has shifted to determining whether ROS-derived autophagy may be used to treat cancer [122–124]. The modulation of the induction of autophagy in malignant tumours has also been demonstrated to directly correlate with the intracellular ROS levels [125, 126]. The process of autophagy is triggered when H2O2 causes the enzyme known as 4A cysteine peptidase (ATG4) to get oxidised. This step is required for the de-lipidation of the ATG8 protein, which is the end result of autophagy being triggered. The process of autophagy is triggered when H2O2 causes the enzyme known as 4A cysteine peptidase (ATG4) to get oxidised. This step is required for the de-lipidation of the ATG8 protein, which is the end result of autophagy being triggered. This H2O2-induced oxidation then renders ATG4 inactive, which causes a rise in the formation of LC3-associated autophagosomes [125]. However, the AMP-activated pathway also contributes significantly to the control of ROS-related autophagy. AMPK activation suppresses mTORC1, causing autophagy. Oxidative stress stimulates AMPKK to control the AMPK pathway (AMPK kinase). This increases the production of H2O2 and leads to the induction of death in the cells. This AMPK activation suppresses mTORC1, which in turn causes autophagy to occur. Additionally, a variety of transcription factors, such as NF-B, have the ability to change the regulation of genes associated by autophagy such as ATG6/Beclin1, which affects ROS-induced autophagy in cancer cells. [127, 128]. In preliminary studies, SOD overproduction suppressed selenite-induced cytotoxic effects (autophagy) in malignant glioma cells [128]. ATG6/7 (autophagy related genes 6 and 7) were also reported to be knocked down by tiny miRNA, which decreased the cytotoxicity caused by selenite [121, 129, 130]. These results have led to the hypothesis that increased ROS levels, and their regulation causes malignant cells to activate autophagy (Fig. 5). Now for therapeutic approaches, many research targeting inhibitions of mTOR signalling attenuate NaF-induced apoptosis and promote viability of neuronal cells by activation of autophagy. Rapamycin probably alleviates this impairment by decreasing the expression of p62, thereby preventing autophagy defects. The protein kinase known as mammalian target of rapamycin (mTOR) is responsible for regulating cell survival, proliferation, and growth. There is a significant amount of interest in the research and development of medications that target the enzyme mTOR, which is commonly elevated in cancer.

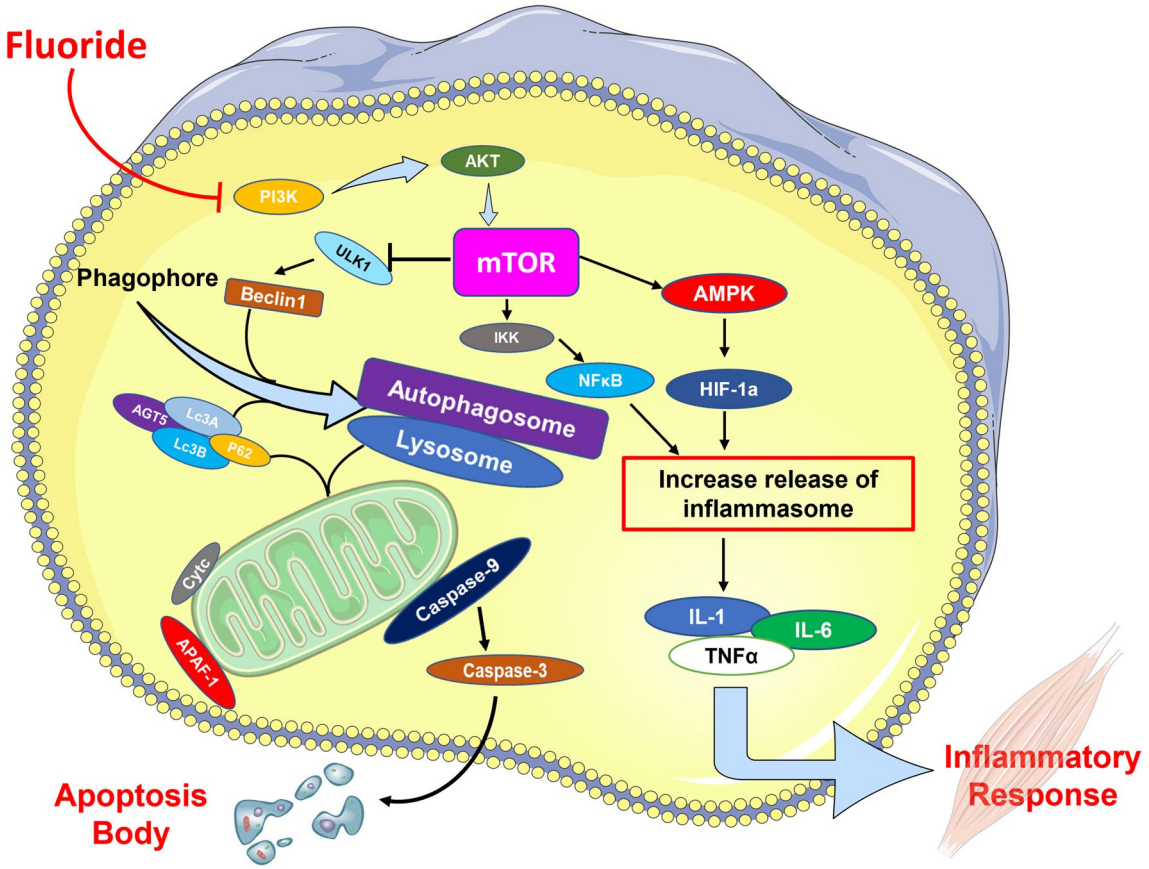

Fig. 5 Autophagy and apoptosis is induced by NaF through the inhibition of PI3K and mTOR activity. This increased the regulation of AKT, which in turn upregulates the LC3 and Beclin1, while decreasing the level of expression for p62.

Fluoride disturbs mitochondrial dynamic cycle: fission and fusion

Mitochondrial dynamics, or building a network through fusion and fission, is related to autophagy, cell signal transcription factors, and iron metabolism. Mitochondrial dynamics is the mechanism by which mitochondria made a network together. Fluorosis can cause mitochondrial dysfunction by disrupting the balance between fission and fusion, leading to abnormal mitochondrial morphology [131]. Fluoride's neurotoxicity is linked to mitochondrial damage [132]. To keep mitochondria functioning properly, it is necessary to have a grasp of the dynamics of mitochondrial fusion and fission [133]. Mitochondrial division requires multiple protein like Drp1, MID49, MID51, Fis-1, Mff, and Dyn2. Mitochondrial members have dynamic protein group known as Mfn1 and Mfn2 which is responsible for mediating the process of mitochondrial outer membrane fusion. One of the proteins of the dynamic's family proteins is responsible for mediating the process by which the inner membranes of mitochondria fuse together. That protein is known as fusion protein OPA1. Under certain physiological settings or when mitochondrial are exposed to detrimental external forces, Drp1 accumulates on the mitochondrial outer membrane, forming a ring that squeezes mitochondria [134]. After then, Dyn2 and Drp1 work together to regulate the last stage of the mitochondrial division process [135]. The fact that a Drp1 deletion can block mitochondrial division and boost mitochondrial networking to generate big mitochondria lends credence to the idea that Drp1 plays a critical role in the process of mitochondrial fission [136]. Overexpression of Drp1 can speed up the process of mitochondrial fission and result in substantial damage to mitochondria. It is abundantly obvious that cells devoid of Dyn2 do not divide because of mitochondrial membranes which are unable to contract in the appropriate manner (Fig. 6) [135]. In rats with persistent fluorosis, the mitochondrion of cortical neurons split and migrated. According to research, the quantities of mRNA and protein produced by Fis1 were decreased by NaF, whereas the levels of Mfn1 and Mfn2 were increased. Increasing drp1 mRNA lowered drp1 protein. An excess of fluoride can cause aberrant mitochondrial division, resulting in a rise in total mitochondria and severe damage to this cytosol. When mitochondria are injured, mPTP opens, which causes the release of cytochrome C from the mitochondria inner membrane into the cytosol [137]. Following this, the intermediate recruiting motif is responsible for activating the Pro-Caspase-9 enzyme. Caspase-9 needs to first cleave and activate the executioner enzyme, Caspase-3, before it can start the apoptotic destruction process [138]. In a dose-dependent way, Cyt C, Caspase-9, and Caspase-3 mRNA expression levels increased as a response to fluoride stimulation. This effect was most pronounced at 100 mg/L. In addition to this, NaF caused a significant shift in the proportion of fusion proteins to fission proteins in the hippocampal of newborn rats, which suggests that fluoride may contribute to an imbalance in the proportion of fission proteins to fusion proteins [139, 140]. When division and fusion equilibrium is disturbed, mitochondria experience some morphological as well as functional alterations. Several studies have been shown that the mitochondrial dynamics fission mechanism inhibition that is generated by NaF in human neuroblastoma cells is mostly responsible for the mitochondrial irregularities, autophagy deficiencies, increased apoptosis, and neuronal damage that are caused by NaF [129]. Contempt the partial retrieval of autophagy, the mechanistically generated mitochondrial abnormalities and cell death caused by NaF are made worse by the pharmacological suppression of mitochondrial fission. This results in an increase in the rate of apoptosis [134]. It has been hypothesised that being exposed to fluoride levels that are typical of the environment can impair memory and learning in addition to causing morphological changes in the mitochondria of the hippocampus. These changes include fission inhibition and accelerated fusion, in addition to deficiencies in autophagy, excessive programmed cell death, and neuronal loss [132]. Children who are subjected to fluoride in drinking water for an extended period of time are at a greater risk of experiencing mental decline. This risk is linked to mitochondrial fission/fusion molecular cycling. In most cases, inhibition of mitochondrial fission leads to abnormalities in the mitochondria membrane, which is lead to improper apoptosis and autophagy which ultimately result in the death of neuron [133]. As a result, targeting the mitochondrial dynamics regulator may provide a possible therapeutic strategy for the treatment of fluoride toxicity. In autoimmune disorders like rheumatoid arthritis, an anti-inflammatory medication called leflunomide can modulate the responses of T cells quite effectively. Its ability to produce pyrimidine pool exhaustion is traditionally credited as being the function that fulfils this role. Leflunomide causes a rise in the quantities of MFN2 and MFN1 transcripts as well as proteins in HeLa and C2C12 muscle cells. This leads to mitochondrial elongation but has no effect on the rate of respiration. Another pharmacological agent, such as mitofusion peptide, SAM-A, epigallocatechin gallate, and liquiritigenin, a flavonoid with cytoprotective effects, was found to be an inducer of mitochondrial fusion in a neuroblastoma cell line. This agent was successful in rescuing mitochondrial fragmentation that was observed in cells lacking Mfn1, Mfn2, and OPA1 (Fig. 6). Importantly, it was demonstrated that liquiritigenin may inhibit mitochondrial fragmentation and cytotoxicity generated by amyloid, so giving a viable therapeutic method for Alzheimer's disease.

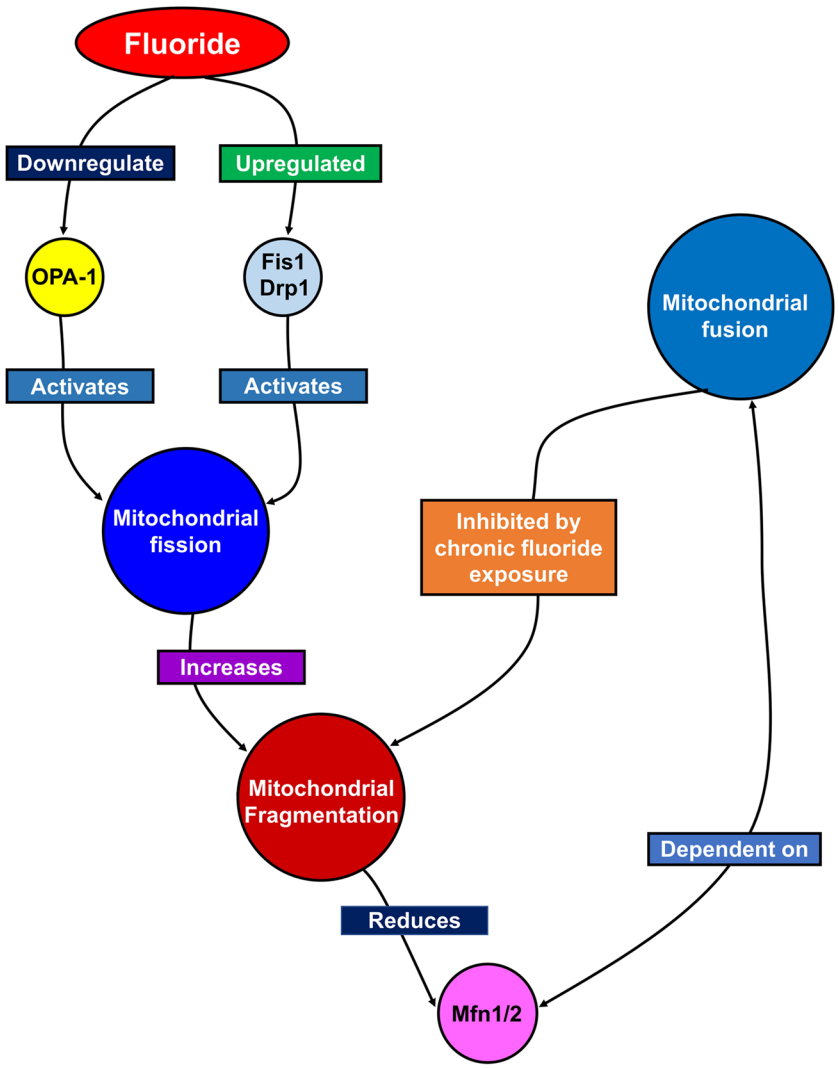

Fig. 6 A representation in schematic developing neuronal damage caused by fluoride exposure. Inhibition of mitochondrial fission contributes to embryonic fluoride neurotoxicity by causing aberrant autophagy and apoptosis associated with mitochondrial abnormalities. These mitochondrial defects are a cause of developmental fluoride neurotoxicity. (1) On the surface of the mitochondria, the expression of Mff, Fis1, and MiD49 are upregulated, and Drp1 protein was recruited from cytoplasm as well as endoplasmic reticulum. The mitochondria are compressed as a result of a significant number of Drp1 molecules forming a circular configuration in the centre of the mitochondria (2). Upregulation of Dyn2 and Drp1 occurs concurrently in order to complete the mitochondrial division process. (3) Excessive mitosis leads to mitochondrial structural damage, which ultimately results in an increased expression of cytochrome c from IMM (inner mitochondrial membrane). Different pharmacological agents like leflunomide stimulate the fusion by increasing the expression of Mfn1, Mfn2, and OPA-1, while some pharmacological agents like SAMBA and liquiritigenin inhibited the fission by suppressing the expression of fis1 and Drp1.

Fluoride binds with calcium and form insoluble fluoride

Fluorine affects bones. Fluorine circulates fast through the bloodstream and accumulates in calcium-rich organs like teeth and bones. Fluoride causes collagen fibres in the tibia to be become loose, heterogeneous, and curved, enlarging the space of bone fossa, decreasing bone flexibility, diminishing tolerance of bone, and increasing fracture risk. Recently, it was shown that the proper calcium intake can treat fluorosis [141]. Numerous academic studies have demonstrated the high affinity between F and Ca. By interacting with F in the colon, supplemental Ca creates the new complex known as insoluble CaF2, which lessens the toxicity and absorption of fluoride [142]. High serum calcium in bone tissue causes hyperosteogeny, hypocalcemia, and increased bone mineral density. In fluorosis, the rate of osteoblast proliferation decreased and apoptosis rose. The mitochondrial route is one of the most crucial apoptosis pathways. The primary energy centres and the primary generator of ATP and ROS are mitochondria. Ca2+ has strong control over

how they behave. Mitochondrial Ca2+ uptake is essential to meet energy needs during fluoride toxicity while maintaining antioxidant capacity to avoid excessive ROS production (Fig. 2) [143]. According to several studies, cells exposed to fluoride had higher fluoride levels and Ca2+ concentrations. This could be the result of fluoride just diffusing into the cell [144]. Fluoride accumulation may promote intracellular Ca2+ release, harming cells. TSCE lowered Ca2+ and fluoride levels in fluoride-exposed cells. Through the mitochondrial Ca2+ unidirectional receptor, mitochondria absorb Ca2+. Unipolar mitochondrial calcium which are the principal mediators of calcium flows into mitochondria, which controls the metabolic process of energy production in the cell. ROS synthesis and programmed cell death are all necessary for fluorosis [143]. According to studies, fluoride may increase endoparasitic reticulum stress, which in turn activates the endoparasitic reticulum pathway generated by calcium, leading to osteoblast apoptosis and mitochondrial malfunction [14]. Ca2+ is primary signalling messenger of the endoplasmic reticulum and is involved in practically all physiological processes. The primary pool of calcium in the osteoblasts is the (ER) endoplasmic reticulum, and endoplasmic reticulum stress can cause an increase in intracellular Ca2+ level. Calpain and Caspase-12 are divided and activated by Ca2+, which also activates Ca2+-dependent enzymes. When Caspase-12 is activated, it interacts with Caspase-9's promoter and Caspase-3's and Caspase-7's effectors to cause apoptosis [145]. Recent research has specifically shown the connection between the endoplasmic reticulum, mitochondria autophagy, and calcium-apoptotic process. During mitochondrial-associated Caspase activation, pro-apoptotic BCL-2 family members (Bax and Bak) successfully convey the increase in intracellular Ca2+ level to mitochondria, functioning unwittingly as a significant upregulating signal of apoptosis mechanism. The production of pro-apoptotic molecules like CtyC was increased by the rise in mitochondrial calcium levels [143]. In addition, multiple Caspase-3 and Caspase-7 were separated in the cytoplasmic and reticulum lumen as a consequence of CtyC and APAF-1 treating pro-Caspase-9 and producing apoptotic bodies. This occurred as a result of the treatment of pro-Caspase-9 by CtyC and APAF-1 [145].

Discussion

The potential molecular mechanisms of steady-state caused fluorosis, such as ROS production, energy metabolism, cell damage, and apoptosis, were the main topics of this review. These pathways are related to. It was found that fluorosis can cause significant damage to the configuration of a cell's mitochondria; disrupt the dynamic equilibrium between fusion and fission; block the transmission of the mitochondrial electron transport chain; let a few free electrons escape from the respiratory chain; alter the potential of a mitochondrial inner membrane; enhance the levels of ATP, ROS, and Ca2+; and initiate a cascade reaction and ultimately result in cell apoptosis. Utilising molecular mechanisms such as energy metabolism pathway, mitochondrial dynamics, generation of reactive oxygen species, cell death, and other pathways, it is feasible to explore the likely molecular mechanism by which fluorosis causes damage to cells. This can be done in a number of ways. It has been discovered that the specific mechanism of the common regulation route of mitophagy following fluorosis cannot be substantiated when considering the cytotoxicity action of fluoride from the standpoint of mitochondrial malfunction. This was discovered after it was found that fluorosis prevented validation of this mechanism. At this moment, it is also unknown what molecular targets will be used in fluorosis diagnosis, therapy, and interventional procedures. The interplay between various trade-off mechanisms in mitochondrial cycle, oxidative stress, mitochondrial biogenesis, death of cells, and mitochondrial homeostasis—all of which are controlled by calcium ion homeostasis—is obscure, and the precise mechanisms require further study. Leflunomide is promote the fusion mechanism while liquiritigenin, BGP-15 are suppressing the fission that result showing protective effect on the mitochondria its dynamic and biogenesis. Rapamycin is a drug which is used as anticancer and suppresses the immune system; they are helpful in treatment of fluoride toxicity by inhibiting the mTOR activity. Some other antioxidant and phytochemical like festin, curcumin, and quercetin helped in neutralising the fluoride toxicity if includes in diet.

Data availability All the data used from publicly available search engines namely PubMed, Scopus, Web of Science. These articles are available online.

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Declarations

Competing interests The authors declare no competing interests.

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