UNIVERSITI PUTRA MALAYSIA

ANTI-ARTHRITIC EFFECTS OF 6-MERCAPTOPURINE AND ITS DERIVATIVES IN ARTHRITIS-INDUCED MODEL, IN VITRO AND IN VIVO

CHE KU DAHLAN BIN CHE KU DAUD

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By

CHE KU DAHLAN BIN CHE KU DAUD

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

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Rheumatoid arthritis (RA) is a chronic inflammatory and autoimmune diseases which causes synovia and joint deformity characterized by abnormal immune condition implicating the synovial fibroblast cell layers and synovium infiltrates further resulting in progressive joints destruction. In this study, four thiopurine compounds namely, 6-mercaptopurine (6-MP), 6-MP riboside, 6-thioguanine (6-TG) and 6-thioxanthine (6-TX) with diclofenac (a non-steroidal anti-inflammatory drug; NSAID) as positive control were screened for their cytotoxicity and anti-inflammatory properties by evaluating the cell cytotoxicity and the nitric oxide (NO) inhibitory activities upon activated fibroblast synoviocytes (HIG-82) and macrophage (RAW 264.7) cell lines with phorbol-12-myristate acetate (PMA) and lipopolysaccharide (LPS), respectively. The preliminary screening results have shown that all the thiopurine compounds did not show any cytotoxic effect on both cell lines at low and medium concentrations. Inhibitory effect of the compounds on nitric oxide production PMA-stimulated HIG-82 had only a small inhibition effect, however excellent inhibition and suppressive activity were observed on RAW 264.7 cell. Meanwhile, at the highest concentration (100 μM) 6-TG and diclofenac had a cytotoxic effect to RAW 264.7 and HIG-82 cell respectively. Further, *in vivo* study using completed Freund's adjuvant (CFA)-induced arthritis animal model was conducted to evaluate the therapeutic and toxicity effects of selected thiopurine compounds (6-MP and 6-MP riboside) selected based on *in vitro* study with different dosages (3, 6 and 10 mg/kg). A repeated oral administration of both compounds showed less toxicity in rats manifested by less alteration in body and organs (liver and kidney) weight, no significant change in full blood count parameters, no significant changes in pivotal liver and kidney biochemical parameters except at high dosage of 6-MP riboside on the liver marker, medium and high dosages of 6-MP on creatinine kidney biomarker, however, no significant toxicity remarks on microscopic histopathology evaluation of both organs. Besides, further experiments were conducted to investigate the pro-inflammatory, suppressive and antioxidative effects of 6-MP and 6-MP riboside on inflammation arthritis induced rats model. 6-MP and 6-MP riboside were observed to inhibit the production of pro-inflammatory cytokines such as TNF-α and IL-6 on the rat blood plasma. Oral repetition treatments of 6-MP at 6 and 10 mg/kg showed a significantly

decreased production of pro-inflammatory cytokines, which was similar to diclofenac used. A significant reduction ($P<0.05$) in the concentration of PGE_2 at 6 and 10 mg/kg dosages on plasma-treated 6-MP, respectively when compared to control arthritic also demonstrated. Moreover, plasma peroxide and reduced glutathione showed a significantly better improvement level after treatments. Collectively, this present study suggested that the anti-arthritic and suppressive actions of 6-MP and 6-MP riboside of both *in vitro* and *in vivo* model are attributed through interferences in inflammatory mediators and antioxidative regulatory system in the body. *In vitro* study was obtained a promising where the thiopurine compounds especially 6-MP and 6-MP riboside exhibited the proliferation of HIG-82 and RAW 264.7 cells at suitable dosages. This finding opens new avenues for treating RA during synovial inflammation of RA and the inhibitory effects of 6-MP and 6-MP riboside to suppress inflammatory cells marker such as synovial fibroblast and macrophages by proliferating healthy synoviocytes. The selected dosages of 6-MP and 6-MP riboside *in vivo* study could be suitable and safer, contributed the best dosages for recovery. A novel knowledge on the pathophysiology of arthritis and its prevention by 6-MP and 6-MP riboside had been revealed throughout this study. Thus, suggests that 6-MP and 6-MP riboside have anti-inflammatory effects by inhibiting the production of pro-inflammatory mediators, enhanced the antioxidant defence system during pathologic condition. 6-MP and 6-MP riboside have therapeutic activity and potentially useful for treating inflammatory conditions as served as a new promising disease-modifying anti-rheumatic drugs (DMARDS) in treating early inflammation arthritis in the future.

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

KESAN ANTI-ARTRITIK DARI 6-MERCAPTOPURINE DAN TERBITANNYA DALAM MODEL ARTHRITIS TERINDUKSI, *IN-VITRO* DAN *IN VIVO*

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Artritis Reumatoid adalah penyakit radang dan autoimun kronik sinovia dan sendi akibat keadaan imun yang tidak normal yang melibatkan lapisan sel sinovial fibroblas dan sinovium sehingga mengakibatkan kerosakan sendi yang teruk. Dalam kajian ini, empat sebatian thiopurina iaitu, 6-mercaptopurina (6-MP), 6-MP ribosida, 6-thioguanina (6-TG) dan 6-thioxanthina (6-TX) dan *diclofenac* (ubat antiradang bukan steroid; NSAID, kawalan positif) disaring untuk sifat sitotoksisiti dan anti-radang dengan menilai sitotoksisiti sel dan aktiviti perencatan nitrik oksida (NO) pada sel sinovial fibroblas (HIG-82) dan makrofaj (RAW 264.7) yang masing-masing diaktifkan oleh phorbol-12-myristate asetat (PMA) dan lipopolysaccharide (LPS). Hasil pemeriksaan awal menunjukkan semua sebatian thiopurina tiada kesan sitotoksik terhadap kedua-dua sel pada kepekatan rendah dan sederhana. Kesan penghambatan sebatian pada pengeluaran oksida nitrat pada HIG-82 yang dirangsang oleh PMA hanya mempunyai kesan perencatan kecil, namun aktiviti perencatan yang sangat baik diperhatikan pada sel RAW 264.7. Sementara itu, pada kepekatan tertinggi (100 μM) 6-TG dan *diclofenac* mempunyai kesan sitotoksik kepada sel RAW 264.7 dan HIG-82. Selanjutnya, kajian *in vivo* menggunakan model haiwan artritis yang disebabkan oleh adjuvant Freund (CFA) telah dilakukan untuk menilai kesan terapeutik dan ketoksikan sebatian thiopurina terpilih (6-MP dan 6-MP ribosida) yang dipilih berdasarkan kajian *in vitro* dengan dos yang berbeza (3, 6 dan 10 mg/kg). Pemberian secara oral berulang kedua-dua sebatian menunjukkan ketoksikan yang kurang pada tikus yang ditunjukkan oleh perubahan yang kecil terhadap berat badan dan organ (hati dan ginjal), tidak ada perubahan yang signifikan ($P<0.05$) pada parameter sel darah merah dan sel darah putih, tidak ada perubahan yang signifikan ($P<0.05$) pada parameter biokimia hati dan ginjal yang penting kecuali pada dos tinggi 6-MP ribosida pada penanda hati, dos sederhana dan tinggi 6-MP pada penanda ginjal kreatinin, bagaimanapun, tidak ada ketoksikan yang signifikan pada penilaian histopatologi mikroskopik kedua-dua organ. Selanjutnya, kajian dilakukan untuk menyiasat kesan pro-radang, penindasan dan antioksidan sebatian 6-MP dan 6-MP ribosida pada model tikus yang disebabkan radang artritis. 6-MP dan 6-MP ribosida diperhatikan menghalang pengeluaran sitokin pro-radang seperti TNF-α dan

IL-6 pada plasma darah tikus. Rawatan secara oral berulang-ulang 6-MP pada dos 6 dan 10mg/kg menunjukkan penurunan pengeluaran sitokin pro-radang, yang serupa dengan *diclofenac*. Pengurangan kepekatan PGE_2 yang ketara ($P<0.05$) dalam dos 6 dan 10 mg/kg pada plasma yang dirawat 6-MP, masing-masing jika dibandingkan dengan kumpulan artritis kawalan. Lebih-lebih lagi, peroksida dan glutathione dalam plasma menunjukkan tahap peningkatan positif ($P<0.05$) yang lebih baik selepas rawatan. Secara keseluruhan, kajian ini menunjukkan bahawa tindakan anti-artritis dan penindasan 6-MP dan 6-MP ribosida pada kedua-dua model *in vitro* dan *in vivo* ini dikaitkan dengan gangguan pada mediator keradangan dan sistem pengawalan antioksidan dalam badan. Kajian *in vitro* telah membuktikan, sebatian thiopurina terutamanya 6-MP dan 6-MP ribosida menunjukkan pertumbuhan sel HIG-82 dan RAW 264.7 pada dos yang sesuai. Penemuan ini membuka jalan baru untuk merawat artritis atau radang sinovial dan kesan penghambatan 6-MP dan 6-MP ribosida untuk menindas penanda sel radang seperti sel fibroblas sinovial dan sel makrofaj dengan memperbanyakkan sel synovia yang sihat. Dos 6-MP dan 6-MP ribosida yang terpilih dalam kajian *in vivo* ini boleh menjadi dos yang sesuai, lebih selamat dan menyumbang kepada dos terbaik untuk pemulihan. Pengetahuan baru mengenai patofisiologi artritis dan pencegahannya oleh 6-MP dan 6-MP ribosida telah dinyatakan di sepanjang kajian ini. Oleh itu, kajian ini menunjukkan bahawa 6-MP dan 6-MP ribosida mempunyai kesan anti-radang dengan menghalang pengeluaran mediator pro-radang melalui pengukuhan sistem pertahanan antioksidan semasa keadaan patologi. 6-MP dan 6-MP ribosida mempunyai aktiviti terapeutik dan berpotensi berguna untuk merawat keadaan keradangan yang berfungsi sebagai ubat pengubah suai penyakit (DMARD) dan menjanjikan ubat baharu dalam merawat radang peringkat awal pada masa akan datang.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

AA	Arachidonic acid
ACPA	Anti-citrulinated protein antibody
AP-1	Activator protein-1
APC	Antigen presenting cell
ATP	Adenosine triphosphate
Aza	Azathioprine
BCR	B cell receptor
BiP	Heavy chain binding protein
BSA	Bovine serum albumin
Ca^{2+}	Calcium ion
CCR5	Chemokine receptor 5
CFA	Complete Freund's adjuvant
CIA	Collagen-induced arthritis
cNOS	constitutive NOS
CO_2	Carbon dioxide
COX	Cyclooxygenase
cPGES	Cytocolic PGE synthase
CRP	C-creative protein
CSF	Colony-stimulating factor
DAF	Decay-accelerating factor
DMARD	disease-modifying anti-rheumatic drugs
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
EC	Endothelial cells

ECM	Extracellular matrix
ERK	Extracellular signal-regulated kinase
FAD	flavin adenine dinucleotide
FBS	Fetal bovine serum
FCA	Freund complete adjuvant
Fcγ	Fc gamma
FGF	Fibroblast growth factor
FLS	Fibroblast-like synoviocytes
FMN	Flavin mononucleotide
GADPH	Glyceraldehyde-3-phosphate dehydrogenase
GM-CSF	Granulocytes-macrophage colony stimulating factor
GPCRs	G protein-coupled receptors
GPI	Glucose-6-phosphate isomerase
GSH-Px	Glutathione peroxide
H_2O_2	Hydrogen peroxide
HCI	Hydrochloride acid
HIG-82	Rabbit synovial fibroblast cell line
HLA	Human leukocytes antigen
HRP	Horseradish peroxidase
IBD	Inflammatory bowel disease
ICAM	Intercellular adhesion molecule
ICE	The Caspase-1 or IL-1β converting enzyme
IFN	Interferon
IFN-γ	Interferon-gama
IgG	Immunoglobulin G

IKK	IκB kinase
IL	Interleukin
IL-1Ra	Interleukin-1 receptor antagonist
iNOS	Inducible nitric oxide synthases
IRF	Interferon regulator factor
IκB	Inhibitory factor *kappa*-B
IκBα	Nuclear factor of *kappa* light polypeptide gene enhancer in B-cells inhibitor, Alpha
JNK	C-Jun NH_2-terminal kinase
LPS	Lipopolysaccharide
M.W.	Molecular weight
MAPK	Mitogen activator protein kinase
MAPKK	MAPK kinase
MAPKKK	MAPK kinase kinase
MCP-1	Monocytes chemoattractant protein-1
MHC-II	Major histocmpability complex class II
MIC	Minimum inhibitory concentration
MIF	Macrophage inhibitory factor
MMP	Matrix metalloproteinases
MMP	Matrix metalloproteinase
MP	Mercaptopurine
mPGES	Microsomal PGE synthase
MPR	Mercaptopurine riboside
mRNA	Messenger ribonucleic acid
MSK1	Mitogen and stress activated protein kinase-1
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide

NADPH	Nicotinamide adenine dinucleotide phosphate
NaOH	Sodium hydroxide
NEMO	NF-*kappa* B essential modulator
NF-κB	Nuclear factor *kappa*-light-chain enhancer of activated B cells
NLR	NOD-like receptor
NO	Nitric oxide
NOD	Nucleotide-binding oligomerization domain
NSAID	Nonsteroidal anti-inflammatory drugs
OD	Optical density
$ONOO^-$	Peroxynitrite ion
PAMP	Pathogen-associated molecular pattern
PBS	Phosphate buffer saline
PDGF	Platelet-derived growth factor
PGE_2	Prostaglandin E2
PMA	Phorbol-12-myristate acetate
RA	Rheumatoid arthritis
RANKL	Receptor activator of nuclear factor *kappa* B ligand
RANTES	Regulated upon activation, normal T cell expressed and secreted protein
RAW 264.7	Macrophage abelsen murine leukaemia virus transformed cell/ Murine monocytic monocytes cell
RF	Rheumatoid factor
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
SAA	Serum amyloid A
SCID	Severe combined immunodeficiency
SF	Synovial fibroblast

SLE	Systemic lupus erythematosus
TCR	T cell receptor
TGF-β	Transforming growth factor-*beta*
TIMP-1	Tissue inhibitor of metalloproteinase-1
TLR	Toll-like receptor
TNF	Tumor necrosis factor
TNF-R	Tumor necrosis factor-receptor
TNF-α	Tumor necrosis factor-*alpha*
TRAF-1	TNF-receptor associated factor-1
TRAF-6	TNF-receptor associated factor-6
TREG	T Cell Regulator
VCAM	Vascular cell adhesion molecule
VEGF	Vascular endothelial growth factor

LIST OF SYMBOLS/ANNOTATIONS

Annotation	Description
<	Lesser than
%	Percent/percentage
>	More than
±	Plus-minus
°	Degree
° C	Degree Celsius
µ	Micro
µL	Microliter
µM	Micromolar
g	Gram
h	Hour
Hz	Hertz
kDa	Kilo Dalton
kg	Kilogram
L	Liter
MΦ	Macrophage
mg/kg	Miligram per kilogram
mg/mL	Milligram per mililiter
min	Minute
mmol	Milimole
nM	Nanomolar
pg/mL	Picogram per milligram
U	Units

v/v	Volume per volume
w/v	Weight per volume
α	*Alpha*
β	*Beta*
γ	*Gamma*

CHAPTER 1

INTRODUCTION

1.1 Research background

Rheumatoid arthritis (RA) is a chronic inflammatory and autoimmune multi-system disease that affects the joints and is characterized by synovial membrane inflammation, pain, and limited joint movement (Sharad *et. al.,* 2011; Parada-Turska *et. al.,* 2006). RA is a serious health problem worldwide that affects an estimated 0.5-1.0% of adults in developed countries (Parada-Turska *et. al.,* 2006; Wang *et. al.,* 2006). In the USA alone, more than 20 million RA patients are having severe limitations to function daily, and an estimated of $100 billion is accounted for the total annual cost of arthritis to society (Rubinstein and Weinberg, 2012). According to the Arthritis Foundation of Malaysia, RA affects about 5 in 1000 adult Malaysians which is comparable with the international prevalence of RA worldwide (Shahrir *et. al.,* 2008). RA has a big significant impact on the physical, emotional, psychological, and social activities of patients on the daily basis; they restricted in most functioning on works as well reducing life expectancy, premature mortality further causing a massive economic burden to society. The onset of the disease on the local inflammatory joint site is believed causes by many factors involved in multi-complexes interrelated connection including, infectious, genetic, environmental, and homeostasis imbalance in the body by hormonal factors. The disease affected the synovium with extended pannus existing in the inflammation fluid with several types of mononuclear cells present in the pannus junction such as macrophages, fibroblasts, T cells, B cells, dendritic, natural killer cell, and other pro-inflammatory mediators or cytokines (Knedla *et. al.,* 2007). The progressive deterioration of joint structures resultant from articular cartilage destruction leading to deformation and disability (Sharad *et. al.,* 2011; Parada-Turska *et. al.,* 2006; Wang *et. al.,* 2006).

The pathogenesis of rheumatoid arthritis involves the release of pro-inflammatory cytokines, such as tumour necrosis factor (TNF-α), interleukin-1 (IL-1) and interleukin-6 (IL-6), which act synergistically to release matrix metalloproteinases (MMPs) from cells such as fibroblast-like synoviocytes and macrophages (Huang *et. al.,* 2011; McInnes and Schett, 2011). Besides, inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX 2) genes are activated (Jungbauer and Medjakovic, 2012; Crielaard *et. al.,* 2011). At the site of inflammation, free radicals such as nitric oxide (NO), peroxide, singlet oxygen and hypochlorite are involved in the pathogenesis of RA through the degradation of membrane lipids, proteins, DNA and cartilage (Jawed *et. al.,* 2010). Excessive accumulation of reactive oxygen species (ROS) and nitrogen species may cause tissue damage, contributing to many pathological conditions such as cancer, cardiovascular diseases, atherosclerosis and rheumatoid arthritis (Jawed *et. al.,* 2010). Several defence mechanisms, including superoxide dismutase, glutathione peroxidase, catalase, glutathione and ascorbate, usually protect cells against these species (Sakuma *et. al.,* 2004). Nevertheless, in RA patients they are subjected to oxidative stress-induced tissue degradation through overproduction of ROS and decreased rates of

superoxide dismutase and glutathione. Radical superoxide and hydrogen peroxide not only induce the development of interleukins and TNF-α from T cells but also stimulate endothelial cells which then influence the production of growth factor, inflammatory cytokines and adhesive molecules on the immune cells, thereby exacerbating tissue destruction and inflammation (Jawed *et. al.,* 2010; Sakuma *et. al.,* 2004).

The current medication treatments available are non-steroidal anti-inflammatory drugs (NSAIDs) and disease-modifying anti-rheumatoid arthritic drugs (DMARDs) (Wang *et. al.,* 2011; Parada-Turska *et. al.,* 2006). However, up to 30% of patients respond inadequately to these treatments or become refractory to drug therapy (Jungbauer and Medjakovic, 2012). Besides, some of these treatments only provide relief from the signs and symptoms of RA however do not prevent the long-term progression of RA (Wang *et. al.,* 2011). For patients who respond to NSAIDs or DMARDs, long-term use of these drugs often is associated with serious adverse events (Jungbauer and Medjakovic, 2012). Biological therapy which targets on molecules and cells specific for processes associated with the pathogenesis of RA has become a breakthrough in the treatment of RA (Šenolt *et. al.,* 2009). Yet it is still unable to induce remission and may cause severe immunology adverse events (Buch *et. al.,* 2007). Hence, there is an urgent need to develop a new drug compound for RA that target the inflamed joints yet avoid collateral damage to healthy tissues with minimal toxicity.

Purinethol or Mercaptopurine (MP)(e.g; 6-MP and 6-MP riboside) is a purine sulfur derivative approved by the Food and Drug Administration (FDA) as an antitumor drug in 1953 (Pilar *et. al.,* 1996). In comparison with other anti-tumour drugs, 80% of children's leukaemia diseases are treated with 6-MP. 6-MP and gold together have shown cytotoxicity activity against cancer cells with a more potent cytotoxic action than free 6-MP alone and even cisplatin (Pilar *et. al.,* 1996). This complex also displayed an excellent anti-bacterial benefit against *M. tuberculosis* in addition to the anti-tumour activity (Pilar *et. al.,* 1996). To date, there is no related report regarding the effects of 6-MP and 6-MP riboside on anti-inflammatory and anti-rheumatic properties regardings to the role of 6-MP and 6-MP riboside in suppressing synoviocytes inflammation induced by both PMA in HIG-82 cells and CFA in rats. This study provided us with a better understanding on joint degeneration and destruction as well as synovial inflammation caused by rheumatoid arthritis and whether 6-MP and 6-MP riboside possess the inhibitory effects to suppress inflammatory events of the pathogenesis of rheumatoid arthritis.

1.2 Objective(s) of study

1.2.1 General objective

This study aims to evaluate the therapeutic effects of 6-mercaptopurine and its major derivatives mainly 6-mercaptopurine riboside in the PMA-induced synovial fibroblast and adjuvant-induced rat arthritic models.

1.2.2 Specific objectives

1. To examine the effects of thiopurine compounds on cell viability of phorbol myristate acetate (PMA)-activated HIG-82 synoviocytes fibroblast and *Escherichia coli* lipopolysaccharide (LPS)-induced RAW 264.7 murine macrophage cell lines.
2. To examine inhibitory effects of thiopurine on inducible nitric oxide production of phorbol myristate acetate (PMA)-activated HIG-82 synoviocytes fibroblast and *Escherichia coli* lipopolysaccharide (LPS)-induced RAW 264.7 murine macrophage cell lines due to nitric oxide production in responding to compound concentrations.
3. To assess the effects of 6-mercaptopurine and 6-mercaptopurine riboside on arthritis physical parameters and complete blood count (CBC) on CFA-induced *Sprague dawley* rats.
4. To investigate the effects of 6-mercaptopurine and 6-mercaptopurine riboside on blood liver and kidney-induced toxicity biomarkers and the histopathological changes on CFA-induced *Sprague dawley* rats.
5. To examine the inhibitory effects of 6-mercaptopurine and 6-mercaptopurine riboside on the cytokines production, oxidative stress biomarkers and pathogenic inflammatory mediator, prostaglandin E2 (PGE_2) concentrations on plasma CFA-induced arthritis in rat.

1.3 Hypothesis

6-mercaptopurine is postulated to demonstrate anti-arthritic effects by reducing the paw oedema, suppressed the systemic pro-inflammatory cytokines such as prostaglandins E2 (PGE_2), tumour necrosis factor-alpha (TNF-α), interleukin-1 (IL-1) and interleukin-6 (IL-6) and also restored the oxidative stress biomarkers such as glutathione and peroxide to normal level incomplete Freund adjuvant (CFA)-induced *Spraque dawley* rats model.

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