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ATTENUATION OF SODIUM FLUORIDE INDUCED NEPHROTOXICITY BY FRESH ORANGE JUICE IN MICE

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ABSTRACT

Fluoride is natural contaminant of underground water and targets the living organisms through drinking water. Fruits are well known for being rich in antioxidants to combat toxins. This study was aimed to explore the ameliorative strength of freshly squeezed orange juice against the reno-toxicity induced by sodium fluoride in mice. For this purpose, 4 weeks old male albino mice were divided randomly into five groups of 5 mice each. Group C was intact, untreated control given 0.00µg/g BW of sodium fluoride, while DI and DII were the groups of animals treated with 0.1 ml of 5.0 and 7.5µg/g BW of sodium fluoride administered for 30 days respectively. Groups D III and D IV were treated with 0.1 ml of 5.0 and 7.5µg/g BW of sodium fluoride administered orally for first 30 days and then 0.1 ml of freshly squeezed orange juice (50% in distilled water) for next 30 days respectively. Whole study was conducted under controlled environmental conditions of temperature 25±1°C and humidity 40-50%. At the end of experiment, mice of each group were weighed, anaesthetized and processed for recovery of kidneys with subsequent fixation using Bouin's fixative. Morphometric analysis showed an overall significant ($p<0.05$) reduction in body weight of mice of group DI(23.2g) and DII(20.8g) as compared to group C(29g). While bodyweight of group DIII(27.40g) and DIV (26.80g)treated with orange juice as antidote was in close adherence to those of group C. Almost similar trend was observed for kidney length and diameter. Kidney length of group DI (9.088mm), DII (8.528mm) and DIV (8.826mm) was reduced significantly as compared to group C (9.948mm). Non-significant difference for kidney length in group DIII (9.774mm) as compared to control is indicative of ameliorative potential of orange juice. Diameter of kidney was also found significantly different for group DI (5.188mm), DII(4.886mm), and DIV (5.182mm) as compared to group C (5.728mm). Group DIII (5.620mm) again was insignificantly different for kidney diameter against group C. In micrometric study, the mean cross sectional area of glomeruli was found reduced significantly in group DI(2043μ^2)and DII(14287.6μ^2) as compared to control group C (37565.55μ^2) while a significant increase was observed for group DIII(21846.1 μ^2) and DIV(21731.9 μ^2) as compared to groups DI and DII. In histopathological analysis, glomerular shrinkage was observed in groups DI and DII. Fresh orange juice has been found to improve this deterioration in group DIII and DIV. These results suggest that sodium fluoride is reno- toxic at different sub lethal doses and orange juice having a variety of natural anti-oxidants, is a potential candidate to attenuate these toxicities.

Key words: Sodium fluoride, Reno toxicity, Mice, Shrunken Glomeruli, *Musmusculus.*

INTRODUCTION

Fluoride is an anion of fluorine which is inorganic in nature and may occur as compound in underground water (Brahman *et al*., 2013). It gets bio accumulated from contaminated soil into crops and ultimately in human (Samal *et al*., 2014; Li *et al*., 2015). It has been reported in infant juices (Omar *et al*., 2014), bottled drinking water, flavored beverages and soft drinks (Dhingra *et al*., 2013; Ha *et al*., 2014). It is used for the treatment of erosive wear (Huysmans *et al*., 2014), dental caries (Zheng *et al.,* 2015); various cardiovascular diseases, obesity, as antibacterial agents, and in antifungal therapy(Kirk, 2006).

Besides such usefulness, fluoride is accused of causing chronic abdomen pain (Chahal *et al*., 2014), oxidative stress(Al-Anazi *et al*., 2015);nephrotoxicity (Song *et al*., 2017); neuropathological alterations (Balaji *et al*., 2015); immunotoxicity (Reddy *et al*., 2014); skeletal disruptions (Yan *et al*., 2015); and apoptosis in erythrocytes (Agalakova and Gusev 2013). Being ubiquitous anion, it blocks a wide variety of metabolic processes (Nelson *et al*., 2015).

Various levels of toxicities of fluoride have been documented in experimental studies conducted in different animals. In rat, hepatotoxicity (Kanagaraj *et al*., 2015), reduced total antioxidant activity in liver (Hamza *et al*., 2015), oxidative stress (Hassan and Yousef 2009), apoptosis, DNAas well as skeletal damage have been recorded (Song *et al*., 2015).Mice (*Musmusculus*) are also found to be at more or less same risk of nephrotoxicity (Basha and Saumya 2013), hepatotoxicity (Chattopadhyay *et al*., 2011), severe oxidative stress

(Bouaziz *et al*., 2007), gonadotoxicity, and infertility as well (Wei *et al*., 2016).

Fresh juices are well reputed for controlling the oxidative stress (Tonin *et al*., 2015) which is maintained for up to 90 minutes post-consumption (Ko *et al*., 2005). Fresh orange juice contains vitamin C and A, folic acid, hesperidin, naringenin, gallic acid, ferulic acid, citric acid (Ohrvik and Witthoft 2008; Galaverna and Dall'Asta 2014; Olayinka*et al*.,2015; Pereira-Caro *et al*., 2015; El-Bassossy *et al*., 2016; Arabi *et al*., 2017; Pereira-Caro *et al*., 2017; Rampersaud and Valim 2017). Hesperidin is a potent antioxidant (Ahmadi and Shadboorestan 2016). Citric acid is found to be effective against toxicity induced by Cd and Hg in rat (Tang *et al*., 2013).Vitamin C is well known for its ameliorative potential against oxidative stress in liver and kidney (Raina *et al*., 2015; El-Sayed *et al*., 2016).Gallic acid extract is antioxidant and effective against d-galactose induced toxicity in mice (Zhuang *et al*., 2017). Folic acid accelerates spermatogenesis in rat (Ibrahim *et al*., 2011). Ferulic acid is anti-oxidant, anti-inflammatory, hepato, and cardio protective in mice and rat (Gerin *et al*., 2016; Shen *et al*., 2016; Song *et al*., 2016).

MATERIALS AND METHODS

Rising of colony: Five male and ten female mice (*Musmusculus*) were bought from Veterinary Research Institute, Lahore. To raise colony, each male was kept with two females in separate cages (14″ × 10″ × 7″) having wood shavings as bedding. They were fed with protein and vitamin rich diet (Feed No.12, National Feeds Lahore) along with fresh drinking water ad libitum in controlled conditions of temperature (25±1°C), humidity (40-50%) and 12 hour light/ dark cycles. On conceiving, females were separated to deliver the young ones. After spending four weeks with mothers, male and female off springs were separated from each other and only male mice were used further in experiment. These mice were also fed with Feed No.12 along with fresh drinking water *ad libitum* under controlled conditions of temperature (25±1°C), humidity (40-50%) and 12 hour light/ dark cycles.

Preparation of fresh orange juice: Fresh seasonal oranges (Kino) were obtained from local market of Lahore, Pakistan. Fully ripened and healthy oranges were sorted out and washed thoroughly following peeling, squeezing and straining to get pulp free juice, and further 50% diluting in distilled water.

Dose grouping and rearing of animals: White powdered form of Sodium fluoride (NaF) made by BDH, Pakistan was obtained and doses of 0.00, 5.00 and 7.50µg/kg BW were prepared in sterilized distilled water. Before drug administration, mice were weighed (12-15g)and randomly divided into 5 groups of 5 animals each as follows:

C: Intact control (0.00 µg of NaF/g of BW) on normal diet for 60 days.

DI: 5.00 µg of NaF/g of BW treated for first 30 days and only on normal diet for next 30 days.

DII: 7.50 µg of NaF/g of BW treated for first 30 days and only on normal diet for next 30 days.

DIII: 5.00 µg of NaF/g of BW treated for first 30 days and with orange juice along with normal dietfor next 30 days.

DIV: 7.50 µg of NaF/g of BW treated for first 30 days and with orange juice along with normal diet for next 30 days.

Dose of NaF as well as orange juice (0.1ml of each per day) was administered orally through a special syringe.

Recovery of organs and histological preparations: At the end of 60thday, animals of all groups were weighed and anaesthetized with anesthetic ether using protocol of University Bioethical Committee. Kidneys were dissected out and placed immediately in normal saline to keep the tissue intact. Pieces of kidney of about 3mm^3 were cut with sharp cutter and immediately shifted to Bouin's fixative (combination of 70 ml of supernatant of water saturated Picric acid, 25 ml of formalin and 5ml of glacial acetate) for fixation for 48 hours and subsequently preserved in ethanol (70%). Sectioning of these organs was done using paraffin wax and staining with hematoxylin and eosin.

Morphometric Analysis: Kidneys were studied morphometrically for bodyweight, length and diameter of kidneys.

Digital photography and processing: The sections were observed and selected for microphotography (100 and 400x) at microscope (M400-D) connected with digital camera (BUC2-500C Bestscope). These images were used for histopathological and micrometric analysis.

Micrometric study: Randomly 100 glomeruli were selected for measuring the cross sectional area (CSA) for each animal in each group. Then 05 average CSA values for each group were obtained (one for each member of the group) to calculate mean CSA±SEM for each group as follows(Ahmad *et al*., 2016):

Cross sectional area of glomeruli= $\pi \times \frac{D}{2} \times \frac{D}{2}$

D1= glomerular diameter 1 and D2= glomerular diameter 2

The diameter of each glomerulus was digitally measured by two lines perpendicular to each other

Statistical analysis: Morphometric as well as micrometric data were analyzed by applying Tuckey's Multiple Comparison Test (One way ANOVA) using Prism Graph Pad 5 Software (San Diego,CA).

RESULTS

Morphometric observations: Body weights of groupDI and DII were reduced significantly as compared to control (groupC), however orange juice had effective role in recovering body weight in groups DIII and DIV (Table 1). Significant difference in kidney length and diameter was observed among groupC, DI and DII while non-significant difference was observed between group C and DIII as well as DII and DIV.

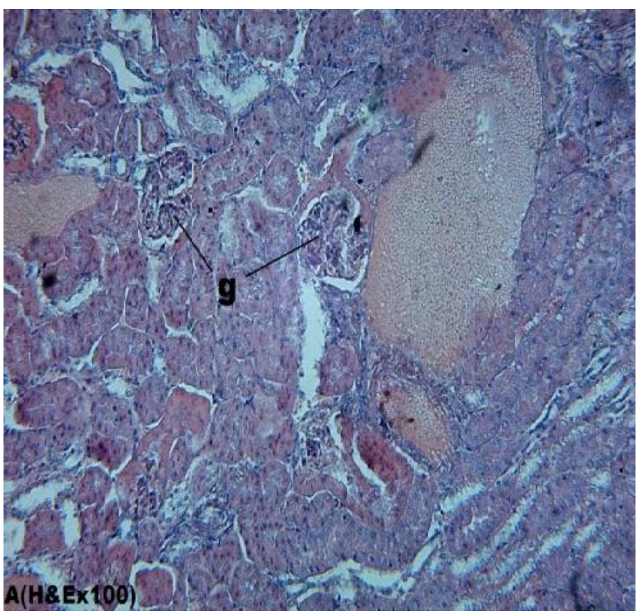
Histological observations: Shrunken glomeruli were observed in groupDI and DII. The intensity of this histopathology has been reduced by orange juice in group DIII and DIV (Fig 1).

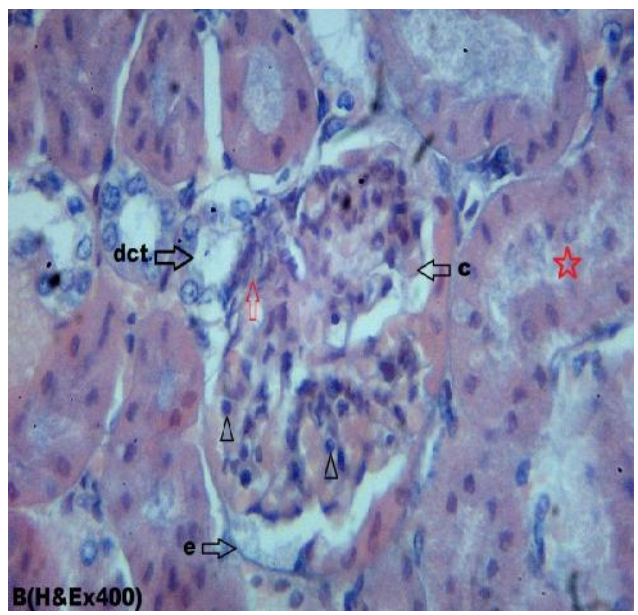
Micrometric observations: The mean cross sectional area of glomeruli is reduced in dose dependent manner in group DI and DII; however recovery is seen in group DIII and DIV (Table 1).

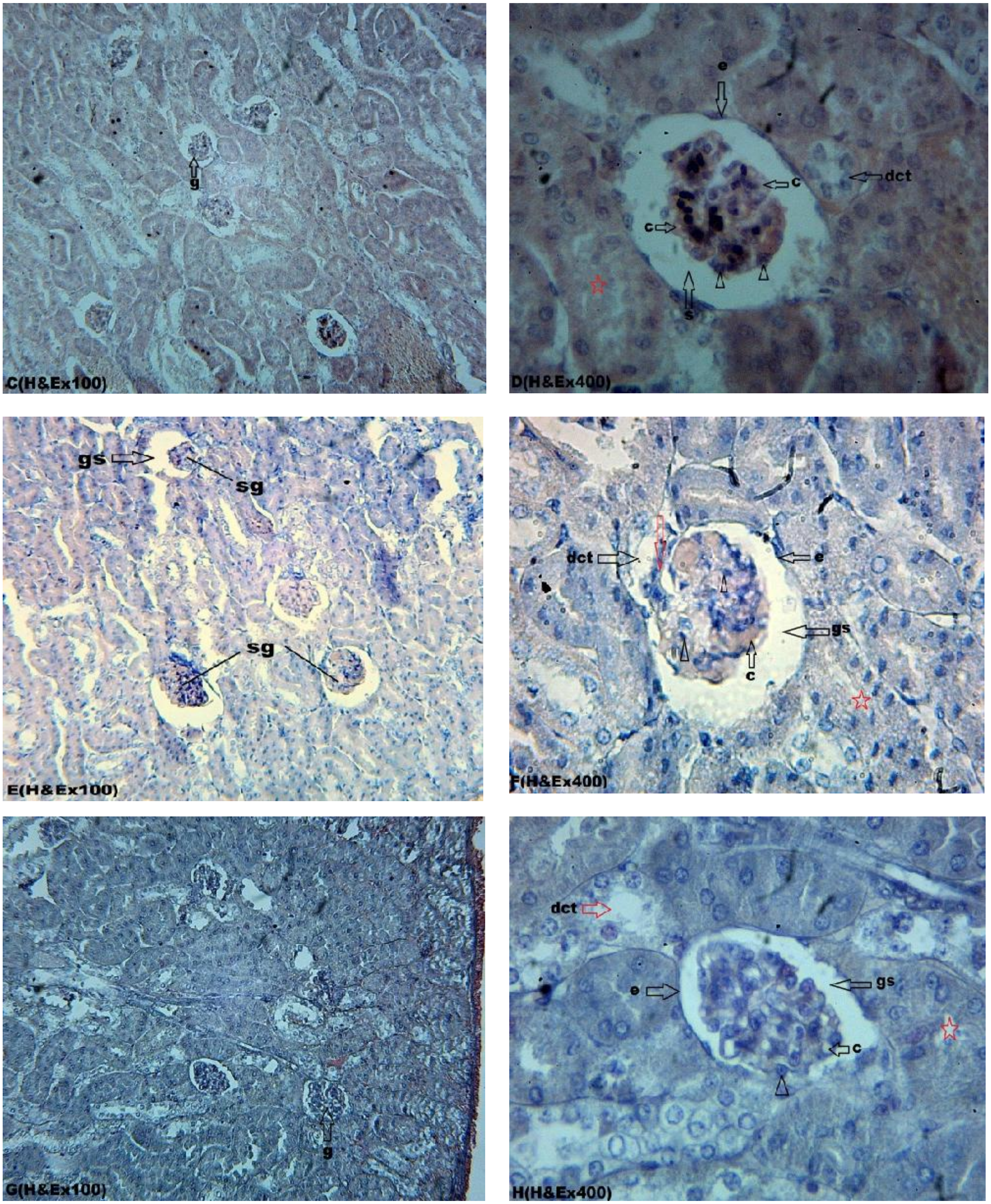
Table1. Morphometric and micrometric results of 90 daysoldmice exposed to different concentrations of Sodium Fluoride.

Groups	C	DI	DII	DIII	DIV
Body Weight (grams±SEM)	29±0.7071^{a}	23.2±0.5831^{b}	20.80±0.3742^{c}	27.40±0.4000^{a}	26.80±0.4899^{a}
Kidney Length (mm±SEM)	9.948±0.07392^{a}	9.088±0.05860^{b}	8.528±0.5305^{c}	9.774±0.07427^{a}	8.826±0.05870^{b}
Kidney Diameter (mm±SEM)	5.728±0.02083^{a}	5.188±0.01393^{b}	4.886±0.04545^{c}	5.620±0.02665^{a}	5.182±0.04283^{b}
Mean CSA of glomeruli (μ^2 ±SEM)	37565.55±7943.78^{a}	20431±3833^{b}	14287.6±2791.8^{c}	21846.1±2074.02^{d}	21731.9±1027.7^{d}

Groups not sharing similar alphabets are different significantly from each other ($p < 0.05$)



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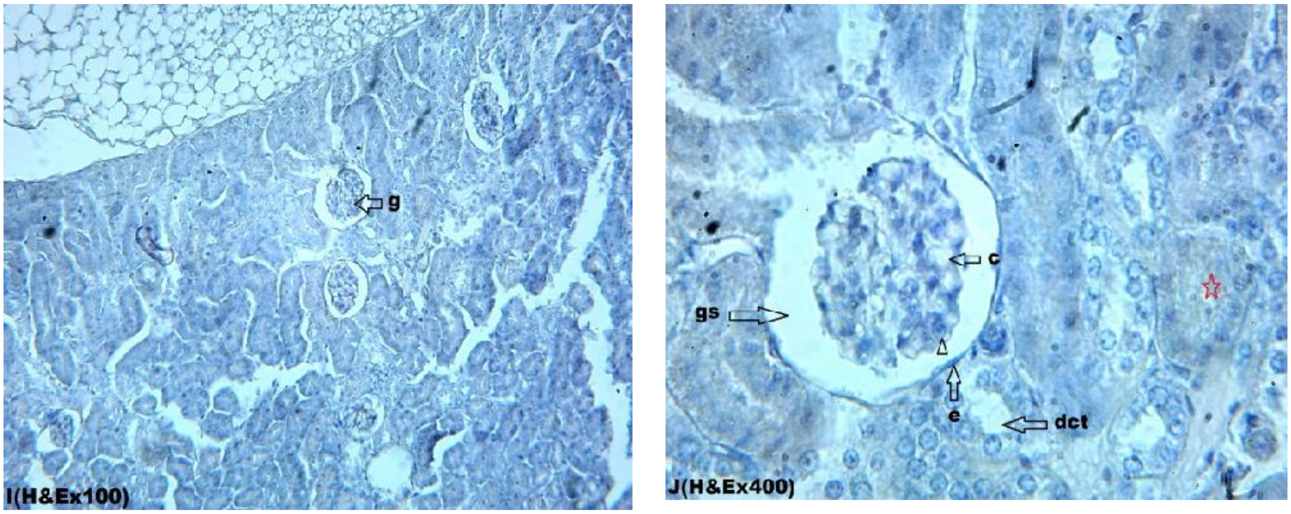

Figure 1(A-J): Selected histological sections of kidney from Control (A-B), Dose group DI (C-D), Dose group DII (E-F), Dose-antidote group DIII (G-H), Dose-antidote group DIV (I-J). g:glomerulus; dct: distal convoluted tubule; c: capillary; e: parietal epithelium of bowman's capsule; gs: glomerular space; sg: shrunken glomerulus; Δ:podocyte; red arrow: macula densa; red star: proximal convoluted tubule.

DISCUSSION

Morphometric results including reduced body weight in group DI and DII indicate the toxic strength of fluoride. However, orange juice has successfully reversed this toxicity in DIII and IV. Significant difference in kidney length and diameter of group DI and DII against C again agrees with the hazardous nature of fluoride, while non-significant difference of C and DIII indicates that orange juice has protective effect while, at the same time, similar trend between group DII an IV indicates that higher dose (7.5ug) perhaps needs more time to be attenuated by orange juice (Table 1).

In present study, fluoride exposure has been investigated to induce shrinkage of glomeruli contrary to findings of Luo *et al*. (2017) where glomerular swelling was observed. Recovery of mean CSA of glomeruli in groups DIII and IV established the confirmation of amelioration by orange juice. Renal damage in terms of granular dystrophy of the renal tubules, necrosis of the endothelial cells and of the mesangial cells is declared on account of fluoride exposure (Dimcevici *et al*., 2014; Baba *et al*., 2016).Orange juice is comprised of many nutrients and each one is strong antioxidant to combat this oxidative stress. Present results of ameliorations are may be owing to any of these nutrients. Gallic acid, citric acid and vitamin C are promising protective agent against fluoride intoxication in the form of oxidative stress(Song *et al*., 2017). Folic acid is known as the main protective factor of neural tube defects (Wolff *et al*., 2009) being effective against oxidative stress (Salama *et al*., 2013). Ferulic acid is also a challenging antioxidant to deal with the oxidative stress through multiple ways including translocation of Nrf2, hunting ROS, and triggering DNA repair (Das *et al*., 2017). Naringenin can reduce oxidative stress and improve mitochondrial dysfunction via activation of the Nrf2/ARE signaling pathway in neurons (Wang *et al*.,2017). Hesperidin can cut down atherosclerosis pleiotropically, including improvement of insulin resistance, amelioration of lipid profiles, inhibition of macrophage foam cell formation, anti-oxidative effect and anti-inflammatory action(Sun *et al*., 2017).

Results of present study indicate that fluoride can affect the health adversely with modulating intensities. Although potential attenuating effects of orange juice is challenging for fluoride intoxication, however, use of fluoridein food should be discouraged especially from infant foods (Steele *et al*. 2014).

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