



## Effect of yogurt on fluoride induced toxicity of plasma markers of kidney in rabbits

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## Authors' Contribution

Sallam, A., S. Bughio &amp; R. Buriro designed the study, M.B. Arain, S. Bughio &amp; M.A. Jamali analyzed the data, Z. Lanjar experimented

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## ABSTRACT

Review Process: Peer review

Fluoride (F) is one of the major chemical substances that damage the renal tissue prevention tubular reabsorption, increasing the excretion of sodium (Na<sup>+</sup>) and chloride (Cl<sup>-</sup>), and enhancing creatinine (Cr), uric acid (UA), blood urea nitrogen (BUN) and potassium (K<sup>+</sup>) level. Results revealed that on 16<sup>th</sup> day in groups B, D, E and G, Cr. values were significantly (P<0.05) increased on 31<sup>st</sup> day in group-F, Cr. value was significantly (P<0.05) decreased, whereas, in groups-B, D, E and G, Cr. values were significantly increased (P<0.05). On 16<sup>th</sup> and 31<sup>st</sup> day, in yogurt-treated groups i.e.- C and F, UA values were significantly (P<0.05) decreased, whereas, in groups B, D, E and G, UA values were significantly (P<0.05) increased. On 16<sup>th</sup> and 31<sup>st</sup> day, in groups-B, D, E and G BUN level was significantly (P<0.05) increased. On 16<sup>th</sup> and 31<sup>st</sup> day in groups-B and E, Na<sup>+</sup> level was significantly (P<0.05) decreased. Whereas, in groups C, D, F and G, Na<sup>+</sup> level was significantly (P<0.05) increased. Likewise, on 16<sup>th</sup> and 31<sup>st</sup> day, in groups-B, D, E and G, K<sup>+</sup> level was significantly (P<0.05) increased. On 16<sup>th</sup> day in groups-B and E, Cl<sup>-</sup> level was significantly (P<0.05) decreased. While, in groups- F and G Cl<sup>-</sup> level were significantly (P<0.05) increased. On 31<sup>st</sup> in groups-B & E, Cl<sup>-</sup> level was significantly (P<0.05) decreased. While, in groups-C, D, F and G, Cl<sup>-</sup> levels was significantly (P<0.05) increased. It has been concluded that increased levels of sCr, UA, BUN, K<sup>+</sup> and reduced levels of Na<sup>+</sup> and Cl<sup>-</sup> were observed in fluoride treated groups. Yogurt-treated groups showed decreased levels of Cr, UA, BUN and K<sup>+</sup> and increased levels of Na<sup>+</sup> and Cl<sup>-</sup> in experimental rabbits.

**Keywords:** Yogurt, fluoride, toxicity, renal functions, rabbits.

**INTRODUCTION** Fluoride is extensively used and broadly distributed throughout the world in numerous forms. The presence of fluoride in environment could vary depending on its chemical nature. The elemental fluorine (F) never occurs in nature in a free state due to its chemically active properties. It is a component of minerals found in rocks and soil, that are created when it reacts with a variety of other elements (Barbier *et al.*, 2010). Fluoride is present in the environment, and it comes from natural sources such as rocks and soils, as well as from industrial activities. It is toxic if the concentration is high. Drinking water from deep wells may have excessive quantities of fluoride in some places (Li *et al.*, 2015). One of the most essential organs for removing fluoride from the body is the kidney. Approximately 60% of the daily fluoride taken by healthy people is eliminated through urine under normal physiological conditions. As a result, the kidney is one of the soft tissues that is most exposed to fluoride concentrations (Dharmaratne, 2019).

In atmosphere, Fluoride compounds exist in various forms such as hydrogen fluoride, carbon tetrafluoride and sodium fluoride (Mattsson and Paulus, 2020). In different countries, more than 260 million people suffer from fluorosis due to improper use of fluoride, among them China is one of the major countries with the most fluorosis cases (Herath *et al.*, 2018). Fluoride entry into human body via respiration, fluoride containing product such as, fluoride gel, dental products, mouthwash, toothpaste and fluoride supplements (tablets, chewing gums, etc.) (Singh *et al.*, 2020). The absorption of fluoride takes place through intestinal mucosa and then inhibit metabolic pathway (Zhou *et al.*, 2020). Reportedly, serum creatinine level increased after giving 20 parts/ million sodium fluoride in rats (Al Salhen and Mahmoud, 2016). The amount of urinary N-acetyl glycosaminidase activity, serum creatinine (sCr), uric acid (UA), and blood urea nitrogen (BUN) levels as well kidney lactate dehydrogenase (LDH) was elevated and also lower renal function. Fluoride treatment lower the renal function as seen by the activity of renal Na<sup>+</sup>/K<sup>+</sup>-ATPase and ACP (phosphate acid) decreasing (Xiong *et al.*, 2007).

Yogurt is one of the most widely consumed fermented dairy products in the world, with a high level of public acceptance due to its health advantages (Weerathilake *et al.*, 2014). *Streptococcus thermophilus* and *Lactobacillus delbrueckii* sub species *bulgaricus* are the most active bacterial strains in yoghurt. Lactic acid bacteria (LAB) aid in the absorption of nutrients, vitamin production, and the prevention of unwanted microflora in the gut (Brodziak and Król, 2016). A harmful uremic toxin known as indoxyl sulphate accumulates in the plasma those people suffering from chronic kidney diseases CKD (Niwa, 2010). This substance damage the cellular structure of renal tubular cells, glomerular mesangial cells, and vascular smooth muscle cell (Ng *et al.*, 2014). In vitro

studies reported that *Streptococcus thermophilus* reduces indoxyl sulphate. Combinations of *Streptococcus thermophilus* have shown great effectiveness in CKD, by decreases in the buildup of circulating uremic toxins (Pisano *et al.*, 2018). Some probiotic bacteria consume urea, uric acid, creatinine and another toxin as a nutrition for growth. These harmful waste buildup in the circulation because of overworked and damaged kidney (Ranganathan, 2015).

**OBJECTIVES:** The aim of the study was to investigate the fluoride induced toxicity and influence of yogurt on relieving fluoride induced renal toxicity in rabbits.

**MATERIAL AND METHODS: Experimental animals and adaptation:** Forty-two adult male and female rabbits (Dutch species) average body weight (BW) is one kilogram were bought from market. The controlled environment (temperature 17- 23 °C, humidity 45%- 60%) was given to the rabbits. The rabbits were reared in cages at animal house, at Sindh Agriculture University, Tandojam and protocol approved No. DAS/936/2022. Before starting experiments, all animals were dewormed and kept under hygienic conditions for 02 weeks as an acclimatization period.

**Experimental design:** Animals were divided into seven experimental groups (6 rabbits/group). Group-A (Control), Group-B (F 50mg/ kg B.W rabbit), Group-C (yogurt 15gm/ kg B.W rabbit), Group-D (F 50mg+yogurt 15gm/ kg B.W rabbit), Group-E (F 100mg/ kg B.W rabbit), Group-F (yogurt 30gm/ kg B.W rabbit), Group-G (F 100mg + yogurt 30gm/kg B.W. rabbit). Standard feeding (grass and vegetables) and water was given ad libitum to them. Animals in all treatment groups received the prescribed treatment once daily orally maximum volume and of yogurt and in similar volume of fluoride was dissolved in water then given to rabbit for 30 days. Fluoride was purchased from the company Asia Commodities and Minerals Pakistan and fresh yogurt from Nestle was used in this study.

**Assessment of Renal function:** On 16<sup>th</sup> and 31<sup>st</sup> day, two ml blood sample was collected from jugular vein in plain vacutainer tubes (red top). The serum was separated through centrifugation. After centrifugation, serum was kept at -4°C. Thereafter, following parameters were examined i.e., serum uric acid, blood urea nitrogen, serum creatinine, and electrolytes (Sodium, potassium, chloride). These parameters were determined by spectrophotometer analyzer using biosystem BTS -350 kits.

**Statistical analysis:** The data was analyzed Statistically and tabulated by using computer software Student Edition of Statistics (SXW), Version. 8.1 (Copyright 2005, Analytical Software, USA).

**RESULTS AND DISCUSSIONS: Creatinine level:** Result revealed the Serum creatinine concentration in control and treatment groups of rabbits. Result shows that on day 16<sup>th</sup> In groups B, D, E and G, serum creatinine values were significantly increased (P<0.05). Whereas, on day 31<sup>st</sup> in group-F, serum creatinine values were

significantly decreased ( $P < 0.05$ ). Whereas, in groups B, D, E and G, serum creatinine value ( $P < 0.05$ ) was significantly increased as compared to control (figure.1).

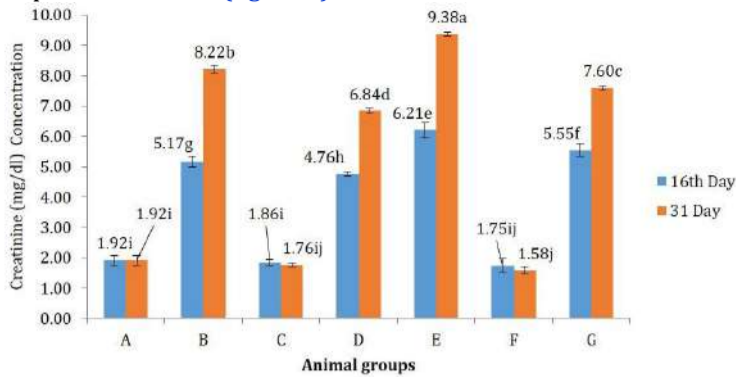


Figure 1: Serum creatinine concentration (mg/dL) in fluoride induced toxicity and yogurt supplemented amelioration in rabbits.

The value of serum creatinine in rabbits increases when the dose and time duration are increased. Yogurt containing beneficial bacteria reduced the concentration of creatinine. Similarly this investigation agreed with Xiong *et al.*, (2007), observed the concentration of serum creatinine (sCr) increased in the mice, and resulting that fluoride reduced or impaired renal function in mice. Al-safei and Al-Mashhadane (2021) recorded that sodium fluoride at 20mg/kg in rabbits increased creatinine concentration. Yang *et al.* (2020) observed that probiotics in gastrointestinal tract, metabolized creatinine and decreased its level, this rise was as a result of chronic kidney disease. Because these substances pass through across a concentration gradient from the blood stream to gastrointestinal tract would aid in lowering blood level of creatinine. Probiotics including *Lacticaseibacillus paracasei*, *S. thermophilus* and *Lactiplantibacillus plantarum* reduced the level of creatinine in plasma.

**Uric acid level:** Data shown in (figure 2) the serum uric acid concentration in control and treatment groups of rabbits.

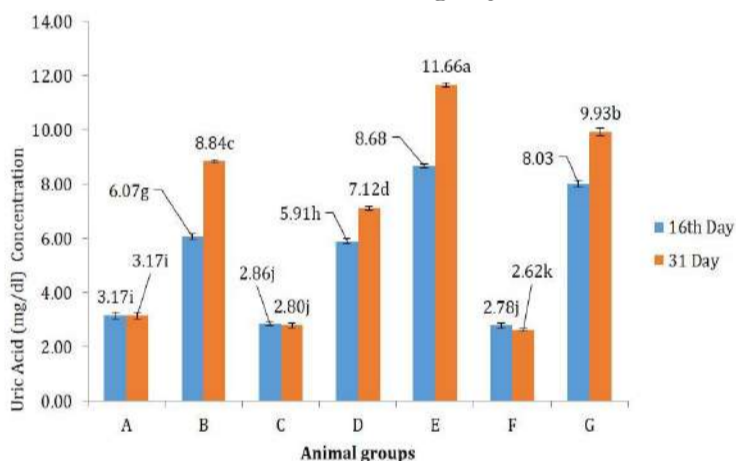


Figure 2: Serum uric acid concentration (mg/dL) in fluoride induced toxicity and yogurt supplemented amelioration in rabbits.

Results indicated that serum uric acid on 16<sup>th</sup> day, in yogurt treated groups i.e., groups-C and F, serum uric acid level were significantly decreased ( $P < 0.05$ ). Whereas, in fluoride treated groups i.e., groups-B, D, E and G, serum uric acid level were significantly increased ( $P < 0.05$ ). However, on day 31<sup>st</sup> Statistically, similar trend was noticed as indicated on 16<sup>th</sup> day i.e., in groups-C and F, serum uric acid level were significantly decreased ( $P < 0.05$ ), whereas, in groups-B, D, E and G, serum uric acid level were significantly increased ( $P < 0.05$ ) as compared to control. Xiong *et al.* (2007) recorded that 12, 24, and 48 mg/kg fluoride in mice increased the concentration of uric acid in serum by increasing the dose of sodium fluoride. In current study, yogurt containing beneficial bacteria reduced serum uric acid concentration. The present findings are consistent with Choi *et al.* (2005) that there is a substantial inverse connection between dairy intake and serum uric acid level. Milk protein (casein and lactalbumin) have been demonstrated to lower blood uric acid level in healthy people due to the uricosuric impact of these protein. Yamanaka *et al.* (2019) found that *Lactobacillus gasseri* lowered serum uric acid level in individual with hyperuricemia and gout, which is characterized by a reduction in uric acid excretion or an increase in uric acid buildup due to aberrant purine metabolism. Reportedly, Hamada *et al.* (2022) observed that *Lactobacillus gasseri* containing yogurt (85g) twice daily reduced the serum uric acid level in patients suffering from marginal hyperuricemia.

**Blood urea nitrogen level:** Serum blood urea nitrogen concentration in control and treated groups of rabbits is shown in figure 3.

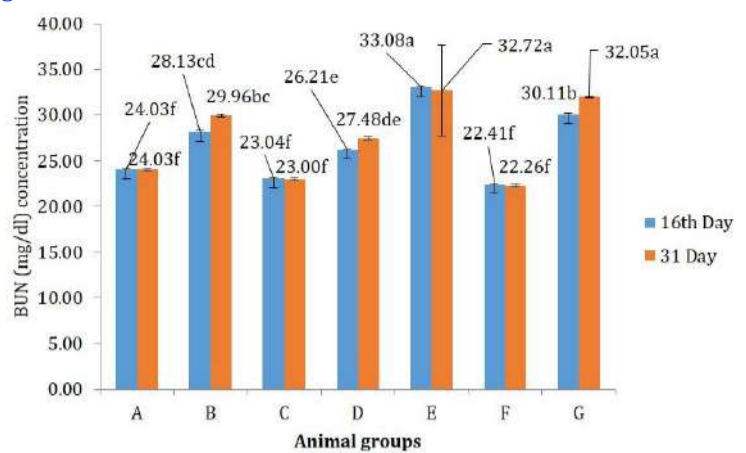


Figure 3: Serum blood urea nitrogen concentration (mg/dL) in fluoride induced toxicity and yogurt supplemented protection in rabbits.

Results indicated that on day 16<sup>th</sup> In groups-B, D, E and G blood urea nitrogen level was significantly increased ( $P < 0.05$ ). On 31<sup>st</sup> day, mean blood urea nitrogen values similarly increased as on 16<sup>th</sup> day i.e., groups-B, D, E and G blood urea nitrogen level was significantly increased ( $P < 0.05$ ) in comparison to control. Present study showed agreement with previous studies that the Piglets fed fluoride 100 and 250mg/kg for 50 days with a base diet showed increased level of BUN (Zhan *et al.*, 2006). Furthermore, in agreement, that the concentration of BUN level increased when mice were treated with fluoride 12, 24 and 48 mg/kg, resulting declined the function of kidney (Xiong *et al.*, 2007). It has also reported that the short term administration of probiotics reduced the serum Blood urea nitrogen concentration and reduced the renal chances of renal disease by improve renal function, microorganisms from the *Lactobacillus* and *Bifidobacterium* have been shown to reduce the concentration of blood urea nitrogen (Fagundes *et al.*, 2018).

**Serum sodium level:** Data shown in figure 4 revealed the serum Na<sup>+</sup> concentration in control and treated groups of rabbits.

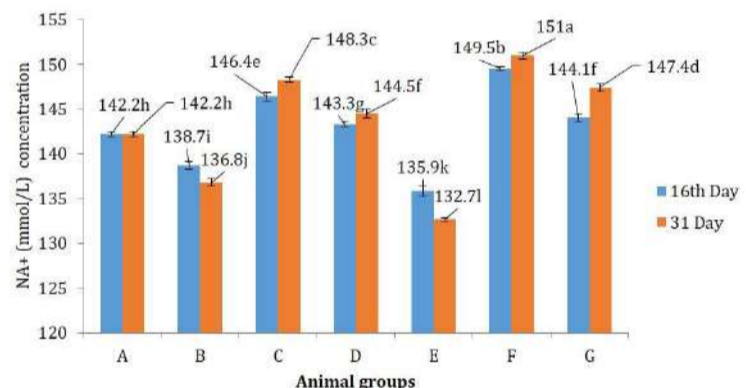


Figure 4: Serum Na<sup>+</sup> concentration (mmol/L) in fluoride induced toxicity and yogurt supplemented betterment in rabbits.

Results indicated that, on 16<sup>th</sup> day, in groups-B and E, Na<sup>+</sup> level was significantly decreased ( $P < 0.05$ ). Whereas, in groups-C, D, F and G Na<sup>+</sup> level was significantly increased ( $P < 0.05$ ). On day 31<sup>st</sup>, in groups-B & E, Na<sup>+</sup> level was significantly decreased ( $P < 0.05$ ). Whereas, in groups-C, D, F and G Na<sup>+</sup> level was significantly increased ( $P < 0.05$ ) following treatment as compared to control. In agreement with current results, it has been reported that Piglet fed for 50 days with a base diet containing 100 and 250mg/kg, show decreased serum Na<sup>+</sup> level. ion may be effected via tubular reabsorption and osmotic disequilibrium between the luminal and medullary interstitial fluid (Agrawal *et al.*, 2008). In agreement, Barai *et al.* (2018) observed that the level of Na<sup>+</sup> increased when treated with yogurt 50ml,100ml and 150ml/kg B.W. Girard *et al.* (2005) observed that the ingestion of castor oil considerably reduced net Na<sup>+</sup> absorption from  $-196 \pm 39 \mu\text{m}$ , in basal condition to  $401 \pm 100 \mu\text{mole}$  in experimental condition. In a dose dependent manner, pre-treatment with *S. boulardii* at concentration ranging from  $1.2-12.0 \times 10^{10}$ CFU /kg reduced the sodium secretory action of castor oil. The net sodium secretion was lowered to  $89 \pm 124$  and  $32 \pm 86 \mu\text{moles}$  at the two highest doses, respectively.

**Serum potassium level:** Data shown in (figure 5) revealed the serum K<sup>+</sup> concentration in control and treated groups of rabbits. Results indicated on the 16<sup>th</sup> day, in treated groups-B, D, E and G,

mean serum potassium values level was significantly increased ( $P < 0.05$ ).

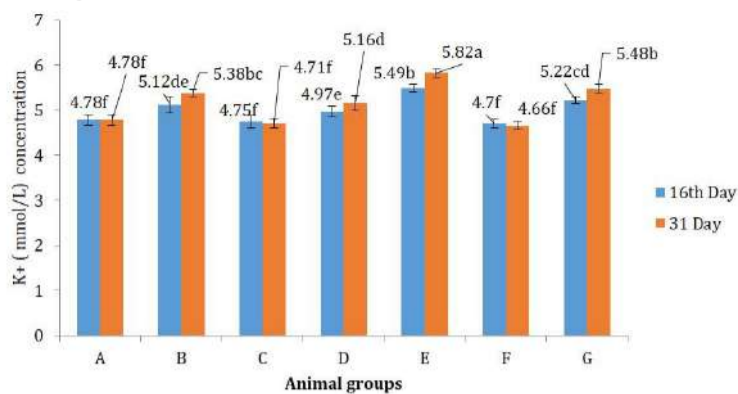


Figure 5: Serum K<sup>+</sup> concentration (mmol/L) in fluoride induced toxicity and yogurt supplemented betterment in rabbits.

Additionally, on the 31<sup>st</sup> day, a similar increasing trend was noticed i.e., in groups-B, D, E and G mean serum potassium values level was significantly increased ( $P < 0.05$ ) after treatment in comparison to control. Reportedly, in agreement *Dalamaga et al. (2008)* recorded that increased fluoride consumption in humans and other vertebrate induced electrolyte imbalance resulting in increased level of potassium in serum. In another study, *Emejulu et al. (2016)* detected that the Piglet fed for 50 days with a base diet containing 100 and 250mg/kg, increased levels of K<sup>+</sup> in serum. The rise in K<sup>+</sup> concentration generated by Na-F may suggest that membrane channel have been damaged and renal function has been affected. This study is contrast with the *Barai et al. (2018)* that 50mg/kg yogurt in mice reduced the level of potassium in serum induced after oral administration of loperamide (3mg/kg). The secretory action of castor oil was inhibited by pre-treatment with *S. boulardii* at doses ranging from 1.2-12.0 x 10<sup>10</sup>CFU /kg. the yeast did not restore the net potassium content observed in the basal condition at the two largest doses, but it did significantly lower the castor oil induced net potassium secretion, with the net potassium secretion of 65.3 ± 43.6 and 51.5 ± 10.5 μmoles respectively (*Girard et al., 2005*).

**Serum chloride level:** Data shown in (figure 6) reveals the serum Cl<sup>-</sup> concentration in control and treated groups of rabbits.

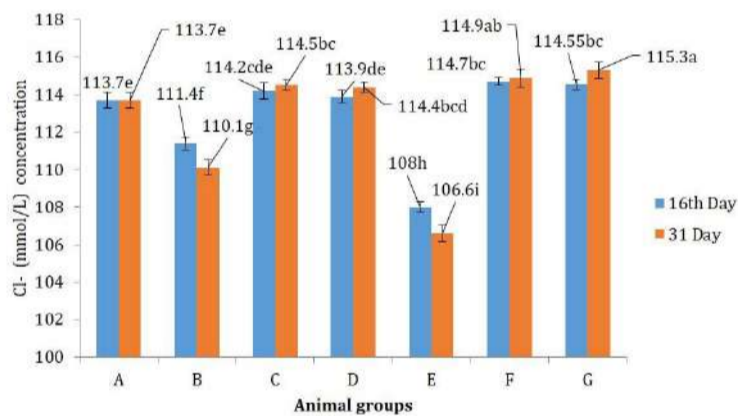


Figure 6: Serum Cl<sup>-</sup> concentration (mmol/L) in fluoride induced toxicity and yogurt supplemented amelioration in rabbit.

Results indicated that on 16<sup>th</sup> day in groups-B and E serum chloride level ( $P < 0.05$ ) decreased. While, in groups-F and G serum chloride level was significantly increased ( $P < 0.05$ ). On 31<sup>st</sup> day in groups-B and E serum chloride level was significantly decreased ( $P < 0.05$ ), while, in groups-C, D, F and G serum chloride level was significantly increased ( $P < 0.05$ ) following treatment as compared to control. The current study showed agreement with *Lehnhardt and Kemper (2011)* that the level of chloride was reduced after the administration of sodium fluoride. Administration of Fluoride decreased in Cl<sup>-</sup> ion concentration in experimental animals. It has been observed that the level of Cl<sup>-</sup> elevated when treated with 50ml yogurt/kg body weight. This study is agreement with the (*Al-Daihan and Bhat, 2019*).

**CONCLUSION:** Based on the results of present study, it was concluded that fluoride caused impaired renal function that is evident in fluoride treated groups increased in blood urea nitrogen, uric acid, creatinine, K<sup>+</sup> in a dose dependent manner. Yogurt supplementation decreased elevated renal profile caused by fluoride intake in rabbit. Fluoride treatment decreased Cl<sup>-</sup> and Na<sup>+</sup> while yogurt supplementation inhibited it. Yoghurt as an economical probiotic produced nephro-protective effect and could be incorporated in the diet of people with fluoride toxicity complaints.

**CONFLICT OF INTEREST:** Authors have no conflict of interest.

**ACKNOWLEDGEMENT:** Thankful to Department of Veterinary Pathology, Sindh Agriculture University Tandojam, assisted to gives platform for performed lab test.

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