UNIVERSITI PUTRA MALAYSIA

ANTI-ARTHRITIC ACTION OF CARDAMONIN IN RHEUMATOID ARTHRITIS-INDUCED RAT MODEL

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FPSK(M) 2016 44

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By

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

May 2016

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

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May 2016

Chairman: Professor Mohd Roslan Sulaiman, PhD
Faculty: Medicine and Health Sciences

Rheumatoid arthritis (RA) is a chronic autoimmune disease which causes joint deformity. The well-being and productivity of RA patients are negatively affected as they constantly experience painfulness in their swollen joints. Current treatments for RA such as disease-modifying anti-rheumatic drugs (DMARDs), glucocorticoids, and non-steroidal anti-inflammatory drugs (NSAIDs) cause adverse effects such as bone marrow suppression, gastrointestinal upset, etc. Therefore, novel substances that possess potential anti-arthritic effect are of research interest. Cardamonin (2',4'-dihydroxy-6'-methoxychalcone) is a naturally occurring chalcone. It is frequently found in plants of Zingiberaceae family such as ginger, a common cooking ingredient for Asians. Cardamonin was reported to suppress the secretion of tumour necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) in induced cell lines. Also, cardamonin had shown antinociceptive activity in chemical-induced mice abdominal writhing test. Thus, cardamonin was chosen to investigate its anti-arthritic effect on complete Freund's adjuvant (CFA)-induced RA rat model of joint inflammation. Preliminary studies included acetic acid-induced abdominal writhing test, carrageenan-induced acute paw inflammation test, and repeated dose 28-day toxicity test. Anti-arthritic experiment utilised six groups (n=6) of male *Sprague Dawley* rats weighing 200g to 250g. RA was induced in the rats through intraplantar (i.pl.) injection of CFA at the right hind paws. On the ninth day after arthritis induction, treatments at dosages of 0.625, 1.25, 2.5, and 5.0 mg/kg were given daily for 22 days through intraperitoneal (i.p.) injection. The positive control group was treated with dexamethasone (3.0mg/kg, i.p.) while the negative control group was given only vehicle (10.0ml/kg, i.p.). CFA-induced inflammatory response was evaluated via volume of paw oedema using plethysmometer, while pain response was evaluated via mechanical allodynia using von Frey anesthesiometer as well as thermal hyperalgesia using plantar test instrument. Evaluation of paw volume, mechanical allodynia, and thermal hyperalgesic responses were done at three-day intervals

throughout the experiment. Blood samples were collected at the end of the experiment to investigate the blood components and systemic cytokines of cardamonin-treated rats. Right hind paws of the rats were harvested for histological examination. Cardamonin significantly inhibited acetic acid-induced abdominal writhing in experimental animals. Also, cardamonin significantly reduced the acute paw inflammation in carrageenan-induced acute paw inflammation test. Repeated dose 28-day toxicity test showed that 5.0mg/kg of cardamonin did not cause toxicity effect in rats. In anti-arthritic study, plethysmometry, von Frey anesthesiometry, and plantar test measurement showed that cardamonin resulted in significant inhibition on CFA-induced inflammatory and pain responses at the doses of 0.625, 1.25, 2.5, and 5.0 mg/kg (i.p.). The complete blood count showed that cardamonin caused significant effect on the blood components of CFA-induced rats. Enzyme-linked immunosorbent assay (ELISA) demonstrated that there was significant inhibition in TNF-α, IL-1β, and IL-6 in cardamonin-treated RA rats. Besides, histological study showed that cardamonin has the potential to suppress the growth of pannus invasion in the joint cavity. The present study revealed that 0.625, 1.25, 2.5, and 5.0 mg/kg of cardamonin caused significant inhibition on CFA-induced RA rats.

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

TINDAKAN ANTI-REUMATIK CARDAMONIN KE ATAS ARTRITIS REUMATOID YANG DIARUH DALAM MODEL TIKUS

Oleh

VOON FUI LING

Mei 2016

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Artritis reumatoid (RA) merupakan penyakit autoimun kronik yang menyebabkan kecacatan sendi. Tahap kesihatan dan produktiviti pesakit RA adalah terjejas kerana mereka sentiasa mengalami kesakitan pada sendi yang bengkak. Rawatan untuk RA seperti ubat-ubatan pengubahsuaian penyakit anti-reumatik (DMARDs), glukokortikoid, dan ubat anti-radang bukan berasaskan steroid (NSAID) menyebabkan kesan buruk seperti menghalang pertumbuhan sumsum tulang, gangguan gastrousus, dan lain-lain. Oleh itu, bahan-bahan baru yang berpotensi untuk memberikan kesan anti-artritis adalah penting. Cardamonin (2',4'-dihydroxy-6'-methoxychalcone) adalah chalcone yang wujud secara semula jadi. Ia biasanya terdapat dalam tumbuhan dari keluarga Zingiberaceae seperti halia, sejenis bahan masak yang digunakan oleh orang Asia. Cardamonin dilaporkan telah menyekat rembesan tumor nekrosis faktor-α (TNF-α) dan interleukin- 1β (IL-1β) dalam sel teraruh. Juga, cardamonin telah menunjukkan kesan anti-sakit dalam ujian menggeliat perut yang diaruh dengan bahan kimia dalam mencit. Oleh itu, cardamonin telah dipilih untuk dikaji kesan anti-artritisnya dalam model tikus keradangan sendi yang diaruh oleh Freund adjuvan lengkap (CFA). Kajian awal termasuk ujian menggeliat perut yang diaruh oleh asid asetik, ujian keradangan akut yang diaruh oleh carrageenan, dan ujian toksisiti 28 hari dos berulang. Eksperimen anti-reumatik menggunakan enam kumpulan (*n*=6) tikus jantan *Sprague Dawley* seberat 200g ke 250g. RA telah diaruh dalam tikus melalui suntikan CFA secara intraplantar (i.pl.) pada tapak kaki kanan. Pada hari kesembilan selepas arthritis diaruh, rawatan pada dos 0.625, 1.25, 2.5, dan 5.0 mg/kg diberikan setiap hari selama 22 hari melalui suntikan intraperitoneal (i.p.). Kumpulan kawalan positif dirawat dengan dexamethasone (3.0mg/kg, i.p.) manakala kumpulan kawalan negatif hanya diberikan pembawa (10.0ml/kg, i.p.). Tindak balas keradangan yang diaruh oleh CFA dinilai melalui isipadu edema pada kaki tikus dengan menggunakan pletismometer, manakala tindak balas kesakitan dinilai melalui alodinia

mekanikal menggunakan von Frey anesthesiometer serta hiperalgesia haba menggunakan instrumen ujian plantar. Penilaian isipadu kaki tikus, alodinia mekanikal, dan tindak balas haba hiperalgesia dilakukan selang tiga hari sepanjang eksperimen. Sampel darah telah diambil pada akhir eksperimen untuk menilai komponen darah dan sitokin sistemik tikus yang telah dirawat dengan cardamonin. Kaki kanan belakang tikus diambil untuk penilaian histologi. Cardamonin telah mengurangkan penggeliatan perut yang diaruh dengan asid asetik dalam haiwan kajian. Juga, cardamonin telah mengurangkan keradangan kaki tikus yang diaruh carrageenan. Ujian toksisiti 28 hari dos berulang menunjukkan 5.0mg/kg cardamonin tidak menghasilkan kesan keracunan terhadap tikus. Dalam kajian anti-artritis, ujian pletismometer, von Frey anesthesiometer, dan pengukuran ujian plantar menunjukkan cardamonin telah mengurangkan tahap keradangan serta tindak balas kesakitan yang diaruh CFA pada dos 0.625, 1.25, 2.5, dan 5.0 mg/kg (i.p.). Kiraan darah lengkap telah menunjukkan kesan yang ketara dalam rawatan cardamonin ke atas komponen-komponen darah tikus RA. Esei yang berkaitan dengan enzim imunoserapan (ELISA) telah menunjukkan bahawa terdapat kesan perencatan yang ketara dalam TNF-α, IL-1β, dan IL-6 dalam plasma darah tikus RA yang telah dirawat dengan cardamonin. Selain itu, kajian histologi menunjukkan bahawa cardamonin mempunyai potensi untuk menyekat penumbuhan pannus dalam rongga sendi. Kajian ini menunjukkan bahawa 0.625, 1.25, 2.5, dan 5.0 mg/kg cardamonin mampu menghasilkan kesan signifikan dalam merencat RA yang diaruh oleh CFA dalam tikus.

ACKNOWLEDGEMENT

First and foremost, I would like to express my deepest gratitude to the chairman of my supervisory committee, Professor Dr. Mohd Roslan bin Sulaiman, who had given me the opportunity to further my study under his guidance and supervision. Sincere appreciation is also extended to Dr. Lee Ming-Tatt who had given me valuable advices throughout my study. I would like to thank Professor Dr. Daud Ahmad Israf Ali, Dr. Ahmad Akira Omar Farouk, and Dr. Enoch Kumar Perimal who were willing to be part of my supervisory committee members.

I would like to extend my gratitude to my seniors and colleagues in the laboratory of physiology: Ms. Jacklin Suloon, Mdm. Noor Azlina Abu Bakar, Mdm. Nor 'Adilah Makhtar, Ms. Ong Hui Ming, Ms. Chung Pui Ping, Mr. Fauzi Idris, Ms. Ee Ai Chin, Ms. Banulata Gopalsamy, Ms. Nurul Atiqah binti Zulalmi, Mr. Mohd Amirudin Efendi, Ms. Tein Yaren, and many more for their invaluable advices, guidance, and support. They had given me a very great help in sacrificing laboratory animals, collecting and fixing the organ samples as well as sending the blood samples of experimental animals to the Faculty of Veterinary Medicine regardless how busy they were. Special thanks to Banulata Gopalsamy who is very kind to proofread my thesis.

Not to forget the laboratory staffs, Mdm. Normayati Sulaiman, Mdm. Hasnijah Alias, Mr. Nasrul Ridzal Zainal Abidin, Mr. Zulkhairi Zainol, and Mdm. Nora Asyikin Mohd Salim who constantly keep the laboratory a clean and safe environment for me to carry out my experiments.

Last but not least, I am very grateful to have the continuous support from my family members: my parents, my elder sister Fui-Chin, and my younger sister Fui-Kiun.

Thank you.

I certify that a Thesis Examination Committee has met on 13 May 2016 to conduct the final examination of Voon Fui Ling on her thesis entitled 'Anti-arthritic Action of Cardamonin in Rheumatoid Arthritis-induced Rat Model' 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 Master of Science.

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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

ACPA	Anti-citrullinated peptide antibodies
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic
ANOVA	Analysis of variance
APC	Antigen-presenting cell
B19	Human parvovirus B19
cAMP	Cyclic adenosine monophosphate
CBC	Complete blood count
CFA	Complete Freund's adjuvant
CNS	Central nervous system
COX	Cyclooxygenase
CREB	cAMP response element-binding
DC	Dendritic cell
DHODH	Dihydroorotate dehydrogenase
DMARDs	Disease-modifying Anti-rheumatic Drugs
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DRG	Dorsal root ganglion
EBV	Epstein - Barr virus
ECM	Extracellular matrix
ED_{50}	Median effective dose
EDTA	Ethylenediaminetetraacetic acid
ELAM-1	Endothelial-leukocyte adhesion molecule-1
ELISA	Enzyme-linked immunosorbent assay
Fc	Fragment crystallisable
FLS	Fibroblast-like synoviocyte
GLUT-4	Glucose transporter type 4
GM-CSF	Granulocyte-macrophage colony-stimulating factor
Hb	Haemoglobin
HIV-1	Human immunodeficiency virus type 1
HLA	Human leukocyte antigen
H&E	Haematoxylin and eosin
i.p.	Intraperitoneal
i.pl.	Intraplantar
ICAM-1	Intercellular adhesion molecule-1
IFN-γ	Interferon-gamma
Ig	Immunoglobulin
IL	Interleukin
IL-1β	Interleukin-1 beta
IL-1Ra	Interleukin-1 receptor antagonist
IL-6	Interleukin-6
iNOS	Inducible nitric oxide synthase
LOX	Lipooxygenase
LPS	Lipopolysaccharide
MHC	Major histocompatibility complex
MMP	Matrix metalloproteinase
NFκB	Nuclear factor-kappa B
NK	Natural killer
NMDA	N-methyl-D-aspartate

NO	Nitric oxide
NSAIDs	Non-steroidal anti-inflammatory drugs
PBQ	Phenylbenzoquinone
PG	Prostaglandin
PGE_2	Prostaglandin E_2
PGI_2	Prostacyclin
PMN	Polymorphonuclear leukocyte
p.o.	Oral administration - per os
QKRAA	glutamine-leucine-arginine-alanine-alanine
RA	Rheumatoid arthritis
RANK	Receptor activator of nuclear factor kappa-B
RANKL	Receptor activator of nuclear factor kappa-B ligand
RBC	Red blood cell
RF	Rheumatoid factor
SE	Shared epitope
S.E.M.	Standard error of mean
Th1	T helper cells type 1
TNF	Tumour necrosis factor
TNFR	Tumour necrosis factor-alpha receptor
TNFSF11	Tumour necrosis factor ligand superfamily member 11
TRPV1	Transient receptor potential vanilloid 1
VCAM-1	Vascular cell adhesion molecule-1
VEGF	Vascular endothelial growth factor
WBC	White blood cell

CHAPTER 1

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease which causes chronic systemic joint inflammation. RA patients experience swollen and painful joints which seriously affect their normal well-being. As RA develops into the later stage, the cartilage and bones start to erode due to the attacking of the autoimmune cells, leading to joint deformity. About 1% of the population worldwide is currently affected by RA while 5 out of 1000 Malaysians are diagnosed with this disease (Arthritis Foundation Malaysia, 2012; Gibofsky, 2012; Chandirasekar *et al.*, 2015).

The early symptoms of RA include joint pain and stiffness, malaise, as well as the symmetrical occurrence of joint inflammation in both the left and right side of the body (Suresh, 2004). Smaller joints at wrists and fingers are usually the first target, followed by larger joints. However, not all patients will show these clear symptoms during the onset of the disease. Some of the patients may present only asymmetrical joint inflammation and thus the early onset of RA is not easy to be detected. As a consequence, many patients miss the chance to inhibit the rapid worsening of RA (Fautrel *et al.*, 2011).

Current treatments available for RA could not totally cure this disease. They are only able to reduce pain as well as slow down the progress of joint damage. The common drug therapies for RA include non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and disease modifying anti-rheumatic drugs (DMARDs). In the past, these drugs were prescribed according to the 'pyramid therapeutic' sequence, in which patients were initially suggested to take NSAIDs, and when the condition deteriorated, glucocorticoids and DMARDs would be given. However, the therapeutic procedure for RA has changed in recent years. Rheumatologists are no longer following the 'pyramid therapeutic' sequence, instead, more robust drugs such as DMARDs or cocktail regimens are prescribed once RA is diagnosed in order to achieve earlier improvement and less joint damage (Kavanaugh, 2007; Upchurch and Kay, 2012). Nevertheless, drugs especially DMARDs are not prescribed for long term usage as the drugs could be very toxic (Emery, 2006).

Researchers are now shifting their attention to find alternatives for treating RA in a more effective way. Besides identifying the real cause of RA, new drug discovery is also in the list of research interest today so that patients could be offered with more choices of drugs other than the three main RA prescriptions (Quan *et al.*, 2008). Natural products and their extracts or compounds are given priority in RA research as their therapeutic potential in medical field has yet to be fully unlocked (Sen and Samanta, 2015).

In the present research, cardamonin was chosen as the treatment compound for chemical induced-rheumatoid arthritis in animal model. Cardamonin is a compound commonly found in Zingibereceae plant species (Israf *et al.*, 2007). It has been reported that cardamonin produced favourable results in antinociceptive as well as anti-inflammatory studies (Park *et al.*, 2014; Li *et al.*, 2015). Therefore, cardamonin might possess anti-arthritic activity and this study was carried out on RA-induced rat model to find out the possible therapeutic effect of cardamonin as the first step in discovering a better anti-arthritic drug option for RA patients.

1.1 Objectives

This research was conducted to evaluate the anti-arthritic effect of cardamonin on complete Freund's adjuvant (CFA)-induced rheumatoid arthritis in rat model.

The specific objectives of this study include the following:

1. To evaluate the anti-oedematous effect of cardamonin on complete Freund's adjuvant (CFA)-induced RA rat paws.

2. To evaluate the pain-reduction effect of cardamonin on mechanical allodynia and thermal hyperalgesia in CFA-induced RA rat paws.

3. To assess the effect of cardamonin on complete blood count (CBC) of CFA-induced RA rats specifically on red blood cell (RBC), haemoglobin (Hb), lymphocyte, and monocyte count.

4. To investigate the effect of cardamonin on the systemic cytokines specifically tumour necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and IL-6 in CFA-induced RA rats.

5. To investigate the effect of cardamonin on the histopathological changes of CFA-induced RA rat joints.

1.2 Hypothesis

Cardamonin was postulated to present anti-arthritic effects by reducing the paw oedema, mechanical allodynia, thermal hyperalgesia, as well as the systemic pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) in CFA-induced RA rat model.

REFERENCES:

Agbanoma, G., Li, C., Ennis, D., Palfreeman, A. C., Williams, L. M., and Brennan, F. M. 2012. Production of TNF-alpha in Macrophages Activated by T Cells, Compared with Lipopolysaccharide, Uses Distinct IL-10-Dependent Regulatory Mechanism. *The Journal of Immunology* 188: 1307-1317.

Ahmad, S., Israf, D. A., Lajis, N. H., Shaari, K., Mohamed, H., Wahab, A. A., Ariffin, K. T., Hoo, W. Y., Aziz, N. A., and Kadir, A. A. 2006. Cardamonin, inhibits pro-inflammatory mediators in activated RAW 264.7 cells and whole blood. *European Journal of Pharmacology* 538: 188-194.

Alamanos, Y. and Drosos, A. A. 2005. Epidemiology of adult rheumatoid arthritis. *Autoimmunity reviews* 4: 130-136.

Allard, S. A., Muirden, K. D., and Maini, R. N. 1991. Correlation of histopathological features of pannus with patterns of damage in different joints in rheumatoid arthritis. *Annals of the Rheumatic Diseases* 50: 278-283.

Aloisi, F. 1999. The role of microglia and astrocytes in CNS immune surveillance and immunopathology. *The Functional Roles of Glial Cells in Health and Disease: Springer* 123-133.

Altomonte, M., Fonsatti, E., Visintin, A., and Maio, M. 2003. Targeted therapy of solid malignancies via HLA class II antigens: a new biotherapeutic approach? *Oncogene* 22: 6564-6569.

Aoki, S., Yoshikawa, K., Yokoyama, T., Nonogaki, T., Iwasaki, S., Mitsui, T., and Niwa, S. 1996. Role of enteric bacteria in the pathogenesis of rheumatoid arthritis: evidence for antibodies to enterobacterial common antigens in rheumatoid sera and synovial fluids. *Annals of the Rheumatic Diseases* 55: 363-369.

Arend, W. P., Malyak, M., Guthridge, C. J., and Gabay, C. 1998. Interleukin-1 receptor antagonist: role in biology. *Annual Review of Immunology* 16: 27-55.

Armstrong, C. P. and Blower, A. L. 1987. Non-steroidal anti-inflammatory drugs and life threatening complications of peptic ulceration. *Gut* 28: 527-532.

Arner, E. C., Hughes, C. E., Decicco, C. P., Caterson, B., and Tortorella, M. D. 1998. Cytokine-induced cartilage proteoglycan degradation is mediated by aggrecanase. *Osteoarthritis and Cartilage* 6: 214-228.

Arthritis Foundation Malaysia. 2012. Retrieved 30 August 2015 from www.afm.org.my

Askling, J., Fahrbach, K., Nordstrom, B., Ross, S., Schmid, C. H., and Symmons, D. 2011. Cancer risk with tumor necrosis factor alpha (TNF) inhibitors: meta-analysis of randomized controlled trials of adalimumab, etanercept, and infliximab using patient level data. *Pharmacoepidemiology and Drug Safety* 20: 119-130.

Auffray, C., Kuo, J., DeMars, R., and Strominger, J. L. 1983. A minimum of four human class II alpha-chain genes are encoded in the HLA region of chromosome 6 *Nature* 304: 174-177.

Bacon, K., Baggiolini, M., Broxmeyer, H., Horuk, R., Lindley, I., Mantovani, A., Matsushima, K., Murphy, P., Nomiyama, H., and Oppenheim, J. 2001. Chemokine/chemokine receptor nomenclature. *Journal of Leukocyte Biology* 70: 465-466.

Bajgai, S. P., Prachyawarakorn, V., Mahidol, C., Ruchirawat, S., and Kittakoop, P. 2011. Hybrid flavan-chalcones, aromatase and lipoxygenase inhibitors, from Desmos cochinchinensis. *Phytochemistry* 72: 2062-2067.

Bancroft, J. D. and Gamble, M. 2008. *Theory and practice of histological techniques*: Elsevier Health Sciences.

Barnes, P. J. and Adcock, I. M. 2009. Glucocorticoid resistance in inflammatory diseases. *The Lancet* 373: 1905-1917.

Bendele, A., McComb, J., Gould, T. Y., McAbee, T., Sennello, G., Chlipala, E., and Guy, M. 1999. Animal models of arthritis: relevance to human disease. *Toxicologic Pathology* 27: 134-142.

Billiau, A. and Matthys, P. 2001. Modes of action of Freund's adjuvants in experimental models of autoimmune diseases. *Journal of Leukocyte Biology* 70: 849-860.

Breedveld, F. C. and Dayer, J. M. 2000. Leflunomide: mode of action in the treatment of rheumatoid arthritis. *Annals of the Rheumatic Diseases* 59: 841-849.

Brenn, D., Richter, F., and Schaible, H.-G. 2007. Sensitization of unmyelinated sensory fibers of the joint nerve to mechanical stimuli by interleukin-6 in the rat: an inflammatory mechanism of joint pain. *Arthritis and Rheumatism* 56: 351-359.

Brennan, F. M. and McInnes, I. B. 2008. Evidence that cytokines play a role in rheumatoid arthritis. *The Journal of clinical investigation* 118: 3537.

Butler, D. M., Maini, R. N., Feldmann, M., and Brennan, F. M. 1994. Modulation of proinflammatory cytokine release in rheumatoid synovial membrane cell cultures. Comparison of monoclonal anti TNF-alpha antibody with the interleukin-1 receptor antagonist. *European Cytokine Network* 6: 225-230.

Celerier, E., Gonzalez, J. R., Maldonado, R., Cabanero, D., and Puig, M. M. 2006. Opioid-induced hyperalgesia in a murine model of postoperative pain: role of nitric oxide generated from the inducible nitric oxide synthase. *Anesthesiology* 104: 546-555.

Cha, H. S., Ahn, K. S., Jeon, C. H., Kim, J., Song, Y. W., and Koh, E. M. 2002. Influence of hypoxia on the expression of matrix metalloproteinase-1,-3 and tissue inhibitor of metalloproteinase-1 in rheumatoid synovial fibroblasts. *Clinical and Experimental Rheumatology* 21: 593-598.

Chandirasekar, R., Kumar, B. L., Jayakumar, R., Uthayakumar, V., Jacob, R., and Sasikala, K. 2015. Evaluation of clinical and cytogenetic parameters in rheumatoid arthritis patients for effective diagnosis. *Clinica Chimica Acta* 439: 77-83.

Chantry, D., Turner, M., Brennan, F., Kingsbury, A., and Feldmann, M. 1990. Granulocyte-macrophage colony stimulating factor induces both HLA-DR expression and cytokine production by human monocytes. *Cytokine* 2: 60-67.

Choi, B.-T., Kang, J., and Jo, U.-B. 2005. Effects of electroacupuncture with different frequencies on spinal ionotropic glutamate receptor expression in complete Freund's adjuvant-injected rat. *Acta Histochemica* 107: 67-76.

Chow, Y.-L., Lee, K.-H., Vidyadaran, S., Lajis, N. H., Akhtar, M. N., Israf, D. A., and Syahida, A. 2012. Cardamonin from Alpinia rafflesiana inhibits inflammatory responses in IFN-gamma/LPS-stimulated BV2 microglia via NF-kappa B signalling pathway. *International Immunopharmacology* 12: 657-665.

Collier, H. O. J., Dinneen, L. C., Johnson, C. A., and Schneider, C. 1968. The abdominal constriction response and its suppression by analgesic drugs in the mouse. *British Journal of Pharmacology and Chemotherapy* 32: 295-310.

Croia, C., Serafini, B., Bombardieri, M., Kelly, S., Humby, F., Severa, M., Rizzo, F., Coccia, E. M., Migliorini, P., and Aloisi, F. 2013. Epstein-Barr virus persistence and infection of autoreactive plasma cells in synovial lymphoid structures in rheumatoid arthritis. *Annals of the Rheumatic Diseases* 72: 1559-1568.

Cronstein, B. N., Kimmel, S. C., Levin, R. I., Martiniuk, F., and Weissmann, G. 1992. A mechanism for the antiinflammatory effects of corticosteroids: the glucocorticoid receptor regulates leukocyte adhesion to endothelial cells and expression of endothelial-leukocyte adhesion molecule 1 and intercellular adhesion molecule 1. *Proceedings of the National Academy of Sciences* 89: 9991-9995.

Cronstein, B. N. 1995. The antirheumatic agents sulphasalazine and methotrexate share an anti-inflammatory mechanism. *Rheumatology* 34: 30-32.

Cunha, F. Q., Poole, S., Lorenzetti, B. B., and Ferreira, S. H. 1992. The pivotal role of tumour necrosis factor a in the development of inflammatory hyperalgesia. *British Journal of Pharmacology* 107: 660-664.

Daughton, C. G. and Ruhoy, I. S. 2013. Lower-dose prescribing: minimizing "side effects" of pharmaceuticals on society and the environment. *Science of the Total Environment* 443: 324-337.

Deraedt, R., Jouquey, S., Delevallee, F., and Flahaut, M. 1980. Release of prostaglandins E and F in an algogenic reaction and its inhibition. *European Journal of Pharmacology* 61: 17-24.

Di Giuseppe, D., Orsini, N., Alfredsson, L., Askling, J., and Wolk, A. 2013. Cigarette smoking and smoking cessation in relation to risk of rheumatoid arthritis in women. *Arthritis Research and Therapy* 15: R56.

Di Rosa, M., Giroud, J. P., and Willoughby, D. A. 1971. Studies of the mediators of the acute inflammatory response induced in rats in different sites by carrageenan and turpentine. *The Journal of Pathology* 104: 15-29.

Diallo, A., Eklu-Gadegkeku, K., Agbono, A., Aklikokou, K., Creppy, E. E., and Gbeassor, M. 2010. Acute and sub-chronic (28-day) oral toxicity studies of hydroalcohol leaf extract of Ageratum

conyzoides L (Asteraceae). *Tropical Journal of Pharmaceutical Research* 9.

Doan, Q. V., Chiou, C.-F., and Dubois, R. W. 2006. Review of eight pharmacoeconomic studies of the value of biologic DMARDs (adalimumab, etanercept, and infliximab) in the management of rheumatoid arthritis. *Journal of managed care pharmacy: JMCP* 12: 555-569.

Doz, E., Lombard, R., Carreras, F., Buzoni-Gatel, D., and Winter, N. 2013. Mycobacteria-infected dendritic cells attract neutrophils that produce IL-10 and specifically shut down Th17 CD4 T cells through their IL-10 receptor. *The Journal of Immunology* 191: 3818-3826.

Dubois, R. N., Abramson, S. B., Crofford, L., Gupta, R. A., Simon, L. S., Van De Putte, L. B. A., and Lipsky, P. E. 1998. Cyclooxygenase in biology and disease. *The Federation of American Societies for Experimental Biology Journal* 12: 1063-1073.

Ebbinghaus, M., Uhlig, B., Richter, F., von Banchet, G. S., Gajda, M., Brauer, R., and Schaible, H.-G. 2012. The role of interleukin-1beta in arthritic pain: Main involvement in thermal, but not mechanical, hyperalgesia in rat antigen-induced arthritis. *Arthritis and Rheumatism* 64: 3897-3907.

Eddarir, S., Cotelle, N., Bakkour, Y., and Rolando, C. 2003. An efficient synthesis of chalcones based on the Suzuki reaction. *Tetrahedron Letters* 44: 5359-5363.

Emery, P. 2006. Treatment of rheumatoid arthritis. *British Medical Journal* 7534: 152.

Epstein, F. H. and Harris, E. D. 1990. Rheumatoid arthritis: pathophysiology and implications for therapy. *New England Journal of Medicine* 322: 1277-1289.

Everett, J., Gravallese, E., and Mix, K. S. 2015. NR4A2 Expression Patterns in Mouse Models of Rheumatoid Arthritis. *Journal of Student Research* 4: 136-143.

Fassbender, H. G. and Simmling-Annefeld, M. 1983. The potential aggressiveness of synovial tissue in rheumatoid arthritis. *The Journal of Pathology* 139: 399-406.

Fautrel, B., Combe, B., Rincheval, N., and Dougados, M. 2011. Level of agreement of the 1987 ACR and 2010 ACR/EULAR rheumatoid arthritis classification criteria: an analysis based on ESPOIR cohort data. *British Medical Journal (Clinical Research Ed.)*.

Fichter, M., Korner, U., Schomburg, J., Jennings, L., Cole, A. A., and Mollenhauer, J. 2006. Collagen degradation products modulate matrix metalloproteinase expression in cultured articular chondrocytes. *Journal of Orthopaedic Research* 24: 63-70.

Firestein, G. S., Alvaro-Gracia, J. M., Maki, R., and Alvaro-Garcia, J. M. 1990. Quantitative analysis of cytokine gene expression in rheumatoid arthritis. *The Journal of Immunology* 144: 3347-3353.

Firestein, G. S. and Zvaifler, N. J. 1990. How important are T cells in chronic rheumatoid synovitis? *Arthritis and Rheumatism* 33: 768-773.

Fox, R. I. 1993. Mechanism of action of hydroxychloroquine as an antirheumatic drug. *Seminars in Arthritis and Rheumatism* 23: 82-91.

Freund, J. 1947. Some aspects of active immunisation. *Annual Review Microbiology* 1: 295-301.

Friederichs, K., Schmitz, J., Weissenbach, M., Heinrich, P. C., and Schaper, F. 2001. Interleukin-6-induced proliferation of pre-B cells mediated by receptor complexes lacking the SHP2/SOCS3 recruitment sites revisited. *European Journal of Biochemistry* 268: 6401-6407.

Fusi, F., Cavalli, M., Mulholland, D., Crouch, N., Coombes, P., Dawson, G., Bova, S., Sgaragli, G., and Saponara, S. 2010. Cardamonin is a bifunctional vasodilator that inhibits Cav1. 2 current and stimulates KCa1. 1 current in rat tail artery Myocytes. *Journal of Pharmacology and Experimental Therapeutics* 332: 531-540.

Galon, J., Franchimont, D., Hiroi, N., Frey, G., Boettner, A., Ehrhart-Bornstein, M., O'shea, J. J., Chrousos, G. P., and Bornstein, S. R. 2002. Gene profiling reveals unknown enhancing and suppressive actions of glucocorticoids on immune cells. *The Federation of American Societies for Experimental Biology Journal* 16: 61-71.

Ganz, T. 2003. Hepcidin, a key regulator of iron metabolism and mediator of anemia of inflammation. *Blood* 102: 783-788.

Gardam, M. A., Keystone, E. C., Menzies, R., Manners, S., Skamene, E., Long, R., and Vinh, D. C. 2003. Anti-tumour necrosis factor agents and tuberculosis risk: mechanisms of action and clinical management. *The Lancet: Infectious Diseases* 3: 148-155.

Geborek, P., Forslind, K., and Wollheim, F. A. 1989. Direct assessment of synovial blood flow and its relation to induced hydrostatic pressure changes. *Annals of the Rheumatic Diseases* 48: 281-286.

Geborek, P., Bladstrom, A., Turesson, C., Gulfe, A., Petersson, I. F., Saxne, T., Olsson, H., and Jacobsson, L. T. H. 2005. Tumour necrosis factor blockers do not increase overall tumour risk in patients with rheumatoid arthritis, but may be associated with an increased risk of lymphomas. *Annals of the Rheumatic Diseases* 64: 699-703.

Gibofsky, A. 2012. Overview of epidemiology, pathophysiology, and diagnosis of rheumatoid arthritis. *The American Journal of Managed Care* 18: S295-302.

Gilani, S. T., Khan, D. A., Khan, F. A., and Ahmed, M., 2012: Adverse effects of low dose methotrexate in rheumatoid arthritis patients. *Journal of the College of Physicians and Surgeons Pakistan,* 22: 101-104.

Goncalves, L. M., Valente, I. M., and Rodrigues, J. A. 2014. An Overview on Cardamonin. *Journal of Medicinal Food* 17: 633-640.

Gouwy, M., Struyf, S., Catusse, J., Proost, P., and Van Damme, J. 2004. Synergy between proinflammatory ligands of G protein-coupled receptors in neutrophil activation and migration. *Journal of Leukocyte Biology* 76: 185-194.

Gravallese, E. M., Harada, Y., Wang, J.-T., Gorn, A. H., Thornhill, T. S., and Goldring, S. R. 1998. Identification of cell types responsible for bone resorption in rheumatoid arthritis and juvenile rheumatoid arthritis. *The American Journal of Pathology* 152: 943.

Gregersen, P. K., Silver, J., and Winchester, R. J. 1987. The shared epitope hypothesis. An approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis. *Arthritis and Rheumatism* 30: 1205-1213.

Grober, J. S., Bowen, B. L., Ebling, H., Athey, B., Thompson, C. B., Fox, D. A., and Stoolman, L. M. 1993. Monocyte-endothelial adhesion in chronic rheumatoid arthritis. In situ detection of selectin and integrin-dependent interactions. *Journal of Clinical Investigation* 91: 2609.

Gryglewski, R. J. 2008. Prostacyclin among prostanoids. *Pharmacological Reports* 60: 3-11.

Guay, J., Bateman, K., Gordon, R., Mancini, J., and Riendeau, D. 2004. Carrageenan-induced paw edema in rat elicits a predominant prostaglandin E_2 (PGE_2) response in the central nervous system associated with the induction of microsomal PGE_2 synthase-1. *Journal of Biological Chemistry* 279: 24866-24872.

Guerne, P.-A., Zuraw, B. L., Vaughan, J. H., Carson, D. A., and Lotz, M. 1989. Synovium as a source of interleukin 6 in vitro. Contribution to local and systemic manifestations of arthritis. *Journal of Clinical Investigation* 83: 585.

Hachicha, M., Rathanaswami, P., Schall, T. J., and McColl, S. R. 1993. Production of monocyte chemotactic protein-1 in human type B synoviocytes. synergistic effect of tumor necrosis factor-alpha and interferon-gamma? *Arthritis and Rheumatism* 36: 26-34.

Haleagrahara, N., Tudawe, D., Chakravarthi, S., and Kutty Radhakrishnan, A. 2013. Amelioration of collagen-induced arthritis in female Dark Agouti rats by glucosamine treatment. *International Scholarly Research Notices: Pharmacology* 2013.

Hamilton, J. A. 2008. Colony-stimulating factors in inflammation and autoimmunity. *Nature Reviews Immunology* 8: 533-544.

Hansen, M. S. and Schuman, S. 2011. Hydroxychloroquine-induced retinal toxicity, *EyeNet* Ophthalmic Pearls American Academy of Ophthalmology.

Hargreaves, K., Dubner, R., Brown, F., Flores, C., and Joris, J. 1988. A new and sensitive method for measuring thermal nociception in cutaneous hyperalgesia. *Pain* 32: 77-88.

Haruna, Y. 2014. Acute and Sub-chronic (28-day) intraperitoneal toxicity studies of the Methanol Root Extract of Securidaca longepedunculata Fresen (Polygalaceae) in Rats. *Journal of Advances in Biotechnology* 2: 89-93.

Hashizume, M., Hayakawa, N., and Mihara, M. 2008. IL-6 trans-signalling directly induces RANKL on fibroblast-like synovial cells and is involved in RANKL induction by TNF-α and IL-17. *Rheumatology* 47: 1635-1640.

Hatziieremia, S., Gray, A. I., Ferro, V. A., Paul, A., and Plevin, R. 2006. The effects of cardamonin on lipopolysaccharide-induced

inflammatory protein production and MAP kinase and NFkB signalling pathways in monocytes/macrophages. *British Journal of Pharmacology* 149: 188-198.

Haynes, D. R., Barg, E., Crotti, T. N., Holding, C., Weedon, H., Atkins, G. J., Zannetino, A., Ahern, M. J., Coleman, M., and Roberts-Thomson, P. J. 2003. Osteoprotegerin expression in synovial tissue from patients with rheumatoid arthritis, spondyloarthropathies and osteoarthritis and normal controls. *Rheumatology* 42: 123-134.

Hecht, C., Englbrecht, M., Rech, J., Schmidt, S., Araujo, E., Engelke, K., Finzel, S., and Schett, G. 2014. Additive effect of anti-citrullinated protein antibodies and rheumatoid factor on bone erosions in patients with RA. *Annals of the Rheumatic Diseases* 2151-2156.

Hemminki, K., Li, X., Sundquist, J., and Sundquist, K. 2009. Familial associations of rheumatoid arthritis with autoimmune diseases and related conditions. *Arthritis and Rheumatism* 60: 661-668.

Hendiani, J. A., Westlund, K. N., Lawand, N., Goel, N., Lisse, J., and McNearney, T. 2003. Mechanical sensation and pain thresholds in patients with chronic arthropathies. *The Journal of Pain* 4: 203-211.

Hsiao, C. H., Cheng, A., Huang, Y. T., Liao, C. H., and Hsueh, P. R. 2013. Clinical and pathological characteristics of mycobacterial tenosynovitis and arthritis. *Infection* 41: 457-464.

Hutchinson, D., Shepstone, L., Moots, R., Lear, J. T., and Lynch, M. P. 2001. Heavy cigarette smoking is strongly associated with rheumatoid arthritis (RA), particularly in patients without a family history of RA. *Annals of the Rheumatic Diseases* 60: 223-227.

Isaacs, J. D. and Moreland, L. W. 2011. *Fast Facts: Rheumatoid Arthritis*. 2nd Edition ed. Abingdon, United Kingdom: Health Press Limited.

Israf, D. A., Khaizurin, T. A., Syahida, A., Lajis, N. H., and Khozirah, S. 2007. Cardamonin inhibits COX and iNOS expression via inhibition of p65NF-κB nuclear translocation and Iκ-B phosphorylation in RAW 264.7 macrophage cells. *Molecular Immunology* 44: 673-679.

Janeway, C. A., Travers, P., Walport, M., and Capra, J. D. 1999. *Immunobiology: The Immune System in Health and Disease*: Current Biology Publications New York.

Janeway, C. A., Travers, P., Walport, M., and Shlomchik, M. J. 2001. The major histocompatibility complex and its functions, *Immunobiology: The Immune System in Health and Disease. 5th edition.* New York: Garland Science.

Ji, R.-R., Kohno, T., Moore, K. A., and Woolf, C. J. 2003. Central sensitization and LTP: do pain and memory share similar mechanisms? *Trends in Neurosciences* 26: 696-705.

Jin, H., Arase, N., Hirayasu, K., Kohyama, M., Suenaga, T., Saito, F., Tanimura, K., Matsuoka, S., Ebina, K., and Shi, K. 2014. Autoantibodies to IgG/HLA class II complexes are associated with rheumatoid arthritis susceptibility. *Proceedings of the National Academy of Sciences* 111: 3787-3792.

Joosten, L. A. B., Radstake, T. R. D., Lubberts, E., van den Bersselaar, L. A. M., van Riel, P. L. C. M., van Lent, P. L. E. M., Barrera, P., and van den Berg, W. B. 2003. Association of interleukin-18 expression with enhanced levels of both interleukin-1 beta and tumor necrosis factor-alpha in knee synovial tissue of patients with rheumatoid arthritis. *Arthritis and Rheumatism* 48: 339-347.

Joshi, C. S., Priya, E. S., and Venkataraman, S. 2007. Acute and subacute toxicity studies on the polyherbal antidiabetic formulation diakyur in experimental animal models. *Journal of Health Science* 245-249.

Kakurina, N., Kadisa, A., Lejnieks, A., Mikazane, H., Kozireva, S., and Murovska, M. 2015. Use of exploratory factor analysis to ascertain the correlation between the activities of rheumatoid arthritis and infection by human parvovirus B19. *Medicina* 51: 18-24.

Kavanaugh, A. 2007. Current treatments for rheumatoid arthritis. *American Journal of Orthopedics (Belle Mead, N.J.)* 36: 4.

Kawahito, Y., Ichinose, S., Sano, H., Tsubouchi, Y., Kohno, M., Yoshikawa, T., Tokunaga, D., Hojo, T., Harasawa, R., and Nakano, T. 2008. Mycoplasma fermentans glycolipid-antigen as a pathogen of rheumatoid arthritis. *Biochemical and Biophysical Research Communications* 369: 561-566.

Kawasaki, Y., Zhang, L., Cheng, J.-K., and Ji, R.-R. 2008. Cytokine mechanisms of central sensitization: distinct and overlapping role of interleukin-1b, interleukin-6, and tumor necrosis factor-a in regulating synaptic and neuronal activity in the superficial spinal cord. *The Journal of Neuroscience* 28: 5189-5194.

Kay, J. and Calabrese, L. 2004. The role of interleukin-1 in the pathogenesis of rheumatoid arthritis. *Rheumatology-Oxford* 43: iii2-iii9.

Keith, J. C., Albert, L. M., Leathurby, Y., Follettie, M., Wang, L., Borges-Marcucci, L., Chadwick, C. C., Steffan, R. J., and Harnish, D. C. 2005. The utility of pathway selective estrogen receptor ligands that inhibit nuclear factor-kB transcriptional activity in models of rheumatoid arthritis. *Arthritis Research and Therapy* 7: R427-R438.

Kim, S.-H., Han, S.-Y., Azam, T., Yoon, D.-Y., and Dinarello, C. A. 2005. Interleukin-32: a cytokine and inducer of TNF-alpha. *Immunity* 22: 131-142.

Kinne, R. W., Stuhlmuller, B., and Burmester, G.-R. 2007. Cells of the synovium in rheumatoid arthritis. Macrophages. *Arthritis Research and Therapy* 9: 224.

Kirwan, J. R. 1995. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. *New England Journal of Medicine* 333: 142-147.

Klein, J. 1979. The major histocompatibility complex of the mouse. *Science* 203: 516-521.

Koch, A. E., Polverini, P. J., Kunkel, S. L., Harlow, L. A., DiPietro, L. A., Elner, V. M., Elner, S. G., and Strieter, R. M. 1992. Interleukin-8

as a macrophage-derived mediator of angiogenesis. *Science* 258: 1798-1801.

Kotake, S., Udagawa, N., Hakoda, M., Mogi, M., Yano, K., Tsuda, E., Takahashi, K., Furuya, T., Ishiyama, S., and Kim, K. 2001. Activated human T cells directly induce osteoclastogenesis from human monocytes: possible role of T cells in bone destruction in rheumatoid arthritis patients. *Arthritis and Rheumatism* 44: 1003-1012.

Krishna, B. M. and Chaganty, R. B. 1973. Cardamonin and alpinetin from the seeds of Alpinia speciosa. *Phytochemistry* 12: 238.

Kuruvilla, J., Leitch, H. A., Vickars, L. M., Galbraith, P. F., Li, C. H., Al-Saab, S., and Naiman, S. C. 2003. Aplastic anemia following administration of a tumor necrosis factor-alpha inhibitor. *European Journal of Haematology* 71: 396-398.

Lee, K. H., Chen, Y. S., Judson, J. P., Chakravarthi, S., Sim, Y. M., and Er, H. M. 2008. The effect of water extracts of Euphorbia hirta on cartilage degeneration in arthritic rats. *Malaysian Journal of Pathology* 30: 95-102.

Lee, M.-Y., Seo, C.-S., Lee, J.-A., Shin, I.-S., Kim, S.-J., Ha, H., and Shin, H.-K. 2012. *Alpinia katsumadai* HAYATA seed extract inhibit LPS-induced inflammation by induction of heme oxygenase-1 in RAW264. 7 cells. *Inflammation* 35: 746-757.

Leffler, A., Kosek, E., Lerndal, T., Nordmark, B., and Hansson, P. 2002. Somatosensory perception and function of diffuse noxious inhibitory controls (DNIC) in patients suffering from rheumatoid arthritis. *European Journal of Pain* 6: 161-176.

Lester, R. S., Knowles, S. R., and Shear, N. H. 1998. The risks of systemic corticosteroid use. *Dermatologic Clinics* 16: 277-288.

Li, S. Y., Birnbaum, A. D., and Goldstein, D. A. 2010. Optic neuritis associated with adalimumab in the treatment of uveitis. *Ocular Immunology and Inflammation* 18: 475-481.

Li, Y.-Y., Huang, S.-S., Lee, M.-M., Deng, J.-S., and Huang, G.-J. 2015. Anti-inflammatory activities of cardamonin from *Alpinia katsumadai* through heme oxygenase-1 induction and inhibition of NF-κB and MAPK signaling pathway in the carrageenan-induced paw edema. *International Immunopharmacology* 25: 332-339.

Lin, E., Lin, W.-H., Wang, S.-Y., Chen, C.-S., Liao, J.-W., Chang, H.-W., Chen, S.-C., Lin, K.-Y., Wang, L., and Yang, H.-L. 2012. Flavokawain B inhibits growth of human squamous carcinoma cells: Involvement of apoptosis and cell cycle dysregulation in vitro and in vivo. *The Journal of Nutritional Biochemistry* 23: 368-378.

Linn-Rasker, S. P., Van Der Helm-van Mil, A. H. M., Van Gaalen, F. A., Kloppenburg, M., de Vries, R. R. P., le Cessie, S., Breedveld, F. C., Toes, R. E. M., and Huizinga, T. W. J. 2006. Smoking is a risk factor for anti-CCP antibodies only in rheumatoid arthritis patients who carry HLA-DRB1 shared epitope alleles. *Annals of the Rheumatic Diseases* 65: 366-371.

Lolignier, S., Eijkelkamp, N., and Wood, J. N. 2015 Mechanical allodynia. *Pflugers Archiv European Journal of Physiology* 467: 133-139.

MacGregor, A. J., Snieder, H., Rigby, A. S., Koskenvuo, M., Kaprio, J., Aho, K., and Silman, A. J. 2000. Characterizing the quantitative genetic contribution to rheumatoid arthritis using data from twins. *Arthritis and Rheumatism* 43: 30.

Mackie, S. L., Taylor, J. C., Martin, S. G., Wordsworth, P., Steer, S., Wilson, A. G., Worthington, J., Emery, P., Barrett, J. H., and Morgan, A. W. 2012. A spectrum of susceptibility to rheumatoid arthritis within HLA-DRB1: stratification by autoantibody status in a large UK population. *Genes and immunity* 13: 120-128.

Makrygiannakis, D., af Klint, E., Lundberg, I. E., Lofberg, R., Ulfgren, A. K., Klareskog, L., and Catrina, A. I. 2006. Citrullination is an inflammation-dependent process. *Annals of the Rheumatic Diseases* 65: 1219-1222.

Manfredsdottir, V. F., Vikingsdottir, T., Jonsson, T., Geirsson, A. J., Kjartansson, O., Heimisdottir, M., Sigurdardottir, S. L., Valdimarsson, H., and Vikingsson, A. 2006. The effects of tobacco smoking and rheumatoid factor seropositivity on disease activity and joint damage in early rheumatoid arthritis. *Rheumatology* 45: 734-740.

Marmor, M. F., Kellner, U., Lai, T. Y. Y., Lyons, J. S., and Mieler, W. F. 2011. Revised recommendations on screening for chloroquine and hydroxychloroquine retinopathy. *Ophthalmology* 118: 415-422.

Matsuno, H., Yudoh, K., Katayama, R., Nakazawa, F., Uzuki, M., Sawai, T., Yonezawa, T., Saeki, Y., Panayi, G. S., and Pitzalis, C. 2002. The role of TNF-a in the pathogenesis of inflammation and joint destruction in rheumatoid arthritis (RA): a study using a human RA/SCID mouse chimera. *Rheumatology* 41: 329-337.

McDermott, A. J., Frank, C. R., Falkowski, N. R., McDonald, R. A., Young, V. B., and Huffnagle, G. B. 2014. Role of GM-CSF in the inflammatory cytokine network that regulates neutrophil influx into the colonic mucosa during Clostridium difficile infection in mice. *Gut Microbes* 5: 10-19.

McDonough, A. K., Curtis, J. R., and Saag, K. G. 2008. The epidemiology of glucocorticoid-associated adverse events. *Current Opinion in Rheumatology* 20: 131-137.

McInnes, I. B., Leung, B. P., Sturrock, R. D., Field, M., and Liew, F. Y. 1997. Interleukin-15 mediates T cell-dependent regulation of tumor necrosis factor-alpha production in rheumatoid arthritis. *Nature Medicine* 3: 189-195.

Minagar, A. and Alexander, J. S. 2003. Blood-brain barrier disruption in multiple sclerosis. *Multiple Sclerosis* 9: 540-549.

Mladenovic, V., Domljan, Z., Rozman, B., Jajic, I., Mihajlovic, D., Dordevic, J., Popovic, M., Dimitrijevic, M., Zivkovic, M., and Campion, G. 1995. Safety and effectiveness of leflunomide in the treatment of patients with active rheumatoid arthritis. *Arthritis and Rheumatism* 38: 1595-1603.

Moncada, S., Palmer, R. M. L., and Higgs, E. A. 1991. Nitric oxide: physiology, pathophysiology, and pharmacology. *Pharmacological Reviews* 43: 109-142.

Mor, A., Abramson, S. B., and Pillinger, M. H. 2005. The fibroblast-like synovial cell in rheumatoid arthritis: a key player in inflammation and joint destruction. *Clinical Immunology* 115: 118-128.

Morales-Ducret, J., Wayner, E., Elices, M. J., Alvaro-Gracia, J. M., Zvaifler, N. J., and Firestein, G. S. 1992. Alpha 4/beta 1 integrin (VLA-4) ligands in arthritis. Vascular cell adhesion molecule-1 expression in synovium and on fibroblast-like synoviocytes. *The Journal of Immunology* 149: 1424-1431.

Morgan, A. W., Haroon-Rashid, L., Martin, S. G., Gooi, H.-C., Worthington, J., Thomson, W., Barrett, J. H., and Emery, P. 2008. The shared epitope hypothesis in rheumatoid arthritis: evaluation of alternative classification criteria in a large UK Caucasian cohort. *Arthritis and Rheumatism* 58: 1275-1283.

Morikawa, T., Funakoshi, K., Ninomiya, K., Yasuda, D., Miyagawa, K., Matsuda, H., and Yoshikawa, M. 2008. Medicinal Foodstuffs. XXXIV. Structures of New Prenylchalcones and Prenylflavanones with TNF-α and Aminopeptidase N Inhibitory Activities from *Boesenbergia rotunda*. *Chemical and Pharmaceutical Bulletin* 56: 956-962.

Morris, C. J. 2003. Carrageenan-induced paw edema in the rat and mouse, *Inflammation Protocols: Springer* 115-121.

Murakami, A., Kondo, A., Nakamura, Y., Ohigashi, H., and Koshimizu, K. 1993. Possible anti-tumor promoting properties of edible plants from Thailand, and identification of an active constituent, cardamonin, of Boesenbergia pandurata. *Bioscience, Biotechnology, and Biochemistry* 57: 1971-1973.

Noort, A. R., van Zoest, K. P. M., Koolwijk, P., Tak, P. P., and Tas, S. W. 2013. A9. 11 NF-kB Inducing Kinase (NIK) is a Key Regulator of Inflammation-Induced Angiogenesis. *Annals of the Rheumatic Diseases* 72: A68-A68.

Nukui, Y., Nakamura, H., Ishioka, H., Miyamoto, H., Okamoto, A., Kazumi, Y., Yotsuyanagi, H., Moriya, K., and Hatakeyama, S. 2014. Synovitis of the wrist caused by Mycobacterium florentinum. *Infection* 42: 437-440.

Obreja, O., Rathee, P. K., Lips, K. S., Distler, C., and Kress, M. 2002. IL-1β potentiates heat-activated currents in rat sensory neurons: involvement of IL-1RI, tyrosine kinase, and protein kinase C. *The Federation of American Societies for Experimental Biology Journal* 16: 1497-1503.

Ochaion, A., Bar-Yehuda, S., Cohn, S., Del Valle, L., Perez-Liz, G., Madi, L., Barer, F., Farbstein, M., Fishman-Furman, S., and Reitblat, T. 2006. Methotrexate enhances the anti-inflammatory effect of CF101 via up-regulation of the A3 adenosine receptor expression. *Arthritis Research and Therapy* 8: R169.

OECD. 2008. *Test No. 407: Repeated Dose 28-day Oral Toxicity Study in Rodents*: OECD Publishing.

Oliver, J. E. and Silman, A. J. 2009. Why are women predisposed to autoimmune rheumatic diseases. *Arthritis Research and Therapy* 11: 252.

Ono, K., Kaneko, H., Choudhary, S., Pilbeam, C. C., Lorenzo, J. A., Akatsu, T., Kugai, N., and Raisz, L. G. 2005. Biphasic effect of prostaglandin E2 on osteoclast formation in spleen cell cultures: role of the EP2 receptor. *Journal of Bone and Mineral Research* 20: 23-29.

Opree, A. and Kress, M. 2000. Involvement of the proinflammatory cytokines tumor necrosis factor-a, IL-1β, and IL-6 but not IL-8 in the development of heat hyperalgesia: effects on heat-evoked calcitonin gene-related peptide release from rat skin. *The Journal of Neuroscience* 20: 6289-6293.

Osborn, L., Hession, C., Tizard, R., Vassallo, C., Luhowskyj, S., Chi-Rosso, G., and Lobb, R. 1989. Direct expression cloning of vascular cell adhesion molecule 1, a cytokine-induced endothelial protein that binds to lymphocytes. *Cell* 59: 1203-1211.

Page, T. H., Turner, J. J. O., Brown, A. C., Timms, E. M., Inglis, J. J., Brennan, F. M., Foxwell, B. M. J., Ray, K. P., and Feldmann, M. 2010. Nonsteroidal anti-inflammatory drugs increase TNF production in rheumatoid synovial membrane cultures and whole blood. *The Journal of Immunology* 185: 3694-3701.

Parasuraman, S., Raveendran, R., and Kesavan, R. 2010. Blood sample collection in small laboratory animals. *Journal of pharmacology & Pharmacotherapeutics* 1: 87.

Park, M. K., Lee, H. J., Choi, J. K., Kim, H. J., Kang, J. H., Lee, E. J., Kim, Y. R., Kang, J. H., Yoo, J. K., and Cho, H. Y. 2014. Novel anti-nociceptive effects of cardamonin via blocking expression of cyclooxygenase-2 and transglutaminase-2. *Pharmacology Biochemistry and Behavior* 118: 10-15.

Patil, K. R., Patil, C. R., Jadhav, R. B., Mahajan, V. K., Patil, P. R., and Gaikwad, P. S. 2011. Anti-arthritic activity of bartogenic acid isolated from fruits of Barringtonia racemosa Roxb.(Lecythidaceae). *Evidence-Based Complementary and Alternative Medicine* 2011.

Postlethwaite, A. E., Lachman, L. B., and Kang, A. H. 1984. Induction of fibroblast proliferation by interleukin-1 derived from human monocytic leukemia cells. *Arthritis and Rheumatism* 27: 995-1001.

Qin, Y., Sun, C.-Y., Lu, F.-R., Shu, X.-R., Yang, D., Chen, L., She, X.-M., Gregg, N. M., Guo, T., and Hu, Y. 2012. Cardamonin exerts potent activity against multiple myeloma through blockade of NF-κB pathway in vitro. *Leukemia Research* 36: 514-520.

Quan, L., Thiele, G. M., Tian, J., and Wang, D. 2008. The Development of Novel Therapies for Rheumatoid Arthritis. *Expert Opinion on Therapeutic Patents* 18: 723-738.

Rader, R. A. 2008. (Re) defining biopharmaceutical. *Nature Biotechnology* 26: 743-751.

Raghavendra, V., Tanga, F. Y., and DeLeo, J. A. 2004. Complete Freund's adjuvant-induced peripheral inflammation evokes glial activation and proinflammatory cytokine expression in the CNS. *European Journal of Neuroscience* 20: 467-473.

Rainsford, K. D. 2003. *Ibuprofen: A critical bibliographic review*: CRC Press.

Raymond, L., Eck, S., Mollmark, J., Hays, E., Tomek, I., Kantor, S., Elliott, S., and Vincenti, M. 2006. Interleukin-1 beta induction of matrix metalloproteinase-1 transcription in chondrocytes requires ERK-dependent activation of CCAAT enhancer-binding protein-beta. *Journal of Cellular Physiology* 207: 683-688.

Reith, W. and Mach, B. 2001. The bare lymphocyte syndrome and the regulation of MHC expression. *Annual Review of Immunology* 19: 331-373.

Richter, F., Natura, G., Loser, S., Schmidt, K., Viisanen, H., and Schaible, H.-G. 2010. Tumor necrosis factor causes persistent sensitization of joint nociceptors to mechanical stimuli in rats. *Arthritis and Rheumatism* 62: 3806-3814.

Riksen, N. P., Barrera, P., van den Broek, P. H. H., Van Riel, P., Smits, P., and Rongen, G. A. 2006. Methotrexate modulates the kinetics of adenosine in humans in vivo. *Annals of the Rheumatic Diseases* 65: 465-470.

Rothwell, N., Allan, S., and Toulmond, S. 1997. The role of interleukin 1 in acute neurodegeneration and stroke: pathophysiological and therapeutic implications. *Journal of Clinical Investigation* 100: 2648.

Saal, J. G., Krimmel, M., Steidle, M., Gerneth, F., Wagner, S., Fritz, P., Koch, S., Zacher, J., Sell, S., and Einsele, H. 1999. Synovial Epstein-Barr virus infection increases the risk of rheumatoid arthritis in individuals with the shared HLA-DR4 epitope. *Arthritis and Rheumatism* 42: 1485-1496.

Safieh-Garabedian, B., Poole, S., Allchorne, A., Winter, J., and Woolf, C. J. 1995. Contribution of interleukin-1b to the inflammation-induced increase in nerve growth factor levels and inflammatory hyperalgesia. *British Journal of Pharmacology* 115: 1265-1275.

Sahu, N. K., Balbhadra, S. S., Choudhary, J., and Kohli, D. V. 2012. Exploring pharmacological significance of chalcone scaffold: a review. *Current Medicinal Chemistry* 19: 209-225.

Salvemini, D., Wang, Z.-Q., Wyatt, P. S., Bourdon, D. M., Marino, M. H., Manning, P. T., and Currie, M. G. 1996. Nitric oxide: a key mediator in the early and late phase of carrageenan-induced rat paw inflammation. *British Journal of Pharmacology* 118: 829-838.

Sandkuhler, J. 2009. Models and mechanisms of hyperalgesia and allodynia. *Physiological Reviews* 89: 707-758.

Scheinfeld, N. 2004. A comprehensive review and evaluation of the side effects of the tumor necrosis factor alpha blockers etanercept, infliximab and adalimumab. *Journal of Dermatological Treatment* 15: 280-294.

Scholl, P. R. and Geha, R. S. 1994. MHC class II signaling in B-cell activation. *Immunology Today* 15: 418-422.

Schroder, J., Raiber, S., Berger, T., Schmidt, A., Schmidt, J., Soares-Sello, A. M., Bardshiri, E., Strack, D., Simpson, T. J., and Veit, M. 1998. Plant polyketide synthases: a chalcone synthase-type enzyme which performs a condensation reaction with methylmalonyl-CoA in the biosynthesis of C-methylated chalcones. *Biochemistry* 37: 8417-8425.

Schulz, M., Dotzlaw, H., and Neeck, G. 2014. Ankylosing Spondylitis and Rheumatoid Arthritis: Serum Levels of TNF- and Its Soluble Receptors during the Course of Therapy with Etanercept and Infliximab. *BioMed research international* 2014.

Scott, D. L. and Kingsley, G. H. 2006. Tumor necrosis factor inhibitors for rheumatoid arthritis. *New England Journal of Medicine* 355: 704-712.

Segal, R., Baumoehl, Y., Elkayam, O., Levartovsky, D., Litinsky, I., Paran, D., Wigler, I., Habot, B., Leibovitz, A., and Sela, B. A. 2004. Anemia, serum vitamin B12, and folic acid in patients with rheumatoid arthritis, psoriatic arthritis, and systemic lupus erythematosus. *Rheumatology International* 24: 14-19.

Sen, T. and Samanta, S. K. 2015. Medicinal Plants, Human Health and Biodiversity: A Broad Review, *Biotechnological Applications of Biodiversity: Springer* 59-110.

Sholter, D. E. and Armstrong, P. W. 2000. Adverse effects of corticosteroids on the cardiovascular system. *The Canadian Journal of Cardiology* 16: 505-511.

Silverman, G. J. and Carson, D. A. 2003. Roles of B cells in rheumatoid arthritis. *Arthritis Research and Therapy* 5: S1-6.

Sommer, C. and Kress, M. 2004. Recent findings on how proinflammatory cytokines cause pain: peripheral mechanisms in inflammatory and neuropathic hyperalgesia. *Neuroscience Letters* 361: 184-187.

Sosin, M. and Handa, S. 2003. Lesson of the week: Low dose methotrexate and bone marrow suppression. *British Medical Journal* 326: 266.

Sousa, V. R., Chagas Araujo Sousa, F., Silva Filho, O. F., Rici, G., Eli, R., Neves Diniz, A., Silva Moura, L., Jesus Rosa Pereira Alves, J., Sousa Junior, A., and Angelica Miglino, M. 2014. Comparative study by computed radiography, histology, and scanning electron microscopy of the articular cartilage of normal goats and in chronic infection with caprine arthritis-encephalitis virus. *Microscopy Research and Technique* 77: 11-16.

Srirangan, S. and Choy, E. H. 2010. The role of interleukin 6 in the pathophysiology of rheumatoid arthritis. *Therapeutic Advances in Musculoskeletal Disease* 2: 247-256.

Stevens, C. R., Blake, D. R., Merry, P., Revell, P. A., and Levick, J. R. 1991. A comparative study by morphometry of the microvasculature in normal and rheumatoid synovium. *Arthritis and Rheumatism* 34: 1508-1513.

Suhrbier, A. and Mahalingam, S. 2009. The immunobiology of viral arthritides. *Pharmacology and Therapeutics* 124: 301-308.

Sulaiman, M. R., Zakaria, Z. A., Bujarimin, A. S., Somchit, M. N., Israf, D. A., and Moin, S. 2008a. Evaluation of Moringa oleifera aqueous extract for antinociceptive and anti-inflammatory activities in animal models. *Pharmaceutical Biology* 46: 838-845.

Sulaiman, M. R., Zakaria, Z. A., Daud, I. A., Ng, F. N., Ng, Y. C., and Hidayat, M. T. 2008b. Antinociceptive and anti-inflammatory activities of the aqueous extract of *Kaempferia galanga* leaves in animal models. *Journal of Natural Medicines* 62: 221-227.

Sulaiman, M. R., Zakaria, Z. A., Chiong, H. S., Lai, S. K., Israf, D. A., and Azam Shah, T. M. 2009. Antinociceptive and anti-inflammatory effects of *Stachytarpheta jamaicensis* (L.) Vahl (Verbenaceae) in experimental animal models. *Medical Principles and Practice* 18: 272.

Sulaiman, M. R., Perimal, E. K., Akhtar, M. N., Mohamad, A. S., Khalid, M. H., Tasrip, N. A., Mokhtar, F., Zakaria, Z. A., Lajis, N. H., and Israf, D. A. 2010a. Anti-inflammatory effect of zerumbone on acute and chronic inflammation models in mice. *Fitoterapia* 81: 855-858.

Sulaiman, M. R., Tengku, M. T. A., Shaik, M. W. M., Moin, S., Yusof, M., Mokhtar, A. F., Zakaria, Z. A., Israf, D. A., and Lajis, N. 2010b. Antinociceptive activity of the essential oil of *Zingiber zerumbet*. *Planta Medica* 76: 107-112.

Sulaiman, M. R., Mohd Padzil, A., Shaari, K., Khalid, S., Mossadeq, S., Mastura, W., Mohamad, A. S., Ahmad, S., Akira, A., and Israf, D. 2011. Antinociceptive activity of Melicope ptelefolia ethanolic extract in experimental animals. *BioMed Research International* 2010.

Suresh, E. 2004. Diagnosis of early rheumatoid arthritis: what the non-specialist needs to know. *Journal of the Royal Society of Medicine* 97: 421-424.

Takahashi, A., Yamamoto, N., and Murakami, A. 2011. Cardamonin suppresses nitric oxide production via blocking the IFN-gamma/STAT pathway in endotoxin-challenged peritoneal macrophages of ICR mice. *Life Sciences* 89: 337-342.

Takemura, S., Klimiuk, P. A., Braun, A., Goronzy, J. J., and Weyand, C. M. 2001. T cell activation in rheumatoid synovium is B cell dependent. *The Journal of Immunology* 167: 4710-4718.

Tanaka, E., Taniguchi, A., Urano, W., Nakajima, H., Matsuda, Y., Kitamura, Y., Saito, M., Yamanaka, H., Saito, T., and Kamatani, N. 2002. Adverse effects of sulfasalazine in patients with rheumatoid arthritis are associated with diplotype configuration at the N-acetyltransferase 2 gene. *The Journal of Rheumatology* 29: 2492-2499.

Taylor, P. C. and Sivakumar, B. 2005. Hypoxia and angiogenesis in rheumatoid arthritis. *Current Opinion in Rheumatology* 17: 293-298.

Tewtrakul, S., Subhadhirasakul, S., Puripattanavong, J., and Panphadung, T. 2003. HIV-1 protease inhibitory substances from the rhizomes of *Boesenbergia pandurata* Holtt. *Songklanakarin. Journal of Science and Technology* 25.

Toussirot, E. and Roudier, J. 2007. Pathophysiological links between rheumatoid arthritis and the Epstein-Barr virus: an update. *Joint Bone Spine* 74: 418-426.

Tran, C. N., Lundy, S. K., and Fox, D. A. 2005. Synovial biology and T cells in rheumatoid arthritis. *Pathophysiology* 12: 183-189.

Tuompo, R., Hannu, T., Mattila, L., Siitonen, A., and Leirisalo-Repo, M. 2013. Reactive arthritis following Salmonella infection: a population-based study. *Scandinavian Journal of Rheumatology* 42: 196-202.

Udagawa, N., Takahashi, N., Akatsu, T., Tanaka, H., Sasaki, T., Nishihara, T., Koga, T., Martin, T. J., and Suda, T. 1990. Origin of osteoclasts: mature monocytes and macrophages are capable of differentiating into osteoclasts under a suitable microenvironment prepared by bone marrow-derived stromal cells. *Proceedings of the National Academy of Sciences* 87: 7260-7264.

Unemori, E. N., Ferrara, N., Bauer, E. A., and Amento, E. P. 1992. Vascular endothelial growth factor induces interstitial collagenase expression in human endothelial cells. *Journal of Cellular Physiology* 153: 557-562.

Upchurch, K. S. and Kay, J. 2012. Evolution of treatment for rheumatoid arthritis. *Rheumatology* 51: vi28-vi36.

Verhoef, C. M., van Roon, J. A. G., Vianen, M. E., Lafeber, F. P. J. G., and Bijlsma, J. W. J. 1999. The immune suppressive effect of dexamethasone in rheumatoid arthritis is accompanied by upregulation of interleukin-10 and by differential changes in interferon-gamma and interleukin-4 production. *Annals of the Rheumatic Diseases* 58: 49-54.

Viatte, S., Plant, D., and Raychaudhuri, S. 2013. Genetics and epigenetics of rheumatoid arthritis. *Nature Reviews Rheumatology* 9: 141-153.

Wang, Z. 2009. Claisen-Schmidt Condensation, *Comprehensive Organic Name Reactions and Reagents*. London, United Kingdom: John Wiley & Sons, Inc.

Wei, Z., Yang, J., Xia, Y.-F., Huang, W.-Z., Wang, Z.-T., and Dai, Y. 2012. Cardamonin protects septic mice from acute lung injury by preventing endothelial barrier dysfunction. *Journal of Biochemical and Molecular Toxicology* 26: 282-290.

Weyand, C. M., Hicok, K. C., Conn, D. L., and Goronzy, J. J. 1992. The influence of HLA-DRB1 genes on disease severity in rheumatoid arthritis. *Annals of Internal Medicine* 117: 801-806.

Wilson, A., Yu, H.-T., Goodnough, L. T., and Nissenson, A. R. 2004. Prevalence and outcomes of anemia in rheumatoid arthritis: a systematic review of the literature. *The American Journal of Medicine* 116: 50-57.

Yadav, V. R., Prasad, S., Reuter, S., Sung, B., and Aggarwal, B. B. 2011. Cardamonin Inhibits osteoclastogenesis induced by Tumor Cells through interruption of the signaling pathway activated by receptor activator of NF-κB ligand. *Cancer Letters*.

Yahya, A., Bengtsson, C., Lai, T. C., Larsson, P. T., Mustafa, A. N., Abdullah, N. A., Muhamad, N., Hussein, H., Klareskog, L., and Alfredsson, L. 2012. Smoking is associated with an increased risk of developing ACPA-positive but not ACPA-negative rheumatoid arthritis in Asian populations: evidence from the Malaysian MyEIRA case-control study. *Modern rheumatology* 22: 524-531.

Yamamoto, N., Kawabata, K., Sawada, K., Ueda, M., Fukuda, I., Kawasaki, K., Murakami, A., and Ashida, H. 2011. Cardamonin Stimulates Glucose Uptake through Translocation of Glucose Transporter-4 in L6 Myotubes. *Phytotherapy Research* 25: 1218-1224.

Ziegler-Heitbrock, L. 2007. The $CD14^{+}$ $CD16^{+}$ blood monocytes: their role in infection and inflammation. *Journal of Leukocyte Biology* 81: 584-592.

Zimmermann, M. 1983. Ethical guidelines for investigations of experimental pain in conscious animals. *Pain* 16: 109-110.