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Ameliorative Effects of Amla Fruit Pulp Extract and Selenium on Dimethoate Induced Alteration in Serum Calcium and Phosphate Level of Rats

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Abstract: Wistar rats were divided into 6 numerically equal groups and treated as -- Group A: Control; Group B: dimethoate (20 mg/kg b wt); Group C: dimethoate (20 mg/kg b wt) and selenium (0.5 mg/kg b wt); Group D: dimethoate (20 mg/kg b wt) and amla fruit pulp extract (200 mg/kg b wt); Group E: selenium (0.5 mg/kg b w.) and Group F: amla fruit pulp extract (200 mg/kg b wt). Blood samples were collected on 7 and 14 day and serum calcium and phosphate levels were analyzed. Serum calcium levels of rats treated for 7 day with dimethoate (Group B); dimethoate +selenium (Group C) and dimethoate+amla fruit pulp extract (Group D) decreased as compared to control rats (Group A). The administration of amla fruit pulp extract and selenium did not fully restore the reduced calcium levels caused by dimethoate, despite a slight increase in calcium levels of group C and group D. After 14 day, calcium levels decreased after dimethoate; dimethoate+ selenium; and dimethoate +amla fruit pulp extract treatment. Although serum calcium levels are increased in group C and group D as compared to dimethoate treated group (group B) but the levels (group C and D) are still hypocalcemic as compared to control. Levels in group E (selenium) and F (amla fruit pulp extract) remain unaltered on day 7 and 14. Serum phosphate levels decreased after 7 and 14 day in dimethoate, dimethoate+selenium and dimethoate+amla fruit pulp extract treated rats. In group C (as compared with E) and group F (as compared with F) phosphate level decreased. Phosphate levels of group C and group D increased as compared to group B. This indicates that treatment of amla fruit pulp extract and selenium caused phosphate levels to recover.

Keywords: Dimethoate, Calcium, Phosphate, Amla fruit pulp, Selenium, Pesticide, Amelioration, Organophosphate

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Introduction

Pesticides, which can be physical, biological, or chemical mediators, are substances formulated particularly for the destruction, prevention, and expulsion of animals, pests, and microorganisms (hazardous to plant growth) (Intisar *et al.,* 2022). Organophosphates(OPs) are a crucial component of contemporary agriculture; yet, due to overuse, pesticide residues from OPs are accumulating in the soil and contaminating aquatic and terrestrial food webs through groundwater (Mali *et al.,* 2023). The connection between a high amount of OP exposure and harmful health effects was examined in epidemiological research. Organophosphate acts by phosphorylating the enzyme acetylcholinesterase (AChE), which hydrolyzes acetylcholine in cholinergic synapses and neuromuscular junctions (Badr, 2020). Reactive oxygen species (ROS) are produced excessively as a result of oxidative stress caused by OP chemicals, which may alter antioxidant and scavenging systems. Antioxidant therapy has been demonstrated to reduce oxidative stress and the death rate associated with OP-induced toxicity (Cemek *et al.,* 2010).

Dimethoate (O,O-dimethyl S-methyl-carbamoyl-methyl phosphorodithioate) is an organo-phosphate which is frequently used in agriculture as an insecticide to manage arthropod infestation of agricultural products. Dimethoate has been categorized as a well-known neurotoxic that changes metabolic enzymes in target and non-target species, including mammals, and inhibits acetylcholinesterase (AChE), interrupts cholinergic neurotransmission in the central and peripheral nervous systems (Sharma *et al.,* 2023). As an AChE inhibitor, it is moderately hazardous to mammals and could have negative health effects on both humans and animals, including cattle and pets. Dimethoate can enter the bloodstream after exposure and reach the kidney, brain, myocardium, and other organs (Martínez-Morcillo *et al.,* 2019)

Amla (*Emblica officinalis* Gaertn. or *Phyllanthus emblica* Linn), also known as Indian gooseberry, is a significant medicinal plant used in both conventional and alternative therapies. It produces fruits with significant antioxidant properties as a result of being one of the most abundant natural vitamin C sources and a flavonoids (Mahajan *et al.,* 2023). A few other important chemical components of *E. officinalis* include alkaloids, tannins, and emblicanin A and B. The ellagic acid of this plant has medicinal benefits (Morampud *et al.*, 2023), and the fruits in particular are used to treat inflammation, diarrhoea, and jaundice.

Selenium (Se) is a trace element which is necessary for both human and animal life. It can be consumed in organic (selenomethionine, selenocystein) or inorganic (selenite, selenate) forms through diet. Se's inclusion in selenoproteins such as glutathione peroxidase and thioredoxin reductase is primarily responsible for its physiological effects (Castel *et al.,* 2023). Many enzymes require selenium as a necessary component, some of which have antioxidant properties. Animals that are deficient in this element are more vulnerable to harm from specific forms of oxidative stress (Burk, 2002). Selenium is a vital mineral that is suggested as a dietary supplement for health benefits and is necessary for a variety of processes, such as antioxidant, defense, cellular redox homeostasis, and metabolic cycling (Ozturk Kurt *et al.,* 2023).

Calcium and phosphorus are crucial components of numerous biological processes. While phosphorus is essential in energy metabolism, cellular signaling, nucleic acid synthesis, and the stabilization of cell membranes, calcium is necessary for muscular contraction, hormone production, the blood-clotting cascade, and the excitation of neurons.(Srivastav *et al.,* 2000, Taylor and David Bushinsky, 2009). Calcium concentrations in extracellular components are closely monitored within a narrow physiological range that is ideal for a wide range of cellular functions (Srivastav *et al.,* 2000).

The present study was aimed to investigate the protective effects of amla fruit pulp extract and selenium against dimethoate induced alterations in serum calcium and phosphorus levels.

Materials and Methods

Amla fruit pulp extract preparation:

Amla fruit, *Emblica officinalis* were purchased locally. The amla fruits were washed thoroughly with water and dried in hot air oven at 40℃. After drying, the pulps were cut into small pieces, dried and powdered. Powdered amla fruit pulp were mixed with 90% ethanol in 1:20 ratio (w/v) and kept at orbital shaker for 48 h. Then the samples were filtered through Whatman No. 1 filter paper. The filtrates were dried in oven at 40°C and stored at -20°C. For use, the dried residues of amla pulp were dissolved with ethanol to provide desired dose to be given to rats.

Chemicals:

Dimethoate (Rogor) 30 EC was purchased from Agricultural shop. It was in the form of emulsion and was diluted in water to obtain an effective concentration of dimethoate. Sodium selenite was purchased from Eastern Scientific Emporium (Gorakhpur) and dissolved in distilled water for use in experiments. The dose used in this study for dimethoate, selenium and amla fruit pulp extract are based on the reports of earlier investigators: dimethoate (20 mg/kg b wt- Sayim, 2007; Saafi – Ben Salah *et al.,* 2012; 7, 15 and 28 mg/kg b wt- Farag *et al.,* 2006; 30 mg/kg b wt- Apaydin *et al.,* 2022); selenium (0.25 mg/kg b wt- Adedara *et al.,* 2020; 0.05 and 0.5 mg/kg b wt- Loeschner *et al.,* 2014); amla pulp extract (200 mg/kg b wt- Yadav, 2018).

Animals:

Male Wistar rats were collected from Asia Scientific Emporium, Varanasi, India. The animals were housed in polypropylene cages and were acclimatized for two weeks prior to different treatments. During acclimation and experimental period, rats were provided food and tap water *ad libitum.* Experimental design was approved by Research Degree Committee, D.D.U. Gorakhpur.

Experimental design:

The acclimatized rats were divided into 6 groups (A-F), each group containing 20 rats. The rats were treated (at 10:00 am throughout experiment) as follow:

Group A (Control): No treatment was given

Group B (Dimethoate treated rats): These rats were given daily dose of dimethoate (20 mg/kg b wt)

Group C (Dimethoate + Selenium): These rats were given daily dimethoate (20 mg/kg b wt) and Selenium (0.5 mg/kg b wt)

Group D (Dimethoate + Amla fruit pulp extract): These rats were given daily dimethoate (20 mg/kg b wt) and amla pulp extract (200 mg/kg b wt)

Group E (Selenium): These rats were given daily selenium (0.5 mg/kg b wt)

Group F (Amla fruit pulp extract): These rats were given only amla fruit pulp extract (200 mg/kg b wt)

Rats (10 from each group) from all groups were sacrificed 24 h after last dose on 7th and 14th day after initiation of experiment under light ether anesthesia. Animals were fasted overnight before sacrifice. Blood samples were collected and sera were separated by centrifugation (at 3,000 rpm) and kept at -20 °C and analyzed for serum calcium and serum inorganic phosphate by using Beacon kit (Beacon Diagnostic Private Ltd). Each sample was analyzed in duplicate.

Statistical analysis:

Data are represented as mean ± S.E. for six specimens. Student t-test was used to determine significance level. In all studies, the treatments group are compared with specific control group. Analysis of Variance (ANOVA) was used to observe the significant difference among all treated groups.

Results

Serum calcium level of rat treated with dimethoate (group B) exhibited a decrease after 7 day ($P<0.0001$) and 14 day ($P<0.0001$) (Fig. 1). In dimethoate and selenium treated rats (group C), the serum calcium level increased on 7 day (not significant) and on 14 day ($P<0.0001$) as compared to group B. In group D (dimethoate and amla fruit pulp extract), the serum calcium level showed an insignificant increase on day 7 as compared to group B, however, on day 14 the calcium level were significantly increased ($P<0.01$) as compared to group B (Fig. 1) This indicates that selenium and amla pulp extract are

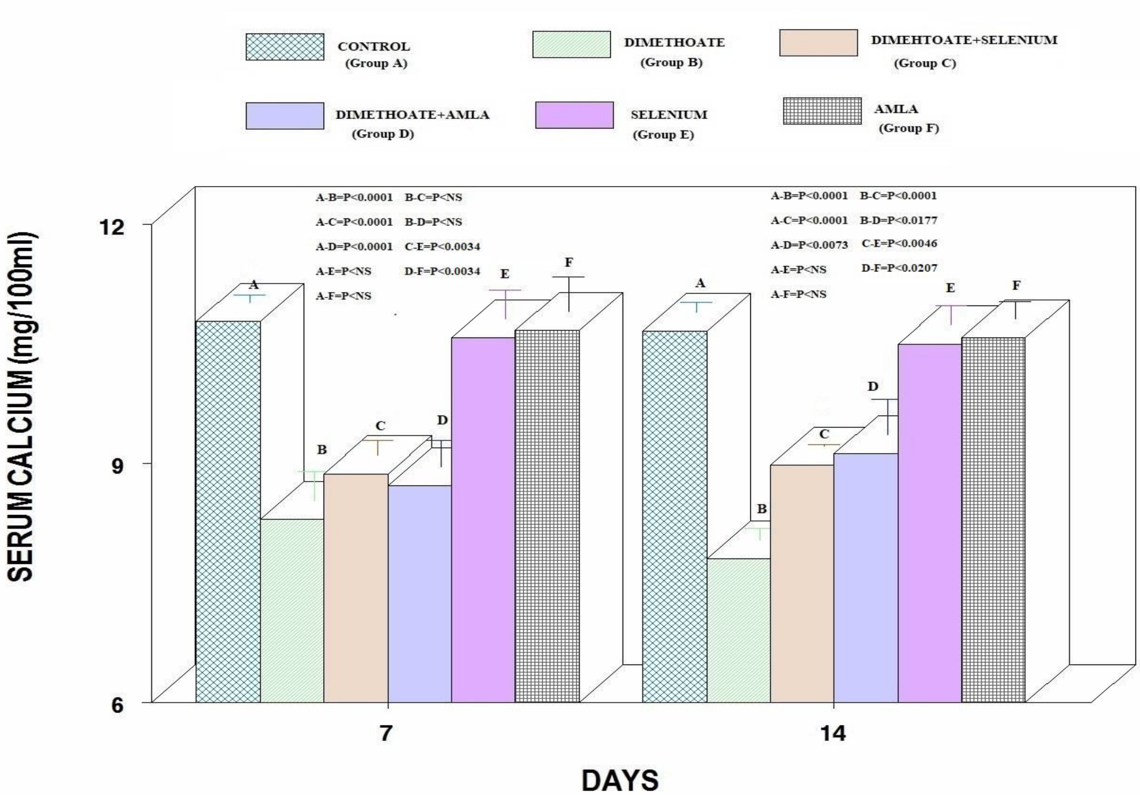

Fig. 1: Serum calcium levels of rats after various treatments. Each value indicates mean±SE (n=6).

effective in recovering the calcium levels which was decreased by treatment with dimethoate. In selenium (Group E) and amla fruit pulp extract (Group F) there was no change in serum calcium levels on 7 and 14 day. Analysis of Variance (ANOVA) indicated that the treatment was significant (7 day – F= 12.976, P<0.0001; 14 day – F= 16.755, P<0.0001).

In dimethoate (group B) exposed rat the serum phosphate levels gradually decreased from 7 day (P<0.0001) to 14 day (P<0.0001) (Fig. 2). In dimethoate and selenium (group C) treated rats, the serum phosphate levels increased at 7 day (P<0.007) which continued till 14 day (P<0.004) as compared to levels of group B. In Group D (dimethoate and amla fruit pulp extract), serum phosphate levels increased on day 7 (P<0.013) and 14 day (P<0.013) as compared to group B (dimethoate treated only) (Fig. 2). In selenium (Group E) and amla fruit pulp extract (Group F) there was no change in serum phosphate levels as compared to control rats (Group A). Analysis of Variance (ANOVA) indicated that treatment was significant (7 day-F= 11.876, P<0.0001; 14 day- F = 10.209, P< 0.0001).

Discussion

In the present study dimethoate treated rats exhibited hypocalcemia. This is in agreement with reports of other investigators who have also noticed hypocalcemia after exposure to different toxicants in rats: diazinon (Rangoonwala *et al.,* 2005), mipcin (Rangoonwala *et al.,* 2007), cypermethrin (Rangoonwala *et al.,* 2008), heroin (Barai *et al.,* 2009), cadmium (Tripathi and Srivastav, 2011b), chlorpyrifos (Tripathi *et al.,* 2013), microcystin LR (Srivastava *et al.,* 2020), cypermetrin (Srivastava *et al.,* 2021); in chickens:

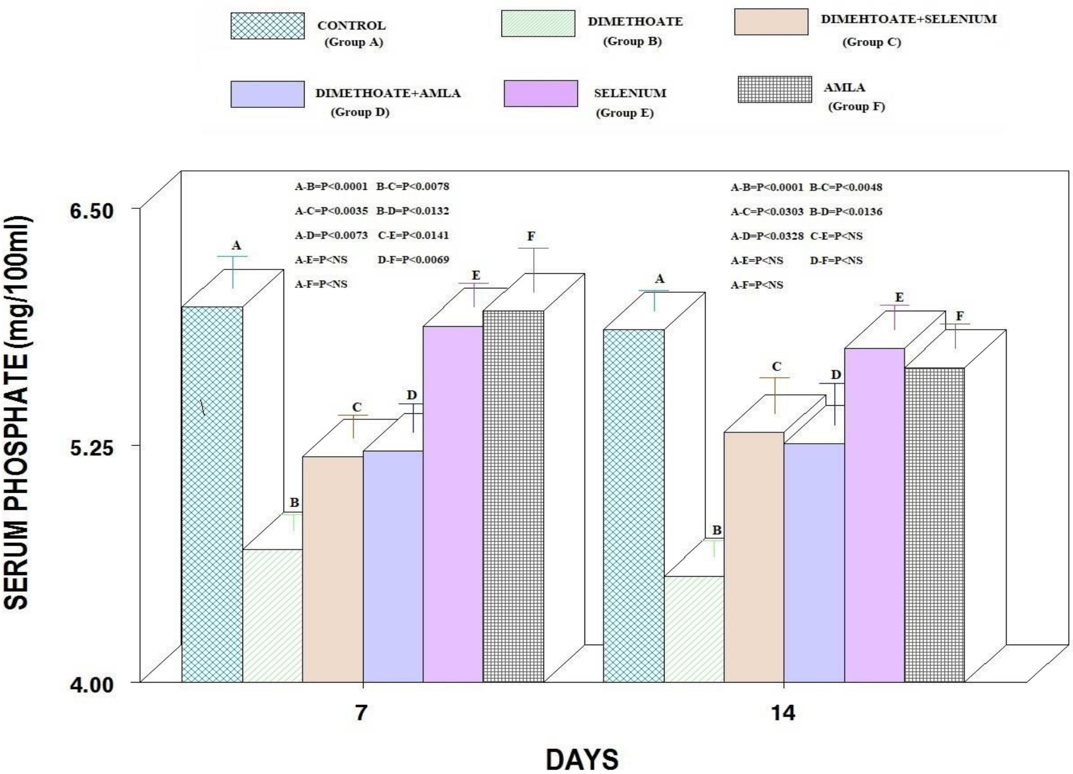

Fig. 2: Serum phosphate levels of rats after various treatments. Each value indicates mean±SE (n=6).

gamma benzene hexachloride and quinalphos (Agarwal *et al.,*2009); and in frogs: chlorpyrifos (Srivastav *et al.,* 2018) and cadmium (Srivastav *et al.,* 2019*).* Hypocalcemia in toxicant exposed fish has also been reported--- deltamethrin (Srivastav *et al*., 1997b, 2010); aldrin (Singh *et al*., 1996); malachite green (Srivastava *et al.,* 1995); formothion (Singh *et al*., 1997); cadmium (Rai and Srivastav, 2003, Chowdhary *et al.,* 2004, Suzuki *et al .,* 2004),), cypermethrin (Mishra *et al.,* 2010), herbal pesticides (Kumar *et al*., 2011 a, b; Prasad *et al.,* 2011 a ,b) and dimethoate (Pandey and Das, 2015). In *Cyprinus carpio* after treatment with nickel no significant changes in serum calcium levels was noticed (Bozorgzahed *et al.,* 2023).

Rat exposed with dimethoate exhibited hypophosphatemia. The decreased level of inorganic phosphate levels have also been reported by other investigators in rats- cadmium (Tripathi and Srivastav, 2011b), chlorpyrifos (Tripathi *et al.,* 2013), microcystin LR (Moreno *et al.,* 2003; Srivastava *et al.,* 2020), cypermetrin (Srivastava *et al.,* 2021); in chickens- gamma benzene hexachloride and quinalphos (Agarwal *et al.,* 2009). In frog hypophosphatemia was recorded after treatment with chlorpyrifos (Srivastav *et al.,* 2018). In fish hypophosphatemia was noticed by exposure to chlorpyrifos (Srivastav *et al.,* 1997 a), deltamethrin (Srivastav *et al.,* 1997 b), cypermethrin (Mishra *et al.,* 2001), cadmium (Rai and Srivastav, 2003), azadirachtin (Kumar *et al*. 2011 a), *Nerium indicum* leaf extract (Prasad *et al.,* 2011a), *Euphorbia royleana* (Prasad *et al*., 2011 b) and *Euphorbia tirucalli* (Kumar *et al*., 2011b), lead (Srivastav *et al*., 2013) and microcystin LR (Prakash *et al.,*2015, 2016). Contrary to it, few investigators failed to notice any alteration in serum/plasma phosphate of rats treated with heptachlor (Rangoonwala *et al.,* 2004), diazinon (Rangoonwala *et al.,* 2005) and mipcin (Rangoonwala *et al.,* 2007). However, Barai *et al.,*(2009) noticed hyperphosphatemia in heroin administered rats.

The observed hypocalcemia in dimethoate treated rats can be explained due to the degeneration of glomeruli and renal tubules in dimethoate exposed rats (our unpublished data). Degeneration of kidney after exposure to various toxicants has been reported in mammals (Chmielnicka *et al*., 1989; Prozialeck *et al*., 2009; Tripathi and Srivastav, 2010, 2011 a). In addition, decreased intestinal calcium absorption has also been reported by Chertok *et al* (1981). After exposure to toxicant increased efflux of calcium (Chmielnicka *et al.,* 1989; Prozialeck *et al*., 2009) may occur due to kidney damage by toxicants which may accounts for the observed hypocalcemia in present study. In past, hypocalcemia has also been attributed to the degenerative changes in the renal tubules in toxicant treated fishes (Koyama and Itazawa, 1977; Roch and Maly, 1979; Larsson *et al.,*1981; Haux and Larsson, 1984). Also, few investigators have attributed the hypocalcemia in mipcin (Rangoonwala *et al.,* 2007) and heroin (Barai *et al.,*2009) to the degenration of parathyroid glands.

Conclusion

The results of this investigation concluded that the rats blood calcium and phosphate levels were adversely affected by dimethoate exposure. Selenium and extracts of amla fruit pulp supplements may help to prevent these essential electrolytes. Giving dietary supplements including amla fruit pulp extract and selenium to organisms exposed to dimethoate is advised in order to reduce their toxic symptoms.

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