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CHRONIC THIACLOPRID EXPOSURE IMPAIRS COGNITIVE FUNCTION AND TRIGGERS MITOCHONDRIAL APOPTOSIS PATHWAY IN RAT STRIATUM AND HIPPOCAMPUS: NEUROPREVENTIVE EFFECT OF BITTER APRICOT KERNELS EXTRACT *(PRUNUS ARMENIACA L.)*

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ABSTRACT

Thiacloprid (THI) is a nicotinic receptor agonist widely used as pesticide in Algeria, however it is susceptible to accumulate in various fruits and vegetables and pouring downstream into food plates and contributes to the development of neurodegenerative diseases. Conversely, several natural compounds are provided with cytoprotective potential and, therefore, are able to act against the harmful effects of toxicants such as pesticides. This study focused on striatum (str) and hippocampus (hipp) mitochondrial toxicity assessment, evaluation of behavioral function and intrinsic apoptosis pathway in rats exposed to THI at low-dose (0.020 mg/kg) for 3 months. In addition, this study examined neuroprotective potential of bitter apricot kernel extract when administered concomitantly with THI at the dose of 50 mg/kg. In current study, assessment of mitochondrial permeability transition pore (mPTP) and swelling, evaluation of mitochondrial redox status, cholinergic function (Ach E) and apoptosis markers (Caspase 9 and 3, Bax and Bcl2, Cytochrome c and cytosolic calcium) were performed in both brain areas, besides behavioral and histopathological examination. The results showed an increase of lipid peroxidation in both of str and hipp with a values of 1,14 ± 0,04 nmol/mg of proteins (pr) and 1,58 ± 0,09 nmol/mg pr. respectively and a significant decrease in GSH (0,09 ± 0,01 mmol/mg pr. in hipp and 0,08±0,01 mmol/mg pr. in str), the results also showed a change in the activity of antioxidants enzymes SOD (16,37±1,09 UI/mg pr. in hipp14,54±1,46 UI/mg pr. in str) , CAT (0,010±0,01 UI/mg pr. in hipp and 0,005±0,004 UI/mg pr. in str), GPx (0,01± 0,001 nmol/mg pr. in both hipp and str) and GST (23,73±1,68 UI/mg pr. in hipp and 17,56± 1,04 UI/mg pr. in str), as well as an abrupt increase in mPTP opening with a value of (0,057±0,005 in str and 0,054±0,005 in hipp) , which leaded to mitochondrial swelling where the level o mitochondrial swelling was (0,016±0,002 in str and 0,106±0,003 in hipp), the swelling was associated also with a high releasing of Cyt-c with a values of (4,48 ± 1,26 µg/ml in str and 5,32 ± 1,08 µg/ml in hipp) and Ca++(2,26±0,06 mmol/l in str and 2,32±0,07 mmol/l in hipp) into the cytosol, the results also showed a significant decreasing of Bcl2 (16,4 ± 1,86 ng/mg pr in str and 14,8± 0,82 ng/mg pr in hipp), in the other hand the rates of caspase-9 were (278±14 mAbs/mg pr.) in str and 212 ±24 mAbs/mg pr. in hipp), caspase3 (184± 16mAbs/mg pr.) in str and 250 ±14mAbs/mg pr. in hipp), and BAX (0,926 ng/mg pr in str and 1,189 ng/mg pr in hipp) were increased. The results of this study revealed also a decrease of memorization processes and learning abilities, at the same time a decrease in Ach E activity (14,02± 0,78 nmol/min/mg pr. in str and 22,35± 1,77 nmol/min/mg pr. in hipp) was recorded. Inversely, bitter apricot kernels extract showed higher cytoprotective potential against THI neurotoxicity, since mitochondrial redox homeostasis and membrane integrity were recovered, cognitive impairment and brain tissue damage were also prevented. In conclusion, THI induced mitochondrial disorders, triggered apoptosis signaling pathway and impaired cognitive functions which were prevented by bitter apricot kernels extract when associated with this pesticide.

Keywords: Thiacloprid, Extract, Striatum, Hippocampus, Cognitive function, Mitochondrial apoptosis

INTRODUCTION

It is recognized that the benefits of pesticides are inherent in crop protection and in increasing economic potential in agriculture and human health by increasing agri-food and crop production and controlling some disease-carrying insects **(Messiad et al. 2015)**. However; The main reason for their toxicity could be the presence of similar targets in both pests and non-target species, including humans. Neonicotinoids (NNs) are considered to be the most important synthetic pesticides used to control harmful insects in plant and animal health over the last few decades and were able to bind to nicotinic acetylcholine receptors (nAChRs), causing excitation, abnormal paralysis and death of harmful organisms, developed to replace organophosphorus and carbamate insecticides **(Schaafsma et al. 2015; Pang et al. 2020)**. However, if these pesticides have a potent agonist against nAChRs of target insects, there is multiple evidence that these pesticides have low affinity for the same receptors in vertebrates **(Costas-Ferreira and Faro 2021)**, raising the question of how neonicotinoids might act for animal non-target organisms can be neurotoxic. It has been reported that the toxicity of NN focuses on the cellular and molecular integrity of the organism, resulting in carcinogenic, endocrine disorders **(Sekeroglu et al. 2014)**, neurotoxic **(Cimino et al. 2017)**, hepatotoxic effects **(Alarcan et al . 2020)**. Among the most commonly used NNs in Algeria is Thiacloprid (THI), (Z)-N-[3-(6-Chloro-pyridin-3-ylmethyl)-thiazolidin-2-ylidene]cyanamide), an organochlorinated insecticide of the family the chloroprynydilic neonicotinoids **(Galdikova et al. 2019)**. This insecticide was registered in 2000 under the trade name Calypso 480SC (480 g.L-1) **(Schwarzbacherov et al. 2019).** The mode of action of this pesticide in target organisms is to interrupt the transmission process of nerve impulses after its binding to nAChRs in neurons **(Galdikova et al. 2019).** Literature data indicate that THI is toxic to mammals at both acute and chronic exposures at low or high doses, causes neurotoxicity and attenuates locomotor activity in rats treated with 3.1 mg/kg body weight THI **(Vivek et al .2020).** In addition, a previous study showed that this pesticide can cause central nervous system disorders (Alzheimer's disease, Parkinson's disease, schizophrenia, depression), which were thought to be associated with a change in the density of the nAChRs subtype in rats who have been exposed to high doses of THI **(Cimino et al. 2017).** It is worth noting that the