UNIVERSITI PUTRA MALAYSIA

NEUROTHERAPEUTIC EFFECTS OF CURCUMIN ON LEAD-INDUCED TOXICITY IN A RAT MODEL WITH EMPHASIS ON CEREBELLAR DAMAGE

ABUBAKAR KABEER

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By

ABUBAKAR KABEER

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Master of Science

October 2019

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DEDICATION

This thesis is dedicated to my beloved parents Alhaji Abubakar Adamu and Hajiya Asma'u Abubakar Mukhtar, for their words of motivation, moral supports, guidance, patient, and reinforcement in search of excellence.

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the degree of Master of Science

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October 2019

Chairman : Associate Professor Ezamin Bin Abdul Rahim, PhD
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Lead (Pb) is a toxic environmental heavy metal that induces serious clinical defect on all organs with the brain, kidney and liver being the primary targets, hence Pb poisoning has been a major threat to public health in developing countries due to human activities. Curcumin is the main active constituent of turmeric rhizome (C*urcuma longa*) with great neuroprotective role as well as being a strong antioxidant and anti-inflammatory properties. This study is aimed at evaluating the therapeutic potentials of curcumin on Pb-induced toxicity in a rat model since the application of chelation therapy is associated with numerous side effects. Thirty-six male Sprague Dawley rats aged 8 weeks weighing between 200 – 250 g were randomly assigned into five (5) groups with 12 rats in Group A (normal saline) and 6 rats each for Group B (LTG) (50 mg/kg of lead acetate for 4 weeks), Group C (RC) (50 mg/kg lead acetate for 4 weeks and left for another 4 weeks without treatment), Group D (Cur100) (50 mg/kg lead acetate for 4 weeks, followed by 100 mg/kg curcumin for 4 weeks) and Group E (Cur200) (50 mg/kg lead acetate, followed by 200 mg/kg curcumin for 4 weeks). All experimental groups received the oral treatment through orogastric-tube on alternate days. Motor functions was assessed using horizontal bar method while Pb concentration in the cerebellum, liver and kidney of the rats were evaluated using inductive coupled plasma mass spectrometry (ICP-MS) techniques. Further, the rats' cerebellum, liver and kidney were fixed in 10% buffered formalin for 5 days and subsequently prepared for histological examination using paraffin method. The Pb-administered rats showed significant decrease in motor activity scores, SOD activity with increase MDA levels and Pb concentration in their cerebellum, liver, kidney and serum with marked alterations in the histological architecture of the cerebellum, liver and kidney. However, treatment with curcumin improved their functional motor activity, reduced Pb concentration in the cerebellum, liver and kidney and ameliorates the markers of oxidative stress as well as attenuating the alterations in the histological architecture of the cerebellum, liver and kidney. Therefore, it is concluded that

curcumin attenuates Pb-induced toxicity via inhibition of oxidative stress and chelating activity in rats.

Keywords: Curcumin, Lead toxicity, ICP-MS, Horizontal bar, Motor coordination, Oxidative stress, Cerebellum.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

KESAN NEUROTERAPEUTIK CURCUMIN KE ATAS KEROSAKAN SEREBELUM DISEBABKAN OLEH PLUMBUM DALAM MODEL TIKUS

Oleh

ABUBAKAR KABEER

Oktober 2019

Pengerusi : Profesor Madya Ezamin Bin Abdul Rahim, PhD
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Plumbum (Pb) adalah logam berat alam sekitar yang toksik yang menyebabkan kecacatan klinikal yang serius pada semua organ-organ badan dimana otak, buah pinggang dan hati menjadi sasaran utama. Curcumin adalah konstituen aktif yang utama dalam kunyit (*curcuma longa*) dengan ciri-ciri antioksidan dan anti-radang yang kuat. Kajian ini bertujuan untuk menilai potensi terapeutik curcumin ke atas ketoksikan yang disebabkan oleh Pb dalam model tikus. Tiga puluh enam ekor tikus iantan jenis Sprague Dawley yang beratnya diantara 200-250g telah dibahagikan secara rawak kepada lima (5) kumpulan dengan 12 ekor tikus dalam kumpulan kawalan (normal saline) dan 6 ekor tikus untuk setiap kumpulan: yang dirawat dengan Pb (LTG) (50 mg / kg plumbum asetat untuk 4 minggu), kumpulan pemulihan (RC) (50 mg / kg plumbum asetat selama 4 minggu dan ditinggalkan untuk 4 minggu lagi tanpa rawatan), kumpulan rawatan 1 (Cur100) (50 mg / kg plumbum asetat selama 4 minggu, diikuti oleh 100 mg / kg curcumin untuk 4 minggu) dan kumpulan rawatan 2 (Cur200) (50 mg / kg plumbum asetat, diikuti oleh 200 mg / kg curcumin untuk 4 minggu). Semua kumpulan eksperimen menerima rawatan selang sehari secara oral melalui tiub orogastrik. Fungsi motor dinilai menggunakan kaedah bar mendatar manakala kepekatan Pb dalam serebelum, hati dan buah pinggang tikus telah dinilai menggunakan teknik ICP-MS. Tikus yang diberi Pb menunjukkan penurunan yang ketara dalam skor aktiviti motor, aktiviti SOD dengan peningkatan tahap MDA dan kepekatan Pb dalam serebelum, hati, buah pinggang dan serum mereka dengan perubahan ketara dalam struktur histologi serebelum, hati dan buah pinggang. Walau bagaimanapun, rawatan dengan curcumin meningkatkan aktiviti fungsi motor mereka, mengurangkan kepekatan Pb dalam serebelum, hati dan buah pinggang dan meningkatkan petanda tekanan oksidatif dan juga memulihkan struktur histologi serebelum, hati dan buah pinggang. Oleh itu, ianya boleh disimpulkan bahawa curcumin melemahkan ketoksikan Pb melalui kekangan tekanan oksidatif dan aktiviti chelating pada tikus.

Kata kunci: Curcumin, ketoksikan plumbum, ICP-MS, bar mendatar, penyelarasan Motor, tekanan oksidatif, Serebelum.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

%	Percentage
µ/mg prot.	Micro/milligram protein
µm	Micrometer
ABLES	Adults Blood Lead Epidemiology and Surveillance
AD	Alzheimer's disease
ADAM-10	A-disintegrin and metalloprotease 10
ALA	alpha-Linolenic acid
ALAS	aminolevulinic acid synthatase
ALAD	δ-aminolevulinic acid dehydratase
ALP	Alkaline phosphatase
ATSDR	Agency for toxic substances and disease registry
APP	amyloid precursor protein
ALT	Alanine transaminase
AST	Aspartate aminotransferase
BACE-1	beta-amyloid enzyme 1
BBB	Blood brain barrier
BLLs	Blood lead levels
BUN	Blood Urea Nitrogen
CAT	Catalase
CDC	Center for Disease Control and Prevention
CKD	Chronic kidney disease
CNS	Central nervous system
COX-2	cyclooxygenase-2
CRE	Creatinine
CREB	cyclic AMP response element binding protein
DNA	Deoxyribonucleic acid
DW	Distilled water
EDTA	Ethylenediaminetetraacetic acid
EGFR	epidermal growth factor receptor
FAK	focal adhesion kinase
g	Gram

GFR	glomerular filtration rate
GSH	glutathione
H & E	Hematoxylin and Eosin
HCL	Hydrochloric acid
HFD	high fat diet
IACUC	International Animal Care Use Committee
iNOS	inducible nitric oxide synthase
IQ	Intelligence quotient
Kg	Kilogram
LD	Lactases dehydrate
LDL	Low density lipoprotein
MAPK	mitogen-activated protein kinase
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCP	monocytes chemoattractant protein
MDA	malondialdehyde
mg	Milligram
Min	Minute
mL	Milliliter
MMP-9	Matrix Metallopeptidase 9
NHANES	National Health and Nutrition Examination
OD	Optical density
OSHA	Occupational Safety and Health Administration
OECD	Organization economic committee development
Pb	lead
PBS	phosphate buffer saline
pH	potential of Hydrogen
PKB	protein kinase B
PLT	platelet
RAGE	receptors for advanced glycation end products
RBC	red blood cell
ROS	Reactive oxygen species

SAH	subarachnoid hemorrhage
STAT3	signal transducer and activator of transcription 3
SOD	superoxide dismutase
TNF-α	tumor necrosis factor-alpha
TrkB	tropomyosin receptor kinase B
UPM	Universiti Putra Malaysia
VSMCs	vascular smooth muscle cells
WBC	White blood count
WHO	World health organization
Wk	Week

CHAPTER 1

INTRODUCTION

1.1 Background

Lead (Pb) is a natural occurring toxic heavy metal that exist in combination with other elements on the earth crust with a relative low melting point, malleable, and a poor conductor, hence due to its above mentioned physicochemical properties its continuous use by man such as in mining, farming and industrialization is inevitable (WHO, 2010). The primary route of exposure to Pb in our environment is through ingestion of Pb contaminated food material and inhalation of fine Pb particles in contaminated atmosphere (Dapul and Laraque, 2014). However, following exposure to Pb in our environment, Pb particles maybe absorbed and distributed to different vital organs such as the kidney, liver, spleen and brain where it alter the normal physiology of the body system, thus excretion is very slow usually through the urinary tract (Shamsudin *et al.*, 2017).

Public health policies and guide against Pb exposure and toxicity in our environment plays a vital role in bringing down blood lead levels (BLLs) drastically among populations, particularly in developed countries, although Pb exposure even at low-level is associated with clinical implications (Camaj *et al.,* 2018).

Pb exposure and toxicity remain a persistent threat to public wellbeing worldwide, accounting for about 0.6% of total global burden of ailment with numerous health implications, particularly among less privileged children, although, sources of Pb, contamination, and exposure among developed and developing countries varies due to socio-demographic factors, with children more at the risk of exposure due to pica behavior and increased absorption (Getso *et al.*, 2013; Tanaka *et al.*, 2018).

Pb-induced toxicity results in serious disease manifestation such as gastro-intestinal symptoms, muscles weakness, anemia, kidney inflammation, brain damage, convulsion, low intelligence quotient (IQ) and liver disease that develops over a period of time due to accumulation of lead in the body system (Getso *et al.*, 2013).

Occupational exposure to Pb is associated with numerous health implications such as cancer and mortality, although even at a low concentration in adults it can results to different adverse health challenges, which may include cognitive impairments, reproductive effects and hypertension (Chowdhury *et al.*, 2014; Kosnett *et al.*, 2007).

Adult exposure to Pb is mostly occupational, usually occur at working place, while pediatric exposure is more or less an environmental exposure which includes peeling or flaking of lead-based paint or weathered powdered paint, pica behavior, and

engaging in hobbies or activities that can increase exposure in the environment (Dapul and Laraque 2014; Murata *et al.*, 2009).

According to the United State Occupational Safety and Health Administration (OSHA) report (2016), an estimated population of 804,000 within the general industry workers and 838,000 among construction industry workers are prone to Pb exposure due to the nature of their occupation, although 2016 data from Adults Blood Lead Epidemiology and Surveillance (ABLES) program reveals a significant reduction in elevated blood lead levels (BLLs) prevalence among adults, thus occupational exposure remains a public health concern with approximately 94% of industrial workers exposed to Pb occupationally (Shaffer and Gilbert, 2017).

However, due to high sensitivity of the nervous system compared to other organ systems, the nervous system becomes the primary target of Pb toxicity, although Pb toxicity affects both the central nervous system and the peripheral nervous system but in adults the effect is mostly on the peripheral nervous system, while the central nervous system is significantly affected in children due to the vulnerability of a developing central nervous system to neurotoxic agent (Flora *et al*., 2012; Needleman 2004; Sanders *et al.* 2009).

The proportion at which circulating Pb gain access to the brain in children is remarkably higher than in adult and prolonged exposed children with high levels of Pb may be subjected to delayed growth, decrease intelligence, convulsions, lack of coordination, paralysis, coma, hearing loss, delirium, encephalopathy and even death (Needleman, 2004). In addition, progressive degeneration of part of the brain is a direct consequence of lead exposure, noticeable symptoms may include poor attention span, headache, muscular tremor, loss of memory, irritability and hallucinations (Flora *et al.* 2012; Ilieva *et al.*, 2009).

The cerebellum is the prominent structure of the hind brain, it is located at the posterior cranial fossa in mammals, and thus cerebellum plays a significant role in motor movement co-ordination. Damage to the cerebellum could lead to loss of motor movement coordination which may include loss of muscle tone, intention tremor, dysmetria, ataxia, dysarthria and other loss of motor coordination (Grimaldi and Manto, 2012).

Curcumin is the principal constituent of turmeric, a spice that is derived from the root of *curcuma longa*, a perennial herb belonging to the family of ginger (*Zingiberaceae*) that is largely cultivated in south and southeast tropical Asia, precisely India, Cambodia, Japan, and China (Wilken *et al*., 2011). Turmeric as a spice in whole, contains a vital chemical compounds called the curcuminoids, which consist of curcumin, demethoxycurcumin and bisdemethoxycurcumin, however, curcumin is the principal curcuminoids (Madhavi and Kagan, 2014).

Curcumin is the most biologically active component of *curcuma longa* that gives the yellow characteristics of the spice, it is lipophilic, phenolic and water insoluble with a well-established evidence of being a strong antioxidant and anti-inflammatory agent that is regarded chiefly as food additive and traditional medicine in Asia (Schiborr *et al.*, 2014).

In vitro and *in vivo* studies reveals that curcumin have a reputable therapeutic benefits that include, anti-inflammatory, antioxidant, anticancer, hepatoprotective, cardiovascular, renal, digestive and neurodegenerative disorder alleviation (Hewlings and Kalman, 2017; Mahmoud *et al*., 2018; Mary *et al.*, 2017). Curcumin as a lipophilic compound have the competency to easily cross the blood-brain barrier, as a result, binds to plaques and inhibit amyloid-β peptide aggregation in the brain which is an important factor in attenuating Alzheimer's disease development in patients (Garcia-Alloza *et al.*, 2007; Shi *et al.*, 2018).

Noteworthy, curcumin can cause a reverse in biliary hyperplasia, necrosis, and fatty changes induced by aflatoxin synthesis, thus hepatoprotective effects of curcumin is attributed to its formidable antioxidant properties and ability to reduce pro-inflammatory cytokines production (Mohiuddin *et al.*, 2010). In addition curcumin have a protective therapeutic effect on the cardiovascular system by inhibiting platelet aggregation, lowering the levels of triglyceride and cholesterol, as well as reducing the vulnerability of low lipoprotein (LDL) peroxidation (Mohiuddin *et al*., 2010).

1.2 Problem Statement

In developing countries, Pb poisoning has been the major threat to public health and it is attributed to human activities such as farming, mining, and industrialization (Abdel-Zaher *et al.*, 2019; Flora *et al.*, 2012). Although several occupational and public health safety measures have been carried out in order to reduce the cases of Pb exposure to the minimal, yet several new cases of Pb poisoning are still documented. Lead toxicity results into various deleterious effects on human and animal health which may include on the nervous system, hematopoietic, renal, reproductive system and even death (Flora *et al.*, 2012; Flora *et al.*, 2013). However, the larger the number of people exposed to Pb globally from different exposure sources, the higher the health and economic costs (Kordas *et al.*, 2018). Further, the Global Burden of Disease (GBD) study 2018, estimates a mean of global economic cost of $3.15-$12.6 billion per year solely for intellectual disability due to Pb poisoning (Landrigan *et al.*, 2018), and $0.776-$1.237 trillion for IQ loss during childhood as well as attributing 143,000 deaths and 0.6% of global burden of disease to Pb poisoning (Kordas *et al.*, 2018; Landrigan *et al.*, 2018).

These deleterious effects play a vital role in disease manifestation and few local herbs extracts shows positive effect against Pb mediated injury both *in vitro* and *in vivo* studies (Flora *et al.*, 2012). The application of chelation therapy in the treatment of heavy metals exposure shows a lot of side effects that can produce several mild to

severe side effects, which may include excessive removal of essential metals in the body, low blood pressure, anemia, fever, headache, nausea and vomiting seizures, brain, kidney and liver damage, hypocalcaemia, and severe allergic reactions such as anaphylactic shock (Flora *et al.*, 2013; Kabeer *et al.*, 2019). In consideration to the risk associated with the application of chelating agents mentioned above, the application is restricted to severe metal poisoning where the benefits is significantly higher than the risks (Flora and Pachauri, 2010).

The central nervous system (CNS) remains the primary target of Pb toxicity during development after exposure. Impairment of neurotransmitters, apoptosis, and alteration in cellular signaling are all direct consequences of neurotoxic effect of lead, in addition, neurotoxic symptoms of Pb exposure may be immediately or delayed, these symptoms may include encephalopathy, mental retardation, visual impairment, loss of memory and cognitive deficit (Sanders *et al.*, 2009).

1.3 Justification of the Study

Previous studies have documented the therapeutic benefits of curcumin in different biological set ups that include on the liver (Um *et al.*, 2013), renal diseases (Ali *et al.*, 2018), nervous and (Yuan *et al.*, 2017), cardiovascular disorder (He *et al.*, 2015), as well as in cancer (Aoki *et al.*, 2007). Therefore, the application and usefulness of natural antioxidants such as curcumin due to its pharmacological safety and prospective therapeutics in management of numerous ailment is aimed to serve as an alternative medicine in the treatment and management of Pb-induced toxicity. Treatment of Pb-induced rats with curcumin is expected to have a neurotherapeutic effect on Pb-induced cerebellar damage due to its high antioxidant and anti-inflammatory properties.

1.4 Significance of the Study

The study is aimed at evaluating the toxic effects caused by Pb-induced toxicity due to exposure and subsequently the neurotherapeutic effects of curcumin. The findings from this study is expected to provide a basis for establishment of reference on the neurotherapeutic effect of curcumin on Pb-induced neurotoxicity, specifically on the cerebellum.

1.5 Hypothesis

I. Curcumin can reduced the amount of Pb accumulated in rats' cerebellum, liver and kidney as well ameliorating Pb-induced cerebellar degeneration.

1.6 General Objective

To determine the neurotherapeutic effects of curcumin on Pb-induced cerebellar damage in a rat model.

1.6.1 Specific Objectives

I. To determine the ameliorative effects of curcumin on motor activity on Pb-induced rats using horizontal bar method.
II. To evaluate the antioxidant and chelating properties of curcumin on the cerebellum and serum of Pb-induced rats via ELISA and ICP-MS techniques respectively.
III. To assess the attenuating effects of curcumin on hematological indexes and histopathological changes via hematology and histological examination using paraffin method in Pb-induced rats.

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BIODATA OF STUDENT

Abubakar Kabeer was born on the 14th of September, 1988 in Zaria. Kaduna State, Nigeria. After completion of his primary and secondary education, he proceed to University of Maiduguri, Borno State, where he received his Bachelor Degree in Human Anatomy (B.Sc.) in 2012 and a National Teachers Institute (NTI) diploma in Postgraduate Education (PGDE) in 2015. He serves as a senior lecturer with School of Nursing and Midwifery Lafia (SONML), Nasarawa State before transferring his service to the Federal University Lafia (FULafia) where he serves as a graduate assistant (GA) in the department of Anatomy. In 2018 he was awarded a scholarship to pursue his Masters in Human Anatomy at Universiti Putra Malaysia (UPM). He registered and undertakes a research titled: Neurotherapeutic Effects of Curcumin on Lead-induced Cerebellar Damage in Rats Model, under the supervision of Prof.Madya.Dr. Ezamin Bin Abdul Rahim, with the aim of developing and evaluating the histological and therapeutic potentials of curcumin on lead-induced toxicity.

Abubakar Kabeer has intent interest in scientific research and writing especially in histology, neuroanatomy and neuroscience.

LIST OF PUBLICATIONS

Kabeer Abubakar; Mailafiya Maryam Muhammad; Danmaigoro Abubakar; Ezamin Abdul Rahim and Md. Zuki Abu Bakar (2019). Therapeutic Potential of Curcumin Against Lead-induced Toxicity : A review. *Biomedical Research and Therapy*, *6* (3), 3053–3066.

Kabeer Abubakar; Mailafiya Maryam Muhammad; Danmaigoro Abubakar; Samaila Musa Chiroma; Ezamin Abdul Rahim and Md. Zuki Abu Bakar (2019). Curcumin Attenuates Lead-induced Cerebellar Toxicity in Rats Via Inhibition of Oxidative Stress and Chelating Activity. *Biomolecules* 9(9) 1- 26 . (JCR Q1 IF 4.694)

Kabeer Abubakar; Mailafiya Maryam Muhammad; Danmaigoro Abubakar; Samaila Musa Chiroma; Ezamin Abdul Rahim and Md. Zuki Abu Bakar (2019). Curcumin improves motor coordination in lead-induced Rats using Horizontal Bar Method. (**Oral presentation**).

Kabeer Abubakar; Mailafiya Maryam Muhammad; Tawfiq Y.T Zyoud, Danmaigoro Abubakar; Samaila Musa Chiroma; Ezamin Abdul Rahim and Md. Zuki Abu Bakar (2019). Ameliorative Effect of Curcumin on Lead-induced Hapato-renal Toxicity in Rat a Model (**Under review**).

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