UNIVERSITI PUTRA MALAYSIA

PATHOLOGICAL RESPONSES TO INTRATRACHEALLY INSTILLED POLYCYCLIC AROMATIC HYDROCARBONS AND EFFECTS OF CURCUMIN TOWARDS THESE RESPONSES IN SPRAGUE DAWLEY RATS

ABDULKARIM JAFAR KARIM

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By

ABDULKARIM JAFAR KARIM

Thesis Submitted to the School of Graduate Studies, Universti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

November 2010

DEDICATED

WITH LOVE AND GRATITUDE

TO

MY BELOVED PARENT

AND

MY SUPERVISOR

Abstract of thesis presented to the Senate of Universiti Putra Malaysia
in fulfilment of the requirement for the degree of Doctor of Philosophy

PATHOLOGICAL RESPONSES TO INTRATRACHEALLY INSTILLED POLYCYCLIC AROMATIC HYDROCARBONS AND EFFECTS OF CURCUMIN TOWARDS THESE RESPONSES IN SPRAGUE DAWLEY RATS

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November 2010

Chairman : Noordin Mohammed Mustapha, PhD

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Increasing attention is diverted to air pollution since its impact is extremely diversified. One of the ubiquitous environmental pollutants is the polycyclic aromatic hydrocarbon (PAH). The aim of this study was to assess several aspects of air pollution on bodily function and morphology.

This study was designed based on the occurrence of the PAHs in the Malaysian 1997 haze episode using four selected PAHs. These were benzo[a]pyrene (BaP), benzo[a]anthracene (BaA), benzo[e]pyrene (BeP) and phenanthrene (Phen). These PAHs were instilled individually by intratracheal (IT) route to male rats and either singly or in combination for a period of one month. Blood was taken at days 0.5, 3, 7, 21, 60 and 180. The same timeline was used to euthanize the rats. Bronchoalveolar lavage (BAL) was conducted and lung sampling was done for H&E, transmission electron microscope (TEM) and TUNEL assay to study apoptosis. Blood and BAL

were used to study the hepatic enzymes, oxidative and immune status of the rats. Curcumin was given *via* diet along with BaP and PAHs combination to test its ability to ameliorate the PAHs injuries.

There was a close relationship between the blood and BAL fluid with histopathological findings. Out of the four PAHs, only BaP produced neoplastic growth in different sites of the body. Microscopic lesions revealed the ability of BaP, and to a lesser extent BaA, to induce hyperplasia, dysplasia and atypia which are pivotal steps into carcinogenesis while Phen resulted in pulmonary fibrosis. The effect BeP and the PAHs combination (Comb) were reversible with no longer than 21 days PI. The TUNEL assay was effective in detecting apoptosis with high percentages in the BeP and Comb groups explaining the reversible trends in these groups.

Carcinogenesis, pulmonary fibrosis and the initiators for lung carcinogenesis is suggested by this study to be oxidative stress dependent. The severity of mitochondrial corruption was proven by TEM in this study to be PAH-dependent. This resulted in significant imbalance in the phase I metabolic enzymes, superoxide dismutase (SOD) and other oxidative enzymes [glutathione peroxidase (GSHpx), glutathione reductase (GR)], which maintain normal levels of reactive oxygen species (ROS). Theoretically, this plays a great part in triggering apoptosis. Practically, ROS was measured by malondialdehyde (MDA) level and the ratio between reduced to oxidized glutathion (GSH:GSSG).

However, owing to the lack of specifity, none of the oxidative enzymes ascertain the exposures to PAHs. Anyway, the MDA and GSH:GSSG are proven by this study to be beneficial in detecting PAH deteriorations.

Following acute response (day 0.5 PI) to PAH exposure, all PAHs were able to produce significant elevations in BALF immunoglobulins (Ig). Chronic responses (day 180 PI) showed a significant drop in Ig in the Phen group due to cytotoxicity marked by the alveolar macrophage activity test. In contrast, IgG in the BaP group was striking due to autoimmune antibodies produced in carcinogenesis.

Dietary supplementation of curcumin showed significant improvement in lung milieu and the oxidant/antioxidant status. It up-regulates the blood oxidative enzymes. Furthermore, curcumin increases the rate of apoptosis, a pathway to get rid of defective cells.

In conclusion, lung tissues have varied responses to PAHs species. The BaP can produce tumorogenesis not only confined to the lung. Combination of PAHs has a mild effect than some individual PAH did. Curcumin has a potent effect in alleviating these deleterious effects.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk Doktor Falsafah

GERAK BALAS AKUT DAN KRONIK HIDROKARBON AROMATIK POLISIKLIK YANG DIINSTILASIKAN SECARA INTRATRAKEA PADA TIKUS

Oleh

ABDULKARIM JAFAR KARIM

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Perhatian yang lebih telah dialihkan kepada pencemaran udara kerana kesannya yang pelbagai. Salah satu bahan pencemar alam sekitar yang sentiasa ada adalah hidrokarbon polisiklik aromatik (PAH). Tujuan kajian ini adalah untuk menilai beberapa aspek pencemaran udara pada fungsi tubuh dan morfologi.

Kajian ini direka berdasarkan kehadiran PAH dalam episod jerebu pada 1997 di Malaysia menggunakan empat PAH yang dipilih. Ianya adalah benzo[a]pirena (BaP), benzo[a]antrasena (BaA), benzo [e] pirena (BeP) dan fenantren (Phen). PAH ini telah diinstilasikan secara berasingan melalui intratrakea (IT) pada tikus jantan dan secara sendiri atau gabungan untuk jangka waktu satu bulan. Darah diambil pada hari 0, 5, 3, 7, 21, 60 dan 180. Jangka masa yang sama digunakan untuk mengorbankan tikus. Lavaj bronkoalveolus (BAL) telah dilakukan dan sampel paru-paru diambil untuk H&E, mikroskop elektron pancaran (TEM) dan asei TUNEL untuk mengkaji

apoptosis. Darah dan lavaj bronkoalveolus digunakan untuk mengkaji enzim hati, status oksidatif dan status keimunan tikus. Kurkumin diberikan melalui diet bersama dengan kombinasi BaP dan PAH bagi menguji kemampuannya untuk memperbaiki kecederaan yang disebabkan oleh PAH.

Terdapat hubungan erat antara darah dan cecair BAL dengan penemuan histopatologi tersebut. Dari empat PAH tersebut, hanya BaP menghasilkan pertumbuhan neoplastik di lokasi yang berbeza pada tubuh. Lesi mikroskopik menunjukkan kemampuan BaP, dan BaA mempunyai sedikit pengaruh, untuk menyebabkan hiperplasia, displasia dan atipia yang merupakan ciri penting dalam karsinogenesis sementara Phen menyebabkan fibrosis paru-paru. Pengaruh BeP dan kombinasi PAH (Comb) boleh diterbalikkan dengan syarat tidak melebihi daripada 21 hari Pl. Asei TUNEL didapati efektif dalam mengesan apoptosis dengan peratusan yang tinggi bagi BeP dan kumpulan Comb menjelaskan keupayaan boleh diterbalikkan dalam kumpulan-kumpulan ini.

Karsinogenesis, fibrosis paru-paru dan inisiator untuk karsinogenesis peparu disarankan oleh kajian ini adalah bergantung kepada tekanan oksidatif. Keparahan kerosakan mitokondria telah dibuktikan dengan TEM dalam kajian ini adalah PAH-bergantung. Hal ini menyebabkan ketidakseimbangan yang ketara dalam enzim metabolic fasa I, dismutase superoksida (SOD) dan enzim oksidatif lain [glutation peroksidas (GSHpx), glutation reduktas (GR)], yang mengekalkan tahap normal spesies oksigen reaktif. Secara praktis, ROS

diukur berdasarkan paras malondialdehid (MDA) dan nisbah antara glutation yang dikurangkan dan yang teroksida (GSH: GSSG).

Namun begitu, kerana kurangnya kekhususan, tidak ada enzim oksidatif yang dapat memastikan kesan dari PAH. Walau bagaimanapun, MDA dan GSH: GSSG telah dibuktikan oleh kajian ini dapat memberi bermanfaat dalam mengesan kecederaan yang diakibatkan oleh PAH.

Berikutan gerak balas akut (hari 0.5 PI) terhadap pendedahan kepada PAH, semua PAH mampu menghasilkan peningkatan yang signifikan dalam imunoglobulin (Ig) BALF. Gerak balas kronik (hari PI 180) menunjukkan penurunan yang signifikan dalam Ig bagi kumpulan Phen kerana kesitotoksikan yang ditunjukkan oleh ujian aktiviti makrofaj alveolar. Sebaliknya, IgG dalam kumpulan BaP dan BaA sangat menonjol disebabkan oleh penghasilan antibodi keautoimunan yang dihasilkan dalam karsinogenesis.

Penambahan kurkumin dalam diet menunjukkan penambahbaikan yang signifikan dalam persekitaran paru-paru dan status oksidan/antioksidan. Ia mengawal atur naik aktiviti enzim oksidatif dalam darah. Selain itu, kurkumin meningkatkan tahap apoptosis, satu cara untuk menyingkirkan sel-sel yang telah rosak.

Sebagai kesimpulan, tisu paru-paru mempunyai gerak balas yang berbeza untuk spesies PAH. BaP dapat menghasilkan tumorogenesis yang tidak hanya

terbatas pada paru-paru. Kombinasi PAH mempunyai kesan yang sederhana berbanding kesan yang dihasilkan oleh beberapa PAH secara individu. Kurkumin mempunyai pengaruh kuat dalam mengurangkan kesan-kesan mudarat tersebut.

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Again, Alhamdulillah.

I certify that an Examination Committee has met on Day Month Year to conduct the final examination of Abdulkarim Jafar Karim on his Doctor of Philosophy thesis entitled "Pathological responses to intratracheally-instilled polycyclic aromatic hydrocarbons and curcumin effects towards these responses in Sprague Dawley RATS" in accordance with Universiti Putra Malaysia (Higher Degree) Act 1980 and Universiti Putra Malaysia (Higher Degree) Regulations 1981. The Committee recommends that the candidate be awarded the relevant degree. Members of the Examination Committee are as follows:

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This thesis was submitted to the Senate of Universiti Putra Malaysia has been accepted as fulfillment of the requirement for the degree of Doctor of Philosophy. The members of the supervisory committee were as follows:

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DECLARATION

I declare that the thesis is my original work except for quotations and citations which have been fully acknowledged. I also declare that it has not been previously and is not concurrently submitted for any other degree at Universiti Putra Malaysia or other institutions.

ABDULKARIM JAFAR KARIM

Date: 4 November 2010

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LIST OF ABBREVIATIONS

Ag	antigen
AhR	aryl hydrocarbon receptor
Alb	albumin
AMØ	Alveolar macrophages
AO	acridine orange
BaA	benzo(a)anthracene
BALF	bronchoalveolar lavage fluid
BALT	bronchus-associated lymphoid tissue
BaP	benzo(a)pyrene
BeP	benzo[e]pyrene
BPDE	BaP-7,8-diol-9,10-epoxide
Bwt	body weight
CAS	chemical abstract service
Comb	PAHs combination
COX-2	cyclooxygenase-2
Curc	Curcumin
CYP450	cytochrome P-450
d	day
DE	diol epoxide
de-H_2O	deionised water
DMBA	7,12-dimethylbenz[a]-anthracene
EC	enzyme code
ELF	epithelial lining fluid
ELISA	Enzyme-linked immunosorbant assay

EPA	Environmental Protection Agency
g	Relative Centrifugal Force (RCF)
GGC	gamma-glutamylcysteine
gm	gram
GR	glutathione reductase
GSH	reduced glutation
GSHpx	glutathione peroxidase
GSSG	oxidized glutathione
GST	glutathione -S- transferase
HSI	hepatosomatic index
Ig	immunoglobulin
IL	interlukin
iNOS	inducible nitric oxide synthases
IT	intratracheal
LPO	lipid peroxidation
MDA	malondialdehyde
µg	microgram
µL	microliter
MMP-9	matrix-metalloproteinase-9
MPO	myeloperoxidase
MWt	molecular weight
ng	nanogram
PAH	polycyclic aromatic hydrocarbon
PEL	pulmonary epithelial lining
Phen	phenanthrene

PI	post instillation
PM	particulate matter
PMN	polymorph nuclear cell
PSI	pulmonary somatic index
Ptdlns	phosphatidylinositol
RNS	reactive nitrogen species
ROS	reactive oxygen species
RPMI	Rosewell Park Memorial Institute
SOD	superoxide dismutase
TBARS	thiobarbituric acid reactive substances
TEM	transmission electron microscope
tGSH	total glutathione
TNF	tumor necrosis factor
TP	total protein
TUNEL	Terminal deoxynucleotidyl transferase dUTP nick end labeling
WW/DW	wet weight/dry weight ratio

CHAPTER I

GENERAL INTRODUCTION

1.1. Air Polution

Air pollution affects millions worldwide and its adverse effects on human health are a serious concern. Previous studies have reported increased morbidity and mortality due to ambient air pollution (Samet *et al.,* 2000), increased risk of lung cancer (Pope *et al.,* 2002), genotoxicity in various tissues (Burgaz *et al.,* 2002), and heritable mutations in mice (Somers *et al.,* 2004). Polycyclic aromatic hydrocarbons (PAHs) which are the products of the incomplete combustion of fossil fuels, have been detected as suspended particulate matter in ambient air in urban areas (Pleil *et al.,* 2004).

Since the early industrial revolution, air quality worsens day by day. Pollution problems have largely resulted from industry and domestic heating, principally due to sulphur dioxide. In recent years, however, the transport sector has become the most significant source of both primary pollutants, such as PAHs and nitrogen dioxide, and secondary pollutants, like ozone. A risky PAHs concentration (above 100 ng/m^3) was recorded in Europe in 1960. Special measurements and precautions that were taken to decrease this value to 4.4 ng/m^3 in 1992. The declines were attributed to increase used of catalytic converters in motor vehicles, reduction in coal and movement to oil and natural gas and improved combustion technology (Dorsey *et al.,* 2006).

1.1.1. Air pollution in Malaysia

Negative impacts on the environment as a whole and on air quality in particular have been resulted from improper plann development and growth, earlier in Malaysia (Sham, 1994). The general air quality of Malaysia since 1970 has deteriorated. Studies have shown that should no effective counter measures be introduced, the emissions of sulphur dioxide, nitrogen oxides, particulate matter and hydrocarbons in the year 2005 would increase by 1.4, 2.12, 1.47 and 2.27 times, respectively, from the 1992 levels (Awang *et al.,* 2000).

1.1.2. Natural pollution due to forest fire

Eight major haze episodes, officially reported in the past twenty years in Malaysia, were associated with a significant increase in total suspended particles (TSP) (Awang *et al.,* 2000). They were in 1980**,** April 1983, August 1990, June 1991, October 1991 and August to October 1994 and the worst was from July to October 1997 in which the levels of TSP reached 1033 gm^{-3} and 2005 (Abdullah *et al.,* 2007). Chemists have identified more than 100 substances in wood smoke, both organic and inorganic, from which a PAH known as benzo[a]pyrene is a potent carcinogen.

1.1.3. Transportation pollution

The diesel engine sector forms a vital part of transportation systems in all developing countries of the world. However, diesel engine exhaust emissions are a major

contributor to environment pollution. Direct measurement of PAH in diesel and gasoline engine emissions has confirmed that primary emissions are responsible for the transport of smaller than 0.5 μm particles which contain higher amounts of aromatics and sulphur, which cause environment pollution (Zielinski *et al.*, 2006). The total number of cars on the road in Peninsular Malaysia was 160000, 264000, 5.2 million and 7 million in 1970, 1976, 1990 and 1996 respectively with nearly double the number of motorcycles. This explosive increase in car number is responsible for the high risky air pollution.

1.1.4. South East Asia Air Pollution

To date, no detailed chemical studies of forest fire (haze) emissions composition have been carried out in SE Asia. Between August and October 1997, the haze from forest fires in Sumatra and Borneo covered largely Indonesia, Malaysia, Singapore and Brunei, as well as southern parts of Thailand and the Philippines, with a potential impact on the lives of several hundred million people. The regional haze in SE Asia has many effects including airport closures, automobile accidents, loss of biodiversity, lower crop productivity, downturn in tourism and economic costs (health effects have caused most concern). More people suffered from upper respiratory tract infections, asthma, conjunctivitis, bronchitis, eye and throat irritations, coughing, breathlessness, blocked and runny noses, skin rashes and cardiovascular disorders (Isobe *et al.*, 2007).

1.1.5. Emergency levels

The US Environmental Protection Agency (EPA) defines 'emergency' level when PM_{10} concentrations exceeded 500 µg/m^3. On 23 September 1997, this value of the Malaysian API was almost 1 mg/m^3. It is therefore clear that the main health hazard posed by the haze from forest fires is from inhaling smoke particles. Particles larger than 10µm in diameter are removed in the nose and do not penetrate the respiratory system (Table 1.1).

Table 1.1. Fate of air dust inside the body

	Size	***Site***	***Residence***
Air dust (Particles)	> 10 µm	Nose, mouth, throat, larynx	Several hours
	< 10 µm	Tracheo-bronchial	24 hours
	6 – 8 µm	Alveolar area	Days to years
	2.5 µm (cigarette smoke)	Deeply in Alveoli – Blood stream	Years

Particles smaller than 10µm (PM_{10}), so-called 'inhalable' particles, can be deposited in the respiratory system. Particles smaller than 2.5µm ($PM_{2.5}$), the 'respirable' particles, can penetrate deep into the pulmonary region which consist of the bronchioles and alveoli. The carcinogenicity of the PAH is dominated by small particles. Currently, air quality monitoring stations only measure PM_{10}, but studies have shown that $PM_{2.5}$ may have even more significant adverse health effects (Gerlofs-Nijland *et al.,* 2007). Studies of forest fires showed that there was a

pronounced concentration peak at a diameter of 0.15µm. Particles in the nasal cavity and the tracheobronchial sections may also be swallowed and enter the gastrointestinal tract. Toxic substances that are present in the particles may be transferred from any of these reservoirs into the bloodstream and then transmitted to other organs via the circulatory system. The physical and chemical characteristics of tropical haze particles resulting from forest fires may be quite different from those of urban aerosols, which originated mainly from vehicle exhausts and industrial sources (Zakaria *et al.*, 2002).

1.2. Objectives

It is hypothesized that PAHs produce different acute & chronic responses in animal model but elicit similar biomarkers. Therefore, the aim of this study is to assess the acute & chronic responses to selected PAHs in an animal model, with the following objectives:

i. to describe/depict the effects of repeated inhalation to selected PAHs
ii. to compare the responses and associated synergistic/antagonistic action to selected PAHs
iii. to describe the associated morphologic changes in tissues due to inhaled PAHs
iv. to assess the systemic and pulmonary defense status due to inhaled PAHs
v. to alleviate PAH-exposure symptoms using curcumin

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