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Evaluation of the neuro-cognitive toxicity of Dimethoate after sub-chronic exposure in male Wistar rat

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بسمه تعالی

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سوگند نامه

اینک که برای پرداختن به پیشه داروسازی آماده هستم با ایمانی کامل و اعتقادی محکم به آفریننده بزرگ جهان هستی و کتاب آسمانی خود سوگند یاد میکنم و در پیشگاه با عظمت او پیمان می بندم و خداوند را در عهد و میثاق پایدار خود شاهد و گواه می گیرم که در این امر خطیر همواره در راه راست و درست انسانی گام بردارم و عزت و حرمت طبابت و مصلحت بیماران و رنجوران را بر هر چیزی برتر بدانم و در برابر فریب هوای نفس از جاده صلاح منحرف نشوم و به هرکاری که با راه و رسم الهی و آئین پرهیزکاری و شرافت انسانی و پزشکی مغایرت دارد دست نیازم. قسم یاد میکنم اسرار بیماران را محفوظ و هرگز داروهایی که موجب مرگ انسان ها و یا سقط جنین می گردد در اختیار افراد جامعه نگذارم. همواره خواهم کوشید بخاطر مسائل مادی بیماران را از خدمات پزشکی و دارویی محروم نسازم تا با روبی گشاده و وجدانی آزاد در پیشگاه خداوند بلند مرتبه حاضر شوم.

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بدینوسیله گواهی می نماییم کلیه نتایج ارایه شده در این پایان نامه حاصل کار اینجانب بوده و با رعایت کلیه اصول علمی و اخلاقی تکارش شده است. تمام یا قسمتی از آن توسط فرد یا مرکز علمی دیگر به هیچ صورتی ارایه یا ثبت نشده است. موارد استفاده شده از آثار دیگران با مشخصات کامل منبع ذکر گردیده است و همچنین پاسخگویی و مسئولیت در قبال نتایج به عهده اینجانب خواهدبود.

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To

My Parents

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Abstract:

Background: Organophosphate pesticides like Dimethoate are widely used in agriculture, posing potential risks to human health, mostly due to dietary and occupational exposure, and the environment. Despite regulatory measures, concerns persist regarding their neurotoxic effects, particularly on cognitive function. The aim of the present study was to evaluate the neuro-cognitive toxicity of Dimethoate after sub-chronic exposure in male Wistar rats.

Methods and Materials: Male Wistar rats were exposed to sub-chronic doses of Dimethoate (2mg/kg and 4mg/kg) via oral gavage for a specified period. Behavioral tests, including the Elevated Plus Maze, Open Field Maze, Novel Object Recognition Memory Test, were conducted to assess cognitive function. Biochemical assays were performed to measure acetylcholinesterase activity, oxidative stress markers, brain-derived neurotrophic factor (BDNF) and glycogen synthase kinase-3 beta (GSK-3β) in hippocampal tissue. Additionally, gene expression of inflammatory factors was evaluated.

Findings: Sub-chronic exposure to Dimethoate resulted in Improvements in learning memory in treated rats according to a significant increase in total exploration time and discrimination ratio in NORM test; also, better performance in anxiety tests in treated rats specially in 4mg/kg dose according to a significant increase in the percentage of time and entries to open arm at 4mg/kg treated rats in EPM test and a significant increase in time and entries to inner zone in treated rat in OFM test. Both doses of Dimethoate led to a significant decrease in acetylcholinesterase activity in plasma and hippocampal tissue. Additionally, oxidative stress markers and inflammatory factors were significantly elevated in Dimethoate-exposed groups compared to control. While there was a nominal decrease in BDNF, GSK-3β levels significantly increased in hippocampal tissue following Dimethoate exposure.

Discussion: Our findings suggest that sub-chronic exposure to Dimethoate adversely affects neuro-cognitive function in male Wistar rats. The observed behavioral changes, along with alterations in biochemical and molecular parameters, indicate potential neurotoxic effects of Dimethoate. These results underscore the need for further investigation into the mechanisms underlying Dimethoate-induced neurotoxicity and the development of strategies to mitigate its adverse effects on neurological health. Additionally, these findings emphasize the importance of regulatory measures to minimize human and environmental exposure to organophosphate pesticides.

Keywords: Dimethoate; Organophosphate; Male Wistar rat; Learning and memory; Anxiety; Oxidative stress; Inflammation

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ABBREVIATIONS

AChE=Acetylcholinesterase

BChE=Butyrylcholinesterase

BDNF=Brain derived neurotrophic factor

cDNA=Complementary Deoxyribonucleic Acid

ChE=Cholinesterase

CNS=Central nervous system

DIM=Dimethoate

DMDTP=dimethyldithiophosphate

DMTP=dimethylthiophosphate

DNA=Deoxyribonucleic Acid

DSM-5=Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

EC=Emulsifiable concentrate

EDTA=Ethylenediamine Tetraacetic Acid

ELISA=Enzyme Linked Immunosorbent Assay

EPM=Elevated Plus Maze

ERK1/2=Extracellular regulated kinase ½

GABA=Gamma-aminobutyric acid

GAPDH= Glyceraldehyde-3-phosphate dehydrogenase

GFAP=Glial fibrillary acidic protein

GPx=glutathione peroxidase

GR=glutathione reductase

GSH=glutathione

GSK-3α=Glycogen synthase kinase-3 alpha

GSK-3β=Glycogen synthase kinase-3 betta

IL-1β=Interlukin-1 betta

IL-6=Interlukin-6

MDA=Malondialdehyde

mRNA= Messenger Ribonucleic Acid

NF-κB=Nuclear Factor-kappa B

NORM=Novel Object Recognition Memory

OFM=Open Field Maze

OP=Organophosphate

PCR=Polymerase Chain Reaction

RNA=Ribonucleic Acid

TBARS=Thiobarbituric Acid Reactive Substance

TNF-α=Tumor necrosis factor-alpha

ULV=Ultra-low volume