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MITIGATIVE EFFECT OF HESPERIDIN ON ACRYLAMIDE PROVOKED NEUROTOXICITY IN RATS

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ABSTRACT
Neurotoxicity can result from exposure to substances used in chemotherapy, radiation treatment, drug therapies, certain drug abuse, and organ transplants, as well as exposure to heavy metals, certain foods and food additives, pesticides, industrial and/or cleaning solvents, cosmetics, and some naturally occurring substances. Symptoms may appear immediately after exposure or be delayed. They may include limb weakness or numbness, loss of memory, vision, and/or intellect, uncontrollable obsessive and/or compulsive behaviors, delusions, headache, cognitive and behavioral problems and sexual dysfunction. Individuals with certain disorders may be especially vulnerable to neurotoxins

Key words: *Neurotoxicity, heavy metals, industrial, cleaning solvents numbness, loss of memory, vision.*

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INRODUCTION

Neurotoxicity is concerned with the adverse changes in the structure or function of the nervous system. Herein, a neurotoxin is considered to be a substance which elicits a pathological response primarily or specifically on the nervous system. The complexity of the nervous system results in a broad range of potential targets and adverse squeal, since the activity of the nervous system maintains a balance between all the various organs in the body. Neurotoxicity occurs when the exposure to natural or artificial toxic substances, which are called neurotoxins, alters the normal activity of the nervous system in such a way as to cause damage to nervous tissue. This can eventually disrupt or even kill neurons, key cells that transmit and process signals in the brain and other parts of the nervous system. Neurotoxicity has been found to be a major cause of neurodegenerative diseases such as Alzheimer's disease [4].

Acrylamide (ACR) is used in the chemical industry to manufacture polymers, as a grouting agent, and in the production of specialty monomers. Humans can be exposed to ACR by ingestion, inhalation, and

skin contact. Recent investigations have indicated that ACR is formed in fried food .Humans exposed to ACR over prolonged periods of time can experience peripheral neuropathy, characterized by a dying back of elongate nerve cell axons [5, 6, 7]. ACR is neurotoxic, genotoxic, and carcinogenic in rodents [8, 9].

MATERIALS AND METHODS

Animals

This study was conducted using male albino wistar rats weighing (150-200 g). Animals were obtained from the Animal House, Mohammed Sathak A.J.College of Pharmacy, The Tamilnadu Dr. M.G.R. Medical University, and Chennai, India. Animals were fed with commercially available standard rat pelleted feed from M/s Hindustan Lever Limited, Bangalore, India. The feed and water were provided *ad libitum*. The animals were deprived of food for 24 h before experimentation but allowed free access to tap water throughout. The rats were housed under conditions of controlled temperature (25±2 °C) and were acclimatized to 12-h light: 12-h dark cycles. Experimental animals were used after obtaining prior permission and handled according to the University and institutional legislation as regulated by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Social Justice and Empowerment, Government of India.

Experimental Protocol:

The experimental animals were randomized into four groups of six rats each as follows:

Group 1: Control rats received normal saline (1 ml/kg, p.o.) for 14 days.

Group 2: Toxic control rats received ACR (50 mg/kg; i.p.) three times per week for 2 weeks.

Group 3: Drug control groups received HDN (100 mg/kg, p.o.) for 14 days

Group 4: Rats treated with ACR (50 mg/kg, i.p) three times per week for 2 weeks and 1 hour

Later after administration of ACR, co treated with HDN (100mg/kg; i.p) for 2 weeks.

Tissue Preparation:

Twenty-four hour after administration of the last dose, the animals were anaesthetized using ether and sacrificed by cervical decapitation. Brain tissues were cleared of adhering fat, cut into small pieces and then homogenized in ice-cold homogenization buffer (10 mM KH_2PO_4 (pH 7.4); 20 mM EDTA; 30 mMKCl) to give 10% homogenate. The homogenate was then made into aliquots and was used for the determination of brain contents GSH and MDA and enzymatic activities of SOD, CAT, GSH-Px, and GST.

Histopathological Examination of the Brain

Two rats from each group were sacrificed under light ether anesthesia (24 h after the last dosing), and brain samples of all groups were preserved in 10% neutral buffered formalin. Brain sections were cut at 5 µmthickness using a rotary microtome and stained with haematoxylin and eosin.Sections were examined and photographed under a light microscope (300X).

RESULTS

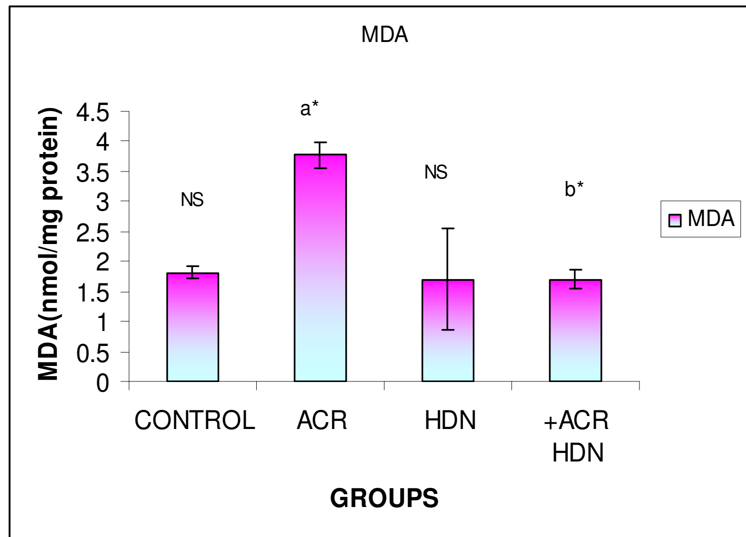
Table I.Effect of Hesperidin and Acrylamide on the activities of brain enzymeantioxidants

Groups	SOD (U/mg of protein)	CAT (U/mg of protein)	GPx (U/mg of protein)	GST (nmoles min^{-1} mg^{-1} protein)
Group 1 (Control)	10.18 ± 0.32	80.04± 3.78	19.65 ± 0.48	5.59±0.45
Group 2 (ACR)	5.14 ± 0.35 [a,*]	44.09 ± 3.58 [a,*]	9.26 ±0.75 [a,*]	3.18 ± 0.21 [a,*]

Group 3 (HDN)	10.61 ± 0.39 NS	80.71 ± 3.90 NS	20.10 ± 0.77 NS	4.95 ± 0.17 NS
Group 4 (ACR + HDN)	8.50± 0.41 b,*	72.36 ± 5.38 b,*	16.51 ± 0.71 b,*	5.43± 0.1 b,*

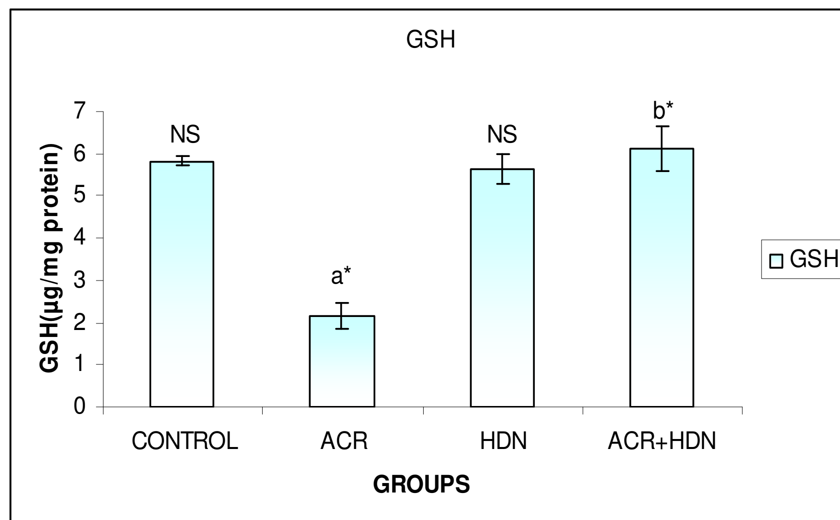
Results are expressed as mean ± S.D. for six rats.

Level of MDA in the brain tissue of experimental animals



Results are given as mean ± S.D. for six rats. Comparisons are made between:
a-Group I (Control) and Group II (ACR)
b-Group II (ACR) and Group IV (ACR+HDN)
NS- Group I(Control) and Group III (HDN)
Statistically significant ($P < 0.05$); NS – non-significant.

Levels of GSH in the brain tissue of experimental animals



Results are given as mean ± S.D. for six rats. Comparisons are made between:
a-Group I (Control) and Group II (ACR)
b-Group II (ACR) and Group IV (ACR+HDN)
NS- Group I(Control) and Group III (HDN)
Statistically significant ($P < 0.05$); NS – non-significant.

Histopathology Section of Brain Tissues

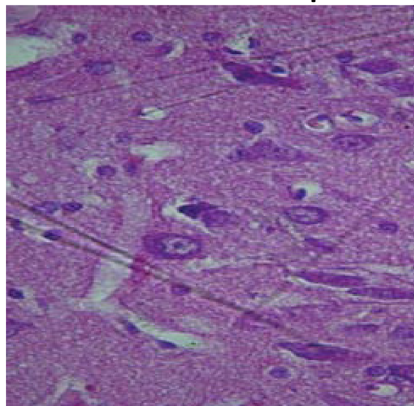


Fig.A.Control (Group 1)

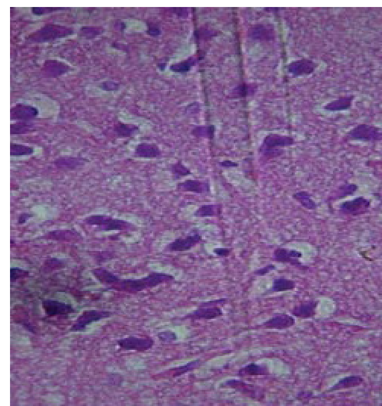


Fig.B. ACR alone (Group 2)

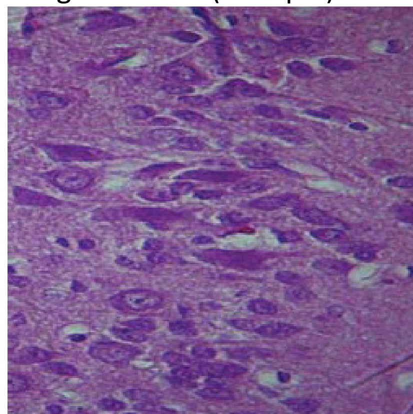


Fig.C. HDN alone (Group 3)

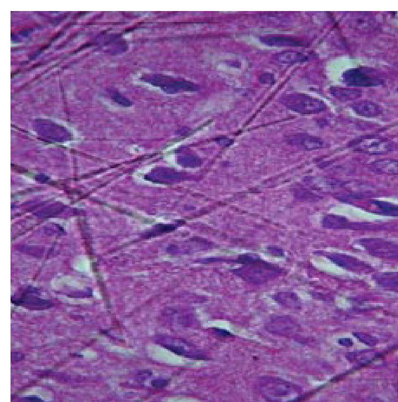


Fig.DACR +HDN (Group 4)

DISCUSSION

The neurotoxicity of ACR and experimental animals as well documented in a series of reports since the Swedish Food Administration alarm in 2002 [10]. ACR has been shown to be carcinogenic in animals, and has been classified by the WHO/IARC among others as 'probably carcinogenic for humans'. The current study deals with the preventive effects of citrus flavonoid hesperidin (HDN) against ACR induced neurotoxicity in rats. Previously, it was reported that ACR induced severe biochemical, histopathological and genotoxic alterations in rats [11]. ACR is a small organic molecule with very high water solubility. The metabolism of ACR in the body may result in the generation of reactive oxygen species (ROS) which play a role in the oxidative stress of ACR and cause oxidative DNA damage, which may play a role in its carcinogenicity [12]. Treatment with HDN increased the activity of SOD, CAT and GPx which may be due to the scavenging of the radicals generated by ACR induced lipid peroxidation thereby decreasing the utilization of these antioxidant enzymes to reduce the ACR induced oxidative insult. This might be responsible for the increased activities of antioxidant enzyme on administration of HDN which is in line with the previous reports that HDN is an effective scavenger of free radicals [13].The histopathological findings demonstrated that administration of ACR induced various degenerative changes in neuronal cells, which confirmed the biochemical evidence of oxidative stress. Treatment with HDN obviously mitigated the histopathological changes induced by ACR.

CONCLUSION

The present data indicate that ACR induced neurotoxicity might be related to oxidative stress. Co administration of HDN lessened the negative effects of ACR on the brain by inhibiting free radical mediated process; an effect that could be attributed to the antioxidant property of HDN.However, future mechanistic studies are

highly warranted to elucidate the protective nature of HDN on ACR provoked oxidative neurotoxicity.

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