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Light and Electron Microscopic Study of Fluoride Induced Gastric Mucosal Damage in Rats

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A B S T R A C T

The present study was carried out to determine the adverse effects of fluoride on the rat gastric mucosa. Twelve albino rats were used. The experimental group was treated with 600 mg/kg b.w./day of sodium fluoride for 40 days via oral gavage. The control group had distilled water for the same period. The rat stomachs were prepared for light microscopic, scanning and transmission electron microscopy. The pathological and ultrastructural changes include loss of surface epithelium, microvilli and structural integrity, along with extensive cell degeneration and mucosal erosion indicating that sodium fluoride has a severe detrimental impact on the gastric tissue, compromising both its protective and functional capabilities.

Introduction

Fluorosis, a condition prevalent in various regions around the world, results from prolonged excessive fluoride intake and poses significant health risks to both humans and animals (Zuo *et al.,* 2018). While fluoride is widely recognized for its effects on bones and teeth, it can also harm other tissues and organs, leading to a range of symptoms and pathological conditions. Chronic exposure to high fluoride levels can lead to serious health issues.

Acute and chronic studies in animals and humans have shown that fluoride causes gastrointestinal damage (Susheela *et al.,* 1992; Shashi, 2002; Rao *et al.,* 2017). Sodium fluoride has been linked to gastrointestinal damage, which can be observed through alterations in biochemical markers, molecular processes, and histopathological changes. The gastrointestinal tract is the main organ that is affected by fluoride-induced toxicity. The first indications of fluorine poisoning are gastrointestinal signs and symptoms, such as vomiting, nausea, diarrhoea, and abdominal discomfort (Susheela *et al.,* 1993; Das *et al.,* 1994; Sharma *et al.,* 2009).

The stomach serves as a primary site of contact for ingested fluoride, making it susceptible to fluoride-induced damage. High fluoride levels can disrupt gastric mucosal integrity and functionality, leading to pathological changes. Several studies have highlighted the potential for fluoride to induce gastric lesions and alter mucosal morphology, which can result in impaired digestive processes and overall gastrointestinal health (Sharma *et al.,* 2020; Gupta *et al.,* 2021).

Scanning and transmission electron microscopy have provided detailed insights into these changes, revealing

disruptions at the cellular level, including loss of microvilli, cellular necrosis, and alterations in gastric folds and pits (Suresh *et al.,* 2013; Singh *et al.,* 2017).

The aim of the present study is to describe the anatomical and histological structures of the stomach of rat, using light and electron microscopy. This study would help to get information regarding the precise cellular structure of various cells lining the stomach of rat.

Materials and Methods

Twelve Wistar albino rats weighing between 150-200 g were randomly assigned to two groups of six rats each. Experimental group received a freshly prepared solution of 600 mg fluoride as sodium fluoride. Control group had distilled water. The animals had free access to food and water. At the end of 40 days of experiment, each animal was anesthetized. The rat abdomens were quickly opened, the stomachs excised, opened along the greater curvature and processed for light, SEM and TEM analysis.

Sample preparation

In light microscopy, the specimens were fixed in alcoholic Bouin's fluid for 24 hours, embedded in paraffin wax and 7µm sections were taken. Haematoxylin and eosin stain was used for cellular details.

For SEM, specimens were dehydrated with graded acetone immersions. They were then critical-point dried using liquid carbon dioxide and mounted on aluminum stubs. Finally, they were thinly coated with gold and examined in scanning electron microscope (JEOL JSM-6510).

For TEM, cross-sectioned stomach specimens were divided into small pieces and fixed in 2.5% phosphate buffered glutaraldehyde (0.1M), post-fixed with 1% phosphate buffered osmium tetraoxide and then dehydrated. After immersion in propylene oxide, the specimens were embedded in epoxy resin mixture.

Semithin sections were stained with toluidine blue and examined by light microscope. Ultrathin sections were stained with uranyl acetate and lead citrate, to be examined by transmission electron microscope (Tecnai 2, Fei Company, The Netherlands) at All India Institute of Medical Sciences, New Delhi, India.

Results and Discussion

Light microscopy

The control specimens showed the fullness of surface mucous cells and their rounded profiles. Most of the mucous epithelial cells were columnar in shape. The gastric pits were lined with surface mucous epithelial cells. The gastric glands and gastric pits were structurally intact. (Fig.1, 2).

The gastric mucosa section of fluoridated rats revealed thickened epithelium with inflammation of gastric layer. (Fig.3). Parietal cell hyperplasia was observed in the gastric mucosa. Additionally, the sub epithelial collagen plate—a layer of connective tissue just beneath the epithelial layer of the stomach was found to be thickened. (Fig.4). The mucosal layers, crucial for protecting the stomach lining and aiding digestion, were significantly disrupted. Erosion areas were observed in gastric mucosa along with necrosis of gastric glands. (Fig.5). The gastric glands appeared disrupted and reduced in number. There was distinctive cellular infiltrate, indicating an inflammatory response within the gastric lining. (Fig.6). There was widening of the concavities between the mucosal folds which suggests a loss of structural integrity within the stomach lining, possibly due to the weakening of the connective tissue or a breakdown in the normal cellular architecture. (Fig.7).

Electron microscopic results

Scanning electron microscopy

SEM analysis of the stomach from control rats revealed well-organized, regular longitudinal mucosal folds, essential for the stomach's flexibility and function. (Fig.8). The luminal surface of the fundic region -the upper part of the stomach appeared smooth and intact. (Fig.9).

In fluorotic rats, the gastric tissue exhibited severe structural damage. The mucosal surface was exfoliated. The gastric pits, essential for secreting digestive enzymes were clearly discernible due to the extensive tissue damage induced by sodium fluoride. (Fig.10). The loss of microvilli suggested a decrease in the stomach's ability to absorb nutrients. The mucosal surface displayed signs of erosion, indicating extensive damage and degradation. (Fig.11).

Deep concavities were evident between the mucosal folds. These concavities, along with irregular gastric folds, disrupted the usual smooth and organized appearance of the stomach. The presence of numerous gastric pits, forming a honeycomb-like structure, highlighted the extent of the damage. (Fig.12, 13).

The stomach tissue of fluoridated rats exhibited significant alterations, most notably the loss of the surface epithelium. Microvilli, essential for nutrient absorption, were also absent. The appearance of discrete furrows and fissures in the tissue indicated breakdown in structural integrity of the stomach lining. (Fig.14).

Extensive cell degeneration, presence of fissures, and a complete absence of microvilli indicated severe damage and compromised structural integrity of the stomach lining due to fluoride exposure. (Fig.15).

Transmission electron microscopy

Examination of ultrathin sections from control animals showed presence of mucous neck cells which secrete mucous to protect the stomach lining, while the glandular lumen exposed to the luminal surface serves as a central space for secretions. Supranuclear granules and flat euchromatin-rich nuclei were present. A tubulovesicular network was observed in the cytoplasm of the supranuclear region, likely facilitating intracellular transport and communication. (Fig.16). A large, oval spherical nucleus was seen, which was located basally. The well-developed secretory vesicles, responsible for transporting and releasing substances from the cell and lysosomes were arranged around the nucleus. (Fig.17).

In the stomach of the fluorotic rats, irregularities in cell shape and structure were present. Cells present at the gastric pits had destroyed apical regions and were exfoliated. (Fig.18). There was an increase in the number of damaged cells. The degenerating cells at the rugae's basal section featured a variety of empty gaps.

The cells exhibited various forms of damage, including interdigitations, dumped mitochondria and destroyed apical regions. (Fig.19). The rugae were severely damaged, showing widespread cell degeneration and the absence of microvilli. Many secretory granules, forming clusters of varied sizes, were present in the supranuclear cytoplasm. (Fig.20). Cells with polymorphic medium-sized granules, tonofilaments and mitochondria were visible. (Fig.21).

Degenerating cells characterized by flattened nuclei and cytoplasm filled with mucous mass were visible. An apical area injury was identified. An irregular nucleus was also seen. (Fig.22, 23).

The stomach is particularly vulnerable to fluoride toxicity due to its acidic environment and prolonged exposure to ingested fluoride. Histopathological examinations have highlighted the adverse histopathological effects of sodium fluoride on the gastric tissues of rats.

One of the most consistent findings is damage to the gastric epithelium. Studies have observed erosion and ulceration of the epithelial lining, which is indicative of an inflammatory response. The fluoridated rats exhibited significant epithelial erosion and ulcer formation in the stomach, suggesting that fluoride can disrupt the mucosal barrier (Ahmed *et al.,* 2022). Fluoride exposure can lead to alterations in gastric glands. Changes such as atrophy or hyperplasia of gastric glands have been reported, which may affect gastric acid secretion and overall digestive function.

Prolonged exposure to sodium fluoride resulted in significant glandular atrophy and altered glandular morphology, indicating a disturbance in normal gastric function (Sharma *et al.,* 2023). Chronic exposure results in the formation of gastric ulcers, erosions and damage to gastric epithelium. Rats exposed to high fluoride concentrations developed severe gastric ulcers, characterized by loss of epithelial integrity and increased necrotic areas (Yang *et al.,* 2022). This damage compromises the mucosal barrier, making the stomach lining more susceptible to further injury and inflammation. Kumar *et al.,* (2023) observed that fluoride-induced changes in the gastric glands led to abnormal secretion patterns and reduced protective mucus production, contributing to increased susceptibility to gastric injury. Prolonged fluoride exposure can lead to fibrosis in the submucosal layer of the stomach. fluoride exposure resulted in significant submucosal fibrosis and altered collagen deposition, leading to reduced gastric wall flexibility and function (Zhang *et al.,* 2022). This fibrosis alters the structural integrity of the stomach and can impact its functional capacity (Siddiqui *et al.,* 2020).

Studies utilizing SEM have revealed significant alterations in the stomachs of rats exposed to fluoride, providing insights into the structural damage induced by fluoride.

Figure.1-4

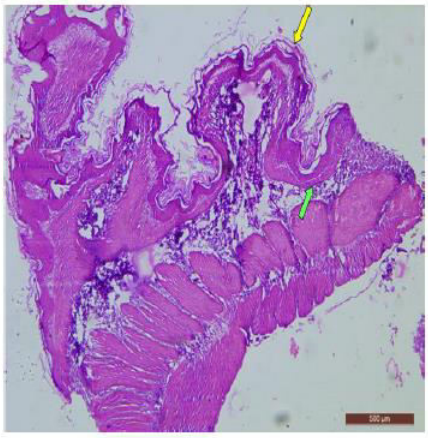

Fig. 1: T.S. of stomach of control rat showing normal structure of stratified squamous epithelium (⇧) with underlying submucosa (⇧). H&E× 40

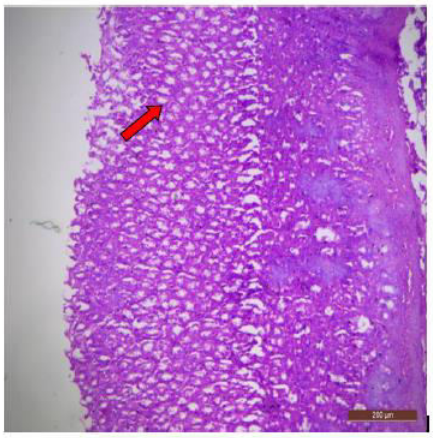

Fig. 2: T.S. of stomach of control rat showing gastric glands (⇧). H&E×100

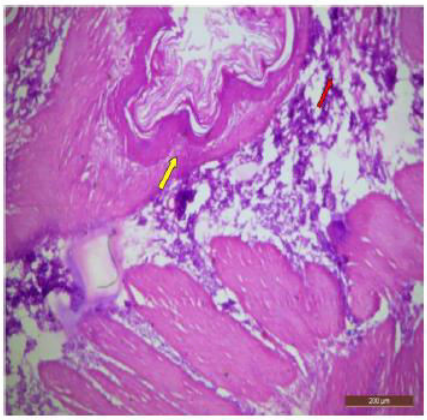

Fig. 3: T.S. of stomach of rat treated with 600 mg NaF/kg bw/day for 40 days showing thickened epithelium (⇧) and inflammatory debris (⇧) in the submucosal region. H&E × 100

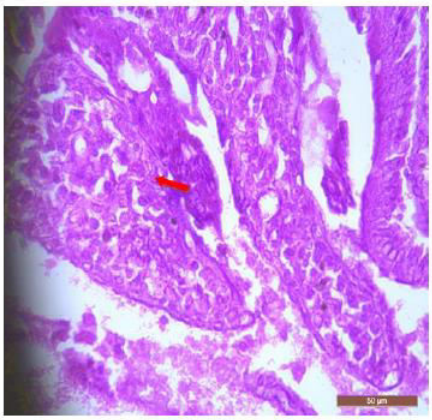

Fig. 4: T.S. of stomach of rat treated with 600 mg NaF/kg bw/day for 40 days showing thickened subepithelial collagen plate (⇧). H&E×400

Figure.5-7

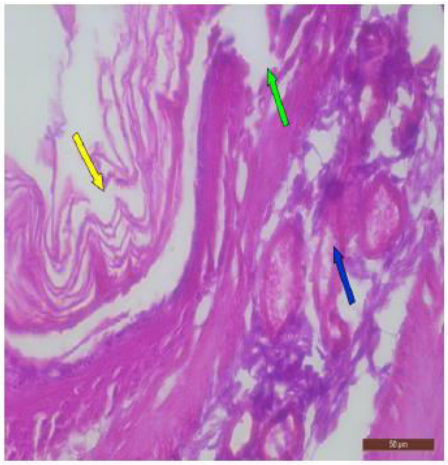

Fig. 5: T.S. of stomach of rat treated with 600 mg NaF/kg bw/day for 40 days showing disrupted mucosal layers (⇧) and gastric folds (⇧) alongwith necrosis of gastric glands (⇧). H&E×400

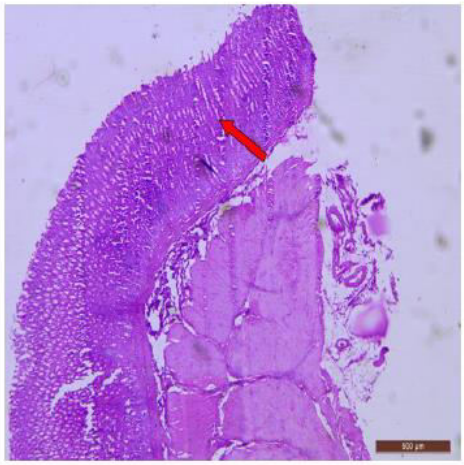

Fig. 6: T.S. of stomach of rat treated with 600 mg NaF/kg bw/day for 40 days showing disrupted and reduced gastric glands (⇧). H&E×400

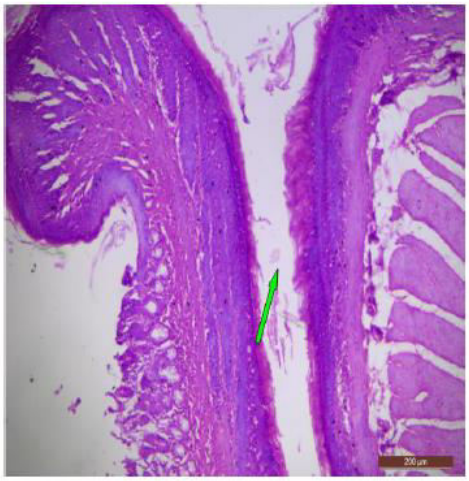

Fig. 7: T.S. of stomach of rat treated with 600 mg NaF/kg bw/day for 40 days showing widened concavities (⇧) between two mucosal folds. H&E×100

Figure.8-11

SCANNING ELECTRON MICROSCOPY:

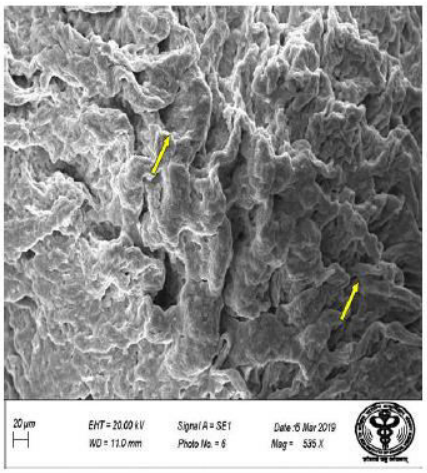

Fig. 8: Scanning electron micrograph of stomach of control rat showing regular longitudinal mucosal folds (⇧). X 535.

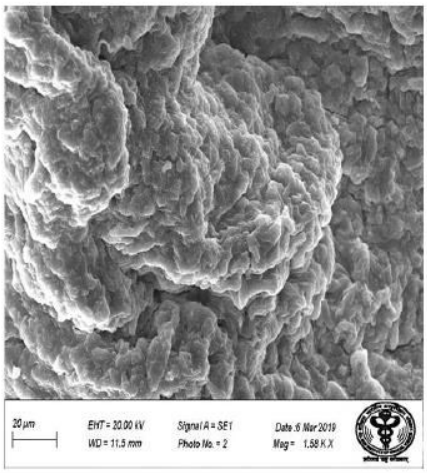

Fig. 9: Scanning electron micrograph of stomach of control rat showing luminal surface of fundic region. X 1580

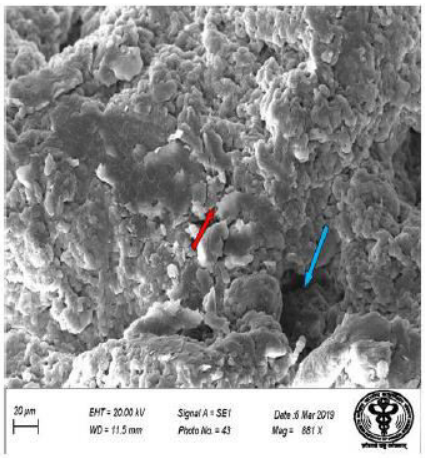

Fig. 10: Scanning electron micrograph of stomach treated with 600 mg sodium fluoride for 40 days showing exfoliated mucosal surface (⇧) and gastric pits (⇧). X 881

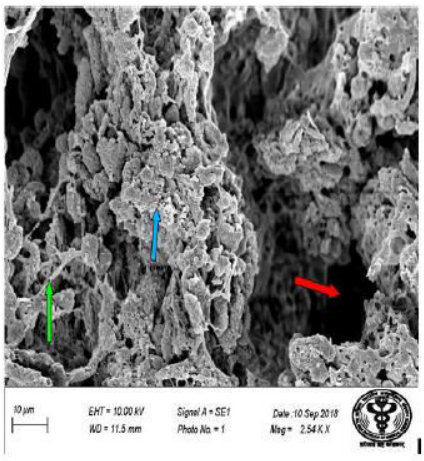

Fig. 11: Scanning electron micrograph of stomach treated with 600 mg sodium fluoride for 40 days showing gastric pits (⇧), loss of microvilli and mucosal erosions (⇧) with numerous exfoliated mucosal strands (⇧). X 2540

Figure.12-15

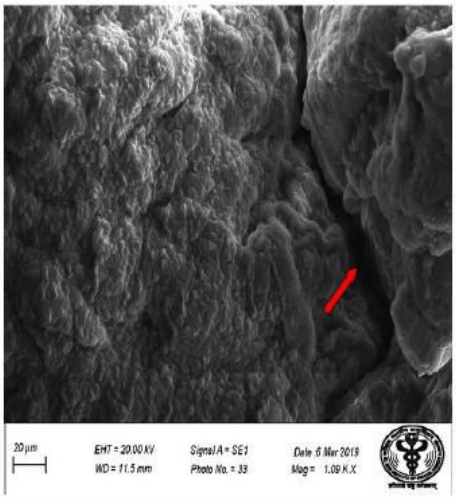

Fig. 12: Scanning electron micrograph of stomach treated with 600 mg sodium fluoride for 40 days showing deep concavities (⇑) in between the mucosal folds on the surface. X 1090

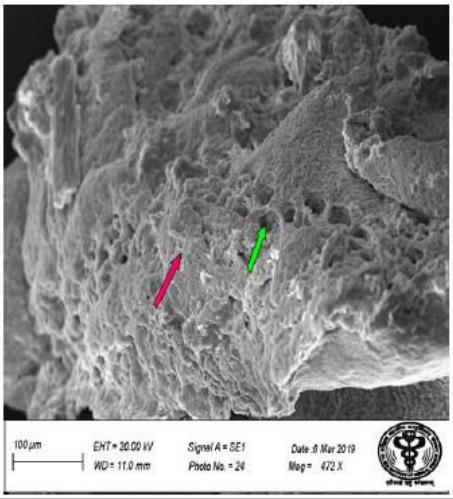

Fig. 13: Scanning electron micrograph of stomach treated with 600 mg sodium fluoride for 40 days showing irregular gastric folds (⇑) and numerous gastric pits (⇑) forming honey comb shaped like structure. X 472

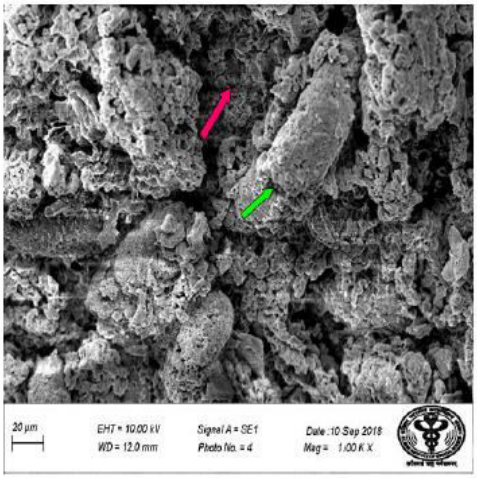

Fig. 14: Scanning electron micrograph of stomach treated with 600 mg sodium fluoride for 40 days showing loss of surface epithelium (⇑) and microvilli and discrete furrows (⇑). X 1000

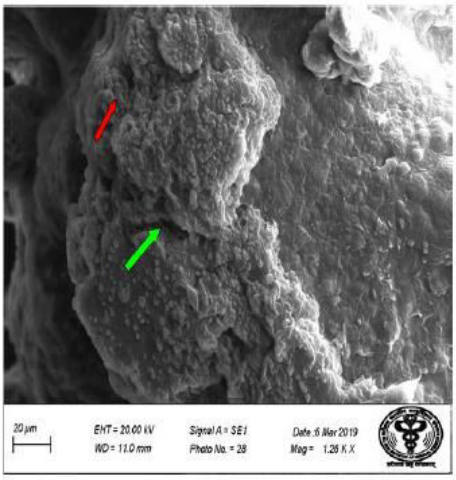

Fig. 15: Scanning electron micrograph of stomach treated with 600 mg sodium fluoride for 40 days showing cell degeneration (⇑), fissures (⇑) and absence of microvilli. X 1260

Figure.16-19

TRANSMISSION ELECTRON MICROSCOPY:

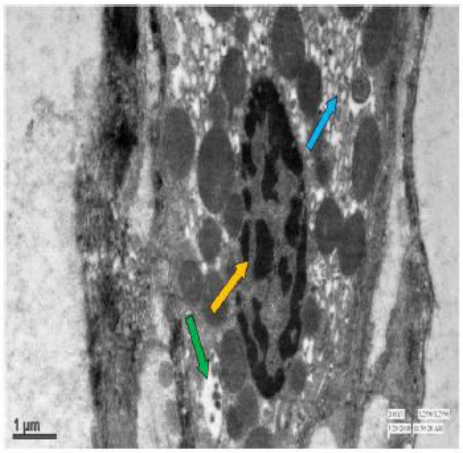

Fig. 16: Transmission electron micrograph of stomach of control rat showing mucous neck cells (⇑) and lumen of the gland (⇑). The supranuclear portion of cytoplasm contained a tubulovesicular network (⇑). X 2550

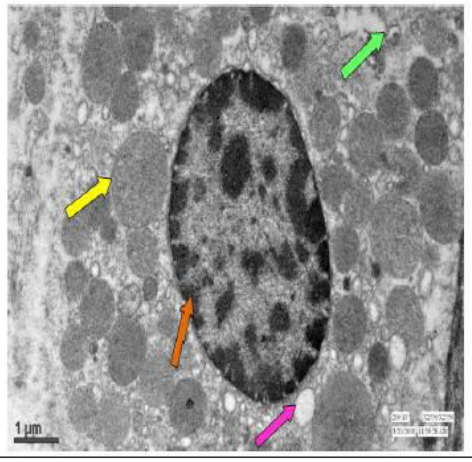

Fig. 17: Transmission electron micrograph of stomach of control rat showing nucleus (⇑), mitochondria (⇑), lysosomes (⇑) and secretory vesicles (⇑). X 2550

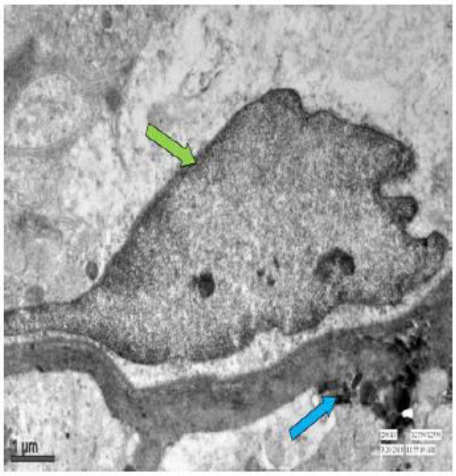

Fig. 18: Transmission electron micrograph of stomach of rat treated with 600 mg/kg b.w./day of NaF for 40 days showing irregular nucleus(⇑) filled with cytoplasm and damaged apical part of rugae (⇑). X 2550

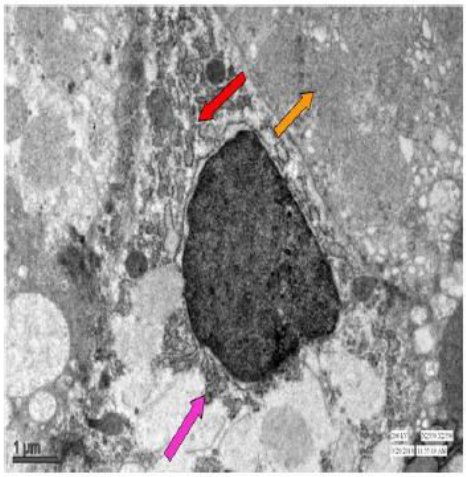

Fig. 19: Transmission electron micrograph of stomach of rat treated with 600 mg/kg b.w./day of NaF for 40 days showing interdigitations (⇑), destroyed apical regions (⇑) and clumping of mitochondria (⇑). X 2550

Figure.20-23

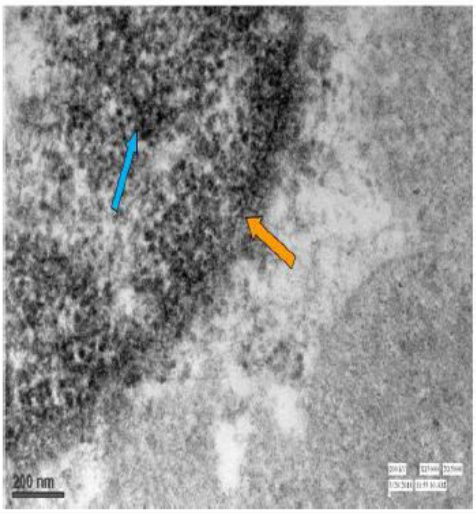

Fig. 20: Transmission electron micrograph of stomach of rat treated with 600 mg NaF/kg b.w./day for 40 days showing damaged rugae (⇧) and clusters of secretory granules (⇧). X 15000

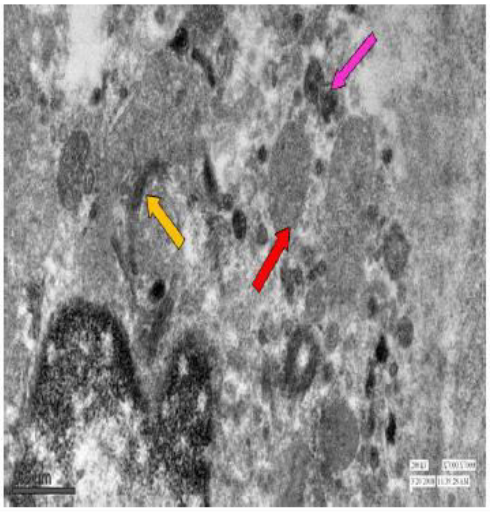

Fig. 21: Transmission electron micrograph of stomach of rat treated with 600 mg NaF/kg b.w./day of for 40 days showing few mitochondria (⇧), polymorphic granules (⇧) and bundles of tonofilaments (⇧). X 7000

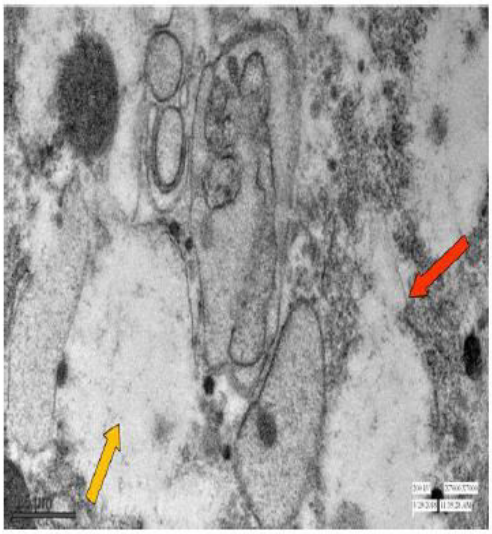

Fig. 22: Transmission electron micrograph of stomach of rat treated with 600 mg/kg b.w./day of NaF for 40 days showing degenerating cells with flattened nuclei and cytoplasm filled by mucous mass (⇧). Destroyed apical regions (⇧) were also visible. X 7000

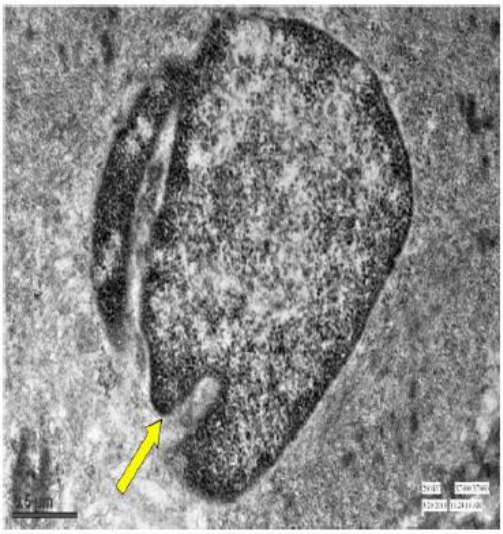

Fig. 23: Transmission electron micrograph of stomach of rat treated with 600 mg/kg b.w./day of NaF for 40 days showing destroyed and irregular shaped nucleus (⇧). X 7000

One of the most notable SEM findings in fluoride-exposed stomach of rat is the disruption of the epithelial surface. Normal gastric epithelium is characterized by smooth, well-organized surface cells with microvilli that enhance absorption.

However, fluoride exposure leads to considerable damage to these structures. In fluoride-treated rats exhibited a loss of microvilli and severe desquamation of epithelial cells, indicating significant structural compromise (Ali *et al.,* 2022). It often revealed the presence of surface lesions such as ulcers and erosions in the gastric mucosa of fluoride-exposed rats.

These lesions are characterized by irregular, eroded surfaces and the presence of cellular debris. The rats exposed to high levels of fluoride developed pronounced surface lesions with uneven and necrotic areas, suggesting a direct impact on mucosal integrity (Kumari *et al.,* 2021).

The structure of gastric glands can also be altered by fluoride exposure. SEM analyses show abnormal glandular architecture, including changes in the shape and arrangement of glandular cells. Singh *et al.,* (2020) reported that fluoride-induced changes in the gastric glands included irregular gland openings and altered gland cell morphology, which could affect gastric secretory functions.

Extensive cellular necrosis in gastric mucosa, loss of microvilli, damaged epithelial and cellular structures of fluoride-exposed rats, contribute to the observed epithelial damage (Hassan *et al.,* 2023).

TEM studies revealed that the endoplasmic reticulum plays a crucial role in protein synthesis and processing. Fluoride exposure leads to alterations in endoplasmic reticulum structure, including dilation and fragmentation.

These changes are indicative of disrupted protein synthesis and cellular stress responses. The present study showed that rats exposed to sodium fluoride showed marked endoplasmic reticulum dilation which may contribute to cellular dysfunction (Patel *et al.,* 2020).

The mitochondria are particularly sensitive to fluoride-induced damage. TEM images show mitochondrial swelling, disrupted cristae, and reduced electron density. This mitochondrial damage can impair cellular energy production and contribute to cell death. Kumar *et al.,* (2021) reported that fluoride exposure caused pronounced mitochondrial swelling and disorganization in the gastric epithelial cells of rats, highlighting the impact on cellular energy metabolism.

Disruptions in tight junctions and desmosomes, leads to compromised barrier function and increased intercellular gaps, which could contribute to mucosal damage and increased susceptibility to pathogens (Wang *et al.,* 2022). Exfoliation of the damaged cells occurred in the gastric pits, and the continuity of the apical cell membrane was lost.

The degraded nucleus has an abnormal shape. It has been shown in this context that high fluoride concentrations in very acidic media may cause gastric lesions, most likely by encouraging acid back-diffusion to the mucosa. The observed delayed gastric emptying caused by fluoride treatment might be the result of the stomach's natural defense mechanism against irritating substances.

The ultrastructural and functional abnormalities observed in the gastrointestinal tissue during this investigation were evident signs of cellular injury and were a direct consequence of acute fluoride exposure.

In conclusion, the current work presents a multi-approach histological assessment of 40 days fluoride toxicity study in stomach of rat through histological supported with both scanning and transmission electron microscopy. Results from the present study could show that fluoride intoxication has profoundly altered the histological structure of gastric mucosa at many levels and revealed several alarming signs as the proliferative and hemorrhagic lesions in addition to several ultrastructural alterations such as absence of microvilli and degeneration of epithelial cells.

Ethical aspects

The experimental protocols were performed under the approval of Institutional Animal Ethical Committee of Punjabi University, Patiala (Animal maintenance and Registration No. 107/GO/ReBi/S/99/CPCSEA/2017-41).

Acknowledgement

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Author Contributions

A. Shashi: Investigation, formal analysis, writing—original draft. Sukhmanjeet Kaur: Validation, methodology, writing—reviewing.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical Approval Not applicable.

Consent to Participate Not applicable.

Consent to Publish Not applicable.

Conflict of Interest The authors declare no competing interests.

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