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Original Article

Ameliorative Effects of Orange Juice on Sodium Fluoride Induced Gastro-Hepatic Toxicity in Mice

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ABSTRACT

Floride toxicity has been under discussion and investigations when taken in excess amounts. Floride leaching into the water bodies as a result of industrialization is a common issue facing most of the developing countries like Pakistan, India, Bangladesh etc. This leached fluoride has the ability to cause a myriad of disorders when incorporated in animal bodies. **Objective:** To find out the ameliorative effect of orange juice against toxic effects of sodium fluoride influencing damaging effect on liver and stomach. **Methods:** The mice were divided in six groups. The control group supplied with Nestle's water, while different concentrations of sodium fluoride (2.50µg/g, 5.00µg/g and 7.50µg/g body weight) were prepared and administered orally in mice for 30 days. Then all treated groups were supplied with fresh natural orange juice for next 30 days to test its ameliorative potential. **Results:** The data revealed the significant reduction of body weight ($p<0.001$), stomach length, stomach diameter ($p < 0.05$) while hepato- somatic and gastro-somatic index increased ($p < 0.05$) in treated groups as compared to control group after sodium fluoride administration. Morphological studies revealed different abnormalities in treated groups such as spots on the liver and stomach, swelling of stomach, constriction of fundic and cardiac regions and lobes of liver. **Conclusions:** This study clearly revealed that sodium fluoride is potentially toxic to organs of albino mice, especially liver and stomach and that orange juice demonstrated ameliorative potential against the toxicity due to sodium fluoride.

INTRODUCTION

Fluorosis is a worldwide endemic disease that affects multiple continents. Fluoride-related health problems in humans are becoming increasingly common due to natural andgeological causes as well as more recently, rising industrialization and the resulting environmental contamination. Worldwide, drinking water containing high amounts of fluoride has been linked to health risks; in India alone, there are an estimated 66.62 million victims. Water that is consumed by humans and animals, along with food to a lesser amount, allows fluoride to enter their bodies [1]. Fluoride exposure produces the anion superoxide (O2-), which raises O2- concentrations and has downstream effects on molecules including H2O2, ONOO- (an isomer of nitrate), and O-H reactive species. These molecules play a key role in mitigating the toxicity of fluoride ions. Vital organs such as kidney, liver, brain etc, are adversely affected, which has been demonstrated by laboratory testing. Fluoride lowers glutathione levels and prevents the actions of antioxidant enzymes such as catalase, glutathione peroxidase, and superoxide dismutase. Oxygen radicals may be produced excessively at the mitochondrial level as a result of glutathione deficiency, which damages various parts of cells. Furthermore, the synthesis of too many oxygen radicals may result in peroxidation of lipids, oxidation of macromolecules, depolarization of the mitochondrial membrane and death

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[2]. Higher fluoride intake has been shown to cause metabolic disorders by interfering with a number of cellular processes such as transcription, translation, mitosis, many cellular chemical reactions and other basic cytological processes. Moreover, it compromises antioxidant defence system of the body [3]. Low amounts of the vital trace element fluoride (F-) have been shown to support the growth of teeth and bones [4]. It exists in the environment in a variety of forms and is widely utilized, as are its compounds. Water use generally accounts for the greatest portion of daily F- intake, either because F- containing rocks and soils runoff into water sources. Some regions use artificial fluoridation of drinking water or groundwater [5]. Thus antioxidant/pro-oxidant multi-organ dysfunctions may result from an imbalance brought on by fluoride intoxication [6]. The amount of fluoride taken up by plants is directly related to the kind of plant involved and also upon the strength of the polarity of nutrient medium upon which it is grown. After a certain threshold level of fluoride ions, the influx of this ion through roots may increase dramatically [7]. In an experiment it was observed that the concentration of fluoride was greater in roots as compared to that in shoots in tomatoes (Lycopersicumesculentum) and oats (Avena sativa) when experimentally grow on substrate media rich in fluoride [8]. Coal mines where fluoride concentrations are dangerously high can produce airborne fluoride particles in the concentrations of 6 µg/m3, which has been observed in parts of China [9]. The innate ability of sodium fluoride to induce procreative and embryological defects has also been investigated in laboratory animals [10, 11]. The blood chemistry and hepatic functions of many test animals exposed to higher levels of fluoride have been shown to cause fluctuations in the normal working of these parts [12]. A short-lived duration inhalation MRL, premised on lower respiratory tract agitation in humans was derived for hydrogen fluoride [13].

METHODS

Sodium fluoride and natural fresh orange juice were used in this experiment for 30 days each.

The chemical composition of fluoride as shown in table 1.

Table 1: Chemical composition of fluoride

Company Name's	BDH
Colour	White
Form	Powder
Highest Percentages of Impurities	
Chloride (Cl)	0.5%
Copper (Cu)	0.05%
Iron (Fe)	0.001%

A group of 15 albino mice (10 females and 5 males) were obtained from Veterinary Research Institute, Lahore, at the beginning of experiment. Colony of albino mice was established to fulfill demands of experiment. These animals were kept in air-conditioned animal house at 25±1°C temperature. Steel racks and cages (14" × 10" × 7") were also available for this purpose. Two females were caged with one male in five different cages. Breeding stock was kept in controlled environmental conditions in the form of 12-hour light/ dark cycles, temperature of 25±1°C and humidity i.e., relative 40-50%. Each cage had wood shavings as bedding material, which was replaced daily. Before the drug administration, animals were weighted and divided. Every group consisted of five animals. The animals were fed drinking water with sodium fluoride indifferent concentrations and drinking water with orange juice (in ml) daily as detailed above. Every animal was weighed weekly. Control group i.e. G-I was supplied with Nestle's water while treated groups (from G-II to G-VI) were first treated with various concentrations of sodium fluoride such as G-II5-µg/g B.W (Body Weight)., G-III with 7.5µg/g, G-IV with 2.5 µg/g, G-V with 2.5 µg/g sodium fluoride for 30 days and after that all treated groups were givenfresh orange juice (50% in distilled water) for next 30days. On the 31st day, animals were weighed and then anaesthetized with ether. The organs were dissected out of the animal, then fixed in Bouin's fluid for 48 hours with subsequent preservation in 70% alcohol. Both control and treated organs were processed for morphological and anatomical studies. The organs were weighed by using digital balance, organ length and diameter were measured by using avernier caliper. The whole data were subjected to mathematical calculations and were analyzed by a computer-based program SPSS. One way ANOVA was used for analysis of data obtained in this study. The study was ethically accredited by Examination branch, University of Education Township Lahore (REF#: 1090, Dated: 15-09-2013)

RESULTS

Morphological Studies

In Group-I, no abnormalities were observed in liver and stomach. All the livers and stomachs of albino male mice were normal and proper in morphological structure.Group-IIrevealed some abnormalities in liver such larger size of posterior right lobe, median lobe, gallbladder, caudate lobe and left lobe and stomach fundic region were narrower than control. InGroup-III, posterior right lobe became small, gall bladder expanded and stomach effected as esophagus, cardia, fore-stomach, body, limiting ridge, region of fundic glands and region of pyloric gland showed abnormal structure. InGroup-IV an infection of liver in posterior right lobe, median lobe, gallbladder, caudate lobe and left lob and stomach regions showed abnormal appearances.InGroup-V, cancer production occurred incardia, fore stomach and

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region of pyloric glands were affected and in Group-VI, Liver posterior right lobe, gallbladder, caudate lobe, right median lobe and left lob expanded in form and spots and hole formation were observed,infection occurred in forestomach, fundus, limiting ridge, region of fundic glands and region of pyloric glands of stomach.

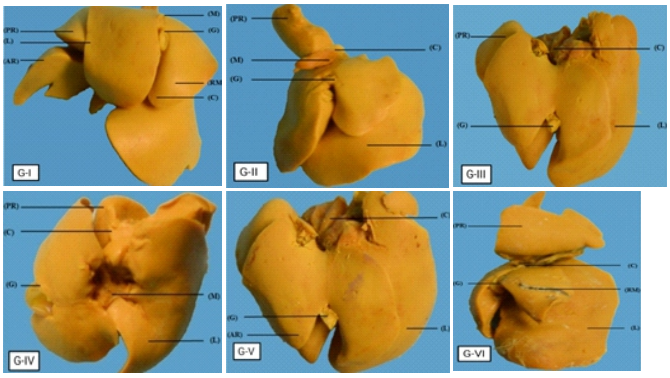

Figure 1: Macrophotograph of liver of albino male mice from G-I to G-VI, showing no abnormalities in control (G-I) while treated Groups showing abnormalities Posterior right lobe (PR), anterior right lobe (AR), median lobe (M), gallbladder (G), caudate lobe (C), right median lobe (RM) and left lob (L)

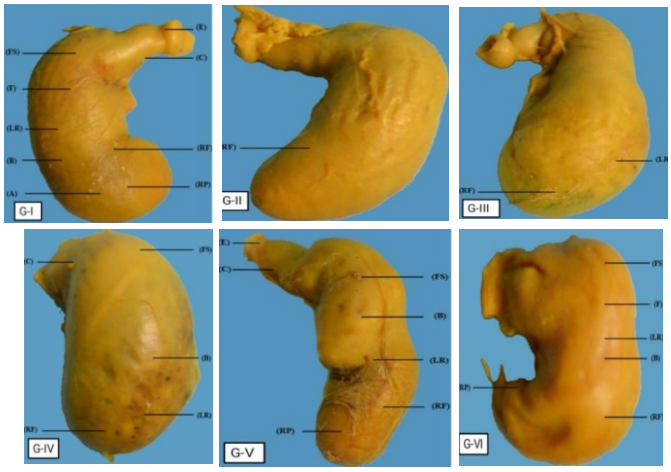

Figure 2: Macrophotograph of stomach of albino male mice. G-I (control) showing no abnormalities while treated Groups showing abnormalities. Esophagus (E), cardia (C), fore stomach (FS), fundus (F), limiting ridge (LR), body (B), antrum (A), region of fundic glands (RF) and region of pyloric glands (RP)

Morphometric Analysis

The organs from all the groups; control and experimental, were subjected to morphometric analysis. The morphometric study of the organs was based on ONE- WAY ANOVA Duncan test by using SPSS-16 software. Analysis of different dose groups was made on the basis of different parameters. These parameters included wet weight, length, diameter and organ-somatic index.

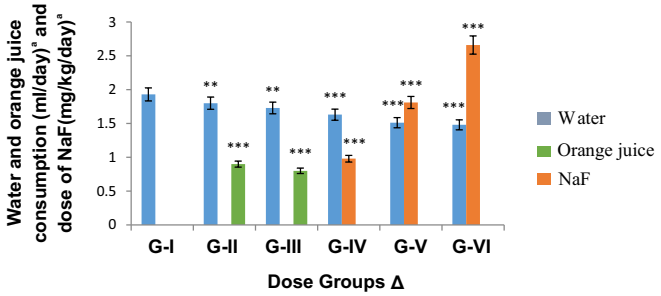

Figure 4: : Histogram showing the water and orange juice consumption of male albino mice (ml/day) [a] and dose of NaF (mg/kg/day)[a] for 30 days

Asterisks indicate significant difference against control

*** =(p < 0.001)

** =(p < 0.01)

The first parameter studied was the weight of all five dosage groups as compared to the control. While the control group stood at 29 ± 1.58 grams, the body weight of male albino mice Group-II (5.00µg/g B.W NaF and orange juice) had decreased significantly from control group. The mean value of body weight was (27 ± 1.00 grams), which was significantly reduced (p<0.001) than the control. The average body weight of Group-III (7.50µg/g B.W NaF and orange juice) was 26.67±1.53 grams), which was significantly reduced (p<0.001) than control. The average body weight Group-IV (2.50µg/g B.W NaF) was 25±0.57 grams which was significantly reduced (p<0.001) than control. The average body weight Group-V (5.00µg/g B.W NaF) was 23.33±1.00 grams, which was significantly reduced (p<0.001) than control. The average body weight Group-VI (7.50 µg/g B.W NaF) was 21±1.00 grams which was significantly reduced (p<0.001) than control. The control group appeared with average gastro-somatic index of 1914.22±131.17 mg. The average gastric somatic index of group-II (5.00µg/g B.W NaF and orange juice) was 1868.73±20.50 mg which was lesser than control. The average gastro-somatic index of group-III (7.50µg/g B.W NaF and orange juice) was 1816.93±68.59 mg which was lesser than control. The average gastro-somatic index of group-IV (2.50µg/g B.W NaF) was 2055.77±27.24 mg which was significantly (p<0.05) more than control. The average gastro-somatic index of Group-V (5.00µg/g B.W NaF) was 2110.88±142.55 mg which was significantly (p<0.01) more than control. The average gastro-somatic index of Group-VI (7.50µg/g B.W NaF) was 2293.91±201.53 mg which was significantly (p<0.001) more than control. The average stomach length of Group-II (5.00µg/g B.W NaF and orange juice) was 12.22±0.59 mm which was lesser than control. The average stomach length of Group-III (7.50µg/g B.W NaF and orange juice) was 12.07±1.38 mm which was lesser than control. The average stomach length of Group-IV (2.50µg/g B.W NaF) was 11.53±0.48 mm which was decreased significantly (p<0.05) than control. The average stomach length of Group-V (5.00µg/g B.W NaF) was 11.48±0.43 mm which was decreased significantly (p<0.05) than control. The average stomach length of Group-VI (7.50µg/g B.W NaF) was 11.47±0.46 mm which was decreased significantly (p<0.05) than control. The average stomach diameter of group-II (5.00µg/g B.W NaF and orange juice) was 6.33±0.71mm which was lesser than control. The average stomach diameter of Group-III (7.50µg/g B.W NaF and orange juice) was 5.99±1.34 mm which was decreased significantly (p<0.05) than control. The average

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stomach diameter of Group-IV (2.50µg/g B.W NaF) was 5.91±0.50 mm which was decreased significantly ($p<0.05$) than control. The average stomach diameter of Group-V (5.00µg/g B.W NaF) was 5.63±0.45 mm which was decreased significantly ($p<0.01$) than control. The average stomach diameter of Group-VI (7.50µg/g B.W NaF) was 5.58±0.35 mm which was decreased significantly ($p<0.01$) than control. The control group appeared with average hepatic somatic index of 4598.95±249.62 mg. The average hepato-somatic index of Group-II (5.00µg/g B.W NaF and orange juice) was 4350.36±830.83 mg which was significantly ($p<0.05$) more than control. The average hepato-somatic index of Group-III (7.50µg/g B.W NaF and orange juice) was 4591.47±252.86 mg, which was lesser than control. The average hepato-somatic index of Group-IV (2.50µg/g B.W NaF) was 4705.18±540.68 mg which was significantly more than control. The average hepato-somatic index of Group-V (5.00µg/g B.W NaF) was 4601.75±390.15 mg which was more than control. The average hepato-somatic index of Group-VI (7.50µg/g B.W NaF) was 4904.72±309.33 mg which was significantly ($p<0.05$) more than control.

Table 2: The effects of sodium fluoride and fresh orange juiceon albino male mice Stomach and Liver for 30 days

Variables	Group I	Group II	Group III	Group IV	Group V	Group VI
Body Weight (Grams ± S.E)	29 ± 1.58	27± 1.00 ***	26.67 ±1.02 ***	25± 0.57 ***	23.33 ±1.00 ***	21± 1.02 ***
Stomach Length (mm ± S.E)	13.21± 1.65	12.22± 0.59	12.07± 1.38	11.53± 0.48*	11.480. 43*	11.47± 0.46*
Stomach Diameter (mm ± S.E)	7.07± 0.71	6.33± 0.71	5.99± 1.34*	5.91± 0.50*	5.63± 0.45**	5.58± 0.35**
Hepato-Somatic Index (mg ± S.E)	4598.95 ±98.65	4350.36 ± 77.12 *	4591.47 ±88.06	4705.18 ±41.77	4601.75 ±190.21	4904.72 ±87.16 *
Gastro- Somatic Index (mg ± S.E)	1914.22 ±91.07	1868.73 ±20.52	1816.93 ±68.59	2055.77 ±27.24 *	2110.88 ±142.08 **	2293.91 ±97.18 ***

Asterisks indicate significant difference against control
**=($p<0.01$)and *=($p<0.05$)

DISCUSSION

The current study aimed at observing the toxic effects of commonly used, industrial/pesticidal products containing different concentrations of NaF on albino male mice organs. It shows clearly howNaF aggregates in the liver and gastric tissues of mice, resulting in stress and preventing auto-oxidation processes, therebydamagingliver and gastric tissuesdue to oxidative ill-effects. NaF also produces obstacles in the normal working of many proteins such as enzymes taking part in energy synthesis, translocation and transport of ions across membranes. Hence the build-up fluoride ions lead to a series of malfunctions resulting in altered functions of muscles, liver along with other organs. The liver, an immensely significant organ and a highly active center of metabolism, is particularly vulnerable to fluoride toxicity [14]. It has been also known that fluoride can pass through cell membranes and find its way into soft tissues which includes the liver, brain, and kidney. Increased lipid peroxidation and lessened antioxidant enzyme activity have been used to show that fluoride poisoning impairs soft tissue function in animals [15]. The sodium potassium ATPase pump plays a vital role in the translocation of these two ions across the membrane. Brain and muscle contain high concentrations of these pumps across their membranes. Murphy and Hoover have reported the inability of this pump to function in presence of excessive Fluoride ions. The ATPase pumps involved in the transport of sodium, potassium and calcium were found to be defunct in rats, after oral introduction of NaF [16]. Fluoride (F) penetrates soft tissues by simple diffusion through cell membranes, where it degrades the tissues. Long-term F intake affects not only the skeletal system but also the soft tissues, including the liver, kidney, gastrointestinal tract, muscle, and various other reproductive and endocrine systems [17-19]. The teeth, bones, and stomach all showed signs of fluoride poisoning; the frequency and degree of these alterations were correlated with the amount of NaF used and the length of exposure [20]. NaF did not change the incidence of preneoplastic and neoplastic lesions at any location in rats of either sex, despite abundant indications of toxicity. This study's findings suggest that NaF is not carcinogenic [20]. The kidney is the organ most important to an animal's ability to withstand prolonged exposure to fluoride [21]. F- excretion in urine is less common in those with renal failure [22]. Even at the typical permissible limits of F in drinking water, they are at significant risk of fluorosis and have increased plasma F levels compared to normal healthy individuals [23]. Animals including humans, have changes in kidney function when exposed to fluoride through their drinking water [24]. Renal tubular injury is indicated by N-acetyl-β-D-glycosaminidase (NAG) and α-glutathione-S-transferase (α-GST) [25]. Studies of F-exposed animals and humans have shown increased levels of NAG and α-GST in urine [26]. It has also been demonstrated that F causes significant histological and ultrastructural alterations in the kidneys of mice and rabbits [27]. A dose-response association between renal tissue damage and fluoride has been observed by researchers. As the kidneys play a major role in eliminating ingested F from the body, decreased renal function raises blood F levels by decreasing urine F excretion [28, 29]. Between 75 and 90 percent of fluoride that is consumed is absorbed. Up to 40% of the fluoride that is swallowed is absorbed from the stomach as hydrogen fluoride (HF), which is created when fluoride is transformed to HF in an acidic stomach. Elevated pH in the stomach reduces the concentration intake of HF, which in turn reduces gastric absorption. The colon absorbs fluoride that is not absorbed in the stomach and is unaffected by pH there [30]. Fluoride is regarded as a

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dangerous substance. It has been demonstrated in this context that high fluoride concentrations in extremely acidic media can cause gastric lesions, most likely by encouraging acid back-diffusion to the mucosa [31]. The gastrointestinal tract's organs are the ones that fluoride exposure negatively affects the most in the body [32]. Fluoride salts have the ability to react with hydrochloric acid (HCl) in the stomach to produce hydrofluoric acid (HF), which can diffuse past the gastric mucosa more easily. Numerous studies in related scientific literature have documented detrimental effects on blood chemistry following consumption of fluoride-enriched water. According to certain research publications, nitric oxide (NO) generation in the blood is boosted when fluorides are taken orally at a dosage of 20 mg/kg [33]. There is proof in scientific literature that long-term fluoride exposure causes oxidative stress and activates lipid peroxidation (LPO) [4]. Due to increased lipid peroxidation and DNA damage in the gastric mucosa, oxidative stress has been linked to the onset of inflammatory bowel disease, peptic ulcers, and gastrointestinal malignancies [6, 34]. In a study it was found that high range of fluoride ions i.e. 150-600 ppm gave way to stress in many important organs especially the heart and kidneys. This included a heightened expression of nuclear kappa factor beta (NF-κB) [35]. Organs of the Group-II (5.00µg/g B.W. of sodium fluoride for 30 days and next 30 days treatment by fresh orange juice) and Group-III (7.50µg/g B.W. of sodium fluoride for 30 days and next 30 days treatment by fresh orange juice) were normal according to the morphology but on the base of morphometric analysis the body weight, hepatic somatic index, gastric somatic index, stomach length and diameter, renal somatic index, (Figure 1 and 2). Organs of Group-IV (2.50µg/g B.W. of sodium fluoride) showed abnormalities the spot on the liver, stomach, (Fig 1and 2). Organs of Group-V (5.00µg/g B.W. of sodium fluoride) and Group-VI (7.50µg/g B.W. of sodium fluoride) showed morphological abnormalities, blackish color spots on the liver, stomach, liver (Figure 1). The more difference on the base of morphometric analysis between control and these treated groups.

CONCLUSIONS

As a conclusion it can clearly be inferred that the oral administration of NaF hashighly toxic attributes, when accumulated in high concentration in albino male mice especially liver and stomachand that orange juice can have healing effects on organs affected by NaF toxicity. Hence, it is suggested that sodium fluoride usage should be monitored in humans especially during sensitive periods such as when a mother is expecting and afterwards when babies start feeding on their mother's milk as it is during the developmental periods that this chemical has the most destructive affects.

Authors Contribution

Conceptualization: AA
Formal analysis: AUMF, AA, AUR, ML
Writing-review and editing: AUMF, FA, HF, RB, SK
All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The author declares no conflict of interest.

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