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IMMUNO- AND GENOTOXICITY INVESTIGATION ON GESAPRIM HERBICIDE IN RABBITS AND THE AMELIORATING ROLE OF AKROPOWER

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ABSTRACT

Atrazine (Gesaprim®) is the most widely used broad-spectrum herbicide in the universe. Unintentional overspray of Atrazine (ATR) poses a potential immune- and genotoxic impacts. Akropower® is a nutritional adjuvant, consists mainly of licorice root extract fermented with Aspergillus oryzae (glycyrrhizic acid); vitamin c (ascorbic acid) and butylated hydroxy toluene (BHT). The molecular mechanisms responsible for ATR-induced immunotoxicity, however, are little understood. We aimed at elucidating the exact immune- and genotoxic mechanisms of ATR in rabbits and the ameliorating role of Akropower® against such toxic effects. Forty male New Zealand white rabbits (1.5 kg ± 20%) were utilized and appointed into 4 equal groups. group 1: control; group 2: Received ATR at 1/10 LD_{50} (2475 ppm) via food; group 3: Received Akropower at 1 ml/liter/day via drinking water; group 4: Received both ATR and Akropower associatively by the same mentioned dosage and course. Atrazine and Akropower exposure was accomplished for 60 days. Both control and treated animals were vaccinated after 4 weeks of experiment by s/c injection of 0.5 ml of rabbit hemorrhagic disease virus (RHDV). Atrazine exposure resulted in significant reduction in lymphoid organs weight; significant decrease in serum total protein and albumin levels; significant decrease in serum RHDV antibody titer only after four weeks of vaccination; up-regulation of spleen Fas and Caspase-3 genes; down-regulation of thymus IL- 9 gene; significant decrease in the diameter and thickness of skin reaction to tuberculin; leucopenia; lymphopenia beside induction of oxidative stress (significantly increased blood MDA and decreased GSH level). Histopathological alterations in liver, spleen and thymus gland were also observed. In addition, marked apoptosis in the spleen and thymus gland were recorded on immunohistochemical examination by Caspase-3 technique. On the other hand, marked improvement of the deteriorated parameters and histopathological alterations were recorded on the co-administration of Akropower with Atrazine. In conclusion, induction of apoptosis by over expression of spleen Fas and Caspase-3 genes that mediate the extrinsic pathway; down regulation of thymus IL-9 gene that suppresses cell proliferation and induction of oxidative stress could give a new explanation for the exact immune- and genotoxic mechanisms of Atrazine. Akropower normalizes ATR-induced immune- and genotoxicity by promoting the antioxidant capability and consequently reinforces the immune function and suppresses apoptosis.

Keywords: Atrazine, Akropower, immunotoxicity, Fas, Caspase-3, IL- 9, rabbits.

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INTRODUCTION

In the present era of green revolution, human population is being expanding swiftly. Forests have been utilized for abode construction, deteriorating environmental balance on one hand **(Ullah, 2014).** On the other hand we are confronted with the emerging and expanding problem of pollutants **(AusAID, 1996; Jacinto, 1997 and Klumpp *et al.,* 2002).**

Pollutants include untreated effluents from industries; domestic wastes and distinctive chemicals such as pesticides used in agriculture or in safety measures **(Gagnaire *et al.,* 2004; Jain *et al.,* 2005; Mustapha, 2008; Naeem *et al.,* 2010 and Abu-Darwish *et al.,* 2011).**

Pesticides are designed to control pests, but they can also be toxic for undesirable plants and mammals **(Nesheim *et al*., 2017)**.

Herbicides, usually known as weed killers, have become an essential part of landscape maintenance since chemical weed control frequently is the more economical route than hand or mechanical weeding **(Kellogg *et al.,* 2000).**

Atrazine "ATR" (Gesaprim®) [(6-chloro-N-ethyl-N'-(1-methylethyl)-triazine-2,4-diamine)] is a selective post-emergence chlorotriazine herbicide worldwide used in many countries for the control of broad leaf and grassy weeds in agricultural crops **(Cerdeira *et al.,* 2005).** It is applied on crops such as corn, sugarcane, sorghum, pineapple and in conifer reforestation plantings **(Dong *et al.,* 2009).**

Environmental or occupational exposure to ATR herbicide can produce toxic consequences in animals and humans **(Hayes *et al*., 2011; Rinsky *et al*., 2012 and Gao *et al*., 2016).**

The immunotoxic potential of ATR was previously studied where it suppressed the innate immune response **(Soltanian, 2016),** and the cell-mediated; humoral and nonspecific immune function **(Chen *et al*., 2013 and Thueson *et al*., 2015).** It causes misbalance in the major organs of the immune system, specifically thymus gland, suggesting that it may be the main target of ATR **(Chen *et al.,* 2013).** Moreover, splenocytes and other lymphoid cells' apoptosis was also recorded following ATR exposure **(Zhang *et al.,* 2011; Sharma *et al.,* 2014; Song *et al*., 2015 and Yuan *et al*., 2017**). The induction of apoptosis can be a possible mechanism of ATR that may compromise the immune function **(Chen *et al.,* 2013).**

Akropower® is a nutritional supplement, consists of licorice root extract fermented with aspergillus oryzae, malic acid, zinc sulfate, vitamins (ascorbic acid, B1, B2, B6, B12, pantothenic acid and biotin), choline chloride, inositol, sodium propionate and butylated hydroxy toluene (BHT) ***(www.akronbio.com).***

Previous studies confirmed the immunostimulant and/or antioxidant actions of the individual Akropower® components including glycyrrhizic acid **(Michaelis *et al.,* 2010);** glycyrrhetinic acid (GA) **(Mohammed *et al.,* 2015 and Abd El-Twab *et al.,* 2016);** ascorbic (**Adikwu and Deo, 2013**) and malic acids **(Al-Qayim and Mashi, 2014).**