CHAPTER 35

MEDICAL SCIENCES
PHARMACOLOGY

Doctoral Theses

01.   BEHL (Tapan)
Evaluate the Effect of Terminalia Catappa Fruit and Seed Extract in Streptozotocin Induced Diabetic Retinopathy in Rats.
Supervisors: Prof. Anita Kotwani and Prof. Thirumurthy Velpandian
Th 23147

Abstract
(Verified)

To evaluate the effect of Terminalia catappa fruit and seed extract in streptozotocin induced diabetic retinopathy in rats. Streptozotocin-induced chronic diabetic rat model was used. Fourteen groups (n=8) including hydro-alcoholic fruit and seed extract of Terminalia catappa in 20mg/kg, 30mg/kg and 40mg/kg were studied for 12 weeks. Blood glucose, body weight and urine volume were measured weekly. Lenticular images, fundus images and retinal vessels tortuosity was evaluated at 2nd, 4th, 6th, 8th, 10th and 12th week. Histological changes, glycosylated hemoglobin, inflammatory, angiogenic and oxidative biomarkers were estimated at 12th week. Fruit and seed extract of T. catappa significantly decreased blood glucose (p<0.001), urine volume (p<0.01) and increased body weight (p<0.01) in a dose-dependent manner in diabetic rats. Treatment with fruit extract of T. catappa 30mg/kg, 40mg/kg, all three doses of seed extract and glibenclamide brought back HbA1c to normal levels. Cataract lens grading: diabetic control-5; glibenclamide, fruit extract of T. catappa 20mg/kg-2, 30mg/kg-1, 40mg/kg-0; seed extract of T. catappa 20mg/kg-1, 30mg/kg, 40 mg/kg-0. Fundus images showed less haziness and neovascularization in treated groups compared to diabetic control. Retinal arteriole and venule tortuosity decreased significantly (p<0.01) in the treatment groups. Terminalia catappa fruit extract in 40mg/kg dose, seed extract in 30mg/kg and 40mg/kg dose showed no thickening of basement membrane of retinal blood vessels. Terminalia catappa fruit and seed extract in all doses showed significant reduction in IL-1β, TNF-α level (anti-inflammatory); significant reduction in VEGF, PKC-β and increase in endostatin levels (angiogenic); reduction in LPO level and increase in GSH, SOD, catalase, T-AOC levels (oxidative). No additive effect of glibenclamide was observed with fruit and seed extract of T. catappa 40mg/kg dose. Hydro-alcoholic fruit and seed extract of Terminalia catappa has multiple actions: anti-glycosylating, anti-hyperglycemic, anti-inflammatory, anti-angiogenic and anti-oxidant and has a potential to be used in diabetes-induced retinopathy.

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1. Introduction 2. Review of literature 3. Aims and objectives 4. Materials and methods 5. Results 6. Discussion 7. Summary and conclusion. References. Annexures. List of Publications.

02.   HALDER (Sumita)
Effect of Cadmium and Chromium Exposure on Neurobhaviour and Gene Expression of Antioxidant Enzymes in F1 and F2 Generation MICE and its Modulation by Quercetin.
Supervisors: Prof. S. K. Bhattacharya, Dr. P. K. Mediratta and Dr. B D Banerjee
Th 23146

Abstract
(Not Verified)

We studied the effect of cadmium and chromium on cognition and oxidative stress in two generations of mice and the modulation of these parameters by quercetin. F_0 mice were treated for 7 days with $CdCl_2$ (1.2mg/kg, i.p), $CrCl_3$ (200μgm/kg, i.p.) or quercetin (25,50,100 mg/kg, i.p.) during their pregnancy, lactation and for a total period of gestation and lactation. F_1 generation mice were reared till 100 days of age. Animals were crossed again to produce F_2 generation. Both F_1 and F_2 generation animals in their adulthood were tested for memory and learning by Morris Water Maze test, passive avoidance paradigm and elevated plus maze test. They were tested for locomotor functions by Rota rod and photoactometer. Brain tissue was tested for glutathione-S-transferase (GST) and catalase activity along with their gene expression. MDA and glutathione levels were also measured. The levels of Cd and Cr in brain tissue was estimated using Atomic Absorption Spectrophotometer.Cd exposure impaired memory which was reversed to some extent on cotreatment with quercetin. Chromium showed an improvement in spatial memory and acquisition and retention memory for the gestation plus lactation group. The activity and expression of antioxidant genes were increased by Cd in most groups and the effect was ameliorated by quercetin co-treatment. Cr however showed a varied response. Cd and Cr levels were high in brain tissue but decreased on cotreatment with quercetin. The MDA and Glutathione levels matched with the metal levels in most groups. Cadmium exposure in the perinatal period altered cognition, the oxidative stress parameters along with the gene expression of the antioxidant enzymes of the F1 generation mice. Chromium showed some improvement in memory in F_1 generation but varied response was seen in oxidative stress parameters. The F_2 generation remained mostly unaffected.

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03.　MD. SHAMSUZZAMAN
Pharmacological Studies on the Possible Mechanisms Involved in Theophylline Induced Cardiotoxicity in Rats.
Supervisors: Prof. A. Ray and Prof. Kavita Gulati
<u>Th 22959</u>

Abstract
(Not Verified)

The study evaluated the cardiotoxic potential of theophylline and investigated the mechanism of action in experimental animals in order to propose and device strategies for its safer use. Rats were injected with aminophylline (the soluble ethylenediamine salt of theophylline) once daily for 7 days and then were anesthetized, dissected and connected to the software based BIO-PAC MP-36 for measuring cardiac parameters viz. heart rate, mean BP and ECG. Blood and heart tissue were collected for various biochemical and immunological assays for oxidative stress and cardiac biomarkers.Interactions of aminophylline with various drugs like 2-choloroadenosine (2-CADO, adenosine agonist), α-tocopherol (antioxidant), L-NAME (NOS inhibitor), and salemeterol (β₂-agonist), as well as effects of restraint stress (RS) on aminophylline induced cardiac and biochemical parameters were also studied. Aminophylline (50, 100 and 150 mg/kg) induced dose dependent tachycardia, with maximal effects at 150 mg/kg. There was also dose related marginal increases in mean BP after the higher dose of the drug tested. Aminophylline also induced consistent T-wave inversions at 150 mg/kg, whereas, no significant changes were seen in the other ECG parameters like PR, RR and QTc intervals. Pretreatment with the anti-oxidant, α-tocopherol (20 and 40 mg/kg) dose dependently attenuated the aminophylline induced tachycardia, and also abolished the appearance of T-waves from the ECG, and reverted the aminophylline induced reductions in T-wave area of ECG interval extraction. Whereas, MDA levels increased, GSH and SOD levels were inhibited but increase in 8-OHdG levels in the serum. Cardiac biomarkers in blood showed that increased CPK-MB,

Troponin-I and ADMA levels but BNP levels were not much affected as compared to controls. Further, in the interaction studies, (a) combined treatment with beta agonists and (b) prior exposure to restraint stress, also potentiated aminophylline induced cardiotoxicity, which were accompanied by predicatable changes in oxidative stress and cardiac biomarkers.

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04.   THAKUR (Tarun)
Pharmacological Studies on the Possible Role of Nitric Oxide (NO) and NO Mediated Signaling Pathways in the Regulation of Stress-Induced Immunological Changes in Rats.
Supervisors: Prof. Kavita Gulati and Prof. A. Ray
Th 22960

Abatract
(Not Verified)

The study evaluated the effects of chronic predictable stress (CPS) and chronic unpredictable stress (CUS) on adaptive immune responses and role of nitric oxide (NO) and NO-mediated signaling pathways during its regulation, in keyhole limpet hemocyanin (KLH)-sensitized rats. Animals were randomly assigned to experimental stress protocols i.e. CPS and CUS for 14 consecutive days. Estimated parameters were: IgG antibody levels, delayed type hypersensitivity (DTH) response, cytokines (IL-1β, IL-6, IFNγ and IL-4), total nitrate and nitrite (NOx) and 3-nitrotyrosine (3-NT, a marker of peroxynitrite formation) and elevated plus maze (EPM) test. Treatments were with nitrergic agents [Isosorbide dinitrate(ISDN): NO donor, aminoguanidine (AMG): iNOS-inhibitor and 7-nitroindazole (7-NI): nNOS-inhibitor and modulators of NO-signaling pathways [Memantine: NMDA-receptor antagonist, pyrrolidinedithiocarbamate (PDTC): NFκB-inhibitor and sildenafil: phosphodiesterase-5-inhibitor]. Exposure to both CPS and CUS-induced decrease in IgG levels, DTH response, IFNγ and IL-4 levels and increased IL-1β, IL-6 as compared to that in control immunized rats, which was accompanied with elevated NOxand 3-NT levels, thus suggesting involvement of NO during immunomodulation. This induced immunosuppression was more in CUS relative to CPS. AMG and PDTC pretreatments caused further reduction in IgG levels, DTH response, attenuated cytokines (IL-1β, IFNγ, IL-4 and IL-6), attenuated NOx, 3-NT levels and reversed behavioral suppression. But ISDN, 7-NI, memantine and sildenafil pretreatments did not produce any significant effect. This study highlights the involvement of iNOS and NFκB-signaling and lesser role of nNOS, via cGMP or NMDA-receptor in adaptive immune responses during chronic stress. Further, differential degree of immunomodulation is observed, which depends on the predictability of the stressor and is supported/corroborated with the findings of pro-inflammatory, TH1 and TH2 cytokines. Thus a better understanding of NO-mediated signaling mechanism is of immense significance, which may have implications for devising strategies, for the pharmacological treatment of stress related disorders.

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