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A Review: Immunological and biochemical studies on imidacloprid toxicity

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Abstract
Imidacloprid and other insecticides are responsible for immunosuppression, hormone disruption, diminished intelligence, reproductive abnormalities, cancer etc. Hepatotoxicity is the primary effect observed in the imidacloprid toxicity however; oxidative stress, nephrotoxic and immunotoxic effects are also observed. Biochemical studies revealed significantly higher activities of mean serum alanine transaminase, aspartate transaminase, lactate dehydrogenase and alkaline phosphatase and serum glucose, creatinine, total lipid and cholesterol level in imidacloprid intoxicated animals and birds. The study of oxidative stress parameters revealed alterations in blood glutathione peroxidase, superoxide dismutase and catalase activities. Immunological studies revealed the significant decrease in delayed type hypersensitivity (DTH) response, stimulation index of T-lymphocytes to PHA, phagocytic activity, chemokinesis and chemotaxis in imidacloprid treated animals. Lymphoid organs such as thymus and spleen tissues showed lymphocytic depletion with pyknotic nuclei in the imidacloprid treated group of experimental animals.

Keywords: Imidacloprid, hepatotoxicity, oxidative stress, lymphocytes

Introduction
India is the largest producer of pesticides in Asia and ranks twelfth in the world for the use of pesticides (Gunnell and Eddleston, 2003) [1]. Only 5% of pesticides reach target and the rest runs off into the water or disperse in the air. The residues of pesticides produce harmful effects on human being, animals, birds, fish and wildlife such as immunosuppression, hormone disruption, diminished intelligence, reproductive abnormalities, cancer etc. (Brouwer *et al*., 1999) [2]. Furthermore, there will be bioaccumulation of persistent pesticides in food products of animal origin such as meat, fat, fish, eggs and milk (Lehotay *et al.*, 2005) [3].

Insecticides are applied on floor litters and walls of the poultry houses, also on equipments within the house or in some cases directly on the birds as vapours, dust or spray leading to the contamination of the external and internal milieu of birds. Indirect exposure of insecticides to the birds occurs through the use of insecticide contaminated poultry litter e.g. rice hulls and wood shavings (Amure and Stuart, 1978) [4] and feed constituents having insecticide residue are used in poultry ration (Naber, 1977) [5].

There is voluminous literature on imidacloprid toxicity in laboratory animals particularly mice (El-Gendy *et al.*, 2010 [6]; Badgujar *et al.*, 2013 [7]; Bagri *et al.*, 2013 [8]) and rat (Jain *et al.*, 2004 [9]; Bhardwaj *et al.*, 2010 [10]; Mohany *et al.*, 2012 [11]; Ranjan *et al.*, 2012 [12]) but limited literature is available on experimental studies on imidacloprid toxicity in chickens (Kammon *et al*., 2010 [13]; Balani *et al*., 2011 [14]). Many insecticides has reported to cause immunosupression but exact cause and mode of suppression is not known, as immune system of animals and birds can be affected by various environmental factors, genetic makeup, species, nutritional status and individual characteristics. Rapid development of agrochemical industries and extensive use of pesticides in agriculture necessitate it to investigate not only the acute and chronic toxicity but also immunotoxicity effects of these compounds.

Many insecticides including imidacloprid have been reported to cause excess production of reactive oxygen species (ROS) in animals and poultry. When the production of ROS exceeds the antioxidant capacity in the target cell, leads to the damage of macromolecules such as nucleic acids, lipids and proteins causing alterations in functions of target cell and ultimately leads to cell death (Bachowski *et al*., 1997) [15].

Imidacloprid Toxicity
Imidacloprid, 1[(6-chloro-3-pyridinyl) methyl]-N-nitro-2-imidazolidinimine is the first

chloronicotyl insecticides to be registered for use (Moriya *et al.*, 1992) [16].

Hematological Studies

Bhardwaj *et al.* (2010) [10] noticed that there were no significant changes in hematological parameters of female rats orally administered imidacloprid (5, 10, 20 mg/kg/day) for 90 days.

Balani *et al.* (2011) [14] reported that sub acute exposure of imidacloprid @ 1.25, 1.67 and 2.5mg/kg body weight for 28 days did not cause significant changes in hematological parameters in white leghorn birds. The study showed that hematological parameters [hemoglobin (Hb), packed cell volume (PCV), total erythrocyte count (TEC)] remained unaffected except total leukocyte count that had decreased at the highest dose of imidacloprid only on 28 thday of experiment in birds.

Bagri *et al*. (2013) [8] observed that maximal tolerated dose of imidacloprid in Swiss albino male mice was 110mg/kg body weight. They revealed that oral administration of imidacloprid did not cause any significant effect hematological in mice.

Biochemical Studies

USEPA (1998) [17] reported that sub chronic oral toxicity of imidacloprid at concentrations of 150, 600 and 2400 parts per million (ppm) in Wistar rats for a period of 13 weeks caused increase in serum alanine amino transferase and alkaline phosphatase activities with slight increase in blood clotting time.

Kaur *et al.* (2006) [18] observed that oral administration of imidacloprid at 1 mg/kg body weight for 21 days in cow calves resulted in elevation of plasma alanine transaminase and serum alkaline phosphatase.

Siddiqui *et al*. (2007) [19] reported the biochemical changes induced by daily oral administration of imidacloprid @ 1 and 2 mg/kg body weight to cockerels for 28 days. There was significant increase in plasma glucose, alanine transaminase and aspartate transaminase activities but total cholesterol had not affected. Imidacloprid did not show any sign of inhibition of cholinesterase activity in plasma. They suggested that short-term exposure of imidacloprid might produce stress in the birds.

Zaahkook *et al*. (2009) [20] observed that after 3 and 6 weeks treatment with 1/50 LD50 of imidacloprid in Japanese quails revealed highly significant increase in serum glucose, creatinine, total lipid and cholesterol level and activities of lactate dehydrogenase, alanine transaminase, aspartate transaminase and alkaline phosphatase. They also found that there was significant decrease in serum total protein, albumin and globulin concentrations.

Bhardwaj *et al.* (2010) [10] observed that 90 days oral toxicity of imidacloprid in female rats with 20 mg/kg/day could cause elevated levels of serum alanine transaminase, aspartate transaminase, glucose and blood urea nitrogen, decrease in serum and brain acetyl choline esterase.

Kammon *et al*. (2010) [13] observed that the chickens given imidacloprid at rate of 139 mg/kg body weight via oral gavages showed significant increase in the activities of serum alanine transaminase, aspartate transaminase, alkaline phosphatase and glucose. But the plasma level of total protein and albumin remained unaltered.

Kapoor *et al.* (2010) [21] observed that oral administration of imidacloprid at the rate of 20 mg/kg body weight for 90 days in female rats resulted in decreased levels of superoxide dismutase, catalase, glutathione peroxidase activity in liver and brain, decreased glutathione levels only in liver and increased levels of melondialdehyde in liver and kidney.

Balani *et al.* (2011) [14] noticed that oral administration of imidacloprid in male white leghorn chicken @ 1.25, 1.67 and 2.5mg/kg body weight for 28 days resulted in hypoglycemia during the entire period of study, which was dose dependent. Imidacloprid treated birds showed significant increase in serum glutamate oxaloacetate transaminase activity at 14 and 28 days of experiment, while no significant change in serum glutamate pyruvate transaminase, total protein, total albumin, total globulin and creatinine was reported.

Mohany *et al.* (2012) [11] observed that treatment of male albino rats with imidacloprid at the rate of 0.21 mg/ kg body weight for 28 days orally caused elevation of serum alanine transaminase, aspartate transaminase and alkaline phosphatase and malondialdehyde.

Ranjan *et al*. (2012) [12] studied the effect of imidacloprid toxicity on lipid peroxidation administered @ 1/10th of LD_{50} in male rats and observed that level of lipid peroxidation (LPO) in terms of melondialdehyde was significantly increased in liver, kidney and heart. They added that the level of melondialdehyde was higher in liver as compared to kidney and heart. Pesticide-mediated toxicity caused excessive production of reactive oxygen species that leads to lipid peroxidation and finally culminating into damage to various vital tissues of liver, kidney and heart.

Ivanova *et al.* (2013) [22] observed that administration of Konfidor® (imidacloprid) 50mg/kg body weight and Aktara® (imidacloprid) 4.6 mg/kg body weight in birds revealed increased blood glucose, total protein, cholesterol and activities of aspartate transaminase and alkaline phosphatase in serum.

Soujanya *et al.* (2013) [23] observed that administration of imidacloprid at 80 mg/kg body weight/day by oral gavages for 28 days in male rats resulted in hepatotoxicity which was evident from increased serum alanine transaminase and aspartate transaminase activities, decreased total protein and reduced glutathione concentration in the liver.

Kumar *et al.* (2014) [24] observed that administration of doses of 25, 50 and 75% LD50 imidacloprid orally in female albino mice produced significant decrease in total protein, acetylcholinesterase and DNA. But there was significant increase in RNA in imidacloprid treated group. The alterations were more in 75% LD50 as compared to other doses.

Immunological Studies

Mohany *et al.* (2011) [25] observed that treatment of male albino rats with imidacloprid at the rate of 0.21 mg/ kg body weight for 28 days orally could cause significant increase in the total leukocyte count, total immunoglobulins especially IgG. In contrast, significant decrease in phagocytic activity, chemokinesis and chemotaxis were observed in imidacloprid treated group as compared to the control group. Histopathologically, the spleen tissues of the imidacloprid treated rats displayed low numbers of lymphocytes, some of which appeared to be pyknotic. However, both fibroblasts and bundles, such as trabeculae, occurred in greater numbers. Similarly, thymus tissues in the imidacloprid treated group showed lymphocytic depletion with pyknotic nuclei.

Kammon *et al*. (2012) [26] observed that imidacloprid treatment @ 5 mg/kg body weight caused immunological deleterious effects in chickens. Imidacloprid produced

significant decline in the titre of antibodies against Newcastle disease vaccine, total immunoglobulin and circulating immune complexes in imidacloprid treated group on day 45 as compared to control group. There were no significant changes in the skin thickness in response to DNCB between treated and control group chickens. Histopathology of the bursa of Fabricius revealed edema, lymphocytic depletion in the medulla and cortex and mild interfollicular fibrosis in imidacloprid treated group. The spleen showed mild hemorrhages and lymphocytic depletion. However, supplementation of vitamin E and selenium resulted in marked improvements in humoral immunity and pathology of lymphoid organs.

Badgujar *et al.*, (2013) [7] observed that administration of imidacloprid daily at 10 and 5 mg/kg body weight over 28 days in female BALB/c mice could cause suppression of cell-mediated immune response as was evident from decreased delayed type hypersensitivity (DTH) response and decreased stimulation index of T-lymphocytes to PHA. In spleen, severe depletion of lymphocytes and congestion in white pulp had noticed. Histopathological analysis of footpad sections of mice revealed suppression of DTH response.

Conclusion

Imidacloprid toxicity causes oxidative stress and immunosupression. Imidacloprid is responsible for hepatotoxicity which leads to significant increase in activities of mean serum alanine transaminase, aspartate transaminase, lactate dehydrogenase and alkaline phosphatase.

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