UNIVERSITI PUTRA MALAYSIA

PHARMACOLOGICAL AND TOXICOLOGICAL EFFECTS OF 6-HYDROXY-2-MERCAPTOPURINE AND 6-THIOGUANINE IN IN VITRO AND IN VIVO MODELS OF ARTHRITIS

NURUL SYUHADA NORDIN

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By

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September 2021

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Rheumatoid arthritis (RA) is a chronic inflammatory and systemic auto-immune disease characterized by symmetrical joint inflammation, destruction of articular cartilage and periarticular tissues leading to loss of joint function and morbidity. The abnormal propagation and activation in many types of immune cells lead to the secretion of the most important pro-inflammatory cytokines mediators such as TNF-α, IL-6, and IL-1 that amplify the inflammation. Current treatment includes non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, disease-modifying anti-rheumatic drugs (DMARDs) and biological agents. However, it has limitations such as poor patient response and risk of toxicity. The thiopurines include 6-mercaptopurine (6-MP), 6-hydroxy-2-mercaptopurine (6H2MP) and 6-thioguanine (6TG) are the immunosuppressive agents used in the treatment of acute lymphoblastic leukaemia, autoimmune disorders and organ transplant recipients. The main objective of this study is to determine the effects of selected thiopurines (6TG and 6H2MP) in phorbol myristate acetate (PMA)-activated rabbit synovial fibroblast cells (HIG-82) and Freund's complete adjuvant (FCA)-activated Sprague Dawley rats. Firstly, the therapeutic effects of thiopurines compounds (6MP, 6TG and 6H2MP) in lipopolysaccharide (LPS)-activated RAW264.7 macrophage and PMA-activated HIG-82 cells were carried out *in vitro*, with diclofenac was used as a positive control drug. The cytotoxicity and nitric oxide inhibition of thiopurines were performed by using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) and Griess assays. 6-thioguanine (6TG) and 6H2MP were chosen to be further investigated for their anti-inflammatory potentials *in vitro* by using various ELISA kit assays to detect the secretion of prostaglandin E2 (PGE2), pro-inflammatory cytokines tumor necrosis factor-alpha (TNF-α), interleukin 1 beta (IL-1β) and interleukin 6 (IL-6). For *in vivo* studies, the sub-chronic toxicity effects of 6TG and 6H2MP were also determined by employing an FCA-induced arthritic model on Sprague Dawley rats. The effects on histological alterations, haematological parameters,

biochemical markers, arthritis severity, secretion levels of enzymes matrix metalloproteinase 1 (MMP1), matrix metalloproteinase 3 (MMP3), cyclooxygenase-2 (COX-2) and pro-inflammatory cytokines (TNF-α, IL-1β & IL-6) in blood serum were determined. The results of LPS-induced RAW 264.7 macrophages demonstrated that 6H2MP and 6TG were able to suppress the production of NO *in vitro*. They also suppressed the release of NO, PGE2 and inflammatory cytokines (TNF-α, IL-1β and IL-6) in PMA-activated HIG-82 synovial fibroblast cells. 6TG was more effective in reducing the inflammatory reactions compared to 6H2MP by showings suppression in lower doses compared to 6H2MP in all experiments, except in PGE2. Further results in 28-days rats *in vivo* study showed that 6TG and 6H2MP by histopathological were prone to show their toxicity in high doses (16 mg/kg) compared to lower doses (4 mg/kg and 8 mg/kg). Both drugs 6TG and 6H2MP decreased the paws volume, and arthritic score and brings the normal mobility of rats. Both compounds also decreased the level of pro-inflammatory cytokines, COX-2 and matrix metalloproteinase enzymes (MMP1 and MMP3). The inhibition of TNF-α, IL-1β and NO is an important mechanism by which 6TG and 6H2MP may affect pain and articular inflammation. Collectively, our findings suggested that both 6TG and 6H2MP could be developed as effective candidates for ameliorating inflammatory-associated complications of autoimmune arthritis, with 6TG showing higher potential to inhibit the inflammation that occurs compared to 6H2MP.

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

KESAN FARMAKOLOGIKAL DAN TOKSIKOLOGIKAL 6-HYDROXY-2-MERCAPTOPURINE DAN 6-THIOGUANINE DI DALAM KAJIAN MODEL ARTHRITIS SECARA *IN VITRO* DAN *IN VIVO*

Oleh

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Rheumatoid arthritis (RA) merupakan penyakit keradangan kronik dan autoimun sistemik yang bercirikan radang pada sendi simetri dan kemusnahan rawan artikular serta tisu peri-artikular. Ia seterusnya membawa kepada kehilangan fungsi sendi dan morbiditi. Perkembangan dan pengaktifan kebanyakan sel imun menyebabkan mediator proinflamasi seperti sitokin TNF-α, IL-6, dan IL-1 meningkatkan kadar keradangan. Rawatan terkini bagi penyakit RA termasuk ubat anti-radang bukan steroid (NSAIDs), glukokortikoid, ubat-ubatan untuk mengelakkan kerosakan sendi (DMARDs) dan agen biologi. Walaubagaimanapun terdapat had-had tertentu yang mempengaruhi kesan rawatan seperti respon pesakit yang rendah dan risiko keracunan. Kumpulan ubatan thiopurine termasuk 6-mercaptopurine, 6-hydroxy-2-mercaptopurine (6H2MP) dan 6-thioguanine (6TG) adalah agen perencat imun yang digunakan di dalam rawatan *acute lymphoblastic leukaemia*, penyakit autoimun dan pemindahan organ. Objektif utama kajian ini ialah untuk mengenalpasti kesan kumpulan ubat thiopurine yang terpilih (6TG dan 6H2MP) di dalam sel sinovial fibroblas arnab (HIG-82) yang diaktifkan oleh phorbol myristate acetate (PMA) dan tikus ujian Sprague Dawley yang disuntik dengan Freund's complete adjuvant (FCA). Pada awalan kajian, kesan terapeutik kompaun thiopurine (6-MP, 6TG dan 6H2MP) di dalam sel makrofaj RAW264.7 yang diaktifkan oleh lipopolisakarida (LPS) dan sel HIG-82 yang diaktifkan oleh PMA telah dijalankan secara *in vitro*, di mana kompaun diclofenac telah digunakan sebagai ubat kawalan positif. Kadar sitotoksik dan perencatan nitric oksida oleh thiopurine diperolehi dengan menjalankan ujian 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) dan ujian Griess. Seterusnya potensi anti-inflamasi ubatan 6TG dan 6H2MP telah dipilih untuk dikaji melalui pelbagai ujian kit ELISA secara *in vitro* dengan mengenalpasti jumlah pengeluaran prostaglandin E2 (PGE2), pro-inflamasi sitokin tumor necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β) dan interleukin 6 (IL-6). Kajian *in vivo* terhadap kesan toksik ubatan 6TG dan 6H2MP secara sub-kronik juga dijalankan

menggunakan model artritis tikus Sprague Dawley yang telah disuntik dengan FCA. Perubahan data terhadap histologi, hematologi, biokimia, tahap artritis, pengeluaran enzim matrix metallo-proteinase 1 (MMP1), matrix metalloproteinase 3 (MMP3), cyclooxygenase-2 (COX-2), dan pro-inflamasi sitokin (TNF-α, IL-1β & IL-6) di dalam serum darah juga diperolehi. Data dianalisa dengan menggunakan perisian GraphPad Prism 5.0 melalui kaedah ANOVA sehala seterusnya melalui ujian post hoc Tukey untuk mengetahui kumpulan yang menunjukkan perbezaan statistik secara signifikan. Keputusan kajian terhadap sel makrofaj RAW264.7 yang diaktifkan oleh LPS menunjukkan 6TG dan 6H2MP berhasil untuk mengurangkan penghasilan NO secara *in vitro*. Kedua-dua kompaun juga berhasil mengurangkan penghasilan NO, PGE2, dan pro-inflammasi sitokin (TNF-α, IL-1 dan IL-6) di dalam sel sinovial fibroblast HIG-82 yang diaktifkan oleh PMA. 6TG didapati lebih berkesan untuk mengurangkan reaksi inflamasi berbanding 6H2MP. Ia menunjukkan pengurangan di dalam dos yang rendah berbanding 6H2MP di dalam kesemua eksperimen kecuali di dalam keputusan kajian PGE2. Kajian histopatologi tikus *(in vivo)* selama 28 hari menunjukkan 6TG dan 6H2MP menunjukkan kadar toksik di dalam dos yang paling tinggi (16 mg/kg) berbanding dos yang rendah (4 mg/kg and 8 mg/kg). Kedua-dua kompaun memulihkan pembengkakan dan menjadikan isipadu kaki, skor artritis dan mobiliti tikus menjadi normal. 6TG dan 6H2MP juga mengurangkan paras peningkatan pro-inflammasi sitokin, enzim COX-2 dan metalloproteinase matriks (MMP1 dan MMP3). Perencatan TNF-α, IL-1β dan NO merupakan mekanisme penting yang membuktikan bahawa 6TG and 6H2MP mungkin memberikan kesan di dalam rawatan kawalan kesakitan dan keradangan artikular. Secara kolektif, dapatan kajian ini mencadangkan bahawa 6TG and 6H2MP adalah calon kompaun yang efektif untuk mengurangkan komplikasi inflammasi dalam artritis autoimun, dengan 6TG didapati lebih berpotensi untuk merencat kadar inflamasi yang berlaku berbanding 6H2MP.

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I certify that a Thesis Examination Committee has met on 30 September 2021 to conduct the final examination of Nurul Syuhada Nordin on her thesis entitled "Pharmacological and toxicological Effects of 6-Hydroxy-2-Mercaptopurine and 6-Thioguanine in *In Vitro* and *In Vivo* Models of Arthritis" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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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 Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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Date: 21 July 2022

Declaration by Members of Supervisory Committee

This is to confirm that:

- the research and the writing of this thesis were done under our supervision;
- supervisory responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2015-2016) are adhered to.

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LIST OF ABBREVIATIONS

6H2MP	6-hydroxy-2-mercaptopurine
6MP	6-mercaptopurine
6-MMP	6-methylmercaptopurine
6TG	6-thioguanine
(6TGuo)	6-thioguanosine
6-TGNs	6-thioguanine nucleotides
6-TGTP	6-thioguanosine triphosphate
AA	Arachidonic acid
ACPA	Anti-citrullinated protein antibody
ACTH	Adrenocorticotropic hormone
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AP-1	Activator protein-1
APC	Antigen-presenting cells
AST	Aspartate aminotransferase
AZA	Azathioprine
CAMs	Cell adhesion molecules
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
CRP	C-reactive protein
DMARD	Disease-modifying anti-rheumatic drug
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DNPS	*de novo* purine synthesis

EBV	Epstein-Barr virus
ECM	Extracellular matrix
EFAs	Essential fatty acids
ERKs	Extracellular signal-regulated kinases
FBS	Fetal bovine serum
FCA	Freund's complete adjuvant
FGF	Fibroblast growth factors
FLS	Fibroblast-like synovial cell
GM-CSF	Granulocyte-macrophage colony-stimulating factor
Hb	Haemoglobin
HGPRT	Hypoxanthine-guanine phosphoribosyl transferase
HIF-1α	Hypoxia-inducible factor 1-alpha
IBD	Inflammatory bowel disease
IL-1	Interleukin 1
IL-6	Interleukin 6
iNOS	inducible NO synthase
HLA-DR4	Human leukocyte antigen (HLA)-DR4
JAK	Janus tyrosine kinase
JNK	c-jun N-terminal kinase
LPS	Lipopolysaccharides
MAPKs	Mitogen-activated protein kinases
MKKs	MAPK kinases
MKKKs	MAPK kinase kinases
MMP1	Matrix metalloproteinase 1
MMP3	Matrix metalloproteinase 3

mRNA	Messenger ribonucleic acid
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide
NADPH	Nicotinamide adenine dinucleotide phosphate
NEMO	NF-κB essential modulator
NETs	Neutrophil extracellular traps
NF-ĸB	Nuclear factor-kappa B
NO	Nitric oxide
NSAIDs	Nonsteroidal anti-inflammatory drugs
PCV	Packed cell volume
PGs	Prostaglandins
PGE2	Prostaglandin E2
PGH2	Prostaglandin H2
PGHS	Prostaglandin endoperoxide H synthase
PMA	Phorbol 12-myristate 13-acetate
PTPN22	Protein tyrosine phosphatase, non-receptor type 22
RA	Rheumatoid arthritis
Rac1	Ras-related C3 botulinum toxin substrate 1
RANKL	Receptor activator of nuclear factor-kappa-B ligand
RBC	Red blood cells
RFs	Rheumatoid factors
RT	Room temperature
STAT	Signal transducer and activator of transcription
TAD	Transactivation domains
TCRs	T cell receptors
TEM	Transmission electron microscopy
TGNs	Thioguanine nucleotides

TNF-α	Tumor necrosis factor-alpha
TLR	Toll-like receptor
TLR4	Toll-like receptor 4
TP	Total protein
TPMT	Thiopurine methyltransferase
VEGF	Vascular endothelial growth factors

CHAPTER 1

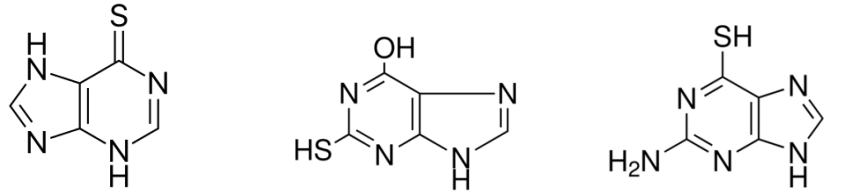
INTRODUCTION

1.1 Background of Study

Rheumatoid arthritis (RA) is a progressive autoimmune disorder that disturbs joints and other tissues in the body. It caused serious disability when it involves synovial tissue inflammation, joint swelling and subsequent cartilage injury (Zahidah and Faizah, 2012). The disease can affect and decrease the quality of life, including psychological well-being, family life, and social relationships. Anxiety and depression often being reported as the main psychiatric disorders related to RA cases (Rezaei et al., 2014).

The regulation of joint inflammation is a useful therapeutic approach in arthritis (Chung et al., 2012). The treatment acquired in RA are including long-duration therapy of disease-modifying anti-rheumatic drug (DMARD), to manage the sign and symptoms and control disease progression. The oral DMARDs used nowadays such as methotrexate, sulfasalazine, hydroxychloroquine, low-dose prednisolone and leflunomide (Highton et al., 2008).

6-mercaptopurine (6MP), 6-hydroxy-2-mercaptopurine (6H2MP) and 6-thioguanine (6TG) are belongs to the thiopurines family of drugs, also categorized as immunosuppressive agents which can inhibit inflammation by deactivating key processes in T lymphocytes, thus lowering the immune system activity (Neurath, 2010). These therapeutic compounds are commonly used for their variety of uses such as in cancer, post-transplant immunosuppression and in autoimmune diseases (Petit et al., 2008).



a) 6MP b) 6H2MP c) 6TG

Figure 1.0: Compounds that are being investigated in this project. (a) 6MP (b) 6H2MP and c) 6TG.

In this study, we were focusing on 6MP, 6H2MP and 6TG (Figure 1.0). These drugs were investigated through various experiments to determine their ability to reduce inflammation by using RAW264.7 macrophages, rabbit synoviocytes (HIG-82) cell culture and male Sprague Dawley rats. Phorbol 12-myristate 13-acetate (PMA) and Freund's complete adjuvant (FCA) were used as inflammation inducers and diclofenac was used as a positive control drug. Both of the drugs were tested separately but with the same doses to make a comparison regarding their potential to produce the effects.

1.2 Research Hypothesis

6TG and 6H2MP can reduce inflammation effects in LPS-induced RAW264.7 macrophages, PMA-induced rabbit synovial fibroblast cells (HIG-82) and FCA-induced arthritic in Sprague-Dawley rats.

1.3 Main Objective

To determine the effects of 6TG and 6H2MP in PMA-induced rabbit synovial fibroblast cells (HIG-82) and FCA-induced arthritic in Sprague-Dawley rats.

1.4 Specific Objectives

1 To determine the cell cytotoxicity effects of 6TG and 6H2MP on macrophages RAW 264.7 cells and rabbit synovial fibroblast cells (HIG-82).
2 To determine the inhibitory effects of 6TG and 6H2MP on inflammatory mediators and cytokines productions upon exposure to LPS in RAW264.7 macrophages and PMA in rabbit synovial fibroblast cells (HIG-82).
3 To examine the inhibitory effects of 6TG and 6H2MP on cytokines production in FCA-induced Sprague-Dawley rats.
4 To determine the levels of protein secretion MMP1, MMP3 and COX-2 after the treatment with 6TG and 6H2MP in FCA-induced Sprague-Dawley rats.
5 To determine the toxicity effects of 6TG and 6H2MP in Sprague-Dawley rats.

1.5 Research Justification

There is no promising report has been made on the effects of 6TG and 6H2MP on anti-rheumatic actions. The study aimed to investigate the activity and function of two thiopurines; 6H2MP (the derivative isomer of 6MP and 6TG in suppressing the inflammation involved with arthritis. Equivalent analyses comparing both drugs were performed since both of them shared a common active metabolite. The inflammation models used were LPS-induced Macrophage 264.7 cells, the synoviocytes from rabbits (HIG-82 cells) induced by phorbol myristate acetate (PMA), and the pharmacology and the toxicity determinations towards the effect of the sub-chronic test on FCA-induced rats. The *in vitro* studies were represented as relevant tools for the evaluation and development of new treatment options, while the animal models of RA can act as a resemblance to descriptive studies of human samples.

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