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# Sodium fluoride: suggestive role in wound healing and cell proliferation with respect to regeneration

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## ABSTRACT

Sodium fluoride is a naturally occurring toxicant. The most common sources of sodium fluoride are municipal water, toothpastes etc. The ever increasing exposure to sodium fluoride may affect various physiological processes including regenerative capabilities. The characteristic events of regeneration include wound healing followed by cell proliferation and differentiation to replace the lost structure or tissue. Lower levels of sodium fluoride may be enhancing wound healing and cell proliferation but higher levels are detrimental for both these processes. Sodium fluoride affects wound healing by altering the expression of various proteins like fibroblast growth factors 2 and 7, Twist1 protein, matrix metalloproteinases 2 and 7, bone morphogenetic protein 7, Bcl-2, p53 etc. Sodium fluoride also influences cell division, migration and matrix synthesis by regulating the expression of bone morphogenetic proteins 2 and 3, alkaline phosphatases etc. which are markers of cell proliferation. Excessive fluoride produces oxidative stress in the cells and leads to conditions like apoptosis, cell cycle arrest and even necrosis. Thus, high levels of sodium fluoride hamper the process of cell proliferation and induce apoptosis via caspase and JNK-mediated pathway. The aim of this review is to understand the role sodium fluoride plays during wound healing and cell proliferation and

its correlation with regenerative capabilities in organisms.

**Keywords:** Sodium fluoride (NaF); Wound healing; Apoptosis; Cell proliferation.

## 1. INTRODUCTION

Sodium fluoride (NaF) is a widespread natural compound and fluoride is one of the trace elements required by the humans for maintaining a good dental health. Fluoride was officially considered as a beneficial element initially and was used on large scale to reduce cavities in humans and thus it was considered an important element for maintaining a good dental health [1]. As a result, sodium fluoride was added in municipal water while sodium fluoride, stannous fluoride (SnF<sub>2</sub>) and sodium monofluorophosphate (Na<sub>2</sub>PO<sub>3</sub>F) were added to toothpastes, to prevent tooth decay in United States [2]. The permitted level of fluoride in drinking water is 1 to 1.5 ppm while 2 ppm is considered toxic [3]. The chronic intake of sodium fluoride results in several serious health conditions like hormonal impairment [4], osteosarcoma [5], problems associated with the male reproductive system [6, 7] and even memory loss [8]. Thus, fluoride may be considered to be an environmental contaminant and its major sources are drinking water, food, pesticides and dental products. Due to the easy exposure to

fluoride from various sources, fluoride enters the body of organisms where it may show several desired and undesired effects. This review focuses on the effects of NaF on wound healing and cell proliferation in order to understand if it might influence the process of regeneration.

## 2. SODIUM FLUORIDE AND WOUND HEALING

The effects of sodium fluoride on wound healing have been seen more commonly during dental procedures in humans. Sodium fluoride in the form of mouthwashes, promotes complication free healing of the wound after tooth extraction [9]. Also, fluoride has been known to reduce cavities in teeth of infants and children [4]. The healing effect of sodium fluoride was also evident when after the topical application of sodium fluoride to the experimental calvarial defects in rats, it led to faster healing as compared to saline treated control group of rats [10].

The mechanism of the mucosal healing can be understood as follows: when the mucosal wound in the oral cavity is healing, the keratinocytes first secrete laminin-5 in their extracellular matrix and further more laminin may be deposited. The keratinocytes start migrating and become hyper-proliferative cells which secrete extracellular matrix components and signaling polypeptides leading to healing of the wound [11]. Sodium fluoride may influence this process in various ways like low dose of sodium fluoride enhances healing of rat skin wounds probably by increasing the levels of key molecules like fibroblast growth factor-2 (FGF-2), fibroblast growth factor-7 (FGF-7) and Twist1 protein which are key proliferative markers and enhance epithelial-mesenchymal interactions, necessary for wound healing [12]. Further, the healing of the wound involves healing of various types of tissues like muscles, blood vessels, bones, epithelium etc. Studies have shown that moderate amount of fluoride improves healing of bone by affecting the expression of vascular endothelial growth factor (VEGF) and bone morphogenetic protein-7 (BMP-7) [13]. Fluoride also affects the levels of matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9), enzymes involved in matrix reorganization, in initial stages of

wound healing as seen during alveolar repair [14]. Thus, during regeneration of a tissue or an organ, the first important event to occur is healing of the wound at the site of injury or site of amputation and sodium fluoride influences this process, thereby enhancing or impeding the process of regeneration in the initial stages. However, once the wound has healed, the pluripotent cells at the site of action start proliferating to replace the lost tissue/organ.

## 3. SODIUM FLUORIDE AND CELL PROLIFERATION

While sodium fluoride is known to enhance proliferation of cells at lower doses, it hampers cell division at higher doses. If sodium fluoride is used in moderate amounts, it stimulates proliferation as has been seen in periodontal ligament cells (PDLs) [15]. Similarly, sodium fluoride also stimulates osteogenesis and chondrogenesis during fracture healing in rabbits [16]. In addition to cell proliferation, the exposure to lower concentrations of fluoride induces migration of cells and matrix synthesis in epithelial cells *in vitro* [11]. To specify, sodium fluoride induces cell proliferation at an optimum concentration of  $5 \times 10^3 \mu\text{mol/l}$  and also increases the expression of BMP-2, BMP-3 and alkaline phosphatases, which are markers of cell proliferation. However, at  $2 \times 10^4 \mu\text{mol/l}$ , sodium fluoride seems to inhibit cell proliferation [17]. It has also been observed that 1 mM sodium fluoride does not hamper cell proliferation, however it influences the expression of several genes in human embryonic stem cells (hESCs) during embryoid body (EB) differentiation i.e. ectoderm marker *NeuroD1* and the mesoderm marker *Brachyury* get upregulated while endoderm marker *AFPI* is down regulated [18]. In human embryonic stem cells (hESCs), the higher dose of sodium fluoride hampers cell proliferation and induces apoptosis via caspase and c-Jun N-terminal kinase (JNK)-mediated, but reactive oxygen species (ROS)-independent pathway [18]. This further suggests that if there is chronic exposure of sodium fluoride, it may interfere with early embryogenesis. These studies demonstrate that at higher doses sodium fluoride may hamper cell division, which is the one of the noteworthy events that contributes to the regeneration of the lost structure.

Humans also possess the ability to regenerate certain tissues, however to a limited capability. Our body gets fluoride from municipal water, toothpastes etc. In such a scenario, there are more chances of fluoride accumulation in various tissues of our body and this fluoride may interfere with the healing capabilities in our body and the scant ability to regenerate the tissues. More than the required levels of fluoride can cause a condition called as fluorosis in humans which is a degenerative disorder affecting bones, teeth and some soft tissues [19, 20]. In case of severe skeletal fluorosis, conditions like extra-osteal calcification and ossification have been seen [21]. Further, fluoride has also been linked to cancer as it is taken up by immature bones and teeth, and is stored in soft tissues like bowels, kidneys, liver, muscles, skin etc. [4]. Thus, from the cited observations it appears that lower sodium fluoride levels probably induce cell proliferation while higher levels deter cell division or induce apoptosis.

#### 4. MECHANISM OF SODIUM FLUORIDE TOXICITY

The exact molecular mechanism by which fluoride shows its toxic effects is precisely not known but apoptosis is one of the manifestations. Fluoride interferes with cell division, stress responses, numerous enzymes, various metabolic pathways etc. Some of the major influences of sodium fluoride have been summarized in Table 1.

Excessive fluoride produces oxidative stress in the cells and leads to conditions like apoptosis, arrest of cell cycle and necrosis [32, 37]. Essentially, at low concentrations fluoride produces oxidative stress while at high concentrations it causes cell death by apoptosis [38]. The oxidative stress can be estimated by the increased lipid peroxidation and lowered levels of antioxidant enzymes like glutathione peroxidase, catalase and superoxide dismutase (SOD). Further, it has been observed that fluoride interferes with the porcine oocyte maturation by inhibiting meiotic resumption, interferes with spindle formation, improper chromosome separation which may lead to aneuploidy and thus ultimately affect female fertility [39]. NaF also affects the splenic development as it reduces the T and B cell population due to cell cycle arrest [40, 41].

**Table 1.** Effects of sodium fluoride on cells at the molecular level.

S. No.	Effects of fluoride
1	Sodium fluoride induces cell proliferation via BMP pathway during skeletal fluorosis [17]
2	High fluoride levels cause hindrance in cell proliferation and growth [22]
3	Fluoride induces G0/G1 arrest, apoptosis and DNA damage in mouse Leydig cells [23]
4	Sodium fluoride induces reorganization of F-actin i.e. podosome formation, in endothelial cells by inducing activation of RhoA, Rac1 and Cdc42 which degrade the extracellular matrix by stimulating local proteolysis [24]
5	Low levels of sodium fluoride induce production of matrix by increasing fibronectin and laminin-5 expression (associated with motility) [11]
6	Fluoride causes reduced cell viability; low protein and DNA synthesis [25-27]
7	Fluoride induces oxidative stress; elevated lipid peroxidation and decreased antioxidant enzymes' activity in human cells [28-30]
8	Fluoride affects the factors associated with stress, signal transduction and apoptosis. High dosage of NaF inhibits proliferation of Leydig cells and causes stress-induced apoptosis which is associated with changes in expression levels of apoptosis related proteins like caspase-3, caspase-9, B cell lymphoma 2 (Bcl-2) and Bax [31, 32]
9	Higher concentrations of fluoride causes exchange aberrations <i>viz</i> due to misrejoining of free ends of different double strand breaks in chromosomes [33, 34]
10	Fluoride causes chromosomal aberrations in human lymphocytes <i>in vitro</i> and bone marrow cells in Swiss albino mice [35, 36]

Apart from inducing oxidative stress, fluoride interferes with expression of genes involved in cell cycle, metabolism, stress response, cellular interactions etc. [42]. Fluoride harms the cell by breaking the mitochondrial outer membrane and thereby releasing cytochrome c which activates caspase-9 and caspase-3 pathways in the cytoplasm leading to apoptosis. Fluoride also decreases the expression of Bcl-2 family proteins which are regulators of apoptosis, and upregulates the expression of p53 proteins which are regulator of cell cycle [43]. Thus,

sodium fluoride influences the proliferation of cells by affecting the cell cycle, metabolism, antioxidant enzymes etc.

## 5. SODIUM FLUORIDE AND REGENERATION

The regeneration of an organ or a part of body, after it is lost, is a remarkable property possessed by only few groups of animals like amphibians, reptiles, fishes, planarians etc. Higher animals, including humans, however, retain the scant capability to regenerate tissues. The regeneration of an organ is accomplished through three well defined stages *viz.* wound healing (the wound heals following inflammation), blastema stage (stem cells are procured and cell proliferation continues) and differentiation stage (the cells get differentiated to replace the lost structure) [44]. The first two stages *viz.* wound healing and cell proliferation, are the hallmarks of regeneration and involve interplay of specific molecules at precise time intervals which procure and push the stem cells to the molecular pathways which ultimately lead to the regeneration of the lost appendage. Some groups of animals possess the ability to regenerate certain tissues as well. The process of regeneration is dependent on several internal and external factors. Sodium fluoride is a common and naturally occurring substance that influences the regeneration of tissues and/or organs. Suresh and Hiradhar [45] have shown that sodium fluoride at a concentration of 50 µg/ml enhances the healing of wound and regeneration of tail in *Hemidactylus flaviviridis* and as the concentrations are increased, sodium fluoride hampers tail regeneration while concentrations of 3000 and 5000 µg/ml are fatal. Fluoride has been shown to have a negative effect on the development of the nervous system during its regeneration, due to inhibition in development of neural ladder, as seen in planarians [46]. Further, it has been seen that low doses of fluoride don't alter the process of fin regeneration but affect the linear pattern of growth of fins in *Poecilia latipinna* [47]. During newt limb regeneration, the presence of sodium fluoride stimulates incorporation of <sup>14</sup>C-leucine by blastema *in vitro* and plays a positive role in limb regeneration. However, if the regenerating limbs are denervated, presence of sodium fluoride does not

stimulate uptake of leucine by such blastemas [48]. Further, sodium fluoride exerts its effects only during later stages of newt limb regeneration [49]. This indicates that the influence of sodium fluoride on newt limb regeneration might be dependent on neural input.

Sodium fluoride also influences tissue regeneration. In humans, sodium fluoride when added into the medication for periodontitis treatment accelerates the periodontal regeneration [50]. Similarly, the regeneration of holes in pinnae in rabbits is upregulated by sodium fluoride as it promotes cell proliferation [51]. Moreover, the pinnae regeneration in rabbits is similar to amphibian regeneration [51]. The events and the gene expression are similar during organ regeneration and embryonic development [52]. It has been observed that during embryonic development of Chinese toad *Bufo gargarizans*, excessive fluoride causes organ malformations, and interferes with embryonic development [53]. Thus, excess of fluoride is detrimental to the process of development as well as regeneration. To summarize, sodium fluoride might be exerting its influence on the tissue and/or organ regeneration by affecting two crucial stages of regeneration *i.e.* wound healing and cell proliferation.

## 6. CONCLUSION

Fluoride or more specifically sodium fluoride, a naturally occurring toxicant in water and various products containing fluoride, when used by humans may lead to accumulation of fluoride in the bodies of humans as well as other organisms, more specifically in aquatic animals. Lower doses of fluoride are perceived to enhance wound healing and cell proliferation, the two hallmark events of regeneration. However, the higher doses have been seen to interfere with both these events. Sodium fluoride affects cell proliferation by directly affecting the cell division or by altering the expression of various cell proliferation markers like BMP-2, BMP-3 etc. Fluoride also influences wound healing by regulating the expression of molecules like FGF-2, FGF-9, BMP-7, Twist1, VEGF, MMP-2, MMP-9 etc. To conclude, sodium fluoride hampers wound healing as well as cell proliferation when present at higher levels in the body of

organisms, thereby impeding the process of regeneration.

## TRANSPARENCY DECLARATION

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