UNIVERSITI PUTRA MALAYSIA

DEVELOPMENT OF QUINONE-RICH FRACTION OF Ardisia crispa (Thunb.) A.DC ROOTS MITIGATES RHEUMATOID ARTHRITIS BY SUPPRESSING ANGIOGENESIS, IN VITRO AND IN VIVO

JOAN ANAK BLIN

FPSK(p) 2021 23

DEVELOPMENT OF QUINONE-RICH FRACTION OF *Ardisia crispa* (Thunb.) A.DC ROOTS MITIGATES RHEUMATOID ARTHRITIS BY SUPPRESSING ANGIOGENESIS, *IN VITRO* AND *IN VIVO*

By

JOAN ANAK BLIN

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

May 2021

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

DEVELOPMENT OF QUINONE-RICH FRACTION OF *Ardisia crispa* (Thunb.) A.DC ROOTS MITIGATES RHEUMATOID ARTHRITIS BY SUPPRESSING ANGIOGENESIS, *IN VITRO* AND *IN VIVO*

By

JOAN ANAK BLIN

May 2021

Chair : Roslida binti Abdul Hamid @ Abdul Razak, PhD
Faculty : Medicine and Health Sciences

Angiogenesis, a process of new blood vessel formation from pre-existing ones, can perpetuate synovial inflammation and joint destruction at its equivocal balance in rheumatoid arthritis (RA). Targeting excessive angiogenesis underlies the early development of RA, a chronic autoimmune joint condition, has therefore become a promising approach for the disease intervention. Limitations of current arthritis therapies have encouraged for rapid development of alternative adjuncts from natural sources. 2-methoxy-6-undecyl-1,4-benzoquinone (BQ) is a *p*-benzoquinone derivative of *Ardisia crispa* roots (Family: Primulaceae), with proven anti-angiogenic properties. However, it is still unclear how BQ is able to inhibit angiogenesis in RA. Hence, this present study investigated the anti-arthritic potential of quinone-rich fraction (QRF) (a rich fraction containing the BQ) from *Ardisia crispa* roots, targeting angiogenesis inhibition *in vitro* and *in vivo*. Preparation of test samples from *Ardisia crispa* roots using *n*-hexane, followed by fractionation and isolation via column chromatography, yielded *Ardisia crispa* roots hexane extract (ACRH) [13.64 g; 24.0%, weight per weight (w/w)], QRF (1.99 g; 14.6%, w/w), and BQ (0.04 g; 1.9%, w/w), respectively. Subsequently, gas chromatography-mass spectrometry (GC-MS) analyses have confirmed the benzoquinonoid content in each sample [ACRH (6.1%, peak-area-percent), QRF (30.5%, peak-area-percent), and BQ (81.4%, peak-area-percent)]. Anti-angiogenic and anti-arthritic activities of ACRH, QRF, and BQ were tested via cell viability MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay, tube formation, cell invasion, and cell apoptosis assays in vascular endothelial growth factor (VEGF)-induced human umbilical vein endothelial cells (HUVECs) and interleukin-1β (IL-1β)-induced human fibroblast-like synoviocytes for

rheumatoid arthritis (HFLS-RA), respectively. ACRH, QRF, and BQ exhibited a narrow therapeutic range in VEGF-induced HUVECs (IC_{50}=1.09±0.18 µg/mL, 3.85±0.26 µg/mL, and 1.34±0.16 µg/mL) and IL-1β-induced HFLS-RA (IC_{50}=3.60±1.38 µg/mL, 4.47±0.34 µg/mL, and 1.09±0.09 µg/mL), respectively. ACRH, QRF, and BQ at 0.05, 0.5, and 5 µg/mL, respectively, significantly inhibited/suppressed (P<0.05) VEGF-induced HUVEC tube formation and IL-1β-induced HFLS-RA invasion, respectively. Moreover, ACRH and BQ at 5 µg/mL, but not QRF, significantly (P<0.05) enhanced apoptosis of IL-1β-induced HFLS-RA. Based on comparable *in vitro* findings of all samples, QRF was chosen for *in vivo* studies by employing a collagen-induced arthritis (CIA) model in male adult Sprague-Dawley rats. QRF at daily doses of 3, 10, and 30 mg/kg, insignificantly (P>0.05) reduced the arthritic scores, ankle swelling, and paw edema in arthritic rats after 13 days treatment, respectively. Additionally, at all doses, QRF also showed no significant (P>0.05) modulation on the body weights and organ weights, i.e., liver, kidney, and spleen, respectively. Protein expression analyses using enzyme-linked immunosorbent assay (ELISA) and multiplex assay demonstrated that QRF at all doses (3, 10, and 30 mg/kg) significantly (P<0.05) attenuated VEGF-A, PI3K, AKT, NF-κB, p38, STAT3, and STAT5 proteins level in arthritic rats in a dose-independent manner. QRF at all doses also significantly (P<0.05) restored synovial microvessel densities (MVD) in arthritic rats to the normal level. Notably, a medium dose of QRF (10 mg/kg) exerted the highest inhibition to the aforementioned biomarkers and MVD than other doses. In conclusion, QRF mitigated RA development by suppressing angiogenesis *in vitro* and *in vivo*, attributed to the benzoquinonoid content and synergism, at least in part, by other phytoconstituents. Further investigation should identify the unknown peaks in the current GC-MS fingerprinting of QRF to better understand the potential involvement/synergism of other compounds in the sample.

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

PEMBANGUNAN FRAKSI KAYA KUINON DARIPADA AKAR *Ardisia crispa* (Thunb.) A.DC MENGURANGKAN ARTRITIS REUMATOID MELALUI PERENCATAN ANGIOGENESIS SECARA *IN VITRO* DAN *IN VIVO*

Oleh

JOAN ANAK BLIN

Mei 2021

Pengerusi : Roslida binti Abdul Hamid @ Abdul Razak, PhD
Fakulti : Perubatan dan Sains Kesihatan

Angiogenesis, suatu proses pembentukan salur darah baharu daripada saluran yang sedia ada, boleh mengekalkan pembengkakan sinovial dan pemusnahan sendi pada ketidakseimbangannya dalam artritis reumatoid (RA). Pensasaran terhadap angiogenesis berlebihan yang mendasari pembentukan awal RA, suatu penyakit sendi kronik autoimun, oleh itu, telah menjanjikan peluang cerah kepada intervensi penyakit tersebut. Keterbatasan rawatan arthritis yang sedia ada telah mendorong pembangunan pesat agen alternatif daripada sebatian semulajadi. 2-metoksi-6-undesil-1,4-benzokuinon (BQ) ialah hasilan *p*-benzokuinon daripada akar *Ardisia crispa* (Famili: Primulaceae), dengan pengesahan ciri-ciri anti-angiogenesis. Namun, masih tidak jelas bagaimana BQ berupaya merencatkan angiogenesis dalam RA. Oleh itu, kajian ini mengkaji potensi anti-artritik fraksi kaya kuinon (QRF) (suatu fraksi kaya mengandungi BQ) daripada akar *Ardisia crispa*, dengan mensasarkan perencatan angiogenesis secara *in vitro* dan *in vivo*. Penyediaan sampel-sampel ujian daripada akar *Ardisia crispa* menggunakan *n*-heksana, diikuti oleh pemfraksian dan pengasingan melalui kromatografi turus, masing-masing menghasilkan extrak heksana akar *Ardisia crispa* (ACRH) [13.64 g; 24.0%, berat per berat (b/b)], QRF (1.99 g; 14.6%, b/b), dan BQ (0.04 g; 1.9%, b/b). Seterusnya, analisis kromatografi gas-spektrometri jisim (GC-MS) telah mengesahkan kandungan benzokuinon di dalam setiap sampel [ACRH (6.1%, peratus kawasan puncak), QRF (30.5%, peratus kawasan puncak), dan BQ (81.4%, peratus kawasan puncak)]. Aktiviti anti-angiogenik dan anti-artritik oleh ACRH, QRF, dan BQ telah diuji melalui asai-asai daya hidup sel MTT [3-(4,5-dimetiltiazol-2-il)-2,5-difeniltetrazolium bromida], pembentukan tiub, invasi sel, dan apoptosis sel, masing-masing pada sel-sel endotelial vena umbilikal manusia (HUVECs) aruhan faktor pertumbuhan endotelial vaskular (VEGF) dan sel-sel artritik reumatoid sinoviosit mirip fibroblas manusia (HFLS-RA) aruhan interleukin-1β (IL-1β). ACRH, QRF, dan BQ mempamerkan julat terapeutik yang sempit pada

HUVECs (IC_{50}=1.09±0.18 µg/mL, 3.85±0.26 µg/mL, dan 1.34±0.16 µg/mL) dan peningkatan ketoksikan pada HFLS-RA (IC_{50}=3.60±1.38 µg/mL, 4.47±0.34 µg/mL, dan 1.09±0.09 µg/mL), masing-masing. ACRH, QRF, dan BQ masing-masing pada 0.05, 0.5, dan 5 µg/mL, dengan signifikannya (P<0.05) merencatkan/mengurangkan pembentukan tiub HUVEC aruhan VEGF and invasi HFLS-RA aruhan IL-1β, masing-masing. Selain itu, ACRH dan BQ pada kepekatan 5 µg/mL, meningkatkan apoptosis HFLS-RA aruhan IL-1β secara ketara (P<0.05). Berdasarkan persamaan keputusan *in vitro* bagi kesemua sampel, QRF telah dilanjutkan dalam kajian *in vivo* menggunakan model artritis aruhan kolagen (CIA) pada tikus jantan dewasa Sprague-Dawley. Dos-dos harian QRF 3, 10, dan 30 mg/kg, masing-masing, secara tidak ketaranya (P>0.05) mengurangkan skor artritis, pembengkakan buku lali, dan edema kaki pada tikus-tikus artritis selepas 13 hari rawatan. Kesemua dos QRF juga menunjukkan tiada perubahan ketara (P>0.05) pada berat badan dan berat organ tikus (i.e., hati, ginjal, dan limpa), masing-masing. Analisis pengekspresan protein melalui kaedah asai imunoserapan terangkai enzim (ELISA) dan asai protein berbilang menunjukkan QRF pada kesemua dos (3, 10, dan 30 mg/kg) menurunkan paras protein-protein VEGF-A, PI3K, AKT, NF-κB, p38, STAT3, dan STAT5 dengan ketara (P<0.05), dalam tikus-tikus artritis tanpa perkadaran dos. Kesemua dos tersebut juga mengembalikan ketumpatan saluran kapilari mikro (MVD) secara ketara (P<0.05) dalam tikus-tikus artritis kepada paras normal. Ternyata, dos sederhana QRF (10 mg/kg) menunjukkan perencatan tertinggi terhadap biomarker yang dinyatakan di atas dan MVD berbanding dos-dos yang lain. Kesimpulannya, QRF mengurangkan pembentukan RA melalui perencatan angiogenesis *in vitro* dan *in vivo*, dikaitkan pada kandungan benzokuinon dan tindakan sinergi, sekurang-kurangnya sebahagian, oleh sebatian bioaktif lain yang terdapat di dalam fraksi kaya tersebut. Penyiasatan lanjut perlu mengenalpasti puncak-puncak yang tidak diketahui pada cap jari GC-MS terkini QRF untuk lebih pemahaman berkaitan potensi penglibatan/tindakan sinergi oleh sebatian lain dalam sampel tersebut.

ACKNOWLEDGEMENTS

Greeting all,

First and foremost, I would like to dedicate my genuine thanks to God for blessing me with patience and determination to complete this study.

I express my deepest gratitude to my advisor, Assoc. Prof. Dr. Roslida Abdul Hamid for her excellent mentorship and professionalism in mapping my PhD journey.

A big thanks to my co-supervisors, Prof. Ts. Dr. Cheah Yoke Kqueen and Dr. Razana Mohd Ali, for their insightful comments and assistance. Special thanks to Dr. Hasiah Abdul Hamid for her professional support in the Drug Metabolism course and Dr. Armania Nurdin for her guidance throughout animal studies.

My utmost gratitude is extended to all staffs of Biomedical laboratories: Puan Normayati Sulaiman, Puan Hasnijah Alias, Encik Nasrul Ridzal Zainal Abidin, Puan Nora Asyikin Mohd Salim, Encik Zain Zailan Hj Kassim, Encik Zulkhairi Zainol, Puan Nurul Munirah Manan, Puan Nor Aishah Norsabarudin, Puan Hazlen Saleh, Encik Shamsul Qamar Alias, Puan Fariza Zainul Abidin; staffs of Histopathology laboratory: Puan Juita Chupri, Puan Zamzarina Ahmad Bajari; and staff of Comparative Medicine And Technology Unit: Encik Saiful Qushairi Suarni. Your assistance and generosity are highly appreciated.

My heartfelt appreciation goes to my beloved family: Blin Sungki, Takik Sawing, Gosstin Blin, Nancy Blin, Edward Blin; and friends: Mohd Rohaizad Roduan, Siti Nur Syuhada Musa, Nurul Asma Mustafa, Nur Hafizah Hashim, Atikah Ibrahim, Mohamad Mahfuz Saharudin, Areej Mohd Taufik, Intan Masyitah Mohd Murad, Shazwani Rosli, Nazri Nayan, Awang Hazmi Awang Junaidi, Annas Salleh, Nur Faseeha Suhaimi, Che Ku Dahlan, Qais Bashir, Aiman Haiqal Ismail, Nurul Syuhada Nordin, Noor Izzah Abd Rahman, Shazleen Sofea Abdullah, Zulzikry Hafiz Abu Bakar, and a long list of others. Thank you for all the small things.

Last but not least, I owe my sincere thanks to the Ministry of Higher Education Malaysia, for the MyBrain15 Scholarship (MyPhD) awarded for my study. Once and for all, thank you and all of you be blessed.

I certify that a Thesis Examination Committee has met on 10 May 2021 to conduct the final examination of Joan anak Blin on his thesis entitled "Development of Quinone-Rich Fraction of *Ardisia crispa* (Thunb.) A.DC Roots Mitigates Rheumatoid Arthritis by Suppressing Angiogenesis, *In Vitro* and *In Vivo*" 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.

Members of the Thesis Examination Committee were as follows:

Mohd Nasir bin Mohd Desa, PhD
Associate Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Chairman)

Tham Chau Ling, PhD
Associate Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Internal Examiner)

Enoch Kumar a/l Perimal, PhD
Associate Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Internal Examiner)

Serafim Kiriakidis, PhD
Senior Research
Institute of Musculoskeletal Sciences
University of Oxford
United Kingdom
(External Examiner)

_____
ZURIATI AHMAD ZUKARNAIN, PhD
Professor Ts. and Deputy Dean
School of Graduate Studies
Universiti Putra Malaysia

Date: 30 September 2021

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:

Roslida binti Abdul Hamid @ Abdul Razak, PhD
Associate Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Chairman)

Cheah Yoke Kqueen, PhD
Professor, Ts.
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

Razana Mohd Ali, MBBS, MPath
Medical Lecturer
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

ZALILAH MOHD SHARIFF, PhD
Professor and Dean
School of Graduate Studies
Universiti Putra Malaysia

Date: 14 October 2021

Declaration by graduate student

I hereby confirm that:

- this thesis is my original work;
- quotations, illustrations and citations have been duly referenced;
- this thesis has not been submitted previously or concurrently for any other degree at any other institutions;
- intellectual property from the thesis and copyright of thesis are fully-owned by Universiti Putra Malaysia, as according to the Universiti Putra Malaysia (Research) Rules 2012;
- written permission must be obtained from supervisor and the office of Deputy Vice-Chancellor (Research and Innovation) before thesis is published (in the form of written, printed or in electronic form) including books, journals, modules, proceedings, popular writings, seminar papers, manuscripts, posters, reports, lecture notes, learning modules or any other materials as stated in the Universiti Putra Malaysia (Research) Rules 2012;
- there is no plagiarism or data falsification/fabrication in the thesis, and scholarly integrity is upheld as according to the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) and the Universiti Putra Malaysia (Research) Rules 2012. The thesis has undergone plagiarism detection software.

Signature: _____ Date: _____

Name and Matric No.: Joan anak Blin (GS43921)

Declaration by Members of Supervisory Committee

This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
- supervision responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) are adhered to.

Signature:	_____
Name of Chairman of Supervisory Committee:	Assoc. Prof. Dr. Roslida binti Abdul Hamid @ Abdul Razak

Signature:	_____
Name of Member of Supervisory Committee:	Prof. Ts. Dr. Cheah Yoke Kqueen

Signature:	_____
Name of Member of Supervisory Committee:	Dr. Razana binti Mohd Ali

TABLE OF CONTENTS

	Page
ABSTRACT	i
ABSTRAK	iii
ACKNOWLEDGEMENTS	v
APPROVAL	vi
DECLARATION	viii
LIST OF TABLES	xiv
LIST OF FIGURES	xvi
LIST OF ABBREVIATIONS	xxiii
CHAPTER	
1 INTRODUCTION	1
1.1 Research background	1
1.2 Problem statement	2
1.3 Justification of study	2
1.4 Objective(s)	3
1.4.1 General objective	3
1.4.2 Specific objectives	3
1.5 Hypothesis	4
2 LITERATURE REVIEW	5
2.1 Rheumatoid arthritis	5
2.1.1 Epidemiology of rheumatoid arthritis	5
2.1.2 Angiogenesis in the pathogenesis of rheumatoid arthritis	6
2.1.3 Fibroblast-like synoviocytes: key effector cells in rheumatoid arthritis	11
2.1.4 Angiogenic roles of endothelial cells in rheumatoid arthritis	14
2.1.5 Signal transduction in rheumatoid arthritis	14
2.1.5.1 Vascular endothelial growth factor (VEGF) signaling	14
2.1.5.2 Phosphatidylinositol 3-kinase (PI3K)/protein kinase-B (AKT) signaling pathway	18
2.1.5.3 Nuclear factor-kappa B (NF-κB) pathway	19
2.1.5.4 Mitogen-activated protein kinase (MAPK) pathway	20
2.1.5.5 JAK/STAT signal transduction pathway	22
2.2 Strategies towards rheumatoid arthritis therapy: the old and the new	24

2.2.1 Surgery 25
2.2.2 Conventional drug therapies 25
2.2.3 Current approaches: DMARDs and paradigm shift by the biological and targeted synthetic DMARDs 25
2.3 Limitation of current therapies 26
2.4 Opting for natural anti-arthritic agents from herbal medicines 29
2.4.1 Quinones and *p*-benzoquinones as potential anti-angiogenic agents for rheumatoid arthritis therapies 34
2.5 *Ardisia crispa* 36
2.5.1 Family Primulaceae 36
2.5.2 Genus *Ardisia* 36
2.5.3 Geographical distribution, habitat, and the name varieties 39
2.5.4 Plant morphology 39
2.5.5 Traditional usages 39
2.5.6 Phytochemical studies of *Ardisia crispa* 41
2.5.7 Pharmacological studies of *Ardisia crispa* 44
2.6 Current tools for screening anti-angiogenic/anti-arthritic agent 48
2.6.1 Human umbilical vein endothelial cells (HUVECs) 48
2.6.2 Human fibroblast-like synoviocytes for rheumatoid arthritis (HFLS-RA) 49
2.6.3 *In vitro* assays and their principles 50
2.6.3.1 Cell viability assay 51
2.6.3.2 Tube formation assay 51
2.6.3.3 Cell apoptosis assay 52
2.6.3.4 Cell invasion assay 52
2.6.4 *In vivo* arthritic model: Collagen-induced arthritis (CIA) in rats 53
2.6.5 Protein expression analysis 55
2.6.5.1 Enzyme-linked immunosorbent assay (ELISA) system 55
2.6.5.2 Multiplex immunosorbent assay system 57

3 THE GAS CHROMATOGRAPHY-MASS SPECTROMETRY FINGERPRINTINGS OF BIOACTIVE FRACTIONS AND COMPOUND OF *Ardisia crispa* ROOTS 59
3.1 Introduction 59
3.2 Material and methods 59
3.2.1 Plant material 59
3.2.2 Preparation of bioactive fractions and compound from *Ardisia crispa* roots 60

	3.2.3	Benzoquinone composition analysis of ACRH, QRF, and BQ by GC-MS	60
3.3	Results		61
	3.3.1	Yields of bioactive fractions and compound of *Ardisia crispa* roots	61
	3.3.2	GC-MS profiles of ACRH, QRF, and BQ	61
3.4	Discussion		66
3.5	Conclusion		68
4	**BIOACTIVE FRACTIONS AND COMPOUND OF *Ardisia crispa* ROOTS EXHIBIT ANTI-ARTHRITIC PROPERTIES MEDIATED VIA ANGIOGENESIS INHIBITION *IN VITRO***		69
4.1	Introduction		69
4.2	Material and Methods		70
	4.2.1	Preparation of test samples	70
	4.2.2	Cell culture	70
	4.2.3	Experimental design	70
	4.2.3.1	Determination of cell viability by MTT assay	71
	4.2.3.2	Tube formation assay on VEGF-induced HUVECs	72
	4.2.3.3	Determination of apoptosis on IL-1β-induced HFLS-RA by Annexin V/PI staining	73
	4.2.3.4	Cell invasion assay on IL-1β-induced HFLS-RA	73
	4.2.4	Statistical analysis	74
4.3	Results		75
	4.3.1	ACRH, QRF, and BQ inhibited VEGF-induced HUVECs and IL-1β-induced HFLS-RA cell viability, respectively	75
	4.3.2	ACRH, QRF, and BQ inhibited VEGF-induced HUVECs tube formation	78
	4.3.3	ACRH and BQ, respectively, promoting apoptosis on IL-1β-induced HFLS-RA	82
	4.3.4	ACRH, QRF, and BQ suppressed IL-1β-induced HFLS-RA invasion	86
4.4	Discussion		90
4.5	Conclusion		96
5	**QUINONE-RICH FRACTION OF *Ardisia crispa* ROOTS (PRIMULACEAE) ALTERS ANGIOGENIC CASCADE IN COLLAGEN-INDUCED ARTHRITIS IN RATS**		97
5.1	Introduction		97
5.2	Materials and methods		97
	5.2.1	Animal model and ethical clearance	98
	5.2.2	Induction of collagen-induced arthritis	98

		5.2.3	A pilot study of collagen-induced arthritis in rats	98
		5.2.4	Experimental design	99
		5.2.5	Morphological evaluation of CIA in arthritic rats	101
			5.2.5.1 Bodyweight	101
			5.2.5.2 Ankle joint diameter	101
			5.2.5.3 Paw volume	101
			5.2.5.4 Arthritic scores	101
		5.2.6	Histopathological examination of microvessel density in rat synovium	104
		5.2.7	Molecular studies	104
			5.2.7.1 Protein extraction	104
			5.2.7.2 Determination of protein concentration	104
			5.2.7.3 Quantification of VEGF-A and PI3K2α protein expression via enzyme-linked immunosorbent assay (ELISA)	105
			5.2.7.4 Quantification of protein expression via multiplex magnetic bead-based immunoassay	106
		5.2.8	Statistical analysis	107
	5.3	Results		107
		5.3.1	Pilot study of CIA in Sprague-Dawley rats	107
		5.3.2	Morphology of CIA in rats	112
		5.3.3	Effect of QRF on bodyweight and organ weights	114
		5.3.4	Effect of QRF on arthritic scores, ankle joint diameter, and paw volume of hind limbs	118
		5.3.5	Effect of QRF on the microvessel density of arthritic synovium	129
		5.3.6	Molecular studies	134
			5.3.6.1 QRF modulated pro-angiogenic proteins expressions in arthritic rats	134
	5.4	Discussion		136
	5.5	Conclusion		148
6	**SUMMARY, CONCLUSION AND RECOMMENDATIONS FOR FUTURE RESEARCH**			150
REFERENCES				154
APPENDICES				211
BIODATA OF STUDENT				223
LIST OF PUBLICATIONS				224

LIST OF TABLES

Table		Page
2.1	Angiogenic elements and mediators in rheumatoid arthritis.	8
2.2	Current approved bDMARDs and tsDMARDs and their role in angiogenesis in rheumatoid arthritis.	28
2.3	Natural agents with anti-angiogenic/anti-arthritic activity.	31
2.4	*Ardisia species*, phytocompounds, and their pharmacological properties.	38
2.5	Pharmacological activities of some extracts/phytochemical constituents of *Ardisia crispa.*	47
3.1	Summary of ACRH, QRF, and BQ yield prepared from the hexane extraction of *Ardisia crispa* roots.	61
4.1	The IC_{50} values of ACRH, QRF, and BQ on VEGF-induced HUVECs and IL-1β-induced HFLS-RA.	75
4.2	Percentage of IL-1β-induced HFLS-RA cell population after 24 h of treatment with ACRH, QRF, and BQ, respectively.	85
5.1	Summary of animal grouping (n = 8) and QRF treatment procedures.	99
5.2	Scoring system for subjective CIA evaluation in immunized rats.	103
5.3	Effect of CIA induction (day 0 – 11) and QRF treatments (day 14 – 26) on the trend of the body weight gain in arthritic rats.	115
5.4	Effect of QRF doses 3, 10, and 30 mg/kg on organ weights of arthritic rats for 13 days of treatments.	117
5.5	Effect of CIA induction (day 0 – 11) and QRF treatments (day 14 – 26) on the trend of the left ankle diameter in arthritic rats.	121
5.6	Effect of CIA induction (day 0 – 11) and QRF treatments (day 14 – 26) on the trend of the right ankle diameter in arthritic rats.	122

5.7	Effect of CIA induction (day 0 – 11) and QRF treatments (day 14 – 26) on the trend of the left hind paw volume in arthritic rats.	125
5.8	Effect of CIA induction (day 0 – 11) and QRF treatments (day 14 – 26) on the trend of the right hind paw volume in arthritic rats.	126
5.9	Effect of QRF treatments on microvessel density (MVD) of arthritic synovium after 13 days post-treatment (day 14 – 26).	130
5.10	Protein expressions quantitated via ELISA and multiplex magnetic bead-based immunoassay, respectively.	135

LIST OF FIGURES

Figure		Page
2.1	Illustration of normal synovium (left half) and arthritic synovium (right half). The arthritic synovium demonstrates pathological processes, including synovial hyperplasia, inflammatory cell recruitment, angiogenesis, cartilage destruction, and bone erosions.	6
2.2	Mechanisms of synovial angiogenesis in rheumatoid arthritis. A: Rheumatoid arthritis is characterized by chronic inflammation of multiple joints, involving particularly metacarpophalangeal and proximal interphalangeal joints. B: The primary sites of inflammation taking place within the synovium (in red) leading to cartilage and bone damage. C-E: Synovial inflammation begins with activation of immune cells (T and B cells), that secrete pro-inflammatory cytokines such as TNF-α and IL-1β within the synovial lining. Sustained release of these mediators activates fibroblast-like synoviocytes (FLS) and residence macrophages. Aggressive FLS can release growth factors, such as VEGF that can bind to its receptors on endothelial cells. F: Synovial endothelium, under the aberrant signal of multiple signaling pathways in inflammation promotes synovial neovascularization.	10
2.3	Mechanisms and consequences of fibroblast-like synoviocytes (FLS) activation in rheumatoid arthritis (RA). In this concept, the loss of proteoglycans from articular cartilage represents a key initial step and, in the context of an as yet poorly understood immunological sensitization, directly triggers the activation, increased adhesion, and invasiveness of RA-FLS that ultimately results in a tumor-like transformation. This transformation includes profound epigenetic changes and results in alterations in growth and apoptosis as well as to migration and invasion. These alterations trigger the homing and survival of immune cells and contribute to increased osteoclastogenesis and angiogenesis as part of the complex pathogenesis of RA. SUMO: small ubiquitin-related modifiers; CXCL: CXC chemokine ligand; RANKL: receptor activator of nuclear factor-κB ligand; SDF-1: stromal cell-derived factor 1.	13
2.4	VEGFR-2 signal transduction and trafficking pathways mediated by VEGF-A (shown in grey). Schematic representation of the signaling pathways elicited by the docking of adaptor proteins to major tyrosine phosphorylation sites. Phosphorylation of Y951 residue leads to the recruitment of TSAd which in turns binds and	17

activates Src. Substrates for Src include molecules related to cell adhesion, vascular permeability, and cell survival (via PI3K/AKT pathway activation). pY1175 mobilizes SHB, which in turn activates FAK (cell attachment and migration). SHB is also one of the Src substrates that are involved in the activation of PI3K/AKT. Moreover, pY1175 residues recruit PLC, triggering $Ca2^{+}$-dependent signaling, which in turn results in transcriptional control of proliferation and cell migration. Cell motility is also regulated by the recruitment of NCK to pY1214 leading to p38MAPK activation. VEGFR-2 activation promotes its own internalization with signaling continuing within endosomal compartments. After being internalized to $RAB5^{+}$ sorting endosomes, VEGFR-2 can be recycled to the cell surface in $RAB4^{+}$ (fast trafficking, persistent intracellular signaling) or $Rab11^{+}$ (slow trafficking, PTP1b-limited intracellular signaling) endosomes. Alternatively, VEGFR-2 undergoes lysosomal degradation in $Rab7^{+}$ endosomes. PLC, phospholipase C; PIP2, phosphatidylinositol bisphosphate; DAG, diacylglycerol; IP3, inositol trisphosphate; PKC, protein kinase C; MAPK, mitogen-activated protein kinase; MEK, MAP/ERK kinase; ERK, extracellular signal–regulated kinases; NFAT, nuclear factor of activated T-cells; TSAd, T cell-specific adaptor protein; PI3K, phosphatidylinositol 3-kinases; PIP3, phosphatidylinositol triphosphate; BAD, Bcl-2-associated death promoter; SHB, Src homology-2 domain containing protein B; FAK, focal adhesion kinase; PTP1b, protein tyrosine phosphatase 1b. The dotted lines refer to signaling pathways that have additional elements to them (e.g., other adaptor proteins/non direct signaling routes) that have not been included due to space. The solid lines are for a direct signaling pathway. The blue arrows refer to the routes through which the receptor trafficked for either recycling or degradation.

2.5 PI3K/AKT pathway and the downstream activation of mTOR signal that regulates protein translation related to cellular processes such as cell proliferation, cell cycle, and angiogenesis. 19

2.6 Schematic diagram of NF-κB activation in rheumatoid arthritis. 20

2.7 MAPK signaling cascades in mammalian cells. 22

2.8 The JAK/STAT pathway as represented via the IL-6 mediated JAK1/STAT3 signal activation. 24

2.9 Quinones at ortho (1,2), meta (1,3), or para (1,4)- position around an aromatic ring. 34

2.10	*Ardisia crispa* plant. (a) whole plant, (b) leaves, and (c) roots. Photos (a) and (b) were captured at the Agricultural Conservatory Park, Institute of Bioscience, Universiti Putra Malaysia by Nordin et al. (2018). Photo (c) was captured during plant collection at the Faculty of Agriculture, Universiti Putra Malaysia.	40
2.11	Chemical structure of ardisiacrispin A ($C_{52}H_{84}O_{22}$) and ardisiacrispin B ($C_{52}H_{86}O_{22}$) isolated from the roots of *Ardisia crispa.*	41
2.12	Chemical structure of 2-methoxy-6-tridecyl-1,4-benzoquinone (AC7-1) isolated from *Ardisia crispa* roots.	41
2.13	Chemical structure of (a) 2-methoxy-6-undecyl-1,4-benzoquinone and (b) viminalol (AC1) isolated from the hexane extract of *Ardisia crispa* roots.	42
2.14	Chemical structure of (a) wogonin; (b) oroxylin A; (c) wogonoside; (d) baicalin; (e) (+) anwulignan; (f) *meso*-dihydroguaiaretic acid; (g) 4-hydroxyvaleric acid; (h) bergenin; (i) *n*-tetradecane; (j) β-sitosterol; and (k) ardisiacrispin C, isolated from the roots of *Ardisia crispa.*	43
2.15	Human umbilical vein endothelial cells (HUVECs) in a “cobblestone” morphology.	49
2.16	Cultured human fibroblast-like synoviocytes for rheumatoid arthritis forming monolayers and have a spindle-shaped appearance.	50
2.17	Overview of a transwell invasion assay setup.	53
2.18	Pathogenesis of collagen-induced arthritis. (A) Collagen type II (CII) emulsified in complete Freund’s adjuvant (CFA) containing oil and heat-killed mycobacteria activate specific T and B cells, resulting in antibody and cell-mediated inflammation in joints. (B) Left panel: Oil and heat-killed mycobacterial act as danger signals evoking myeloid expansion and cytokine production. Right panel: CII and mycobacteria are processed by antigen-presenting cells and elicit adaptive cellular, and humoral immune responses potentiate inflammation in the joints.	54
2.19	ELISA types with their representative chemistry workflows.	56
2.20	Simplified workflow of multiplex bead-based assay system.	58
3.1	Chromatogram of reference compound showing a 2-methoxy-6-undecyl-1,4-benzoquinone at Peak 1 (Rt =	62

64.365 min) along with minor unidentified peaks (Peak 2 and 3).

3.2 Chromatogram of ACRH showing Peak 1, Diethyl Phthalate; Peak 5, Hexadecanoic acid, ethyl ester (CAS) Ethyl pal; Peak 8, Ethyl Oleate; Peak 11, 2 methoxy-6-undecyl-1,4-benzoquinone; Peak 13; Phenol, 2-methoxy-5-acetoxymethyl-, Peak 17, Sebacic acid, di(2,6-dimethoxyphenyl) ester; and other unidentified peaks (Peak 15 & 19). 63

3.3 Chromatogram of QRF showing Peak 1, Phthalate <diethyl->; Peak 2, 2 methoxy-6-undecyl-1,4-benzoquinone Peak 5, 4A.Beta.,13a.Alpha.-Aza-4.Beta.-Ethy; Peak 6, Sebacic acid, di(2,6-dimethoxyphenyl) ester; Peak 7, 2'-dodecyl-5'-allyl-2,5-dimethylpyrrolidine-N-o; and other unidentified peaks (Peak 3, 4, and 8). 64

3.4 Chromatogram of BQ showing Peak 1, 2 methoxy-6-undecyl-1,4-benzoquinone; Peak 2, unidentified peak; Peak 3, Sebacic acid, di(2,6-dimethoxyphenyl) ester. 65

4.1 Concentration-response graphs showing the inhibitory effect of (a) ACRH, (b) QRF, and (c) BQ towards VEGF-induced human umbilical vein endothelial cells (HUVECs) viability after 24 h of incubation. Data were expressed as percentage mean ± SEM (n = 3) of viable cells normalized to 100% cell viability in the negative control and were analyzed using one-way ANOVA followed by Tukey's HSD post hoc test. Significant differences (P<0.05) are indicated by different letters between different concentrations. 76

4.2 Concentration-response graphs showing the inhibitory effect of (a) ACRH, (b) QRF, and (c) BQ, respectively towards IL-1β-induced human fibroblast-like synoviocytes for rheumatoid arthritis (HFLS-RA) viability after 24 h of incubation. Data were expressed as percentage mean ± SEM (n = 3) of viable cells normalized to 100% cell viability in the negative control and were analyzed using one-way ANOVA followed by Tukey's HSD post hoc test. Significant differences (P<0.05) are indicated by different letters between different concentrations. 77

4.3 Representative fluorescent images showing inhibitory activities of ACRH, QRF, and BQ on VEGF-induced HUVECs tube formation. HUVECs (1.5×10^4 cell/well) were plated in a 96-well plate, which was pre-coated with a Matrigel membrane matrix (40 µL/well). Cells were concurrently induced with $VEGF_{165}$ (50 ng/mL) and were treated with various concentrations (0.05, 0.5, and 5 µg/mL) of each sample, respectively. Controls (negative control, 80

vehicle 0.1% DMSO, and suramin 50 µg/mL) were set up accordingly, along with the treatments. After 16 h incubation, cells were stained with calcein-AM (8 µg/mL) and visualized using a fluorescence microscope. Images were photographed using a digital camera under an inverted fluorescence microscope at 40× magnification.

4.4 Quantitative data of VEGF-induced HUVECs tube formation after being treated with various concentrations (0.05, 0.5, and 5 µg/mL) of each ACRH, QRF and BQ for 16 h, respectively. Data were represented as the percentage of tube lengths relative to the negative control (at 100% tubular formation) and expressed as mean ± SEM (n=3). Data were analyzed using one-way ANOVA followed by Tukey's HSD post hoc test. Significant differences were indicated by different superscript letters between concentrations in all groups (*P*<0.05). 81

4.5 The dot plots of IL-1β-induced HFLS-RA distribution as determined by Annexin V-PI staining. The cells were induced with IL-1β (10 ng/mL) plus treated with various concentrations (0.05, 0.5, and 5 µg/mL) of ACRH, QRF, and BQ respectively and incubated for 24 h. Negative control (media only), vehicle control (0.1% DMSO), and suramin (50 µg/mL) were included in the experiments. Flowcytometric data were then analyzed and displayed in a dot plot of Annexin V/FITC (y-axis) against PI (x-axis). 84

4.6 Photographed images showing inhibition of ACRH, QRF, and BQ on IL-1β-induced HFLS-RA invasion. HFLS-RA (1×10^4 cells in serum-free SGM) were seeded on a Transwell chamber that has been pre-coated with 30 µL of Matrigel (125 µg/mL). Cells were concurrently induced with IL-1β (10 ng/mL) then treated with various concentrations (0.05, 0.5, and 5 µg/mL) of ACRH, QRF, and BQ, respectively. Controls (negative control, vehicle 0.1% DMSO, and suramin 50 µg/mL) were set up accordingly, along with the treatments. The upper and lower chamber received equal concentrations of each sample. $VEGF_{165}$ (10 ng/mL) was added to the lower chamber as a chemoattractant. After 22 h incubation, cells were stained with H & E stain and were visualized using an inverted light microscope. Image of cells was photographed with DinoCapture 2.0 camera attached to the inverted light microscope at 10× magnification. 88

4.7 Quantitative data of IL-1β-induced HFLS-RA invasion after being treated with various concentrations (0.05, 0.5, and 5 µg/mL) of each ACRH, QRF, and BQ for 22 h, respectively. All data were the percentage of invaded cells relative to the negative control (at 100% invaded cells) and expressed as 89

mean ± SEM (n = 3). Data were analyzed using one-way ANOVA followed by Tukey's HSD post hoc test. Significant differences were indicated by different superscript letters between concentrations in all groups (*P*<0.05).

5.1 Schematic diagram of QRF treatment in arthritic rats. 100

5.2 Morphological assessment of collagen-induced arthritis (CIA) in arthritic rats at every three days interval. (a) bodyweight, (b) ankle joint diameter, (c) hind paw volume, and (d) arthritic scoring, respectively. Note that the measurement of paw volume was taken at (X) by immersing the rat's hind limb up to 0.5 cm above the ankle joint (Y) in the plethysmometer. 102

5.3 Effect of CIA on arthritic scores in rats. (a) Effect-time curves and (b) the AUC of arthritic scores for 41 days. Data represent the mean ± SEM (n = 3 rats/group). Statistical analysis was performed using one-way ANOVA followed by Tukey's HSD. Different superscript letters indicate statistical significance between different groups (*P*<0.05). 109

5.4 Effect of CIA on body weight in rats. (a) Effect-time curves and (b) the AUC of body weight for 41 days. Data represent the mean ± SEM (n = 3 rats/group). Statistical analysis was performed using one-way ANOVA followed by Tukey's HSD. Different superscript letters indicate statistical significance between different groups (*P*<0.05). 111

5.5 Representative morphological observation of the CIA. (a) Arthritic fore limbs, (b) Arthritic hind limbs, (c) Vehicle control, (d) Arthritic control, (e) Celecoxib 5 mg/kg, (f) QRF 3 mg/kg, (g) QRF 10 mg/kg, and (h) QRF 30 mg/kg. 113

5.6 Effect of QRF on body weight of arthritic rats, expressed as AUC values of day 14 - 26. Data represent the mean ± SEM (n = 6 rats/group). Statistical analysis was performed using one-way ANOVA followed by Tukey's HSD. Different superscript letters indicate statistical significance between different groups (*P*<0.05). 116

5.7 Effect of QRF on arthritic scores. (a) Effect-time curves (day 0 – 26), where 'b' indicates a significant (*P*<0.05) increased arthritic scores in arthritic control, celecoxib 5 mg/kg, QRF 3, 10, and 30 mg/kg compared to vehicle control. There was no significant difference within all treated groups with arthritic control from day 11 onwards, indicated by "b" (b) AUC (day 14 – 26) of the arthritic scores. Data represent the mean ± SEM (n = 6 rats/group). Statistical analysis was performed using one-way ANOVA followed by Tukey's 120

HSD. Different superscript letters indicate statistical significance between different groups (*P*<0.05).

5.8 Effect of QRF on (a) left and (b) right ankle diameter of arthritic rats, expressed as AUC values of day 14 - 26. Data expressed are mean ± SEM of six animals per group (n = 6). One-way analysis of variance (ANOVA) followed by Tukey's HSD post hoc test was used for statistical analyses. Different superscript letters indicate significant differences between different groups (*P*<0.05). 124

5.9 Effect of QRF on (a) left and (b) right hind paw volume of arthritic rats, expressed as AUC values of day 14 - 26. Data expressed are mean ± SEM of six animals per group (n = 6). One-way analysis of variance (ANOVA) followed by Tukey's HSD post hoc test was used for statistical analyses. Different superscript letters indicate significant differences between different groups (*P*<0.05). 128

5.10 Micrograph of H&E synovial membrane tissue sections showing microvessel density (MVD) of inflamed ankle joints in arthritic rats. (a) Group I (vehicle control); (b) Group II (arthritic control); (c) Group III (celecoxib 5 mg/kg); (d) Group IV (QRF 3 mg/kg); (e) Group V (QRF 10 mg/kg), and (f) Group VI (QRF 30 mg/kg) at high magnification, 200×. Note that (S) synovium, (JS) joint space, (MV) microvessels, (C) cartilage, and (B) bone, respectively. The density of microvessels is marked with an arrow (→). 133

5.11 Depiction of the molecular mechanism of the anti-arthritic effect of a quinone-rich fraction (QRF) in collagen-induced arthritis rat model mediated via angiogenic pathway inhibition. A red line (—●) shows the inhibitory roles of QRF; a black arrow (⟶) represents activation of downstream signaling; and a dash arrow line (- - ➤) shows alternative activation (cross-talk) respectively. 149

LIST OF ABBREVIATIONS

%	Percentage
× g	Times gravity
µ	Micro
µg	Microgram
µm	Micrometer
4T1	*Mus musculus* mammary carcinoma cell line
AC1	Isomeric mixture of viminalol (α- and β amyrin)
AC7-1	2-methoxy-6-tridecyl-1,4-benzoquinone
ACRE	*Ardisia crispa* roots ethanolic extract
ACRH	*Ardisia crispa* roots hexane extract
ACUC	Animal Care and Use Committee
AGR	Annual Growth Rate
AIA	Adjuvant-induced arthritis
AKT	Protein kinase B
Ang	Angiopoietin
ANOVA	One-way analysis of variance
AP-1	Activator protein-1
APC	Antigen-presenting cells
ASK	Apoptosis signal-regulating kinase
ATP	Adenosine triphosphate
AUC	area under the dosing curve
bFGF	Basic fibroblast growth factor
BK	Bradykinin
BQ	2-methoxy-6-undecyl-1,4-benzoquinone
℃	Degree of Celcius

CAM	Chorioallantoic membrane
CFA	Complete Freund's adjuvant
CIA	Collagen-induced arthritis
CII	Type II bovine collagen
CMC	Carboxymethylcellulose
CO_2	carbon dioxide
COX	Cyclooxygenase
CREB	Cyclic AMP-responsive element-binding protein
CRP	C-reactive protein
CXCL	CXC chemokine ligand
DMARDs	Disease-modifying anti-rheumatic drugs
DMSO	Dimethyl sulfoxide
EBV-EA	Epstein-Barr virus-early antigen
ECGS	Endothelial cell growth supplement
ECM	Endothelial cell medium
ECs	Endothelial cells
EGF	Epidermal growth factor
EI	electron impact
ELISA	Enzyme-linked immunosorbent assay
ERK	Extracellular signal-regulated kinase
FBS	Fetal bovine serum
FDA	Food and Drug Administration
FGF	Fibroblast growth factor
FITC	Fluorescein isothiocyanate
FLS	Fibroblast-like synoviocytes
g	Gram
GC	Glucocorticoids

GC-MS	Gas chromatography-mass spectrometry
G-CSF	Granulocyte-colony stimulating factor
GM-CSF	Granulocyte-macrophage colony-stimulating factor
H&E	Hematoxylin and eosin
HFLS-RA	human fibroblast-like synoviocytes for rheumatoid arthritis
HGF	Hepatocyte growth factor
HIF-1	Hypoxia-inducible factor-1
HMVEC-1	human microvascular endothelial cell-1
HO-1	heme oxygenase-1
HPLC	high-performance liquid chromatography
HSD	Honest significant difference
HSF	Human skin fibroblasts
HSV	herpes simplex virus
HUVECs	Human umbilical vein endothelial cells
IC_{50}	Half maximal inhibitory concentration
ICAM-2	Intercellular adhesion molecule-2
IFA	Incomplete Freund's adjuvant
IFNγ	Interferon gamma
IκBα	Inhibitor of nuclear factor-kappa B
IKKs	IκB kinases
IL	Interleukin
iNOS	Inducible nitric oxide synthase
JAK	Janus kinase
JNK	c-Jun NH2-terminal kinase
kPa	Kilopascal
L	Liter
LMVEC	Lung microvascular endothelial cells LMVEC

LOX	Lipoxygenase
LPO	lipid peroxidation
MAPK	Mitogen-activated protein kinases
MCP-1	Monocyte chemotactic protein 1
MFI	Median fluorescence intensity
mg	Milligram
MHC	Major histocompatibility
MMP	Matrix metalloproteinase
MSD	Meso Scale Discovery
mTOR	Mammalian/mechanistic target of rapamycin
MTT	3-(4,5-dimethythiazol-2-yl)-2,5- diphenyl tetrazolium bromide
MTX	Methotrexate
MVD	Microvessel density
NAPDH	Nicotinamide adenine dinucleotide phosphate
NFLS	Normal FLS
NF-κB	Nuclear factor kappa B
ng	nanogram
NIH3T3	Normal mouse fibroblast cell line
NMR	nuclear magnetic resonance
NO	Nitric oxide
NSAIDs	Non-steroidal anti-inflammatory drugs
OA-FLS	Osteoarthritis derived FLSs
P	Significant value
P/S	Penicillin/streptomycin
p70S6K	Ribosomal protein S6 kinase beta-1
PBS	Phosphate-buffered saline
PDGF	Platelet derived growth factor

PECAM-1	Platelet endothelial cell adhesion molecule-1
PGE_2	Prostaglandin E_2
PGs	Prostaglandins
PI	propidium iodide
PI3K	Phosphatidylinositol-3-kinase
PIAS	Protein inhibitor of activated STAT
PIP	Phosphatidylinositol-triphosphate
PLCγ1	Phospholipase C gamma1
PLGF	Placenta growth factor
PS	phosphatidylserine
QRF	Quinone-rich fraction
RA	Rheumatoid arthritis
RANKL	Receptor activator of NF-κB ligand
Rf	Retention factor
ROS	reactive oxygen species
rpm	Rotations per minute
Rt	Retention time
RTKs	Receptor tyrosine kinases
SAPE	Streptavidin-Phycoerythrin
SCID	severe combined immunodeficiency
SD	Sprague-Dawley
SDF-1	Stromal cell-derived factor 1
SEM	Standard error of mean
SGM	Synoviocyte growth medium
SHB	Src Homology-2 domain-containing protein B
SOCS	Suppressor of cytokine signaling
Src	Family of proto-oncogenic tyrosine kinases

STAT	Signal transducer and activator of transcription
SUMO	small ubiquitin-related modifiers
TAK1	TGF-beta activated kinase 1
TGF-β	Transforming growth factor-beta
Th	T-helper cell
TIM	Tissue inhibitor matrix metalloproteinase
TLC	Thin layer chromatography
TLR	Toll-like receptor
TNFRII	Tumor necrosis factor receptor II
TNF-α	Tumor necrosis factor-alpha
TQF	Triterpene-quinone faction
Tsad	T cell-specific adapter protein
TSC2	Tuberous sclerosis complex 2
TYK2	Tyrosine kinase 2
UEA-1	Ulex europas agglutinin I
VCAM-1	Vascular cell adhesion molecule-1
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
VWF	von Willebrand factor

CHAPTER 1

INTRODUCTION

1.1 Research background

Rheumatoid arthritis (RA) is an autoimmune disease of chronic joint inflammation and deformities (Smolen et al., 2016). The condition is characterized by inflammatory cell infiltration, synovial hyperplasia, pannus formation, cartilage degradation, and bone destruction (Izquierdo et al., 2011; Mellado et al., 2015; Cajas et al., 2019). This systemic autoimmune disease attacks multiple synovial joints, with its persistent inflammation leading to joint destruction (Tseng et al., 2020). Although the disease itself is non-fatal, its complications usually end with disabilities, thus reducing the quality of life of the affected individuals (Law et al., 2019).

RA occurs in 1% of the global population and affects all ethnicities (WHO, 2020). The disease develops in adult populations, predominantly affecting women more than men (Smolen et al., 2016; Mbiantcha et al., 2017). Like other chronic diseases, this disease burdens the patients and the caregivers economically and debilitates work productivity, particularly in industrialized countries (Osiri & Maetzel, 2010). For the most part, there is scarce data on this lifelong disease in developing countries, including Malaysia, unlike Western countries.

Angiogenesis, a process of new vessel formation, is a key event in the pathogenesis of RA (Elshabrawy et al., 2015; Liu et al., 2019). Current knowledge into the pathophysiology and angiogenesis targeted therapy coupled with an emerging understanding of safer and cost-effective medicines derived from plant sources provides new insights for the search for an effective anti-arthritic agent to treat RA (Zampeli et al., 2015). One of the local plants that have received attention is *Ardisia crispa* (Family: Primulaceae), a medicinal herb widely distributed across Asian countries. Locally known as "*Mata Itik*," this plant has been consumed by local folks as food as well as a traditional remedy. While the leaves are served as a traditional salad, the roots are claimed to treat various illnesses, including rheumatism (Perry and Metzger, 1980; Muhamad & Mustafa, 1994). Compared to its leaves, the plant's roots deemed most beneficial medicinally as reported by various literature through rigorous scientific research (Chaweewan et al., 1987; 1995; Roslida, 2004; Huang, 2007; Yeong et al., 2013; Awang Hamsin et al., 2014; Hamid et al., 2017; Wen Jun et al., 2019).

The roots of *Ardisia crispa* contain phytochemicals such as saponins (Chaweewan et al., 1987), benzoquinone (Kang et al., 2001), triterpene, flavonoid, and tannin (Hamsin et al., 2013). 2 methoxy-6-undecyl-1,4-benzoquinone (BQ) that is isolated from the plant's roots is a bioactive compound that has been reported to yield anti-tumor (Yeong et al., 2013), anti-inflammatory

(Hamsin et al., 2013), and anti-angiogenic properties (Awang Hamsin et al., 2014). Moreover, the extracted *Ardisia crispa* roots hexane fraction (ACRH) was recently reported for their anti-arthritic effect, partly via inhibition of pro-inflammatory biomarkers, i.e., tumor necrosis factor-alpha (TNF-α) and interleukin-1β (IL-1β), in complete Freund's adjuvant (CFA)-induced arthritis model in rats (Hamid et al., 2017).

1.2 Problem statement

Deregulation of angiogenesis is one of the driving forces in the early pathogenesis of human RA that perpetuate chronic inflammation and sustaining pannus growth, resulting in joint damage (Leblond et al., 2017). As of late, it has been discovered that inhibiting synovial angiogenesis has become clinically important to repel the disease at the initial developmental stage (Cantatore et al., 2017; Liu et al., 2019). While managing RA has become more challenging due to the interplay between RA, aging, and comorbidities (van Onna & Boonen, 2016), the major drawback of treating this disease is the limitation in the available treatments. The use of mainstream therapies such as nonsteroidal anti-inflammatory drugs (NSAIDs) and conventional disease-modifying anti-rheumatic drugs (DMARDs) aids in impeding the disease progression, but not in treating the disease (Singh et al., 2016). While the introduction of biologic DMARDs to clinically target angiogenesis has intensely improving RA outcomes (Konttinen et al., 2005), the treatment response failure is anticipated in some patients (Hetland et al., 2010; Favalli et al., 2017; Nguyen et al., 2018). Some of the biologics, along with NSAIDs and conventional DMARDs, are also reported with contraindication and toxicities (Tarp et al., 2016; Favalli et al., 2017). Yet, unfortunately, access to the current biologics, particularly among Asian countries, is scarce due to cost inefficiency (Osiri & Maetzel, 2010). As an alternative approach to existing therapies, options to broadly interfere with angiogenesis signals in RA by a safer and affordable natural compound are very much warranted.

1.3 Justification of study

There has been emerging attention to the potential of phytocompounds from plants as an anti-arthritic agent in recent years. This focus has been a significant interest among scientists, pharmaceutical companies, and government agencies as policymakers. Compared to synthetic drugs, plants are relatively less toxic with comparatively low adverse effects. Indeed, plants offer more splendid therapeutic activities due to their rich phytochemical contents, i.e., polyphenols, terpenoids, flavonoids, etc. (Wang et al., 2015). Quinones, particularly para (*p*)-benzoquinones, are bioactive phenolic compounds attributed to their anti-oxidative, anti-inflammatory, and anti-angiogenic properties (Lin et al., 2016; Silva et al., 2020). Predominantly, natural compounds possessing anti-angiogenic effects could also be an excellent anti-arthritic agent, as extensively reported in the literature (Tabana et al., 2016; Jian-Ping et al., 2018; Feng et al., 2019). *Ardisia crispa* is a plant species reported to contain *p*-benzoquinone

derivatives, specifically a 2-methoxy-6-undecyl-1,4-benzoquinone (BQ) (Roslida, 2004) found in its root parts. Despite being reported as a potent anti-angiogenic agent in the disease models of inflammation and angiogenesis (Awang Hamsin et al., 2014; Wen Jun et al., 2019), the scientific validation of its anti-arthritic potential on the particular effector cells of RA [e.g., fibroblast-like synoviocytes (FLS)] and in polyarthritis animal model, targeting angiogenesis inhibition, is yet to be disclosed. It is ideal for examining the *in vitro* anti-arthritic effect of *Ardisia crispa* roots in modulating the activities of RA-FLS, before more comprehensive *in vivo* studies mimicking excessive angiogenesis microenvironment took place. Whilst the previous *in vivo* studies (using CFA-induced monoarthritic model in rats) reporting the anti-arthritic effect of ACRH mediated in part via its antioxidant and inhibition of pro-inflammatory biomarkers (TNF-α and IL-1β) (Hamid et al., 2017), the present study, targeted on the pro-angiogenic biomarkers/cross-talks inhibition, as the early event underlying RA, tested in collagen-induced arthritis (CIA) in rats, a well-established polyarthritis model that highly resembles human RA-like pathogenesis. Thus, the present study is proposed to fulfill these unmet findings by elucidating the potential of *Ardisia crispa* roots as an anti-arthritic agent targeting angiogenesis biomarkers. Findings from this study are hoped to contribute significantly to the body of knowledge of a new natural anti-arthritic agent affordable to treat RA, especially in Asian countries.

1.4 Objective(s)

1.4.1 General objective

This study investigated the *in vitro* and *in vivo* anti-arthritic potential of bioactive fractions [i.e., *Ardisia crispa* roots hexane extract (ACRH) and quinone-rich fraction (QRF)] and a compound [2 methoxy-6-undecyl-1,4-benzoquinone (BQ)] prepared from hexane extraction of *Ardisia crispa* roots by targeting angiogenesis inhibition.

1.4.2 Specific objectives

a) To prepare ACRH, QRF, and BQ samples from *Ardisia crispa* roots using hexane extraction protocol and silica gel column chromatography, followed by identification of the benzoquinone (compound of interest) content in each sample via gas chromatography-mass spectrometry (GC-MS) analyses.
b) To examine the inhibitory activities and the half maximal inhibitory concentration (IC_{50}) value of ACRH, QRF, and BQ, respectively, on VEGF-induced human umbilical vein endothelial cells (HUVECs) and IL-1β-induced human fibroblast-like synoviocytes for rheumatoid arthritis (HFLS-RA) viability.
c) To assess the suppression/inhibitions of ACRH, QRF, and BQ, respectively, on VEGF-induced HUVEC tube formation, IL-1β-induced

HFLS-RA invasion, and enhancement of IL-1β-induced HFLS-RA apoptotic activity.

d) To determine the anti-arthritic effect of QRF in collagen-induced arthritis (CIA) model in Sprague-Dawley rats by assessing the arthritic scores, ankle diameter of hind limbs, hind paw volume, synovial microvessel density, and changes on bodyweight and organ weights (i.e., kidney, liver, spleen).

e) To quantify the protein expression of pro-angiogenic biomarkers/cross-talk mediators in RA post-treatment with QRF via enzyme-linked immunosorbent assay (ELISA) and multiplex magnetic bead-based immunoassay and elucidated the possible mechanism(s) underlying the anti-arthritic effect of QRF.

1.5 Hypothesis

a) ACRH, QRF, and BQ prepared from the *Ardisia crispa* roots hexane extraction may contain the benzoquinone (compound of interest) within each of the samples.

b) ACRH, QRF, and BQ, respectively, may display significant inhibitions on cell viability of both VEGF-induced HUVECs and IL-1β-induced HFLS-RA.

c) ACRH, QRF, and BQ, respectively, may exhibit significant suppression/inhibitions on the VEGF-induced HUVEC tube formation, IL-1β-induced HFLS-RA invasion, and may enhance the apoptotic activity of IL-1β-induced HFLS-RA.

d) QRF may demonstrate significant reductions of the arthritic scores, ankle diameter of hind limbs, hind paw volume, synovial microvessel density, with an insignificant bodyweight and organ weights (i.e., kidney, liver, spleen) changes in the arthritic rats.

e) QRF may cause significant attenuations of pro-angiogenic biomarkers/cross-talk mediators, including VEGF-A, PI3K2α, ERK/MAPK 1/2, AKT, STAT3, JNK, p70 S6 Kinase, NF-κB, STAT5A/B, CREB, and p38 proteins in the arthritic rats.

REFERENCES

Abraham, I., Joshi, R., Pardasani, P., & Pardasani, R. T. (2011). Recent advances in 1, 4-benzoquinone chemistry. *Journal of the Brazilian Chemical Society, 22*(3), 385-421. doi:10.1590/s0103-50532011000300002

Acharya, B. R., Chatterjee, A., Ganguli, A., Bhattacharya, S., & Chakrabarti, G. (2014). Thymoquinone inhibits microtubule polymerization by tubulin binding and causes mitotic arrest following apoptosis in A549 cells. *Biochimie, 97*, 78-91. https://doi.org/10.1016/j.biochi.2013.09.025

Acosta, M. J., Fonseca, L. V., Desbats, M. A., Cerqua, C., Zordan, R., Trevisson, E., et al. (2016). Coenzyme Q biosynthesis in health and disease. *Biochimica et Biophysica Acta (BBA)-Bioenergetics, 1857*(8), 1079-1085. https://doi.org/10.1016/j.bbabio.2016.03.036

Adcock, I. M., & Mumby, S. (2016). Glucocorticoids. In *Pharmacology and Therapeutics of Asthma and COPD* (pp. 171-196). Springer, Cham. DOI 10.1007/164_2016_98

Aittomäki, S., & Pesu, M. (2014). Therapeutic targeting of the Jak/STAT pathway. *Basic & Clinical Pharmacology & Toxicology, 114*(1), 18-23. Doi: 10.1111/bcpt.12164

Al-Abd, A. M., Alamoudi, A. J., Abdel-Naim, A. B., Neamatallah, T. A., & Ashour, O. M. (2017). Anti-angiogenic agents for the treatment of solid tumors: potential pathways, therapy and current strategies–a review. *Journal of Advanced Research, 8*(6), 591-605. https://doi.org/10.1016/j.jare.2017.06.006

Alam, J., Jantan, I., & Bukhari, S. N. A. (2017). Rheumatoid arthritis: recent advances on its etiology, role of cytokines and pharmacotherapy. *Biomedicine & Pharmacotherapy, 92*, 615-633. https://doi.org/10.1016/j.biopha.2017.05.055

Al-Salama, Z. T., & Scott, L. J. (2018). Baricitinib: a review in rheumatoid arthritis. *Drugs, 78*(7), 761-772. DOI:10.1007/s40265-018-0908-4

Alzahrani, A. S. (2019). PI3K/Akt/mTOR inhibitors in cancer: at the bench and bedside. In *Seminars in Cancer Biology*, 59, 125-132. Academic Press. https://doi.org/10.1016/j.semcancer.2019.07.009

Amalraj, A., Varma, K., Jacob, J., Divya, C., Kunnumakkara, A. B., Stohs, S. J., et al. (2017). A novel highly bioavailable curcumin formulation improves symptoms and diagnostic indicators in rheumatoid arthritis patients: A randomized, double-blind, placebo-controlled, two-dose, three-arm, and parallel-group study. *Journal of Medicinal Food, 20*(10), 1022-1030. DOI: 10.1089/jmf.2017.3930

Angiosperm Phylogeny Group. (2009). An update of the Angiosperm Phylogeny Group classification for the orders and families of flowering plants: APG III. *Botanical Journal of the Linnean Society, 161(2)*, 105-121.

Anh, N. H., Ripperger, H., Schmidt, J., Porzel, A., Van Sung, T., & Adam, G. (1996). Resorcinol derivatives from two *Ardisia* species. *Planta Medica, 62*(05), 479-480. DOI: 10.1055/s-2006-957947

Apte, R. S., Chen, D. S., & Ferrara, N. (2019). VEGF in signaling and disease: beyond discovery and development. *Cell, 176*(6), 1248-1264. https://doi.org/10.1016/j.cell.2019.01.021

Arellano-Garcia, M. E., Hu, S., Wang, J., Henson, B., Zhou, H., Chia, D., et al. (2008). Multiplexed immunobead-based assay for detection of oral cancer protein biomarkers in saliva. *Oral Diseases, 14*(8), 705-712. doi:10.1111/j.1601-0825.2008.01488.x

Arjumand, S., Shahzad, M., Shabbir, A., & Yousaf, M. Z. (2019). Thymoquinone attenuates rheumatoid arthritis by downregulating TLR2, TLR4, TNF-α, IL-1, and NFκB expression levels. *Biomedicine & Pharmacotherapy, 111*, 958-963. https://doi.org/10.1016/j.biopha.2019.01.006

Arnaoutova, I., & Kleinman, H. K. (2010). *In vitro* angiogenesis: endothelial cell tube formation on gelled basement membrane extract. *Nature Protocols, 5*(4), 628. doi:10.1038/nprot.2010.6

Arnaoutova, I., George, J., Kleinman, H. K., & Benton, G. (2009). The endothelial cell tube formation assay on basement membrane turns 20: state of the science and the art. *Angiogenesis, 12*(3), 267-274. DOI:10.1007/s10456-009-9146-4

Aryaeian, N., Shahram, F., Mahmoudi, M., Tavakoli, H., Yousefi, B., Arablou, T., et al. (2019). The effect of ginger supplementation on some immunity and inflammation intermediate genes expression in patients with active rheumatoid arthritis. *Gene, 698*, 179-185. https://doi.org/10.1016/j.gene.2019.01.048

Aslantürk, Ö. S. (2018). *In vitro* cytotoxicity and cell viability assays: principles, advantages, and disadvantages. *Genotoxicity-A predictable risk to our actual world, 2,* 64-80. DOI: 10.5772/intechopen.71923

Asquith, D. L., Miller, A. L., McInnes, I. B., & Liew, F. Y. (2009). Autoimmune disease: rheumatoid arthritis. *European Journal of Immunology, 39*, 1991-2058. DOI 10.1002/eji.200939578

Astry, B., Venkatesha, S. H., Laurence, A., Christensen-Quick, A., Garzino-demo, A., Frieman, M. B., et al. (2015). Celastrol, a Chinese herbal compound, controls autoimmune inflammation by altering the balance of pathogenic and regulatory T cells in the target organ. *Clinical*

Immunology, 157(2), 228-238. https://doi.org/10.1016/j.clim.2015.01.011

Awang Hamsin, D. E. Z., Hamid, A. R., Yazan, S. L., Taib, C. N. M., & Yeong, L. T. (2014). *Ardisia crispa* roots inhibit cyclooxygenase and suppress angiogenesis. *BMC Complement Alternative Medicine*, *14*, 102. https://doi.org/10.1186/1472-6882-14-102

Aydin, S. (2015). A short history, principles, and types of ELISA, and our laboratory experience with peptide/protein analyses using ELISA. *Peptides, 72*, 4-15. https://doi.org/10.1016/j.peptides.2015.04.012

Azizi, G., Boghozian, R., & Mirshafiey, A. (2014). The potential role of angiogenic factors in rheumatoid arthritis. *International Journal of Rheumatic Diseases, 17*(4), 369-383.

Babbar, N., Oberoi, H. S., Sandhu, S. K., & Bhargav, V. K. (2014). Influence of different solvents in extraction of phenolic compounds from vegetable residues and their evaluation as natural sources of antioxidants. *Journal of Food Science and Technology, 51*(10), 2568-2575. https://doi.org/10.1007/s13197-012-0754-4

Baier, A., Meineckel, I., Gay, S., & Pap, T. (2003). Apoptosis in rheumatoid arthritis. *Current Opinion in Rheumatology, 15*(3), 274-279.

Baker, H. N., Murphy, R., Lopez, E., & Garcia, C. (2012). Conversion of a capture ELISA to a Luminex xMAP assay using a multiplex antibody screening method. *Journal of Visualized Experiments, 65*, 4084. doi: 10.3791/4084

Bala, K., Ambwani, K., & Gohil, N. K. (2011). Effect of different mitogens and serum concentration on HUVEC morphology and characteristics: implication on use of higher passage cells. *Tissue and Cell, 43*(4), 216-222. https://doi.org/10.1016/j.tice.2011.03.004

Balogh, E., Biniecka, M., Fearon, U., Veale, D. J., & Szekanecz, Z. (2019). Angiogenesis in inflammatory arthritis. *The Israel Medical Association Journal, 5*(21), 345-352.

Banerjee, S., Biehl, A., Gadina, M., Hasni, S., & Schwartz, D. M. (2017). JAK–STAT signaling as a target for inflammatory and autoimmune diseases: current and future8prospects. *Drugs, 77*(5), 521-546. doi: 10.1007/s40265-017-0701-9

Bartok, B., & Firestein, G. S. (2010). Fibroblast-like synoviocytes: key effector cells in rheumatoid arthritis. *Immunological Reviews, 233*(1), 233-255.

Baudin, B., Bruneel, A., Bosselut, N., & Vaubourdolle, M. (2007). A protocol for isolation and culture of human umbilical vein endothelial cells. *Nature Protocols, 2*(3), 481-485. doi:10.1038/nprot.2007.54

Benjamin O, Bansal P, Goyal A, Lappin, S. L (2020). Disease modifying anti-rheumatic drugs (DMARD) In*: StatPearls. StatPearls Publishing, Treasure Island (FL).*

Bessis, N., Decker, P., Assier, E., Semerano, L., & Boissier, M. C. (2017, June). Arthritis models: usefulness and interpretation. In *Seminars in Immunopathology, 39*(4), 469-486. Springer Berlin Heidelberg.

Bevaart, L., Vervoordeldonk, M. J., & Tak, P. P. (2010). Evaluation of therapeutic targets in animal models of arthritis: how does it relate to rheumatoid arthritis?. *Arthritis & Rheumatism, 62*(8), 2192-2205. DOI 10.1002/art.27503

Bhandarkar, S. S., & Arbiser, J. L. (2007). Curcumin as an inhibitor of angiogenesis. In *The Molecular Targets and Therapeutic Uses of Curcumin in Health and Disease* (pp. 185-195). Springer, Boston, MA.

Bhupinder, K., Reena, G., & Gupta, M. (2017). Natural products in treatment of rheumatoid arthritis. *International Journal of Green Pharmacy, 11*(03), S356.

Billiau, A., & Matthys, P. (2011). Collagen-induced arthritis and related animal models: how much of their pathogenesis is auto-immune, how much is auto-inflammatory?. *Cytokine & Growth Factor Reviews, 22*(5-6), 339-344. https://doi.org/10.1016/j.cytogfr.2011.11.003

Bio-Rad Laboratories. (2020). Bio-Plex Multiplex Immunoassays. Retrieved 15 December 2020 from https://www.bio-rad.com/en-my/applications-technologies/bio-plex-multiplex-immunoassays?ID=LUSM0ZMNI

Borges-Argáez, R. O. C. Í. O., Uc-Cachón, A. N. D. R. É. S., Quintal-Novelo, C. A. R. L. O. S., Canché-Escamilla, G. O. N. Z. A. L. O., & Farfán, M. C. (2013). A selective chemical method for the separation of quinones from the stem bark of *Diospyros anisandra. International Journal of Current Pharmaceutical Research, 5*(4), 13-17. http://cicy.repositorioinstitucional.mx/jspui/handle/1003/42

Bottini, N., & Firestein, G. S. (2013). Duality of fibroblast-like synoviocytes in RA: passive responders and imprinted aggressors. *Nature Reviews Rheumatology, 9*(1), 24–33. https://doi.org/10.1038/nrrheum.2012.190

Bouïs, D., Hospers, G. A., Meijer, C., Molema, G., & Mulder, N. H. (2001). Endothelium *in vitro*: a review of human vascular endothelial cell lines for blood vessel-related research. *Angiogenesis, 4*(2), 91-102.

Bousoik, E., & Montazeri Aliabadi, H. (2018). “Do we know jack” about JAK? A closer look at the JAK/STAT signaling pathway. *Frontiers in Oncology, 8*, 287. https://doi.org/10.3389/fonc.2018.00287

Boyden, S. (1962). The chemotactic effect of mixtures of antibody and antigen on polymorphonuclear leukocytes. *The Journal of Experimental Medicine, 115*(3), 453-466.

Brand, D. D., Latham, K. A., & Rosloniec, E. F. (2007). Collagen-induced arthritis. *Nature protocols, 2*(5), 1269. doi:10.1038/nprot.2007.173

Breier, G., Chavakis, T., & Hirsch, E. (2017). Angiogenesis in metabolic-vascular disease. *Thrombosis and Haemostasis, 117*(07), 1289-1295. https://doi.org/10.1160/TH17-05-0325

Bright, J. J. (2007). Curcumin and autoimmune disease. In *The Molecular Targets and Therapeutic Uses of Curcumin in Health and Disease*, 425-451. Springer, Boston, MA.

Brown, R. M., Meah, C. J., Heath, V. L., Styles, I. B., & Bicknell, R. (2016). Tube-forming assays. In *Angiogenesis Protocols* (pp. 149-157). Humana Press, New York, NY. DOI 10.1007/978-1-4939-3628-1_9

Bugatti, S., Cassione, E. B., De Stefano, L., & Manzo, A. (2020). Established rheumatoid arthritis. The pathogenic aspects. *Best Practice & Research Clinical Rheumatology, 33*(5), 101478. https://doi.org/10.1016/j.berh.2019.101478

Bullock, J., Rizvi, S. A., Saleh, A. M., Ahmed, S. S., Do, D. P., Ansari, R. A., et al. (2018). Rheumatoid arthritis: a brief overview of the treatment. *Medical Principles and Practice,* 27(6), 501-507. https://doi.org/10.1159/000493390

Burkill, I. H. (1996). A dictionary of the economic product of the Malay peninsula. volume 11 (iz) Government of Malaysia and Singapore by the ministry of Agriculture and cooperative. *Kuala Lumpur,* 354-366.

Burska, A., Boissinot, M., & Ponchel, F. (2014). Cytokines as biomarkers in rheumatoid arthritis. *Mediators of Inflammation, 2014*. https://doi.org/10.1155/2014/545493

Burton, J. D. (2005). The MTT assay to evaluate chemosensitivity. In: *Blumenthal R.D. (eds) Chemosensitivity. Methods in Molecular Medicine™, 110*, 69-78. Humana Press. https://doi.org/10.1385/1-59259-869-2:069

Busbee, P. B., Rouse, M., Nagarkatti, M., & Nagarkatti, P. S. (2013). Use of natural AhR ligands as potential therapeutic modalities against inflammatory disorders. *Nutrition reviews, 71*(6), 353-369. doi:10.1111/nure.12024.

Bustamante, M. F., Garcia-Carbonell, R., Whisenant, K. D., & Guma, M. (2017). Fibroblast-like synoviocyte metabolism in the pathogenesis of rheumatoid arthritis. *Arthritis research & therapy, 19*(1), 1-12. https://doi.org/10.1186/s13075-017-1303-3

Cai, L., Li, C. M., Chen, W. N., Qiu, Y. Y., Guo, Y. L., et al. (2019). Penta-acetyl geniposide induces apoptosis of fibroblast-like synoviocytes from adjuvant-induced arthritis rats *in vitro*, associated with inhibition of NF-κB activation. *Pharmacological Reports, 71*(6), 1006-1013. http://dx.doi.org/10.1016/j.pharep.2019.05.014

Cajas, L. J., Casallas, A., Medina, Y. F., Quintana, G., & Rondóna, F. (2019). Pannus and rheumatoid arthritis: Historic and pathophysiological evolution. *Revista Colombiana de Reumatología*, *26*(2), 118–128. http://dx.doi.org/10.1016/j.rcreu.2018.05.003

Cannell, R. J. (1998). How to approach the isolation of a natural product. In *Natural Products Isolation* (pp. 1-51). Humana Press.

Cantatore, F. P., Maruotti, N., Corrado, A., & Ribatti, D. (2017). Anti-angiogenic effects of biotechnological therapies in rheumatic diseases. *Biologics: Targets & Therapy, 11,* 123–128. https://doi.org/10.2147/BTT.S143674

Caporali, R., Caprioli, M., Bobbio-Pallavicini, F., & Montecucco, C. (2008). DMARDS and infections in rheumatoid arthritis. *Autoimmunity Reviews, 8*(2), 139-143. https://doi.org/10.1016/j.autrev.2008.05.001

Caporali, R., Fakhouri, W. K., Nicolay, C., Longley, H. J., Losi, S., & Rogai, V. (2020). New rheumatoid arthritis treatments for 'old'patients: Results of a systematic review. *Advances in Therapy, 37*, 3676–3691. https://doi.org/10.1007/s12325-020-01435-6

Cascão, R., Vidal, B., Lopes, I. P., Paisana, E., Rino, J., Moita, L. F., et al. (2015). Decrease of CD68 synovial macrophages in celastrol treated arthritic rats. *PLoS One, 10*(12), e0142448. https://doi.org/10.1371/journal.pone.0142448

Cathcart, E. S., Hayes, K. C., Gonnerman, W. A., Lazzari, A. A., & Franzblau, C. (1986). Experimental arthritis in a nonhuman primate. I. Induction by bovine type II collagen. *Laboratory Investigation; A Journal of Technical Methods and Pathology, 54*(1), 26-31.

Chaanine, A. H., & Hajjar, R. J. (2011). AKT signalling in the failing heart. *European Journal of Heart Failure, 13*(8), 825-829. doi:10.1093/eurjhf/hfr080

Chandra, S., & Gonzalez de Mejia, E. (2004). Polyphenolic compounds, antioxidant capacity, and quinone reductase activity of an aqueous extract of *Ardisia compressa* in comparison to mate (*Ilex paraguariensis*) and green (*Camellia sinensis*) teas. *Journal of Agricultural and Food Chemistry, 52*(11), 3583-3589. https://doi.org/10.1021/jf0352632

Chandran, B., & Goel, A. (2012). A randomized, pilot study to assess the efficacy and safety of curcumin in patients with active rheumatoid arthritis. *Phytotherapy Research, 26*(11), 1719-1725. DOI: 10.1002/ptr.4639

Chang, L., Feng, X., & Gao, W. (2019). Proliferation of rheumatoid arthritis fibroblast-like synoviocytes is enhanced by IL-17-mediated autophagy through STAT3 activation. *Connective Tissue Research, 60*(4), 358-366. https://doi.org/10.1080/03008207.2018.1552266

Chaplin, S. (2020). Upadacitinib for the treatment of rheumatoid arthritis. *Prescriber, 31*(3), 32-34.

Chaurio, R. A., Janko, C., Muñoz, L. E., Frey, B., Herrmann, M., & Gaipl, U. S. (2009). Phospholipids: key players in apoptosis and immune regulation. *Molecules, 14*(12), 4892-4914. https://doi.org/10.3390/molecules14124892

Chaweewan, J. (1995). Some pharmacological studies of ardisiacrispin B, an utero-contracting saponin, isolated from *Ardisia crispa. Journal of the Science Society of Thailand, 21*, 11-26. doi:10.2306/scienceasia1513-1874.1995.21.011

Chaweewan, J., Baumann, H., Kenne, L., & Samuelsson, G. (1987). Ardisiacrispin A and B, two utero-contracting saponins from *Ardisia crispa*. *Planta Medica*, *53*(05), 405–409. https://doi:10.1055/s-2006-962758

Chen, C., & Pipoly, J. J. (1996). Myrsinaceae. In *'Flora of China'Vol. 15*.

Chen, E. Y., Blanke, C. D., Haller, D. G., Benson, A. B., Dragovich, T., Lenz, H. J., et al. (2018). A phase II study of celecoxib with irinotecan, 5-fluorouracil, and leucovorin in patients with previously untreated advanced or metastatic colorectal cancer. *American Journal of Clinical Oncology, 41*(12), 1193–1198. https://doi.org/10.1097/COC.0000000000000465

Chen, H., Pan, J., Wang, J. D., Liao, Q. M., & Xia, X. R. (2016). Suberoylanilide hydroxamic acid, an inhibitor of histone deacetylase, induces apoptosis in rheumatoid arthritis fibroblast-like synoviocytes. *Inflammation, 39*(1), 39-46. DOI: 10.1007/s10753-015-0220-3

Chen, K., Lin, Z. W., He, S. M., Wang, C. Q., Yang, J. C., Lu, Y., et al. (2019). Metformin inhibits the proliferation of rheumatoid arthritis fibroblast-like synoviocytes through IGF-IR/PI3K/AKT/m-TOR pathway. *Biomedicine & Pharmacotherapy, 115*, 108875. https://doi.org/10.1016/j.biopha.2019.108875

Chen, L. P., Zhao, F., Wang, Y., Zhao, L. L., Li, Q. P., & Liu, H. W. (2011). Antitumor effect of resorcinol derivatives from the roots of *Ardisia brevicaulis* by inducing apoptosis. *Journal of Asian Natural Products Research, 13*(8), 734-743. https://doi.org/10.1080/10286020.2011.587412

Chen, M., Lv, Z., Huang, L., Zhang, W., Lin, X., Shi, J., et al. (2015). Triptolide inhibits TGF-β1-induced cell proliferation in rat airway smooth muscle cells by suppressing Smad signaling. *Experimental Cell Research, 331*(2), 362-368. https://doi.org/10.1016/j.yexcr.2014.10.016

Chen, S. R., Dai, Y., Zhao, J., Lin, L., Wang, Y., & Wang, Y. (2018). A mechanistic overview of triptolide and celastrol, natural products from *Tripterygium wilfordii* Hook F. *Frontiers in Pharmacology, 9*, 104. https://doi.org/10.3389/fphar.2018.00104

Chen, Y. F., Jobanputra, P., Barton, P., Bryan, S., Fry-Smith, A., Harris, G., et al. (2008). Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation. In *NIHR Health Technology Assessment Programme: Executive Summaries. NIHR Journals Library, 12*(11).

Chen, Y. J., Wu, J. Y., Leung, W. C., Liu, Y. X., Fu, X. Q., Zhu, J. Q., et al. (2020). An herbal formula inhibits STAT3 signaling and attenuates bone erosion in collagen-induced arthritis rats. *Phytomedicine, 76*, 153254. https://doi.org/10.1016/j.phymed.2020.153254

Cheon, H., Holvey-Bates, E. G., Schoggins, J. W., Forster, S., Hertzog, P., Imanaka, N., et al. (2013). IFNβ-dependent increases in STAT1, STAT2, and IRF9 mediate resistance to viruses and DNA damage. *The EMBO journal, 32*(20), 2751-2763. doi:10.1038/emboj.2013.203

Cheung, T. T., & McInnes, I. B. (2017). Future therapeutic targets in rheumatoid arthritis?. *Seminars in Immunopathology*, 39(4), 487-500. DOI 10.1007/s00281-017-0623-3

Ching, J., Chua, T. K., Chin, L. C., Lau, A. J., Pang, Y. K., Jaya, J. M., et al. (2010). Beta-amyrin from *Ardisia elliptica* Thunb. is more potent than aspirin in inhibiting collagen-induced platelet aggregation. *Indian Journal of Experimental Biology, 48*(3), 275-279.

Cho, H. D., Kim, J. H., Park, J. K., Hong, S. M., Kim, D. H., & Seo, K. I. (2019). *Kochia scoparia* seed extract suppresses VEGF-induced angiogenesis via modulating VEGF receptor 2 and PI3K/AKT/mTOR pathways. *Pharmaceutical Biology, 57*(1), 684-693. https://doi.org/10.1080/13880209.2019.1672753

Choe, J. Y., Park, K. Y., Park, S. H., Lee, S. I., & Kim, S. K. (2013). Regulatory effect of calcineurin inhibitor, tacrolimus, on IL-6/sIL-6R-mediated RANKL expression through JAK2-STAT3-SOCS3 signaling pathway in fibroblast-like synoviocytes. *Arthritis Research & Therapy, 15*(1), 1-12. https://doi.org/10.1186/ar4162

Choi, D. J., Choi, S. I., Choi, B. R., Lee, Y. S., Lee, D. Y., & Kim, G. S. (2019). Cartilage protective and anti-analgesic effects of ALM16 on monosodium iodoacetate induced osteoarthritis in rats. *BMC Complementary And Alternative Medicine, 19*(1), 1-15. https://doi.org/10.1186/s12906-019-2746-7

Choi, J. S., Park, S. Y., Yi, E. Y., Kim, Y. J., & Jeong, J. W. (2011). Coenzyme Q10 decreases basic fibroblast growth factor (bFGF)-induced angiogenesis by blocking ERK activation. *Oncology Research Featuring Preclinical and Clinical Cancer Therapeutics, 19*(10-11), 455-461. https://doi.org/10.3727/096504012X13285365944256

Choudhary, M., Kumar, V., Malhotra, H., & Singh, S. (2015). Medicinal plants with potential anti-arthritic activity. *Journal of Intercultural Ethnopharmacology, 4*(2), 147–179. https://doi.org/10.5455/jice.20150313021918

Choudhary, N., Bhatt, L. K., & Prabhavalkar, K. S. (2018). Experimental animal models for rheumatoid arthritis. *Immunopharmacology and Immunotoxicology, 40*(3), 193-200. https://doi.org/10.1080/08923973.2018.1434793

Choy, E. (2012). Understanding the dynamics: pathways involved in the pathogenesis of rheumatoid arthritis. *Rheumatology, 51*(supplement 5), v3-v11. https://doi.org/10.1093/rheumatology/kes113

Christenhusz, M. J., & Byng, J. W. (2016). The number of known plants species in the world and its annual increase. *Phytotaxa, 261*(3), 201-217. http://dx.doi.org/10.11646/phytotaxa.261.3.1

Chung, K. C., & Pushman, A. G. (2011). Current concepts in the management of the rheumatoid hand. *The Journal of Hand Surgery, 36*(4), 736-747. https://doi.org/10.1016/j.jhsa.2011.01.019

Claesson-Welsh, L., & Welsh, M. (2013). VEGFA and tumour angiogenesis. *Journal of Internal Medicine, 273*(2), 114-127. https://doi.org/10.1111/joim.12019

Clarimundo, V. S., Farinon, M., Pedó, R. T., Teixeira, V. O. N., Nör, C., Gulko, P. S., et al. (2017). Gastrin-releasing peptide and its receptor increase arthritis fibroblast-like synoviocytes invasiveness through activating the PI3K/AKT pathway. *Peptides, 95*, 57-61. https://doi.org/10.1016/j.peptides.2017.07.008

Colombo, F., Durigutto, P., De Maso, L., Biffi, S., Belmonte, B., Tripodo, C., et al. (2019). Targeting CD34+ cells of the inflamed synovial endothelium by guided nanoparticles for the treatment of rheumatoid arthritis. *Journal of Autoimmunity, 103*, 102288. https://doi.org/10.1016/j.jaut.2019.05.016

Commins, S. P., Borish, L., & Steinke, J. W. (2010). Immunologic messenger molecules: cytokines, interferons, and chemokines. *Journal of Allergy and Clinical immunology, 125*(2), 53-72. https://doi.org/10.1016/j.jaci.2009.07.008

Courtenay, J. S., Dallman, M. J., Dayan, A. D., Martin, A., & Mosedale, B. (1980). Immunisation against heterologous type II collagen induces arthritis in mice. *Nature, 283*(5748), 666-668. https://doi.org/10.1038/283666a0

Coxon, A., Bolon, B., Estrada, J., Kaufman, S., Scully, S., Rattan, A., et al. (2002). Inhibition of interleukin-1 but not tumor necrosis factor suppresses neovascularization in rat models of corneal angiogenesis and adjuvant arthritis. *Arthritis & Rheumatism, 46*(10), 2604-2612. DOI 10.1002/art.10546

Crofford, L. J. (2013). Use of NSAIDs in treating patients with arthritis. *Arthritis Research & Therapy, 15*(S3), S2. https://doi.org/10.1186/ar4174

Croia, C., Bursi, R., Sutera, D., Petrelli, F., Alunno, A., & Puxeddu, I. (2019). One year in review 2019: pathogenesis of rheumatoid arthritis. *Clinical and Experimental Rheumatology, 37*(3), 347-357.

Cuenda, A., & Rousseau, S. (2007). p38 MAP-kinases pathway regulation, function and role in human diseases. *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research, 1773*(8), 1358-1375. https://doi.org/10.1016/j.bbamcr.2007.03.010

Cui, P., Qu, F., Sreeharsha, N., Sharma, S., Mishra, A., & Gubbiyappa, S. K. (2020). Antiarthritic effect of chitosan nanoparticle loaded with embelin against adjuvant-induced arthritis in Wistar rats. *International Union of Biochemistry and Molecular Biology Life, 72*(5), 1054-1064. DOI: 10.1002/iub.2248

Dabitao, D., Margolick, J. B., Lopez, J., & Bream, J. H. (2011). Multiplex measurement of proinflammatory cytokines in human serum: comparison of the Meso Scale Discovery electrochemiluminescence assay and the Cytometric Bead Array. *Journal of Immunological Methods, 372*(1-2), 71-77. https://doi.org/10.1016/j.jim.2011.06.033

Dadoun, S., Zeboulon-Ktorza, N., Combescure, C., Elhai, M., Rozenberg, S., Gossec, L., et al. (2013). Mortality in rheumatoid arthritis over the last fifty years: systematic review and meta-analysis. *Joint Bone Spine, 80*(1), 29-33. https://doi.org/10.1016/j.jbspin.2012.02.005

Dai, Q., Li, J., Yun, Y., & Wang, J. (2018). Toll-like receptor 4–myeloid differentiation primary response gene 88 pathway is involved in the shikonin treatment of CIA by regulating Treg/Th17 expression. *Evidence-Based Complementary and Alternative Medicine, 2018*. https://doi.org/10.1155/2018/2428546

Daily, J. W., Yang, M., & Park, S. (2016). Efficacy of turmeric extracts and curcumin for alleviating the symptoms of joint arthritis: a systematic review and meta-analysis of randomized clinical trials. *Journal of Medicinal Food, 19*(8), 717-729. DOI: 10.1089/jmf.2016.3705

Darwish, H. A., Arab, H. H., & Abdelsalam, R. M. (2014). Chrysin alleviates testicular dysfunction in adjuvant arthritic rats via suppression of inflammation and apoptosis: comparison with celecoxib. *Toxicology and Applied Pharmacology, 279*(2), 129-140. https://doi.org/10.1016/j.taap.2014.05.018

Datta, P., Mukherjee, S., Dasgupta, S. C., Gomes, A., & Gomes, A. (2014). Anti arthritic activity of theaflavin (TF), chief flavonoid of black tea against adjuvant induced rheumatoid arthritis in experimental animal models. *Oriental Pharmacy and Experimental Medicine, 14*(3), 245-253. DOI 10.1007/s13596-013-0144-0

Davis, L. S. (2003). A question of transformation: the synovial fibroblast in rheumatoid arthritis. *The American Journal of Pathology, 162*(5), 1399–1402. https://doi.org/10.1016/S0002-9440(10)64272-1

de Launay, D., van de Sande, M. G., de Hair, M. J., Grabiec, A. M., van de Sande, G. P., Lehmann, K. A., et al. (2012). Selective involvement of ERK and JNK mitogen-activated protein kinases in early rheumatoid arthritis (1987 ACR criteria compared to 2010 ACR/EULAR criteria): a prospective study aimed at identification of diagnostic and prognostic biomarkers as well as therapeutic targets. *Annals of the Rheumatic Diseases, 71*(3), 415-423. doi:10.1136/ard.2010.143529

De Mejía, E. G., & Ramírez-Mares, M. V. (2011). *Ardisia*: health-promoting properties and toxicity of phytochemicals and extracts. *Toxicology Mechanisms and Methods, 21*(9), 667-674. https://doi.org/10.3109/15376516.2011.601355

De, S., Kundu, S., & Chatterjee, M. (2020). Generation of a robust model for inducing autoimmune arthritis in Sprague Dawley rats. *Journal of Pharmacological and Toxicological Methods, 102*, 106659. https://doi.org/10.1016/j.vascn.2019.106659

Deane, K. D., Demoruelle, M. K., Kelmenson, L. B., Kuhn, K. A., Norris, J. M., & Holers, V. M. (2017). Genetic and environmental risk factors for rheumatoid arthritis. *Best Practice & Research Clinical Rheumatology, 31*(1), 3-18. https://doi.org/10.1016/j.berh.2017.08.003

Demchenko, A. P. (2012). The change of cellular membranes on apoptosis: fluorescence detection. *Experimental Oncology, 34*(3), 263–268.

Demoruelle, M. K., & Deane, K. D. (2012). Treatment strategies in early rheumatoid arthritis and prevention of rheumatoid arthritis. *Current*

Rheumatology Reports, 14(5), 472-480. doi: 10.1007/s11926-012-0275-1

Deng, J., Fan, C., Gao, X., Zeng, Q., Guo, R., Wei, Y., et al. (2018). Signal transducer and activator of transcription 3 hyperactivation associates with follicular helper T cell differentiation and disease activity in rheumatoid arthritis. *Frontiers in Immunology, 9*, 1226. https://doi.org/10.3389/fimmu.2018.01226

Deng, Q., Bai, S., Gao, W., & Tong, L. (2015). Pristimerin inhibits angiogenesis in adjuvant-induced arthritic rats by suppressing VEGFR2 signaling pathways. *International Immunopharmacology, 29*(2), 302-313. https://doi.org/10.1016/j.intimp.2015.11.001

Dhillon, A. S., Hagan, S., Rath, O., & Kolch, W. (2007). MAP kinase signalling pathways in cancer. *Oncogene, 26*(22), 3279-3290. https://doi.org/10.1038/sj.onc.1210421

Dinarello, C. A. (2011). Interleukin-1 in the pathogenesis and treatment of inflammatory diseases. *Blood, The Journal of the American Society of Hematology, 117*(14), 3720-3732. doi: 10.1182/blood-2010-07-273417

Dou, Y., Luo, J., Wu, X., Wei, Z., Tong, B., Yu, J., et al. (2018). Curcumin attenuates collagen-induced inflammatory response through the "gut-brain axis". *Journal of Neuroinflammation, 15*(1), 1-15. https://doi.org/10.1186/s12974-017-1047-7

Doyle, M. K., Rahman, M. U., Frederick, B., Birbara, C. A., de Vries, D., Toedter, G., et al. (2013). Effects of subcutaneous and intravenous golimumab on inflammatory biomarkers in patients with rheumatoid arthritis: results of a phase 1, randomized, open-label trial. *Rheumatology, 52*(7), 1214-1219. https://doi.org/10.1093/rheumatology/kes381

Dragos, D., Gilca, M., Gaman, L., Vlad, A., Iosif, L., Stoian, I., et al. (2017). Phytomedicine in joint disorders. *Nutrients, 9*(1), 70. doi:10.3390/nu9010070

Dudics, S., Langan, D., Meka, R. R., Venkatesha, S. H., Berman, B. M., Che, C. T., et al. (2018). Natural products for the treatment of autoimmune arthritis: their mechanisms of action, targeted delivery, and interplay with the host microbiome. *International Journal of Molecular Sciences, 19*(9), 2508. doi:10.3390/ijms19092508

Duggan, S., & Keam, S.J. (2019) Upadacitinib: First Approval. *Drugs 79,* 1819–1828. https://doi.org/10.1007/s40265-019-01211-z

Duke, J. A., & Ayensu, E. S. (1985). Medicinal Plants of China. Medicinal Plants of the World. Vol. 1. Algonac, MI.

Ediriweera, M. K., Tennekoon, K. H., & Samarakoon, S. R. (2019). *In vitro* assays and techniques utilized in anticancer drug discovery. *Journal of Applied Toxicology, 39*(1), 38-71. DOI: 10.1002/jat.3658

El-Ghazaly, M. A., Fadel, N. A., Abdel-Naby, D. H., Abd El-Rehim, H. A., Zaki, H. F., & Kenawy, S. A. (2020). Potential anti-inflammatory action of resveratrol and piperine in adjuvant-induced arthritis: Effect on pro-inflammatory cytokines and oxidative stress biomarkers. *The Egyptian Rheumatologist, 42*(1), 71-77. https://doi.org/10.1016/j.ejr.2019.08.003

El-Ghazaly, M. A., Nada, A. S., El-Hazek, R. M., & Khayyal, M. T. (2010). Effect of selective COX-2 inhibitor, celecoxib on adjuvant-induced arthritis model in irradiated rats. *International Journal of Radiation Biology, 86*(12), 1079-1087. DOI: 10.3109/09553002.2010.501839

Elmore, S. (2007). Apoptosis: a review of programmed cell death. *Toxicologic Pathology, 35*(4), 495-516. DOI: 10.1080/01926230701320337

Elshabrawy, H. A., Chen, Z., Volin, M. V., Ravella, S., Virupannavar, S., & Shahrara, S. (2015). The pathogenic role of angiogenesis in rheumatoid arthritis. *Angiogenesis*, *18*(4), 433-448. https://doi.org/10.1007/s10456-015-9477-2

Elshal, M. F., & McCoy, J. P. (2006). Multiplex bead array assays: performance evaluation and comparison of sensitivity to ELISA. *Methods, 38*(4), 317-323. https://doi.org/10.1016/j.ymeth.2005.11.010

Engvall, E. (2010). The ELISA, enzyme-linked immunosorbent assay. *Clinical Chemistry, 56*(2), 319-320. https://doi.org/10.1373/clinchem.2009.127803

Engvall, E., & Perlmann, P. (1971). Enzyme-linked immunosorbent assay (ELISA) quantitative assay of immunoglobulin G. *Immunochemistry, 8*(9), 871-874. https://doi.org/10.1016/0019-2791(71)90454-X

Ezenduka, E. V., Okorie-Kanu, O. J., & Nwanta, J. A. (2019). Comparative analysis of two microbiological tests in the detection of oxytetracycline residue in chicken using ELISA as gold standard. *Journal of Immunoassay and Immunochemistry, 40*(6), 617-629. https://doi.org/10.1080/15321819.2019.1669639

Faisal, R., Ahmad, N., Fahed, Y. S., & Chiragh, S. (2018). Anti-arthritic effect of thymoquinone in comparison with methotrexate on pristane induced arthritis in female Sprague Dawley Rats. *Journal of Ayub Medical College Abbottabad, 30*(1), 3-7.

Falconer, J., Murphy, A. N., Young, S. P., Clark, A. R., Tiziani, S., Guma, M., et al. (2018). Synovial cell metabolism and chronic inflammation in rheumatoid arthritis. *Arthritis & Rheumatology, 70*(7), 984-999. DOI 10.1002/art.40504

Favalli, E. G. (2020). Tofacitinib's infectious profile: concerns for clinical practice. *The Lancet Rheumatology, 2*(2), 65-67. https://doi.org/10.1016/S2665-9913(20)30001-1

Favalli, E. G., Raimondo, M. G., Becciolini, A., Crotti, C., Biggioggero, M., & Caporali, R. (2017). The management of first-line biologic therapy failures in rheumatoid arthritis: current practice and future perspectives. *Autoimmunity Reviews, 16*(12), 1185-1195. https://doi.org/10.1016/j.autrev.2017.10.002

Fearnley, G. W., Smith, G. A., Odell, A. F., Latham, A. M., Wheatcroft, S. B., Harrison, M. A. et al. (2014). Vascular endothelial growth factor A-stimulated signaling from endosomes in primary endothelial cells. In *Methods in Enzymology*, 535, 265-292. Academic Press. http://dx.doi.org/10.1016/B978-0-12-397925-4.00016

Fechtner, S., Singh, A., Chourasia, M., & Ahmed, S. (2017). Molecular insights into the differences in anti-inflammatory activities of green tea catechins on IL-1β signaling in rheumatoid arthritis synovial fibroblasts. *Toxicology and Applied Pharmacology, 329*, 112-120. https://doi.org/10.1016/j.taap.2017.05.016

Feldmann, M., Andreakos, E., Smith, C., Bondeson, J., Yoshimura, S., Kiriakidis, S., et al. (2002). Is NF-κB a useful therapeutic target in rheumatoid arthritis?. *Annals of the Rheumatic Diseases, 61*(supplement 2), ii13-ii18. http://dx.doi.org/10.1136/ard.61.suppl_2.ii13

Feng, H., Yamaki, K., Takano, H., Inoue, K., Yanagisawa, R., & Yoshino, S. (2007). Effect of sinomenine on collagen-induced arthritis in mice. *Autoimmunity, 40*(7), 532-539. https://doi.org/10.1080/08916930701615159

Feng, Z. T., Yang, T., Hou, X. Q., Wu, H. Y., Feng, J. T., Ou, B. J., et al. (2019). Sinomenine mitigates collagen-induced arthritis mice by inhibiting angiogenesis. *Biomedicine & Pharmacotherapy*, *113,* 108759. https://doi.org/10.1016/j.biopha.2019.108759

Ferrara, N., & Adamis, A. P. (2016). Ten years of anti-vascular endothelial growth factor therapy. *Nature Reviews Drug Discovery, 15*(6), 385-403. DOI10.1038/nrd.2015.17

Fidahic, M., Kadic, A. J., Radic, M., & Puljak, L. (2017). Celecoxib for rheumatoid arthritis. *Cochrane Database of Systematic Reviews,* (6). https://doi.org/10.1002/14651858.CD012095.pub2

Fifi, S. I. (2013). Subchronic toxicity study of *Ardisia crispa* root hexane extract in mice. (Unpublished master dissertation). Universiti Putra Malaya, Malaysia.

Firestein, G. S. (1996). Invasive fibroblast-like synoviocytes in rheumatoid arthritis. Passive responders or transformed aggressors?. *Arthritis & Rheumatism, 39*(11), 1781-1790.

Firestein, G. S. (2005). Immunologic mechanisms in the pathogenesis of rheumatoid arthritis. *JCR: Journal of Clinical Rheumatology, 11*(3), S39-S44. doi: 10.1097/01.rhu.0000166673.34461.33

Fischer, B. D., Adeyemo, A., O'Leary, M. E., & Bottaro, A. (2017). Animal models of rheumatoid pain: experimental systems and insights. *Arthritis Research & Therapy, 19*(1), 146. https://doi.org/10.1186/s13075-017-1361-6

Fleischmann, R., Pangan, A. L., Song, I. H., Mysler, E., Bessette, L., Peterfy, C., et al. (2019). Upadacitinib versus placebo or adalimumab in patients with rheumatoid arthritis and an inadequate response to methotrexate: results of a phase III, double-blind, randomized controlled trial. *Arthritis & Rheumatology, 71*(11), 1788-1800. DOI 10.1002/art.41032

Fragoulis, G. E., McInnes, I. B., & Siebert, S. (2019). JAK-inhibitors. New players in the field of immune-mediated diseases, beyond rheumatoid arthritis. *Rheumatology, 58*, 43-54. https://doi.org/10.1093/rheumatology/key276

Frolov, R. V., & Singh, S. (2014). Celecoxib and ion channels: a story of unexpected discoveries. *European Journal of Pharmacology, 730*, 61-71. https://doi.org/10.1016/j.ejphar.2014.02.032

Fukushima, A., Boyle, D. L., Corr, M., & Firestein, G. S. (2010). Kinetic analysis of synovial signalling and gene expression in animal models of arthritis. *Annals of the Rheumatic Diseases, 69*(5), 918-923. doi: 10.1136/ard.2009.112201

Funk, J. L., Oyarzo, J. N., Frye, J. B., Chen, G., Lantz, R. C., Jolad, S. D., et al. (2006). Turmeric extracts containing curcuminoids prevent experimental rheumatoid arthritis. *Journal of Natural Products, 69*(3), 351-355. https://doi.org/10.1021/np050327j

Galligan, C. L., Siminovitch, K. A., Keystone, E. C., Bykerk, V., Perez, O. D., & Fish, E. N. (2010). Fibrocyte activation in rheumatoid arthritis. *Rheumatology, 49*(4), 640-651. https://doi.org/10.1093/rheumatology/kep265

Ganesan, R., & Rasool, M. (2017). Fibroblast-like synoviocytes-dependent effector molecules as a critical mediator for rheumatoid arthritis: Current status and future directions. *International Reviews of Immunology, 36*(1), 20-30. https://doi.org/10.1080/08830185.2016.1269175

García, S., Liz, M., Gómez-Reino, J. J., & Conde, C. (2010). Akt activity protects rheumatoid synovial fibroblasts from Fas-induced apoptosis by inhibition

of Bid cleavage. *Arthritis Research & Therapy, 12*(1), R33. https://doi.org/10.1186/ar2941

Gasparini, C., & Feldmann, M. (2012). NF-κB as a target for modulating inflammatory responses. *Current Pharmaceutical Design, 18*(35), 5735-5745. https://doi.org/10.2174/138161212803530763

Ge, H. X., Zou, F. M., Li, Y., Liu, A. M., & Tu, M. (2017). JNK pathway in osteoarthritis: pathological and therapeutic aspects. *Journal of Receptors and Signal Transduction, 37*(5), 431-436. https://doi.org/10.1080/10799893.2017.1360353

Gentile, M. T., Pastorino, O., Bifulco, M., & Colucci-D'Amato, L. (2019). HUVEC tube-formation assay to evaluate the impact of natural products on angiogenesis. *Journal of Visualized Experiments, 148*, e58591. doi: 10.3791/58591

Ghannam, K., Gamboa, L. M., Kedor, C., Spengler, L., Kuckelkorn, U., Häupl, T., et al. (2020). Response to abatacept is associated with the inhibition of proteasome β1i expression in T cells of patients with rheumatoid arthritis. *RMD open, 6*(3), e001248. http://dx.doi.org/10.1136/rmdopen-2020-001248

Gholamnezhad, Z., Havakhah, S., & Boskabady, M. H. (2016). Preclinical and clinical effects of *Nigella sativa* and its constituent, thymoquinone: A review. *Journal of Ethnopharmacology, 190*, 372-386. https://doi.org/10.1016/j.jep.2016.06.061

Gilston, V., Jones, H. W., Soo, C. C., Coumbe, A., Blades, S., Kaltschmidt, C., et al. (1997). NF-κB activation in human knee-joint synovial tissue during the early stage of joint inflammation. *Biochemical Society Transactions, 25*(3): 518S. https://doi.org/10.1042/bst025518s

GlobalData. Rheumatoid Arthritis – Epidemiology Forecast to 2027 (2019). GlobalData, London.

Goldbach-Mansky, R., Wilson, M., Fleischmann, R., Olsen, N., Silverfield, J., Kempf, P., et al. (2009). Comparison of *Tripterygium wilfordii* Hook F versus sulfasalazine in the treatment of rheumatoid arthritis: a randomized trial. *Annals of Internal Medicine, 151*(4), 229-240. https://doi.org/10.7326/0003-4819-151-4-200908180-00005

Goldenberg, M. M. (1999). Celecoxib, a selective cyclooxygenase-2 inhibitor for the treatment of rheumatoid arthritis and osteoarthritis. *Clinical Therapeutics, 21*(9), 1497-1513. https://doi.org/10.1016/S0149-2918(00)80005-3

Gomez, I., Foudi, N., Longrois, D., & Norel, X. (2013). The role of prostaglandin E2 in human vascular inflammation. *Prostaglandins, Leukotrienes and*

Essential Fatty Acids, 89(2-3), 55-63. https://doi.org/10.1016/j.plefa.2013.04.004

Gong, L., Thorn, C. F., Bertagnolli, M. M., Grosser, T., Altman, R. B., & Klein, T. E. (2012). Celecoxib pathways: pharmacokinetics and pharmacodynamics. *Pharmacogenetics and Genomics, 22*(4), 310–318. https://doi.org/10.1097/FPC.0b013e32834f94cb

Görtz, B., Hayer, S., Tuerck, B., Zwerina, J., Smolen, J. S., & Schett, G. (2005). Tumour necrosis factor activates the mitogen-activated protein kinases p38α and ERK in the synovial membrane in vivo. *Arthritis Research & Therapy, 7*(5), R1140. https://doi.org/10.1186/ar1797

Gotthardt, D., Putz, E. M., Grundschober, E., Prchal-Murphy, M., Straka, E., Kudweis, P., et al. (2016). STAT5 is a key regulator in NK cells and acts as a molecular switch from tumor surveillance to tumor promotion. *Cancer Discovery, 6*(4), 414-429. DOI: 10.1158/2159-8290.CD-15-0732

Grange, R. D., Thompson, J. P., & Lambert, D. G. (2014). Radioimmunoassay, enzyme and non-enzyme-based immunoassays. *British Journal of Anaesthesia, 112*(2), 213-216. https://doi.org/10.1093/bja/aet293

Grevenstuk, T., Gonçalves, S., Nogueira, J. M., & Romano, A. (2008). Plumbagin recovery from field specimens of Drosophyllum lusitanicum (L.) Link. Phytochemical Analysis: *An International Journal of Plant Chemical and Biochemical Techniques, 19*(3), 229-235. DOI: 10.1002/pca.1034

Griffiths, M. M. (1988). Immunogenetics of collagen-induced arthritis in rats. *International Reviews of Immunology, 4*(1), 1-15. https://doi.org/10.3109/08830188809044766

Guanizo, A. C., Fernando, C. D., Garama, D. J., & Gough, D. J. (2018). STAT3: a multifaceted oncoprotein. *Growth Factors, 36*(1-2), 1-14. https://doi.org/10.1080/08977194.2018.1473393

Gumkowski, F., Kaminska, G., Kaminski, M., Morrissey, L. W., & Auerbach, R. (1987). Heterogeneity of mouse vascular endothelium. *Journal of Vascular Research, 24*(1-2), 11-23. https://doi.org/10.1159/000158667

Guo, K., Bu, X., Yang, C., Cao, X., Bian, H., Zhu, Q., et al. (2019). Treatment effects of the second-generation tyrosine kinase inhibitor dasatinib on autoimmune arthritis. *Frontiers in Immunology, 9*, 3133. https://doi.org/10.3389/fimmu.2018.03133

Guo, S., Lok, J., Liu, Y., Hayakawa, K., Leung, W., Xing, C., et al. (2014). Assays to examine endothelial cell migration, tube formation, and gene expression profiles. *Methods in Molecular Biology, 1135*, 393–402. https://doi.org/10.1007/978-1-4939-0320-7_32

Gupta, S. C., Patchva, S., & Aggarwal, B. B. (2013). Therapeutic roles of curcumin: lessons learned from clinical trials. *Journal of The American*

Association of Pharmaceutical Scientists, 15(1), 195-218. https://doi.org/10.1208/s12248-012-9432-8

Gutierrez, P. L. (2000). The metabolism of quinone-containing alkylating agents: free radical production and measurement. *Frontiers in Bioscience, 5*, 629-638.

Hamid, R. A., Fong, L. M., & Ting, Y. L. (2017). Anti-arthritic and gastroprotective activities of *Ardisia crispa* root partially mediated via its antioxidant effect. *Journal of Complementary and Integrative Medicine, 15*(1). DOI: https://doi.org/10.1515/jcim-2017-0012

Hamid, R. A., Othman, F., Anthony, J. J., & Ting, Y. L. (2013). Chemopreventive effect of *Ardisia crispa* hexane fraction on the peri-initiation phase of mouse skin tumorigenesis. *Medical Principles and Practice, 22*(4), 357-361. https://doi.org/10.1159/000346622

Hamsin, D. E. Z. A., Hamid, R. A., Yazan, L. S., Taib, C. N. M., & Ting, Y. L. (2013). The hexane fraction of *Ardisia crispa* Thunb. A. DC. roots inhibits inflammation-induced angiogenesis. *BMC Complementary and Alternative Medicine, 13*(1), 5. https://doi.org/10.1186/1472-6882-13-5

Han, W., Xiong, Y., Li, Y., Fang, W., Ma, Y., Liu, L., et al. (2013). Anti-arthritic effects of clematichinenoside (AR-6) on PI3K/Akt signaling pathway and TNF-α associated with collagen-induced arthritis. *Pharmaceutical Biology, 51*(1), 13-22. https://doi.org/10.3109/13880209.2012.698287

Haqqi, T. M., Anthony, D. D., Gupta, S., Ahmad, N., Lee, M. S., Kumar, G. K. et al. (1999). Prevention of collagen-induced arthritis in mice by a polyphenolic fraction from green tea. *Proceedings of the National Academy of Sciences, 96*(8), 4524-4529. https://doi.org/10.1073/pnas.96.8.4524

Harborne, A. J. (1998). Phytochemical methods a guide to modern techniques of plant analysis. *Springer Science & Business Media*. DOI: 10.1007/978-94-009-5921-7

Harrison, D. A. (2012). The jak/stat pathway. *Cold Spring Harbor Perspectives in Biology, 4*(3), a011205. doi: 10.1101/cshperspect.a011205

Hashemi Goradel, N., Najafi, M., Salehi, E., Farhood, B., & Mortezaee, K. (2019). Cyclooxygenase-2 in cancer: A review. *Journal of Cellular Physiology, 234*(5), 5683-5699. DOI: 10.1002/jcp.27411

Hawk, E., & Viner, J. L. (2007). The adenoma prevention with celecoxib and prevention of colorectal sporadic adenomatous polyps trials: stepping stones to progress. *Cancer Epidemiology, Biomarkers & Prevention, 16*(2):185 – 187. doi:10.1158/1055-9965.EPI-06-1086

Hawkins, P., Armstrong, R., Boden, T., Garside, P., Knight, K., Lilley, E., et al. (2015). Applying refinement to the use of mice and rats in rheumatoid

arthritis research. *Inflammopharmacology, 23*(4), 131–150. https://doi.org/10.1007/s10787-015-0241-4

Hazlewood, G. S., Barnabe, C., Tomlinson, G., Marshall, D., Devoe, D. J., & Bombardier, C. (2016). Methotrexate monotherapy and methotrexate combination therapy with traditional and biologic disease modifying anti-rheumatic drugs for rheumatoid arthritis: A network meta-analysis. *Cochrane Database of Systematic Reviews,* (8). https://doi.org/10.1002/14651858.CD010227.pub2

He, Z. H., He, M. F., Ma, S. C., & But, P. P. H. (2009). Anti-angiogenic effects of rhubarb and its anthraquinone derivatives. *Journal of Ethnopharmacology, 121*(2), 313-317. https://doi.org/10.1016/j.jep.2008.11.008

Hench, P. (1950). Effects of cortisone in the rheumatic diseases. *Lancet, 2*(6634), 483.

Hetland, M. L., Christensen, I. J., Tarp, U., Dreyer, L., Hansen, A., Hansen, I. T., et al. (2010). Direct comparison of treatment responses, remission rates, and drug adherence in patients with rheumatoid arthritis treated with adalimumab, etanercept, or infliximab: results from eight years of surveillance of clinical practice in the nationwide Danish DANBIO registry. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology, 62*(1), 22-32. https://doi.org/10.1002/art.27227

Hill, R. J., Dabbagh, K., Phippard, D., Li, C., Suttmann, R. T., Welch, M., et al. (2008). Pamapimod, a novel p38 mitogen-activated protein kinase inhibitor: preclinical analysis of efficacy and selectivity. *Journal of Pharmacology and Experimental Therapeutics, 327*(3), 610-619. https://doi.org/10.1124/jpet.108.139006

Ho, K. Y., Cardosa, M. S., Chaiamnuay, S., Hidayat, R., Ho, H. Q. T., Kamil, O., et al. (2020). Practice advisory on the appropriate use of NSAIDs in primary care. *Journal of Pain Research, 13*, 1925. https://doi.org/10.2147/JPR.S247781

Hodge, J. A., Kawabata, T. T., Krishnaswami, S., Clark, J. D., Telliez, J. B., Dowty, M. E., et al. (2016). The mechanism of action of tofacitinib-an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis. *Clinical and Experimental Rheumatology, 34*(2), 318-328.

Hoeben, A. N. N., Landuyt, B., Highley, M. S., Wildiers, H., Van Oosterom, A. T., et al. (2004). Vascular endothelial growth factor and angiogenesis. *Pharmacological Reviews, 56*(4), 549-580. DOI: https://doi.org/10.1124/pr.56.4.3

Hollander, A. P., Corke, K. P., Freemont, A. J., & Lewis, C. E. (2001). Expression of hypoxia-inducible factor 1α by macrophages in the rheumatoid

synovium: Implications for targeting of therapeutic genes to the inflamed joint. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology, 44*(7), 1540-1544. https://doi.org/10.1002/1529-0131(200107)44:7<1540::AID-ART277>3.0.CO;2-7

Horai, Y., Miyamura, T., Shimada, K., Takahama, S., Minami, R., Yamamoto, M., et al. (2012). Eternacept for the treatment of patients with rheumatoid arthritis and concurrent interstitial lung disease. *Journal of Clinical Pharmacy and Therapeutics, 37*(1), 117-121. doi: 10.1111/j.1365-2710.2010.01234.x

Hou, W., Liu, B., & Xu, H. (2019). Triptolide: Medicinal chemistry, chemical biology and clinical progress. *European Journal of Medicinal Chemistry, 176*, 378-392. https://doi.org/10.1016/j.ejmech.2019.05.032

Houser, B. (2012). Bio-Rad's Bio-Plex® suspension array system, xMAP technology overview. *Archives of Physiology and Biochemistry, 118*(4), 192-196. https://doi.org/10.3109/13813455.2012.705301

Howell, G. J., Herbert, S. P., Smith, J. M., Mittar, S., Ewan, L. C., Mohammed, M., et al. (2004). Endothelial cell confluence regulates Weibel-Palade body formation. *Molecular Membrane Biology, 21*(6), 413-421. https://doi.org/10.1080/09687860400011571

Hsu, H. Y., Joos, T. O., & Koga, H. (2009). Multiplex microsphere-based flow cytometric platforms for protein analysis and their application in clinical proteomics–from assays to results. *Electrophoresis, 30*(23), 4008-4019. DOI 10.1002/elps.200900211

Hu, H., Jin, H., Yu, L., & Qu, S. (2018). Inhibition of ERK pathway decreases the synovial hyperplasia and angiogenesis of rheumatoid arthritis rats. *European Journal of Inflammation, 16*,1-7. DOI: 10.1177/2058739218794531

Huang W., Xu K-P., Li F-S., Yuan S., Li Z-K., Xu P., et al. (2009). A new triterpenoid saponin from the roots of *Ardisia crispa. Chinese Journal of Organic Chemistry 29*:1564–1568.

Huang, G., Xu, Z., Huang, Y., Duan, X., Gong, W., Zhang, Y., et al. (2013). Curcumin protects against collagen-induced arthritis via suppression of BAFF production. *Journal of Clinical Immunology, 33*(3), 550-557. DOI:10.1007/s10875-012-9839-0

Huang, J., Zhou, L., Wu, H., Pavlos, N., Chim, S. M., Liu, Q., et al. (2015). Triptolide inhibits osteoclast formation, bone resorption, RANKL-mediated NF-κB activation and titanium particle-induced osteolysis in a mouse model. *Molecular and Cellular Endocrinology, 399*, 346-353. https://doi.org/10.1016/j.mce.2014.10.016

Huang, W. (2007). *Studies on the antitumor active constituents isolated from the root of Ardisia crispa*. (Unpublished master dissertation). Central South University, China.

Huang, W., Tan, G-H., Xu, K-P., Li F-S., Li Z-K., Liu Y-P. (2010). Cytotoxic constituents from the root of *Ardisia Crispa*. *Natural Product Research and Development, 23*(6), 949.

Huber, L. C., Distler, O., Tarner, I., Gay, R. E., Gay, S., & Pap, T. (2006). Synovial fibroblasts: key players in rheumatoid arthritis. *Rheumatology, 45*(6), 669-675. doi:10.1093/rheumatology/kel065

Iannone, F., Lopalco, G., Cantarini, L., Galeazzi, M., & Lapadula, G. (2016). Efficacy and safety of combination therapy for preventing bone damage in rheumatoid arthritis. *Clinical Rheumatology, 35*(1), 19-23. DOI:10.1007/s10067-015-3120-x

Ikari, Y., Isozaki, T., Tsubokura, Y., & Kasama, T. (2019). Peficitinib inhibits the chemotactic activity of monocytes via proinflammatory cytokine production in rheumatoid arthritis fibroblast-like synoviocytes. *Cells, 8*(6), 561. https://doi.org/10.3390/cells8060561

Impellizzeri, D., Siracusa, R., Cordaro, M., Peritore, A. F., Gugliandolo, E., D'amico, R., et al. (2020). Protective effect of a new hyaluronic acid-carnosine conjugate on the modulation of the inflammatory response in mice subjected to collagen-induced arthritis. *Biomedicine & Pharmacotherapy,* 125, 110023. https://doi.org/10.1016/j.biopha.2020.110023

Inoki, K., Li, Y., Zhu, T., Wu, J., & Guan, K. L. (2002). TSC2 is phosphorylated and inhibited by Akt and suppresses mTOR signalling. *Nature Cell Biology, 4*(9), 648-657. DOI: 10.1038/ncb839

Ishiyama, M., Tominaga, H., Shiga, M., Sasamoto, K., Ohkura, Y., & Ueno, K. (1996). A combined assay of cell vability and in vitro cytotoxicity with a highly water-soluble tetrazolium salt, neutral red and crystal violet. *Biological and Pharmaceutical Bulletin, 19*(11), 1518-1520. https://doi.org/10.1248/bpb.19.1518

Isomäki, P., Junttila, I., Vidqvist, K. L., Korpela, M., & Silvennoinen, O. (2015). The activity of JAK-STAT pathways in rheumatoid arthritis: constitutive activation of STAT3 correlates with interleukin 6 levels. *Rheumatology, 54*(6), 1103-1113. https://doi.org/10.1093/rheumatology/keu430

Itatani, Y., Kawada, K., Yamamoto, T., & Sakai, Y. (2018). Resistance to anti-angiogenic therapy in cancer—alterations to anti-VEGF pathway. *International Journal of Molecular Sciences, 19*(4), 1232. doi:10.3390/ijms19041232

Ivashkiv, L. B., & Hu, X. (2003). The JAK/STAT pathway in rheumatoid arthritis: pathogenic or protective?. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology, 48*(8), 2092-2096. DOI 10.1002/art.11095

Iwanaga, T., Shikichi, M., Kitamura, H., Yanase, H., & Nozawa-Inoue, K. (2000). Morphology and functional roles of synoviocytes in the joint. *Archives of Histology and Cytology, 63*(1), 17-31. https://doi.org/10.1679/aohc.63.17

Izquierdo, E., Cañete, J. D., Celis, R., Del Rey, M. J., Usategui, A., Marsal, S., et al. (2011). Synovial fibroblast hyperplasia in rheumatoid arthritis: clinicopathologic correlations and partial reversal by anti–tumor necrosis factor therapy. *Arthritis & Rheumatism, 63*(9), 2575-2583. https://doi.org/10.1002/art.30433

Jabeen, A., Mesaik, M. A., Simjee, S. U., Bano, S., & Faizi, S. (2016). Anti-TNF-α and anti-arthritic effect of patuletin: A rare flavonoid from *Tagetes patula*. *International Immunopharmacology, 36*, 232-240. https://doi.org/10.1016/j.intimp.2016.04.034

Jaffe, E. A. (1987). Cell biology of endothelial cells. *Human Pathology, 18*(3), 234-239. https://doi.org/10.1016/S0046-8177(87)80005-9

Jiang, M., Zha, Q., Zhang, C., Lu, C., Yan, X., Zhu, W., et al. (2015). Predicting and verifying outcome of *Tripterygium wilfordii* Hook F. based therapy in rheumatoid arthritis: from open to double-blinded randomized trial. *Scientific Reports, 5*, 9700. https://doi.org/10.1038/srep09700

Jian-Ping, B. I., LI, P., Xi-Xi, X. U., Ting, W. A. N. G., & Fei, L. I. (2018). Anti-rheumatoid arthritic effect of volatile components in *notopterygium incisum* in rats via anti-inflammatory and anti-angiogenic activities. *Chinese Journal of Natural Medicines, 16*(12), 926-935. https://doi.org/10.1016/S1875-5364(18)30134-1

Jin, J. H., Kim, J. S., Kang, S. S., Son, K. H., Chang, H. W., & Kim, H. P. (2010). Anti-inflammatory and anti-arthritic activity of total flavonoids of the roots of *Sophora flavescens*. *Journal of Ethnopharmacology, 127*(3), 589-595. https://doi.org/10.1016/j.jep.2009.12.020

Jindal, H. M. K., & Mohamad, J. (2012). Antioxidant activity of *Ardisia crispa* (Mata pelanduk). *Sains Malaysiana, 41*(5), 539-545.

Julius, A., Kajita, T., & Utteridge, T. M. (2020). Two new species of *Ardisia* subgenus *Tetrardisia* (Primulaceae-Myrsinoideae) from Borneo. *PhytoKeys, 145*, 139–148. https://doi.org/10.3897/phytokeys.145.48573

Jusman, S. W. A., Sari, D. H., Ningsih, S. S., Hardiany, N. S., & Sadikin, M. (2019). Role of hypoxia inducible factor-1 alpha (HIF-1α) in cytoglobin

expression and fibroblast proliferation of keloids. *Kobe Journal of Medical Sciences, 65*(1), E10-E18.

Kahkhaie, K. R., Mirhosseini, A., Aliabadi, A., Mohammadi, A., Haftcheshmeh, S. M., Sathyapalan, T., et al. (2019). Curcumin: a modulator of inflammatory signaling pathways in the immune system. *Inflammopharmacology,* 1-16. https://doi.org/10.1007/s10787-019-00607-3

Kamarudin, M. S., & Latiff, A. (2002). Tumbuhan Ubatan Malaysia (Malaysian Medicinal Plants).

Kamel, K. M., Gad, A. M., Mansour, S. M., Safar, M. M., & Fawzy, H. M. (2018). Novel anti-arthritic mechanisms of Polydatin in complete Freund's adjuvant-induced arthritis in rats: involvement of IL-6, STAT-3, IL-17, and NF-κB. *Inflammation, 41*(5), 1974-1986. DOI:10.1007/s10753-018-0841-4

Kanai, T., Kondo, N., Okada, M., Sano, H., Okumura, G., Kijima, Y., et al. (2020). The JNK pathway represents a novel target in the treatment of rheumatoid arthritis through the suppression of MMP-3. *Journal of Orthopaedic Surgery and Research, 15*(1), 1-10. https://doi.org/10.1186/s13018-020-01595-9

Kanbe, K., Chiba, J., & Nakamura, A. (2011). Decrease of CD68 and MMP-3 expression in synovium by treatment of adalimumab for rheumatoid arthritis. *International Journal of Rheumatic Diseases, 14*(3), 261-266. https://doi.org/10.1111/j.1756-185X.2011.01643.x

Kang, Y. H., Kim, W. H., Park, M. K., & Han, B. H. (2001). Antimetastatic and antitumor effects of benzoquinonoid AC7-1 from *Ardisia crispa*. *International Journal of Cancer, 93*(5), 736-740. https://doi.org/10.1002/ijc.1384

Kannan, K., Ortmann, R. A., & Kimpel, D. (2005). Animal models of rheumatoid arthritis and their relevance to human disease. *Pathophysiology, 12*(3), 167-181. https://doi.org/10.1016/j.pathophys.2005.07.011

Karar, J., & Maity, A. (2011). PI3K/AKT/mTOR pathway in angiogenesis. *Frontiers in Molecular Neuroscience, 4,* 51. doi: 10.3389/fnmol.2011.00051

Karimi, A., Majlesi, M., & Rafieian-Kopaei, M. (2015). Herbal versus synthetic drugs; beliefs and facts. *Journal of Nephropharmacology, 4*(1), 27–30.

Kelly, S., Bombardieri, M., Humby, F., Ng, N., Marrelli, A., Riahi, S., et al. (2015). Angiogenic gene expression and vascular density are reflected in ultrasonographic features of synovitis in early rheumatoid arthritis: an observational study. *Arthritis Research & Therapy, 17*(1), 58. https://doi.org/10.1186/s13075-015-0567-8

Khayyal, M. T., El-Ghazaly, M. A., Abdallah, D. M., Okpanyi, S. N., Kelber, O., & Weiser, D. (2005). Mechanisms involved in the anti-inflammatory effect of a standardized willow bark extract. *Arzneimittelforschung, 55*(11), 677-687. DOI: 10.1055 / s-0031-1296917

Kim, E. K., Kwon, J. E., Lee, S. Y., Lee, E. J., Moon, S. J., Lee, J., et al. (2018). IL-17-mediated mitochondrial dysfunction impairs apoptosis in rheumatoid arthritis synovial fibroblasts through activation of autophagy. *Cell Death & Disease, 8*(1), e2565-e2565. https://doi.org/10.1038/cddis.2016.490

Kim, K. W., Cho, M. L., Lee, S. H., Oh, H. J., Kang, C. M., Ju, J. H., et al. (2007). Human rheumatoid synovial fibroblasts promote osteoclastogenic activity by activating RANKL via TLR-2 and TLR-4 activation. *Immunology Letters, 110*(1), 54-64. https://doi.org/10.1016/j.imlet.2007.03.004

Kinne, R. W., Boehm, S., Iftner, T., Aigner, T., Vornehm, S., Weseloh, G., et al. (1995). Synovial fibroblast-like cells strongly express jun-B and C-fos proto-oncogenes in rheumatoid-and osteoarthritis. *Scandinavian Journal of Rheumatology, 24*(supplement 101), 121-125. https://doi.org/10.3109/03009749509100913

Kłak, A., Paradowska-Gorycka, A., Kwiatkowska, B., & Raciborski, F. (2016). Personalized medicine in rheumatology. *Reumatologia, 54*(4), 177–186. https://doi.org/10.5114/reum.2016.62472

Kleinman, H. K., & Martin, G. R. (2005). Matrigel: basement membrane matrix with biological activity. In *Seminars in Cancer Biology, 15*(5), 378-386. https://doi.org/10.1016/j.semcancer.2005.05.004

Kobayashi, H., & De Mejía, E. (2005). The genus *Ardisia*: a novel source of health-promoting compounds and phytopharmaceuticals. *Journal of Ethnopharmacology, 96*(3), 347-354. https://doi.org/10.1016/j.jep.2004.09.037

Koch, A. E., Harlow, L. A., Haines, G. K., Amento, E. P., Unemori, E. N., Wong, W. L., et al. (1994). Vascular endothelial growth factor. A cytokine modulating endothelial function in rheumatoid arthritis. *The Journal of Immunology, 152*(8), 4149-4156.

Kong, X., Zhang, Y., Liu, C., Guo, W., Li, X., Su, X., et al. (2013). Anti-angiogenic effect of triptolide in rheumatoid arthritis by targeting angiogenic cascade. *PLoS One, 8*(10), e77513. https://doi.org/10.1371/journal.pone.0077513

Konisti, S., Kiriakidis, S., & Paleolog, E. M. (2012). Hypoxia—a key regulator of angiogenesis and inflammation in rheumatoid arthritis. *Nature Reviews Rheumatology*, *8*(3), 153. doi:10.1038/nrrheum.2011.205

Konttinen, Y. T., Seitsalo, S., Lehto, M., & Santavirta, S. (2005). Current management: Management of rheumatic diseases in the era of biological anti-rheumatic drugs. *Acta Orthopaedica, 76*(5), 614-619. https://doi.org/10.1080/17453670510041673

Korb, A., Tohidast-Akrad, M., Cetin, E., Axmann, R., Smolen, J., & Schett, G. (2006). Differential tissue expression and activation of p38 MAPK α, β, γ, and δ isoforms in rheumatoid arthritis. *Arthritis & Rheumatism, 54*(9), 2745-2756. DOI 10.1002/art.22080

Korb-Pap, A., Bertrand, J., Sherwood, J., & Pap, T. (2016). Stable activation of fibroblasts in rheumatic arthritis—causes and consequences. *Rheumatology, 55*(supplement 2), ii64-ii67. https://doi.org/10.1093/rheumatology/kew347

Kozanidou, V. I., Theocharis, A. D., Georgiadis, A., Voulgari, P. V., Drosos, A. A., & Karamanos, N. K. (2005). Signal transduction by IL-2 and its receptors as target in treatment of rheumatoid arthritis. *Current Drug Targets-Immune, Endocrine & Metabolic Disorders, 5*(1), 41-50. https://doi.org/10.2174/1568008053174741

Kramer, N., Walzl, A., Unger, C., Rosner, M., Krupitza, G., Hengstschläger, M., et al. (2013). *In vitro* cell migration and invasion assays. *Mutation Research/Reviews in Mutation Research, 752*(1), 10-24. https://doi.org/10.1016/j.mrrev.2012.08.001

Krause, J., & Tobin, G. (2013). Discovery, development, and regulation of natural products. *Using old solutions to new problems-natural drug discovery in the 21st century, 1*, 1-35. http://dx.doi.org/10.5772/56424

Kumar, S. J., Prasad, S. R., Banerjee, R., Agarwal, D. K., Kulkarni, K. S., & Ramesh, K. V. (2017). Green solvents and technologies for oil extraction from oilseeds. *Chemistry Central Journal, 11*(1), 9. DOI 10.1186/s13065-017-0238-8

Kuncha, M., Naidu, V. G. M., Sahu, B. D., Gadepalli, S. G., & Sistla, R. (2014). Curcumin potentiates the anti-arthritic effect of prednisolone in Freund's complete adjuvant-induced arthritic rats. *Journal of Pharmacy and Pharmacology, 66*(1), 133-144. https://doi.org/10.1111/jphp.12156

Kuptniratsaikul, V., Dajpratham, P., Taechaarpornkul, W., Buntragulpoontawee, M., Lukkanapichonchut, P., Chootip, C., et al. (2014). Efficacy and safety of Curcuma domestica extracts compared with ibuprofen in patients with knee osteoarthritis: a multicenter study. *Clinical Interventions in Aging, 9*, 451–458. https://doi.org/10.2147/CIA.S58535

Kurien, B. T., & Scofield, R. H. (2015). Western blotting: an introduction. In *Western Blotting* (pp. 17-30). Humana Press, New York, NY. DOI 10.1007/978-1-4939-2694-7_5

Laborde, C. M., Castro-Santos, P., & Díaz-Peña, R. (2020). Contribution of multiplex immunoassays to rheumatoid arthritis management: From biomarker discovery to personalized medicine. *Journal of Personalized Medicine, 10*(4), 202. doi:10.3390/jpm10040202

Lafka, T. I., Lazou, A. E., Sinanoglou, V. J., & Lazos, E. S. (2013). Phenolic extracts from wild olive leaves and their potential as edible oils antioxidants. *Foods, 2*(1), 18-31. doi:10.3390/foods2010018

Lafyatis, R., Remmers, E. F., Roberts, A. B., Yocum, D. E., Sporn, M. B., & Wilder, R. L. (1989). Anchorage-independent growth of synoviocytes from arthritic and normal joints. Stimulation by exogenous platelet-derived growth factor and inhibition by transforming growth factor-beta and retinoids. *The Journal of Clinical Investigation, 83*(4), 1267-1276. https://doi.org/10.1172/JCI114011.

Langdon, K., & Haleagrahara, N. (2018). Regulatory T-cell dynamics with abatacept treatment in rheumatoid arthritis. *International Reviews of Immunology, 37*(4), 206-214. https://doi.org/10.1080/08830185.2018.1465943

Laragione, T., & Gulko, P. S. (2010). mTOR regulates the invasive properties of synovial fibroblasts in rheumatoid arthritis. *Molecular Medicine, 16*(9), 352-358. https://doi.org/10.2119/molmed.2010.00049

Lau, M. F., Roslida, A. H., Sabrina, S., & Nhareet, S. M. (2009). Anti-inflammatory and anti-pyretic effects of hexane fraction of *Ardisia crispa* Thunb. DC. *Pharmacologyonline, 3,* 29-39.

Law, S. T., & Taylor, P. C. (2019). Role of biological agents in treatment of rheumatoid arthritis. *Pharmacological Research, 150*, 104497. https://doi.org/10.1016/j.phrs.2019.104497

Lawson, B. R., Belkowski, S. M., Whitesides, J. F., Davis, P., & Lawson, J. W. (2007). Immunomodulation of murine collagen-induced arthritis by N, N-dimethylglycine and a preparation of *Perna canaliculus*. *BMC Complementary and Alternative Medicine, 7*(1), 1-9. https://doi.org/10.1186/1472-6882-7-20

Lazarovici, P., Lahiani, A., Gincberg, G., Haham, D., Fluksman, A., Benny, O., et al. (2018). Nerve growth factor-induced angiogenesis: 1. Endothelial cell tube formation assay. In *Neurotrophic Factors* (pp. 239-250). Humana Press, New York, NY. https://doi.org/10.1007/978-1-4939-7571-6_18

Leblond, A., Allanore, Y., & Avouac, J. (2017). Targeting synovial neoangiogenesis in rheumatoid arthritis. *Autoimmunity Reviews, 16*(6), 594-601. https://doi.org/10.1016/j.autrev.2017.04.005

Lee, A., Choi, S. J., Park, K., Park, J. W., Kim, K., Choi, K., et al. (2013). Detection of active matrix metalloproteinase-3 in serum and fibroblast-like synoviocytes of collagen-induced arthritis mice. *Bioconjugate Chemistry, 24*(6), 1068-1074. https://doi.org/10.1021/bc4001273

Lee, I. S., Cho, D. H., Kim, K. S., Kim, K. H., Park, J., Kim, Y., et al. (2018). Anti-inflammatory effects of embelin in A549 cells and human asthmatic airway epithelial tissues. *Immunopharmacology and immunotoxicology, 40*(1), 83-90. https://doi.org/10.1080/08923973.2017.1414836

Lee, J., Hong, Y. S., Jeong, J. H., Yang, E. J., Jhun, J. Y., Park, M. K., et al. (2013). Coenzyme Q10 ameliorates pain and cartilage degradation in a rat model of osteoarthritis by regulating nitric oxide and inflammatory cytokines. *PLoS One, 8*(7), e69362. https://doi.org/10.1371/journal.pone.0069362

Lee, S. Y., Kwok, S. K., Son, H. J., Ryu, J. G., Kim, E. K., Oh, H. J., et al. (2013). IL-17-mediated Bcl-2 expression regulates survival of fibroblast-like synoviocytes in rheumatoid arthritis through STAT3 activation. *Arthritis Research & Therapy, 15*(1), 1-10. https://doi.org/10.1186/ar4179

Lefèvre, S., Knedla, A., Tennie, C., Kampmann, A., Wunrau, C., Dinser, R., et al. (2009). Synovial fibroblasts spread rheumatoid arthritis to unaffected joints. *Nature Medicine, 15*(12), 1414-1420. https://doi.org/10.1038/nm.2050

Levieux, D., & Venien, A. (1994). Rapid, sensitive two-site ELISA for detection of cows' milk in goats' or ewes' milk using monoclonal antibodies. *Journal of Dairy Research, 61*(1), 91-99. doi:10.1017/S0022029900028089

Li, G. Q., Zhang, Y., Liu, D., Qian, Y. Y., Zhang, H., Guo, S. Y., et al. (2013). PI3 kinase/Akt/HIF-1α pathway is associated with hypoxia-induced epithelial–mesenchymal transition in fibroblast-like synoviocytes of rheumatoid arthritis. *Molecular and Cellular Biochemistry, 372*(1-2), 221-231. https://doi.org/10.1007/s11010-012-1463-z

Li, M., Wei, S. Y., Xu, B., Guo, W., Liu, D. L., Cui, J. R., et al. (2008). Pro-apoptotic and microtubule-disassembly effects of ardisiacrispin (A+ B), triterpenoid saponins from *Ardisia crenata* on human hepatoma Bel-7402 cells. *Journal of Asian Natural Products Research, 10*(8), 729-736. https://doi.org/10.1080/10286020802016198

Li, Q., Li, W., Hui, L. P., Zhao, C. Y., He, L., & Koike, K. (2012). 13, 28-Epoxy triterpenoid saponins from *Ardisia japonica* selectively inhibit proliferation of liver cancer cells without affecting normal liver cells. *Bioorganic & Medicinal Chemistry Letters, 22*(19), 6120-6125. https://doi.org/10.1016/j.bmcl.2012.08.027

Li, X., Kim, K. W., Cho, M. L., Ju, J. H., Kang, C. M., Oh, H. J., et al. (2010). IL-23 induces receptor activator of NF-κB ligand expression in fibroblast-like synoviocytes via STAT3 and NF-κB signal pathways. *Immunology Letters, 127*(2), 100-107. https://doi.org/10.1016/j.imlet.2009.10.012

Li, Y., Wu, S., Li, Y., Jiang, S., Lin, T., Xia, L., et al. (2016). Interleukin-35 (IL-35) inhibits proliferation and promotes apoptosis of fibroblast-like synoviocytes isolated from mice with collagen-induced arthritis. *Molecular Biology Reports, 43*(9), 947-956. DOI:10.1007/s11033-016-4034-7

Li, Y., Yang, B., Bai, J. Y., Xia, S., Mao, M., Li, X., et al. (2019). The roles of synovial hyperplasia, angiogenesis and osteoclastogenesis in the protective effect of apigenin on collagen-induced arthritis. *International Immunopharmacology, 73*, 362-369. https://doi.org/10.1016/j.intimp.2019.05.024

Lim, W. J. (2017). *Antiangiogenic effect of Ardisia crispa root hexane extract mediated via its angiogenic signaling cascades*. (Unpublished master dissertation). Universiti Putra Malaysia, Malaysia.

Lin, D., Xiao, M., Zhao, J., Li, Z., Xing, B., Li, X., et al. (2016). An overview of plant phenolic compounds and their importance in human nutrition and management of type 2 diabetes. *Molecules, 21*(10), 1374. https://doi.org/10.3390/molecules21101374

Lin, J. X., & Leonard, W. J. (2000). The role of Stat5a and Stat5b in signaling by IL-2 family cytokines. *Oncogene,* 19(21), 2566-2576. https://doi.org/10.1038/sj.onc.1203523

Lin, J., Wei, L., Xu, W., Hong, Z., Liu, X., & Peng, J. (2011). Effect of *Hedyotis Diffusa Willd* extract on tumor angiogenesis. *Molecular Medicine Reports, 4*(6), 1283-1288. DOI: 10.3892/mmr.2011.577

Lin, N., Sato, T., & Ito, A. (2001). Triptolide, a novel diterpenoid triepoxide from *Tripterygium wilfordii* Hook. f., suppresses the production and gene expression of pro–matrix metalloproteinases 1 and 3 and augments those of tissue inhibitors of metalloproteinases 1 and 2 in human synovial fibroblasts. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology, 44*(9), 2193-2200. https://doi.org/10.1002/1529-0131(200109)44:9<2193::AID-ART373>3.0.CO;2-5

Littlejohn, E. A., & Monrad, S. U. (2018). Early Diagnosis and Treatment of Rheumatoid Arthritis. *Primary Care, 45*(2), 237-255. DOI: 10.1016/j.pop.2018.02.010

Liu, C., Kong, X., Li, X., Guo, W., Zhang, C., Sun, Y., et al. (2013). Wen Luo Yin inhibits angiogenesis in collagen-induced arthritis rat model and *in vitro.*

Journal of Ethnopharmacology, 149(2), 478-489. https://doi.org/10.1016/j.jep.2013.07.002

Liu, C., Zhang, Y., Kong, X., Zhu, L., Pang, J., Xu, Y., et al. (2013). Triptolide prevents bone destruction in the collagen-induced arthritis model of rheumatoid arthritis by targeting RANKL/RANK/OPG signal pathway. *Evidence-Based Complementary and Alternative Medicine,* 2013. https://doi.org/10.1155/2013/626038

Liu, H., Zhao, F., Yang, R., Wang, M., Zheng, M., Zhao, Y., et al. (2009). Dimeric 1, 4-benzoquinone derivatives and a resorcinol derivative from *Ardisia gigantifolia*. *Phytochemistry, 70*(6), 773-778. https://doi.org/10.1016/j.phytochem.2009.04.004

Liu, N., Chen, L., & Cai, N. (2015). Celecoxib attenuates retinal angiogenesis in a mouse model of oxygen-induced retinopathy. *International Journal of Clinical and Experimental Pathology, 8*(5), 4990-4998.

Liu, S., Li, Y., Xia, L., Shen, H., & Lu, J. (2019). IL-35 prevent bone loss through promotion of bone formation and angiogenesis in rheumatoid arthritis. *Clinical and Experimental Rheumatology, 37*, 820-825.

Liu, T., Zhang, L., Joo, D., & Sun, S. C. (2017). NF-κB signaling in inflammation. *Signal Transduction and Targeted Therapy, 2*(1), 1-9. https://doi.org/10.1038/sigtrans.2017.23

Liu, W., Wu, Y. H., Zhang, L., Xue, B., Wang, Y., Liu, B., et al. (2018). MicroRNA-146a suppresses rheumatoid arthritis fibroblast-like synoviocytes proliferation and inflammatory responses by inhibiting the TLR4/NF-kB signaling. *Oncotarget, 9*(35), 23944–23959. https://doi.org/10.18632/oncotarget.24050

Lo Iacono, N., Pangrazio, A., Abinun, M., Bredius, R., Zecca, M., Blair, H. C., et al. (2013). RANKL cytokine: from pioneer of the osteoimmunology era to cure for a rare disease. *Clinical and Developmental Immunology, 2013*. http://dx.doi.org/10.1155/2013/412768

Lu, Q., Lu, S., Gao, X., Luo, Y., Tong, B., Wei, Z., et al. (2012). Norisoboldine, an alkaloid compound isolated from *Radix Linderae*, inhibits synovial angiogenesis in adjuvant-induced arthritis rats by moderating Notch1 pathway-related endothelial tip cell phenotype. *Experimental Biology and Medicine, 237*(8), 919-932. doi: 10.1258/ebm.2012.011416

Lu, Y., Wang, W. J., Leng, J. H., Cheng, L. F., Feng, L., & Yao, H. P. (2008). Inhibitory effect of triptolide on interleukin-18 and its receptor in rheumatoid arthritis synovial fibroblasts. *Inflammation Research, 57*(6), 260-265. DOI:10.1007/s00011-007-7128-9

Lundstedt, S., Bandowe, B. A. M., Wilcke, W., Boll, E., Christensen, J. H., Vila, J., et al. (2014). First intercomparison study on the analysis of

oxygenated polycyclic aromatic hydrocarbons (oxy-PAHs) and nitrogen heterocyclic polycyclic aromatic compounds (N-PACs) in contaminated soil. *TrAC Trends in Analytical Chemistry, 57*, 83-92. https://doi.org/10.1016/j.trac.2014.01.007

Lv, Q. W., Zhang, W., Shi, Q., Zheng, W. J., Li, X., Chen, H., et al. (2015). Comparison of *Tripterygium wilfordii* Hook F with methotrexate in the treatment of active rheumatoid arthritis (TRIFRA): a randomised, controlled clinical trial. *Annals of the Rheumatic Diseases, 74*(6), 1078-1086. DOI:10.1136/annrheumdis-2013-204807

Ma, J. D., Jing, J., Wang, J. W., Yan, T., Li, Q. H., Mo, Y. Q., et al. (2019). A novel function of artesunate on inhibiting migration and invasion of fibroblast-like synoviocytes from rheumatoid arthritis patients. *Arthritis Research & Therapy, 21*(1), 153. https://doi.org/10.1186/s13075-019-1935-6

Ma, S. N., Zaman Huri, H., & Yahya, F. (2019). Drug-related problems in patients with rheumatoid arthritis. *Therapeutics and Clinical Risk Management, 15,* 505–524. https://doi.org/10.2147/TCRM.S194921

MacDonald, I. J., Liu, S. C., Su, C. M., Wang, Y. H., Tsai, C. H., & Tang, C. H. (2018). Implications of angiogenesis involvement in arthritis. *International Journal of Molecular Sciences, 19*(7), 2012. doi:10.3390/ijms19070012

MacFarlane, L. A., & Todd, D. J. (2014). Kinase inhibitors: the next generation of therapies in the treatment of rheumatoid arthritis. *International Journal of Rheumatic Diseases, 17*(4), 359-368. https://doi.org/10.1111/1756-185X.12293

Madhu, K. D., & Harindran, J. (2014). Antiarthritic potential of *Ocimum gratissimum* L. in collagen induced arthritic Sprague-Dawley rats. *Biomedicine & Aging Pathology, 4*(3), 191-196. http://dx.doi.org/10.1016/j.biomag.2014.02.003

Makarov, S. S. (2001). NF-κB in rheumatoid arthritis: a pivotal regulator of inflammation, hyperplasia, and tissue destruction. *Arthritis Research & Therapy, 3*(4), 1-7. https://doi.org/10.1186/ar300

Malemud, C. J. (2007). Growth hormone, VEGF and FGF: involvement in rheumatoid arthritis. *Clinica Chimica Acta, 375*(1-2), 10-19. https://doi.org/10.1016/j.cca.2006.06.033

Malemud, C. J. (2013). Intracellular signaling pathways in rheumatoid arthritis. *Journal of Clinical & Cellular Immunology, 4*, 160. doi: 10.4172/2155-9899.1000160

Malemud, C. J. (2015). The PI3K/Akt/PTEN/mTOR pathway: a fruitful target for inducing cell death in rheumatoid arthritis?. *Future Medicinal Chemistry, 7*(9), 1137-1147. https://doi.org/10.4155/fmc.15.55

Malemud, C. J. (2018). The role of the JAK/STAT signal pathway in rheumatoid arthritis. *Therapeutic Advances in Musculoskeletal Disease*, *10*(5-6), 117-127. https://doi.org/10.1177/1759720X18776224

Mali, S. M., Sinnathambi, A., Kapase, C. U., Bodhankar, S. L., & Mahadik, K. R. (2011). Anti-arthritic activity of standardised extract of *Phyllanthus amarus* in Freund's complete adjuvant induced arthritis. *Biomedicine & Aging Pathology, 1*(3), 185-190. doi:10.1016/j.biomag.2011.09.004

Malone, M., & Tsai, G. (2018). The evidence for herbal and botanical remedies, Part 2. *Clinician Reviews, 28*(5), 22-28.

Mamat, N., Jamal, J. A., Jantan, I., & Husain, K. (2014). Xanthine oxidase inhibitory and DPPH radical scavenging activities of some Primulaceae species. *Sains Malaysiana, 43*(12), 1827-1833.

Management of rheumatoid arthritis. (2019). Malaysia Health Technology Assessment Section (MaHTAS), Putrajaya, Malaysia.

Mao, S. Z., & Hu, C. M. (2013). *Ardisia rubricaulis* sp. nov.(Primulaceae) from Guangxi, China. *Phytotaxa, 138*(1), 39-42. http://dx.doi.org/10.11646/phytotaxa.138.1.5

Marchetti, D., Reiland, J., Erwin, B., & Roy, M. (2003). Inhibition of heparanase activity and heparanase-induced angiogenesis by suramin analogues. *International Journal of Cancer, 104*(2), 167-174. DOI 10.1002/ijc.10930

Markovics, A., Ocskó, T., Katz, R. S., Buzás, E. I., Glant, T. T., & Mikecz, K. (2016). Immune recognition of citrullinated proteoglycan aggrecan epitopes in mice with proteoglycan-induced arthritis and in patients with rheumatoid arthritis. *PloS One, 11*(7), e0160284. https://doi.org/10.1371/journal.pone.0160284

Martínez, M. J. A., & Benito, P. B. (2005). Biological activity of quinones. In *Studies in Natural Products Chemistry, 30*, 303-366. Elsevier. https://doi.org/10.1016/S1572-5995(05)80036-5

Martins, T. B., Welch, R. J., Hill, H. R., & Litwin, C. M. (2009). Comparison of a multiplexed herpes simplex virus type-specific immunoglobulin G serology assay to immunoblot, Western blot, and enzyme-linked immunosorbent assays. *Clinical and Vaccine Immunology, 16*(1), 55-60. doi:10.1128/CVI.00351-08

Mbiantcha, M., Almas, J., Shabana, S. U., Nida, D., & Aisha, F. (2017). Anti-arthritic property of crude extracts of *Piptadeniastrum africanum* (Mimosaceae) in complete Freund's adjuvant-induced arthritis in rats.

BMC Complementary and Alternative Medicine, 17(1), 1-16. https://doi.org/10.1186/s12906-017-1623-5

Mc Ardle, A., Flatley, B., Pennington, S. R., & FitzGerald, O. (2015). Early biomarkers of joint damage in rheumatoid and psoriatic arthritis. *Arthritis Research & Therapy, 17*(1), 141. https://doi.org/10.1186/s13075-015-0652-z

McNamee, K., Williams, R., & Seed, M. (2015). Animal models of rheumatoid arthritis: how informative are they?. *European Journal of Pharmacology, 759*, 278-286. https://doi.org/10.1016/j.ejphar.2015.03.047

Melincovici, C. S., Bosca, A. B., Susman, S., Marginean, M., Mihu, C., Istrate, M., et al. (2018). Vascular endothelial growth factor (VEGF)-key factor in normal and pathological angiogenesis. *Romanian Journal of Morphology and Embryology, 59*(2), 455-467.

Mellado, M., Martínez-Muñoz, L., Cascio, G., Lucas, P., Pablos, J. L., & Rodríguez-Frade, J. M. (2015). T cell migration in rheumatoid arthritis. *Frontiers in Immunology, 6*, 384. https://doi.org/10.3389/fimmu.2015.00384

Mitra, A., Raychaudhuri, S. K., & Raychaudhuri, S. P. (2012). IL-22 induced cell proliferation is regulated by PI3K/Akt/mTOR signaling cascade. *Cytokine, 60*(1), 38-42. https://doi.org/10.1016/j.cyto.2012.06.316

Moeenfard, M., Cortez, A., Machado, V., Costa, R., Luís, C., Coelho, P., et al. (2016). Anti-angiogenic properties of Cafestol and Kahweol palmitate diterpene esters. *Journal of Cellular Biochemistry, 117*(12), 2748-2756. DOI 10.1002/jcb.25573

Mokotedi, L., Millen, A. M., Mogane, C., Gomes, M., Woodiwiss, A. J., Norton, G. R., et al. (2019). Associations of inflammatory markers and vascular cell adhesion molecule-1 with endothelial dysfunction in collagen-induced arthritis. *European Journal of Pharmacology, 865*, 172786. https://doi.org/10.1016/j.ejphar.2019.172786

Moore, A. R. (2003). Collagen-induced arthritis. In *Inflammation Protocols* (pp. 175-179). Humana Press. https://doi.org/10.1385/1-59259-374-7:175

Mori, T., Miyamoto, T., Yoshida, H., Asakawa, M., Kawasumi, M., Kobayashi, T., et al. (2011). IL-1β and TNFα-initiated IL-6–STAT3 pathway is critical in mediating inflammatory cytokines and RANKL expression in inflammatory arthritis. *International Immunology, 23*(11), 701-712. https://doi.org/10.1093/intimm/dxr077

Moser, C., Ruemmele, P., Gehmert, S., Schenk, H., Kreutz, M. P., Mycielska, M. E., et al. (2012). STAT5b as molecular target in pancreatic cancer—inhibition of tumor growth, angiogenesis, and metastases. *Neoplasia, 14*(10), 915-925. DOI 10.1593/neo.12878

Mossiat, C., Laroche, D., Prati, C., Pozzo, T., Demougeot, C., & Marie, C. (2015). Association between arthritis score at the onset of the disease and long-term locomotor outcome in adjuvant-induced arthritis in rats. *Arthritis Research & Therapy, 17*(1), 184. https://doi.org/10.1186/s13075-015-0700-8

Mu, L. H., Feng, J. Q., & Liu, P. (2013). A new bergenin derivative from the rhizome of *Ardisia gigantifolia*. *Natural Product Research, 27*(14), 1242-1245. https://doi.org/10.1080/14786419.2012.724415

Mu, N., Gu, J., Huang, T., Zhang, C., Shu, Z., Li, M., et al. (2016). A novel NF-κB/YY1/microRNA-10a regulatory circuit in fibroblast-like synoviocytes regulates inflammation in rheumatoid arthritis. *Scientific Reports, 6*(1), 1-14. https://doi.org/10.1038/srep20059

Mu, X., Shi, W., Sun, L., Li, H., Jiang, Z., & Zhang, L. (2012). Pristimerin, a triterpenoid, inhibits tumor angiogenesis by targeting VEGFR2 activation. *Molecules, 17*(6), 6854-6868. https://doi.org/10.3390/molecules17066854

Muhamad, Z., & Mustafa, A. M. (1994). Plants in traditional medicine. Traditional Malay medicinal plants, 104. Kuala Lumpur (MY): 765 Fajar Bakti; 1994 p. 39-41

Müller-Ladner, U., Kriegsmann, J., Franklin, B. N., Matsumoto, S., Geiler, T., Gay, R. E., et al. (1996). Synovial fibroblasts of patients with rheumatoid arthritis attach to and invade normal human cartilage when engrafted into SCID mice. *The American Journal of Pathology, 149*(5), 1607.

Muraoka, S., Kusunoki, N., Takahashi, H., Tsuchiya, K., & Kawai, S. (2013). Leptin stimulates interleukin-6 production via janus kinase 2/signal transducer and activator of transcription 3 in rheumatoid synovial fibroblasts. *Clinical and Experimental Rheumatology, 31*(4), 589-595.

Muslim, N. S., Nassar, Z. D., Aisha, A. F., Shafaei, A., Idris, N., Majid, A., & Ismail, Z. (2012). Antiangiogenesis and antioxidant activity of ethanol extracts of *Pithecellobium jiringa*. *BMC Complementary and Alternative Medicine, 12*(1), 1-10. https://doi.org/10.1186/1472-6882-12-210

Nanjundaiah, S. M., Venkatesha, S. H., Yu, H., Tong, L., Stains, J. P., & Moudgil, K. D. (2012). Celastrus and its bioactive celastrol protect against bone damage in autoimmune arthritis by modulating osteoimmune cross-talk. *Journal of Biological Chemistry, 287*(26), 22216-22226. DOI 10.1074/jbc.M112.356816

Narayanaswamy, R., Shymatak, M., Chatterjee, S., Wai, L. K., & Arumugam, G. (2014). Inhibition of angiogenesis and nitric oxide synthase (NOS), by embelin & vilangin using *in vitro, in vivo* & *in silico* studies. *Advanced Pharmaceutical Bulletin, 4*(Supplement 2), 543–548. https://doi.org/10.5681/apb.2014.080

Narazaki, M., Tanaka, T., & Kishimoto, T. (2017). The role and therapeutic targeting of IL-6 in rheumatoid arthritis. *Expert Review of Clinical Immunology, 13*(6), 535-551. https://doi.org/10.1080/1744666X.2017.1295850

Nguyen, D. X., Cotton, A., Attipoe, L., Ciurtin, C., Doré, C. J., & Ehrenstein, M. R. (2018). Regulatory T cells as a biomarker for response to adalimumab in rheumatoid arthritis. *Journal of Allergy and Clinical Immunology, 142*(3), 978-980. https://doi.org/10.1016/j.jaci.2018.04.026

Noedl, H., Yingyuen, K., Laoboonchai, A., Fukuda, M., Sirichaisinthop, J., & Miller, R. S. (2006). Sensitivity and specificity of an antigen detection ELISA for malaria diagnosis. *The American Journal of Tropical Medicine and Hygiene, 75*(6), 1205-1208.

Nolan, J. P., & Mandy, F. (2006). Multiplexed and microparticle-based analyses: Quantitative tools for the large-scale analysis of biological systems. *Cytometry Part A, 69*(5), 318-325. https://doi.org/10.1002/cyto.a.20266

Noort, A. R., Tak, P. P., & Tas, S. W. (2015). Non-canonical NF-κB signaling in rheumatoid arthritis: Dr Jekyll and Mr Hyde?. *Arthritis Research & Therapy, 17*(1), 1-10. https://doi.org/10.1186/s13075-015-0527-3

Nordin, M. L., Abdul Kadir, A., Zakaria, Z. A., Othman, F., Abdullah, R., & Abdullah, M. N. H. (2017). Cytotoxicity and apoptosis induction of *Ardisia crispa* and its solvent partitions against *Mus musculus* mammary carcinoma cell line (4T1). *Evidence-Based Complementary and Alternative Medicine, 2017*. https://doi.org/10.1155/2017/9368079

Nordin, M. L., Kadir, A. A., Zakaria, Z. A., Abdullah, R., & Abdullah, M. N. H. (2018). *In vitro* investigation of cytotoxic and antioxidative activities of *Ardisia crispa* against breast cancer cell lines, MCF-7 and MDA-MB-231. *BMC Complementary and Alternative Medicine, 18*(1), 1-10. https://doi.org/10.1186/s12906-018-2153-5

Nowak-Sliwinska, P., Alitalo, K., Allen, E., Anisimov, A., Aplin, A. C., Auerbach, R., et al. (2018). Consensus guidelines for the use and interpretation of angiogenesis assays. *Angiogenesis, 21*(3), 425-532. https://doi.org/10.1007/s10456-018-9613-x

O'Donnell, J. S., Massi, D., Teng, M. W., & Mandala, M. (2018). PI3K-AKT-mTOR inhibition in cancer immunotherapy, redux. In *Seminars in Cancer Biology*, *48*, 91-103. Academic Press. https://doi.org/10.1016/j.semcancer.2017.04.015

Ogawa, H., & Natori, S. (1968). Hydroxybenzoquinones from myrsinaceae plants-II.: Distribution among myrsinaceae plants in Japan. *Phytochemistry, 7*(5), 773-782. https://doi.org/10.1016/S0031-9422(00)84831-1

Ogoina, D. (2011). Fever, fever patterns and diseases called 'fever'–a review. *Journal of Infection and Public Health, 4*(3), 108-124. https://doi.org/10.1016/j.jiph.2011.05.002

Ohori, M., Kinoshita, T., Okubo, M., Sato, K., Yamazaki, A., Arakawa, H., et al. (2005). Identification of a selective ERK inhibitor and structural determination of the inhibitor–ERK2 complex. *Biochemical and Biophysical Research Communications, 336*(1), 357-363. https://doi.org/10.1016/j.bbrc.2005.08.082

Oike, T., Sato, Y., Kobayashi, T., Miyamoto, K., Nakamura, S., Kaneko, Y., et al. (2017). Stat3 as a potential therapeutic target for rheumatoid arthritis. *Scientific Reports, 7*(1), 1-9. https://doi.org/10.1038/s41598-017-11233-w

Okazaki, Y., Sawada, T., Nagatani, K., Komagata, Y., Inoue, T., Muto, S., et al. (2005). Effect of nuclear factor-kappaB inhibition on rheumatoid fibroblast-like synoviocytes and collagen induced arthritis. *The Journal of Rheumatology, 32*(8), 1440-1447.

Oliveira, P. G., Farinon, M., Sanchez-Lopez, E., Miyamoto, S., & Guma, M. (2019). Fibroblast-like synoviocytes glucose metabolism as a therapeutic target in rheumatoid arthritis. *Frontiers in Immunology, 10*, 1743. https://doi.org/10.3389/fimmu.2019.01743

Olivieri, M., Gerardi, M. C., Spinelli, F. R., & Di Franco, M. (2012). A Focus on the Diagnosis of Early Rheumatoid Arthritis. *International Journal of Clinical Medicine, 3*, 650-654. http://dx.doi.org/10.4236/ijcm.2012.37116

Olson, J. M., Haas, A. W., Lor, J., McKee, H. S., & Cook, M. E. (2017). A comparison of the anti-inflammatory effects of cis-9, trans-11 conjugated linoleic acid to celecoxib in the collagen-induced arthritis model. *Lipids, 52*(2), 151-159. DOI 10.1007/s11745-016-4228-8

Ong, H. C. (2004). Tumbuhan liar: khasiat ubatan & kegunaan lain. Utusan Publications.

Ong, H. C., Faezah, A. W., & Milow, P. (2012). Medicinal plants used by the jah hut orang asli at kampung pos penderas, Pahang, Malaysia. *Studies on Ethno-Medicine, 6*(1), 11-15. https://doi.org/10.1080/09735070.2012.11886414

Ong, Y. S., Saiful Yazan, L., Ng, W. K., Noordin, M. M., Sapuan, S., Foo, J. B., et al. (2016). Acute and subacute toxicity profiles of thymoquinone-loaded nanostructured lipid carrier in BALB/c mice. *International Journal of Nanomedicine, 11*, 5905–5915. https://doi.org/10.2147/IJN.S114205

Orr, C., Vieira-Sousa, E., Boyle, D. L., Buch, M. H., Buckley, C. D., Cañete, J. D., et al. (2017). Synovial tissue research: a state-of-the-art review.

Nature Reviews Rheumatology, 13(8), 463-475. https://doi.org/10.1038/nrrheum.2017.115

O'Shea, J. J., & Plenge, R. (2012). JAK and STAT signaling molecules in immunoregulation and immune-mediated disease. *Immunity, 36*(4), 542-550. https://doi.org/10.1016/j.immuni.2012.03.014

Osiri, M., & Maetzel, A. (2010). The economic burden of rheumatoid arthritis: Asia/Thailand perspective. In Handbook of disease burdens and quality of life measures (pp. 1733-1750). Springer Science+ Business Media New York.

Ostrowska, M., Maśliński, W., Prochorec-Sobieszek, M., Nieciecki, M., & Sudoł-Szopińska, I. (2018). Cartilage and bone damage in rheumatoid arthritis. *Reumatologia, 56*(2), 111–120. https://doi.org/10.5114/reum.2018.75523

Overvad, K., Diamant, B., Holm, L., Hølmer, G., Mortensen, S. A., & Stender, S. (1999). Coenzyme Q 10 in health and disease. *European Journal of Clinical Nutrition, 53*(10), 764-770. https://doi.org/10.1038/sj.ejcn.1600880

Pandya, N. M., Dhalla, N. S., & Santani, D. D. (2006). Angiogenesis—a new target for future therapy. *Vascular Pharmacology, 44*(5), 265-274. https://doi.org/10.1016/j.vph.2006.01.005

Parama, D., Boruah, M., Kumari, Y., Rana, V., Banik, K., Harsha, C., et al. (2020). Diosgenin, a steroidal saponin, and its analogues: Effective therapies against different chronic diseases. *Life Sciences, 260*, 118182. https://doi.org/10.1016/j.lfs.2020.118182

Park, C., Moon, D. O., Choi, I. W., Choi, B. T., Nam, T. J., Rhu, C. H., et al. (2007). Curcumin induces apoptosis and inhibits prostaglandin E2 production in synovial fibroblasts of patients with rheumatoid arthritis. *International Journal of Molecular Medicine, 20*(3), 365-372. https://doi.org/10.3892/ijmm.20.3.365

Pascual-Salcedo, D., Plasencia, C., Ramiro, S., Nuño, L., Bonilla, G., Nagore, D., et al. (2011). Influence of immunogenicity on the efficacy of long-term treatment with infliximab in rheumatoid arthritis. *Rheumatology, 50*(8), 1445-1452. https://doi.org/10.1093/rheumatology/ker124

Patwardhan, B., Warude, D., Pushpangadan, P., & Bhatt, N. (2005). Ayurveda and traditional Chinese medicine: a comparative overview. *Evidence-Based Complementary and Alternative Medicine, 2*(4), 465–473. doi:10.1093/ecam/neh140

Pawar, A., Desai, R. J., Gautam, N., & Kim, S. C. (2020). Risk of admission to hospital for serious infection after initiating tofacitinib versus biologic DMARDs in patients with rheumatoid arthritis: a multidatabase cohort

study. *The Lancet Rheumatology, 2*(2), 84-98. https://doi.org/10.1016/S2665-9913(19)30137-7

Peach, C. J., Mignone, V. W., Arruda, M. A., Alcobia, D. C., Hill, S. J., Kilpatrick, L. E., et al. (2018). Molecular pharmacology of VEGF-A isoforms: binding and signalling at VEGFR2. *International Journal of Molecular Sciences, 19*(4), 1264. https://doi.org/10.3390/ijms19041264

Pei, J., Wang, Y., & Yu, K. (2018). Sensitive determination of quinones by high-performance liquid chromatography–electrospray ionization–tandem mass spectrometry with methanol derivatization. *Analytical Sciences, 34*(3), 335-340. https://doi.org/10.2116/analsci.34.335

Peng, L., Liu, A., Shen, Y., Xu, H. Z., Yang, S. Z., Ying, X. Z., et al. (2013). Antitumor and anti-angiogenesis effects of thymoquinone on osteosarcoma through the NF-κB pathway. *Oncology Reports, 29*(2), 571-578. https://doi.org/10.3892/or.2012.2165

Perry, L. M., & Metzger, J. (1980). Medicinal plants of east and southeast Asia: attributed properties and uses. MIT press.

Phung, M. W., & Dass, C. R. (2006). *In-vitro* and *in-vivo* assays for angiogenesis-modulating drug discovery and development. *Journal of Pharmacy and Pharmacology, 58*(2), 153-160. DOI 10.1211/jpp.58.2.0001

Pietrosimone, K. M., Jin, M., Poston, B., & Liu, P. (2015). Collagen-Induced Arthritis: A model for murine autoimmune arthritis. *Bio-protocol, 5*(20). DOI: 10.21769/bioprotoc.1626

Pober, J. S., & Cotran, R. S. (1990). The role of endothelial cells in inflammation. *Transplantation, 50*(4), 537-544. doi:10.1097/00007890-199010000-0000

Podolak, I., Mynarski, A., Wróbel, D., Grabowska, K., & Galanty, A. (2019). Bioactive benzoquinones content variability in red-berry and white-berry varieties of *Ardisia crenata* Sims. and assessment of cytotoxic activity. *Natural Product Research, 35*(1), 157-161. https://doi.org/10.1080/14786419.2019.1614575

Pompura, S. L., & Dominguez-Villar, M. (2018). The PI3K/AKT signaling pathway in regulatory T-cell development, stability, and function. *Journal of Leukocyte Biology, 103*(6), 1065-1076. DOI: 10.1002/JLB.2MIR0817-349R

Ponce, M. L. (2009). Tube formation: an *in vitro* matrigel angiogenesis assay. In *Angiogenesis Protocols*, 183-188. Humana Press. doi: 10.1007/978-1-59745-241-0_10

Pope, R. M. (2002). Apoptosis as a therapeutic tool in rheumatoid arthritis. *Nature Reviews Immunology, 2*(7), 527-535. https://doi.org/10.1038/nri846

Prabhu, K. S., Achkar, I. W., Kuttikrishnan, S., Akhtar, S., Khan, A. Q., Siveen, K. S., et al. (2018). Embelin: a benzoquinone possesses therapeutic potential for the treatment of human cancer. *Future Medicinal Chemistry, 10*(8), 961-976. https://doi.org/10.4155/fmc-2017-0198

Qi, L. V., Xian-Yang, Z. H. U., Yu-Feng, X. I. A., Yue, D. A. I., & Zhi-Feng, W. E. I. (2015). Tetrandrine inhibits migration and invasion of rheumatoid arthritis fibroblast-like synoviocytes through down-regulating the expressions of Rac1, Cdc42, and RhoA GTPases and activation of the PI3K/Akt and JNK signaling pathways. *Chinese Journal of Natural Medicines, 13*(11), 831-841. https://doi.org/10.1016/S1875-5364(15)30087-X

Qian, X., Zhao, Z., Shang, W., Xu, Z., Zhang, B., & Cai, H. (2018). Serum proteomic analysis of the anti-arthritic effects of sinomenine on rats with collagen-induced arthritis. *Molecular Medicine Reports, 18*(1), 49-58. https://doi.org/10.3892/mmr.2018.8959

Radhakrishnan, N., Gnanamani, A., & Mandal, A. B. (2011). A potential antibacterial agent Embelin, a natural benzoquinone extracted from *Embelia ribes*. *Biology and Medicine, 3*(2), 1-7.

Ramírez, J., Ruíz-Esquide, V., Pomés, I., Celis, R., Cuervo, A., Hernández, M. V., et al. (2014). Patients with rheumatoid arthritis in clinical remission and ultrasound-defined active synovitis exhibit higher disease activity and increased serum levels of angiogenic biomarkers. *Arthritis Research & Therapy, 16*(1), R5. https://doi.org/10.1186/ar4431

Ramírez-Mares, M. V., Fatell, S., Villa-Trevino, S., & de Mejía, E. G. (1999). Protection of extract from leaves of *Ardisia compressa* against benomyl-induced cytotoxicity and genotoxicity in cultured rat hepatocytes. *Toxicology In Vitro, 13*(6), 889-896. https://doi.org/10.1016/S0887-2333(99)00071-5

Ramírez-Mares, M. V., Sánchez-Burgos, J. A., & Hernández-Carlos, B. (2010). Antioxidant, antimicrobial and antitopoisomerase screening of the stem bark extracts of *Ardisia compressa*. *Pakistan Journal of Nutrition, 9*(4), 307-313.

Rana, A. K., Li, Y., Dang, Q., & Yang, F. (2018). Monocytes in rheumatoid arthritis: Circulating precursors of macrophages and osteoclasts and, their heterogeneity and plasticity role in RA pathogenesis. *International Immunopharmacology, 65*, 348-359. https://doi.org/10.1016/j.intimp.2018.10.016

Ranganathan, P. (2008). An update on pharmacogenomics in rheumatoid arthritis with a focus on TNF-blocking agents. *Current Opinion in Molecular Therapeutics, 10*(6), 562-567.

Rau, R. (2014). Glucocorticoid treatment in rheumatoid arthritis. *Expert opinion on pharmacotherapy, 15*(11), 1575-1583. https://doi.org/10.1517/14656566.2014.922955

Razawy, W., Alves, C. H., Molendijk, M., Asmawidjaja, P. S., Mus, A. M. C., & Lubberts, E. (2017). Experimental arthritis mouse models driven by adaptive and/or innate inflammation. In *Inflammation*, 391-410. Humana Press, New York, NY. DOI 10.1007/978-1-4939-6786-5_27

Reslova, N., Michna, V., Kasny, M., Mikel, P., & Kralik, P. (2017). xMAP technology: applications in detection of pathogens. *Frontiers in Microbiology, 8*, 55. https://doi.org/10.3389/fmicb.2017.00055

Rigante, D., Bosco, A., & Esposito, S. (2015). The etiology of juvenile idiopathic arthritis. *Clinical Reviews in Allergy & Immunology, 49*(2), 253-261. https://doi.org/10.1007/s12016-014-8460-9

Roman-Blas, J. A., & Jimenez, S. A. (2006). NF-κB as a potential therapeutic target in osteoarthritis and rheumatoid arthritis. *Osteoarthritis and Cartilage, 14*(9), 839-848. https://doi.org/10.1016/j.joca.2006.04.008

Romão, V. C., & Fonseca, J. E. (2019). Major challenges in rheumatology: Will we ever treat smarter, instead of just harder?. *Frontiers in Medicine, 6*, 144. https://doi.org/10.3389/fmed.2019.00144

Roskoski Jr, R. (2017). Vascular endothelial growth factor (VEGF) and VEGF receptor inhibitors in the treatment of renal cell carcinomas. *Pharmacological Research, 120*, 116-132. https://doi.org/10.1016/j.phrs.2017.03.010

Roslida, A. H. (2004). *Anti-inflammatory and analgesic effects of AC-2 isolated from Ardisia crispa are mediated via COX-2 inhibition*. (Unpublished doctoral dissertation). Universiti Malaya, Malaysia.

Roslida, A. H., Fezah, O., & Yeong, L. T. (2011). Suppression of DMBA/croton oil-induced mouse skin tumor promotion by *Ardisia crispa* root hexane extract. *Asian Pacific Journal of Cancer Prevention, 12*(3), 665-669.

Roslida, A. H., Teh, Y. H., & Kim, K. H. (2009). Evaluation of anti-ulcer activity of *Ardisia crispa* Thunb. DC. *Pharmacognosy Research, 1*(5), 250.

Roslida, A., & Kim, K. (2008). Anti-inflammatory and anti-hyperalgesic effects of *Ardisia crispa* Thunb. DC. *Pharmacognosy Magazine, 4*(16), 262.

Rucker, M. (2011). Quinone Structure; Let's Learn More. Retrieved 25 December 2020 from https://michaelrucker.com/functional-supplements/quinone-structure/

Rui, X., Pan, H. F., Shao, S. L., & Xu, X. M. (2017). Anti-tumor and anti-angiogenic effects of Fucoidan on prostate cancer: Possible JAK-STAT3

pathway. *BMC Complementary and Alternative Medicine, 17*(1), 378. https://doi.org/10.1186/s12906-017-1885-y

Ruiz-Limón, P., Ortega, R., de la Rosa, I. A., del Carmen Abalos-Aguilera, M., Perez-Sanchez, C., Jimenez-Gomez, Y., et al. (2017). Tocilizumab improves the proatherothrombotic profile of rheumatoid arthritis patients modulating endothelial dysfunction, NETosis, and inflammation. *Translational Research, 183*, 87-103. https://doi.org/10.1016/j.trsl.2016.12.003

Ruschitzka, F., Borer, J. S., Krum, H., Flammer, A. J., Yeomans, N. D., Libby, P., et al. (2017). Differential blood pressure effects of ibuprofen, naproxen, and celecoxib in patients with arthritis: the PRECISION-ABPM (Prospective Randomized Evaluation of Celecoxib Integrated Safety Versus Ibuprofen or Naproxen Ambulatory Blood Pressure Measurement) Trial. *European Heart Journal, 38*(44), 3282-3292. https://doi.org/10.1093/eurheartj/ehx508

Sabio, G., & Davis, R. J. (2014). TNF and MAP kinase signalling pathways. *Seminars in Immunology*, *26*(3), 237-245. https://doi.org/10.1016/j.smim.2014.02.009

Sabir, J. S., Omri, A. E., Banaganapalli, B., Al-Shaeri, M. A., Alkenani, N. A., Sabir, M. J., et al. (2019). Dissecting the role of NF-κB protein family and its regulators in rheumatoid arthritis using weighted gene co-expression network. *Frontiers in Genetics, 10,* 1163. https://doi.org/10.3389/fgene.2019.01163

Saibu, M., Sagar, S., Green, I., Ameer, F., & Meyer, M. (2014). Evaluating the cytotoxic effects of novel quinone compounds. *Anticancer Research, 34*(8), 4077-4086.

Saranadasa, M., & Wang, E. S. (2011). Vascular endothelial growth factor inhibition: conflicting roles in tumor growth. *Cytokine, 53*(2), 115-129. https://doi.org/10.1016/j.cyto.2010.06.012

Saxena, P., Sharma, P. K., & Purohit, P. (2020). A journey of celecoxib from pain to cancer. *Prostaglandins & Other Lipid Mediators, 147*, 106379. https://doi.org/10.1016/j.prostaglandins.2019.106379

Scanzello, C. R., Figgie, M. P., Nestor, B. J., & Goodman, S. M. (2006). Perioperative management of medications used in the treatment of rheumatoid arthritis. *HSS Journal: The Musculoskeletal Journal of Hospital for Special Surgery, 2*(2), 141–147. https://doi.org/10.1007/s11420-006-9012-5

Schett, G., Stach, C., Zwerina, J., Voll, R., & Manger, B. (2008). How antirheumatic drugs protect joints from damage in rheumatoid arthritis. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology, 58*(10), 2936-2948. DOI 10.1002/art.23951

Schett, G., Zwerina, J., & Firestein, G. (2008). The p38 mitogen-activated protein kinase (MAPK) pathway in rheumatoid arthritis. *Annals Of The Rheumatic Diseases, 67*(7), 909–916. https://doi.org/10.1136/ard.2007.074278

Schmajuk, G., Trivedi, A. N., Solomon, D. H., Yelin, E., Trupin, L., Chakravarty, E. F., et al. (2011). Receipt of disease-modifying antirheumatic drugs among patients with rheumatoid arthritis in Medicare managed care plans. *Journal of the American Medical Association, 305*(5), 480-486. doi:10.1001/jama.2011.67

Schnitzer, T. J., Kong, S. X., Mitchell, J. H., Mavros, P., Watson, D. J., Pellissier, J. M., et al. (2003). An observational, retrospective, cohort study of dosing patterns for rofecoxib and celecoxib in the treatment of arthritis. *Clinical Therapeutics, 25*(12), 3162-3172. https://doi.org/10.1016/S0149-2918(03)90100-7

Schroeder, M., Viezens, L., Fuhrhop, I., Rüther, W., Schaefer, C., Schwarzloh, B., et al. (2013). Angiogenic growth factors in rheumatoid arthritis. *Rheumatology International, 33*(2), 523-527. http://dx.doi.org/10.1007/s00296-011-2210-6

Scian, R., Barrionuevo, P., Giambartolomei, G. H., De Simone, E. A., Vanzulli, S. I., Fossati, C. A., et al. (2011). Potential role of fibroblast-like synoviocytes in joint damage induced by *Brucella abortus* infection through production and induction of matrix metalloproteinases. *Infection and Immunity,* 79(9), 3619-3632. doi:10.1128/IAI.05408-11

Scott, D. L., Wolfe, F., & Huizinga, T. W. (2010). Rheumatoid arthritis. *Lancet*, *376*(9746), 1094-1108. DOI: 10.1016/S0140-6736(10)60826-4

Seetharaman, R., Mora, A. L., Nabozny, G., Boothby, M., & Chen, J. (1999). Essential role of T cell NF-κB activation in collagen-induced arthritis. *The Journal of Immunology, 163*(3), 1577-1583.

Seif, F., Khoshmirsafa, M., Aazami, H., Mohsenzadegan, M., Sedighi, G., & Bahar, M. (2017). The role of JAK-STAT signaling pathway and its regulators in the fate of T helper cells. *Cell Communication and Signaling, 15*(1), 1-13. https://doi.org/10.1186/s12964-017-0177-y

Serasanambati, M., & Chilakapati, S. R. (2016). Function of nuclear factor kappa B (NF-kB) in human diseases-a review. *South Indian Journal of Biological Sciences, 2*(4), 368-387.

Shahrir, M., Shahdan, M., Shahid, M., Sulaiman, W., Mokhtar, A. M., Othman, M., et al. (2008). Multicentre survey of rheumatoid arthritis patients from Ministry of Health Rheumatology Centers in Malaysia. *International Journal of Rheumatic Diseases, 11*(3), 287-292. https://doi.org/10.1111/j.1756-185X.2008.00379.x

Shao, R., & Guo, X. (2004). Human microvascular endothelial cells immortalized with human telomerase catalytic protein: a model for the study of *in vitro* angiogenesis. *Biochemical and Biophysical Research Communications, 321*(4), 788-794. https://doi.org/10.1016/j.bbrc.2004.07.033

Sharma, A. R., Jagga, S., Chakraborty, C., & Lee, S. S. (2020). Fibroblast-like-synoviocytes mediate secretion of pro-inflammatory cytokines via ERK and JNK MAPKs in Ti-particle-induced osteolysis. *Materials, 13*(16), 3628. https://doi.org/10.3390/ma13163628

Sharma, S., Sahu, D., Das, H. R., & Sharma, D. (2011). Amelioration of collagen-induced arthritis by *Salix nigra* bark extract via suppression of pro-inflammatory cytokines and oxidative stress. *Food and Chemical Toxicology, 49*(12), 3395-3406. doi:10.1016/j.fct.2011.08.013

Shaterzadeh-Yazdi, H., Noorbakhsh, M. F., Hayati, F., Samarghandian, S., & Farkhondeh, T. (2018). Immunomodulatory and anti-inflammatory effects of thymoquinone. *Cardiovascular & Haematological Disorders-Drug Targets (Formerly Current Drug Targets-Cardiovascular & Hematological Disorders), 18*(1), 52-60. DOI:10.2174/1871529X18666180212114816

Shih, Y. H., Chang, K. W., Chen, M. Y., Yu, C. C., Lin, D. J., Hsia, S. M., et al. (2013). Lysyl oxidase and enhancement of cell proliferation and angiogenesis in oral squamous cell carcinoma. *Head & Neck, 35*(2), 250-256. DOI 10.1002/hed.22959

Shu, Q., Amin, M. A., Ruth, J. H., Campbell, P. L., & Koch, A. E. (2012). Suppression of endothelial cell activity by inhibition of TNFα. *Arthritis Research & Therapy, 14*(2), R88. https://doi.org/10.1186/ar3812

Silva, T. L., Maria de Lourdes, S. G., Ferreira, F. R., Santos, D. C., Amatore, C., & Goulart, M. O. (2020). Quinone-based molecular electrochemistry and their contributions to medicinal chemistry: a look at the present and future. *Current Opinion in Electrochemistry, 24*, 79-87. https://doi.org/10.1016/j.coelec.2020.06.011

Singh, A. K., Umar, S., Riegsecker, S., Chourasia, M., & Ahmed, S. (2016). Regulation of TAK1 activation by epigallocatechin-3-gallate in RA synovial fibroblasts: Suppression of K63-linked autoubiquitination of TRAF6. *Arthritis & Rheumatology, 68*(2), 347–358. https://doi.org/10.1002/art.39447

Singh, J. A., Saag, K. G., Bridges Jr, S. L., Akl, E. A., Bannuru, R. R., Sullivan, M. C., et al. (2016). 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis & Rheumatology, 68*(1), 1-26. https://doi.org/10.1002/art.39480

Singh, K., Deshpande, P., Pryshchep, S., Colmegna, I., Liarski, V., Weyand, C. M., et al. (2009). ERK-dependent T cell receptor threshold calibration in

rheumatoid arthritis. *The Journal of Immunology, 183*(12), 8258-8267. doi: 10.4049/jimmunol.0901784

Smith, M. D. (2011). The normal synovium. *The Open Rheumatology Journal, 5*, 100–106. https://doi.org/10.2174/1874312901105010100

Smith, M. D., Barg, E., Weedon, H., Papengelis, V., Smeets, T., Tak, P., et al. (2003). Microarchitecture and protective mechanisms in synovial tissue from clinically and arthroscopically normal knee joints. *Annals of The Rheumatic Diseases, 62*(4), 303-307. http://dx.doi.org/10.1136/ard.62.4.303

Smolen, J. S., Aletaha, D., & McInnes, I. B. (2016) Rheumatoid arthritis. *The Lancet, 388*(10055), 2023–2038. https://doi:10.1016/s0140-6736(16)30173-8

Smolen, J. S., Breedveld, F. C., Burmester, G. R., Bykerk, V., Dougados, M., Emery, P., et al. (2016). Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. *Annals of the Rheumatic Diseases, 75*(1), 3-15. http://dx.doi.org/10.1136/annrheumdis-2015-207524

Sockalingam, S., Khuan, C. S., & Sthaneshwar, P. (2009). Prevalence of anti cyclic citrullinated peptide antibodies in Malaysian rheumatoid arthritis patients and its correlation with disease activity. *International Journal of Rheumatic Diseases, 12*(3), 211-215. https://doi.org/10.1111/j.1756-185X.2009.01412.x

Solinas, M., Massi, P., Cantelmo, A. R., Cattaneo, M. G., Cammarota, R., Bartolini, D., et al. (2012). Cannabidiol inhibits angiogenesis by multiple mechanisms. *British Journal of Pharmacology, 167*(6), 1218-1231. https://doi.org/10.1111/j.1476-5381.2012.02050.x

Solomon, D. H., Shao, M., Wolski, K., Nissen, S., Husni, M. E., & Paynter, N. (2019). Derivation and validation of a major toxicity risk score among nonsteroidal Antiinflammatory drug users based on data from a randomized controlled trial. *Arthritis & Rheumatology, 71*(8), 1225-1231. DOI 10.1002/art.40870

Somchit, M. N., Adam, Y., Yee, H. C., Zuraini, A., Arifah, A. K., & Zakaria, Z. A. (2011). Anti-fungal activity of *Ardisia crispa* (Thunb.) A. DC. against several fungi responsible for athletes foot. *African Journal of Microbiology Research, 5*(15), 2008-2010. DOI: 10.5897/AJMR10.454

Song, H. P., Li, X., Yu, R., Zeng, G., Yuan, Z. Y., Wang, W., et al. (2015). Phenotypic characterization of type II collagen-induced arthritis in Wistar rats. *Experimental and Therapeutic Medicine, 10*(4), 1483-1488. https://doi.org/10.3892/etm.2015.2667

Song, Y. W., & Kang, E. H. (2010). Autoantibodies in rheumatoid arthritis: rheumatoid factors and anticitrullinated protein antibodies. QJM: *An International Journal of Medicine, 103*(3), 139-146. https://doi.org/10.1093/qjmed/hcp165

Sreepriya, M., & Bali, G. (2006). Effects of administration of Embelin and Curcumin on lipid peroxidation, hepatic glutathione antioxidant defense and hematopoietic system during N-nitrosodiethylamine/Phenobarbital-induced hepatocarcinogenesis in Wistar rats. *Molecular and Cellular Biochemistry, 284*(1), 49-55. https://doi.org/10.1007/s11010-005-9012-7

Staton, C. A., Reed, M. W., & Brown, N. J. (2009). A critical analysis of current in vitro and *in vivo* angiogenesis assays. *International Journal of Experimental Pathology, 90*(3), 195-221. doi: 10.1111/j.1365-2613.2008.00633.x

Steinbild, S., Arends, J., Medinger, M., Häring, B., Frost, A., Drevs, J., et al. (2007). Metronomic antiangiogenic therapy with capecitabine and celecoxib in advanced tumor patients–results of a phase II study. *Oncology Research and Treatment, 30*(12), 629-635. DOI: 10.1159/000110580

Strunk, J., Bundke, E., & Lange, U. (2006). Anti-TNF-α antibody Infliximab and glucocorticoids reduce serum vascular endothelial growth factor levels in patients with rheumatoid arthritis: a pilot study. *Rheumatology International, 26*(3), 252-256. http://dx.doi.org/10.1007/s00296-005-0619-5

Sulaiman, H., Hamid, R. A., Ting, Y. L., & Othman, F. (2012). Anti-tumor effect of *Ardisia crispa* hexane fraction on 7, 12-dimethylbenz [α] anthracene-induced mouse skin papillomagenesis. *Journal of Cancer Research and Therapeutics, 8*(3), 404. DOI: 10.4103/0973-1482.103521

Sultan, M. T., Buttxs, M. S., Qayyum, M. M. N., & Suleria, H. A. R. (2014). Immunity: plants as effective mediators. *Critical Reviews in Food Science and Nutrition, 54*(10), 1298-1308. https://doi.org/10.1080/10408398.2011.633249

Sumino, M., Sekine, T., Ruangrungsi, N., Igarashi, K., & Ikegami, F. (2002). Ardisiphenols and other antioxidant principles from the fruits of *Ardisia colorata*. *Chemical and Pharmaceutical Bulletin, 50*(11), 1484-1487. https://doi.org/10.1248/cpb.50.1484

Sun, H. N., Luo, Y. H., Meng, L. Q., Piao, X. J., Wang, Y., Wang, J. R., et al. (2019). Cryptotanshinone induces reactive oxygen species-mediated apoptosis in human rheumatoid arthritis fibroblast-like synoviocytes. *International Journal of Molecular Medicine, 43*(2), 1067-1075. https://doi.org/10.3892/ijmm.2018.4012

Sun, K., Luo, J., Guo, J., Yao, X., Jing, X., & Guo, F. (2020). The PI3K/AKT/mTOR signaling pathway in osteoarthritis: a narrative review. *Osteoarthritis and Cartilage, 28*(4), 400-409. https://doi.org/10.1016/j.joca.2020.02.027

Sundriyal, M., & Sundriyal, D. C. (2001). Wild edible plants of the Sikkim Himalaya: Nutritive values of selected species. *Economic Botany, 55*(3), 377. https://doi.org/10.1007/BF02866561

Sweeney, S. E., & Firestein, G. S. (2004). Signal transduction in rheumatoid arthritis. *Current Opinion in Rheumatology, 16*(3), 231-237.

Świerkot, J., Nowak, B., Czarny, A., Zaczyńska, E., Sokolik, R., Madej, M., et al. (2016). The activity of JAK/STAT and NF-κB in patients with rheumatoid arthritis. *Advances in Clinical and Experimental Medicine, 25*(4), 709-717. doi: 10.17219/acem/61034

Szekanecz, Z., & Koch, A. E. (2009). Angiogenesis and its targeting in rheumatoid arthritis. *Vascular Pharmacology, 51*(1), 1-7. https://doi.org/10.1016/j.vph.2009.02.002

Szekanecz, Z., Vegvari, A., Szabo, Z., & Koch, A. E. (2010). Chemokines and chemokine receptors in arthritis. *Frontiers in Bioscience (Scholar Edition), 2*, 153-167. doi:10.2741/s53

Tabana, Y. M., Al-Suede, F. S. R., Ahamed, M. B. K., Dahham, S. S., Hassan, L. E. A., Khalilpour, S. et al. (2016). Cat's whiskers (*Orthosiphon stamineus*) tea modulates arthritis pathogenesis via the angiogenesis and inflammatory cascade. *BMC Complementary and Alternative Medicine, 16*(1), 480. https://doi.org/10.1186/s12906-016-1467-4

Tanaka Y. (2016). Current concepts in the management of rheumatoid arthritis. *The Korean Journal of Internal Medicine, 31*(2), 210–218. https://doi.org/10.3904/kjim.2015.137

Tanaka, Y., & Ohira, T. (2018). Mechanisms and therapeutic targets for bone damage in rheumatoid arthritis, in particular the RANK-RANKL system. *Current Opinion in Pharmacology, 40*, 110-119. https://doi.org/10.1016/j.coph.2018.03.006

Taneja, V., Mangalam, A., & David, C. S. (2013). Genetic predisposition to autoimmune diseases conferred by the Major Histocompatibility Complex: Utility of animal models. In *The Autoimmune Diseases: Fifth Edition* (pp. 365-380). Elsevier Inc.. https://doi.org/10.1016/B978-0-12-384929-8.00027-7

Tanwar, A., Chawla, R., Ansari, M. M., Thakur, P., Chakotiya, A. S., Goel, R., et al. (2017). *In vivo* anti-arthritic efficacy of *Camellia sinensis* (L.) in collagen induced arthritis model. *Biomedicine & Pharmacotherapy, 87*, 92-101. https://doi.org/10.1016/j.biopha.2016.12.089

Tao, L., & Xue, J. F. (2018). Effects of TNF-α in rheumatoid arthritis via attenuating α1 (I) collagen promoter. *European Review for Medical and Pharmacological Sciences, 22*(12), 3905-3912.

Tao, X., Schulze-Koops, H., Ma, L., Cai, J., Mao, Y., & Lipsky, P. E. (1998). Effects of *Tripterygium wilfordii* hook F extracts on induction of cyclooxygenase 2 activity and prostaglandin E2 production. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology, 41*(1), 130-138.

Tarp, S., Eric Furst, D., Boers, M., Luta, G., Bliddal, H., Tarp, U., et al. (2017). Risk of serious adverse effects of biological and targeted drugs in patients with rheumatoid arthritis: a systematic review meta-analysis. *Rheumatology, 56*(3), 417-425. https://doi.org/10.1093/rheumatology/kew442

Tawfik, M. K. (2015). Combination of coenzyme Q10 with methotrexate suppresses Freund's complete adjuvant-induced synovial inflammation with reduced hepatotoxicity in rats: effect on oxidative stress and inflammation. *International Immunopharmacology, 24*(1), 80-87. https://doi.org/10.1016/j.intimp.2014.11.018

Taylor, P. C. (2002). VEGF and imaging of vessels in rheumatoid arthritis. *Arthritis Research & Therapy, 4*(S3), S99. https://doi.org/10.1186/ar582

Taylor, P. C. (2019). Clinical efficacy of launched JAK inhibitors in rheumatoid arthritis. *Rheumatology, 58*(Supplement 1), i17-i26. https://doi.org/10.1093/rheumatology/key225

Thairu, N., Kiriakidis, S., Dawson, P., & Paleolog, E. (2011). Angiogenesis as a therapeutic target in arthritis in 2011: learning the lessons of the colorectal cancer experience. *Angiogenesis, 14*(3), 223-234. DOI 10.1007/s10456-011-9208-2

Thalhamer, T., McGrath, M. A., & Harnett, M. M. (2008). MAPKs and their relevance to arthritis and inflammation. *Rheumatology, 47*(4), 409-414. https://doi.org/10.1093/rheumatology/kem297

Thiel, M. J., Schaefer, C. J., Lesch, M. E., Mobley, J. L., Dudley, D. T., Tecle, H., et al. (2007). Central role of the MEK/ERK MAP kinase pathway in a mouse model of rheumatoid arthritis: potential proinflammatory mechanisms. Arthritis & Rheumatism: *Official Journal of the American College of Rheumatology, 56*(10), 3347-3357. DOI 10.1002/art.22869

Tighe, P. J., Ryder, R. R., Todd, I., & Fairclough, L. C. (2015). ELISA in the multiplex era: potentials and pitfalls. *PROTEOMICS–Clinical Applications, 9*(3-4), 406-422. DOI 10.1002/prca.201400130

Tong, L., Nanjundaiah, S. M., Venkatesha, S. H., Astry, B., Yu, H., & Moudgil, K. D. (2014). Pristimerin, a naturally occurring triterpenoid, protects against

autoimmune arthritis by modulating the cellular and soluble immune mediators of inflammation and tissue damage. *Clinical Immunology, 155*(2), 220-230. https://doi.org/10.1016/j.clim.2014.09.014

Trentham, D. E., Townes, A. S., & Kang, A. H. (1977). Autoimmunity to type II collagen an experimental model of arthritis. *The Journal of Experimental Medicine, 146*(3), 857-868.

Trentham, D. E., Townes, A. S., Kang, A. H., & David, J. R. (1978). Humoral and cellular sensitivity to collagen in type II collagen-induced arthritis in rats. *The Journal of Clinical Investigation, 61*(1), 89-96.

Tseng, C. C., Chen, Y. J., Chang, W. A., Tsai, W. C., Ou, T. T., Wu, C. C., et al. (2020). Dual Role of Chondrocytes in Rheumatoid Arthritis: The Chicken and the Egg. *International Journal of Molecular Sciences, 21*(3), 1071. https://doi.org/10.3390/ijms21031071

Tuncel, J., Haag, S., Hoffmann, M. H., Yau, A. C., Hultqvist, M., Olofsson, P., et al. (2016). Animal models of rheumatoid arthritis (I): pristane-induced arthritis in the rat. *PLoS One, 11*(5), e0155936. https://doi.org/10.1371/journal.pone.0155936

Ulus, G., Koparal, A. T., Baysal, K., Anacak, G. Y., & Yavaşoğlu, N. Ü. K. (2018). The anti-angiogenic potential of (±) gossypol in comparison to suramin. *Cytotechnology, 70*(6), 1537-1550. doi: 10.1007/s10616-018-0247-z

Umar, S., Hedaya, O., Singh, A. K., & Ahmed, S. (2015). Thymoquinone inhibits TNF-α-induced inflammation and cell adhesion in rheumatoid arthritis synovial fibroblasts by ASK1 regulation. *Toxicology and Applied Pharmacology, 287*(3), 299-305. https://doi.org/10.1016/j.taap.2015.06.017

Umar, S., Zargan, J., Umar, K., Ahmad, S., Katiyar, C. K., & Khan, H. A. (2012). Modulation of the oxidative stress and inflammatory cytokine response by thymoquinone in the collagen induced arthritis in Wistar rats. *Chemico-biological Interactions, 197*(1), 40-46. https://doi.org/10.1016/j.cbi.2012.03.003

Valmas, C., Grosch, M. N., Schümann, M., Olejnik, J., Martinez, O., Best, S. M., et al. (2010). Marburg virus evades interferon responses by a mechanism distinct from ebola virus. *PLOS Pathogens, 6*(1), e1000721. https://doi.org/10.1371/journal.ppat.1000721

Van Meerloo, J., Kaspers, G. J., & Cloos, J. (2011). Cell sensitivity assays: the MTT assay. In *Cancer Cell Culture* (pp. 237-245). Humana Press.

van Onna, M., & Boonen, A. (2016). The challenging interplay between rheumatoid arthritis, ageing and comorbidities. *BMC Musculoskeletal Disorders, 17*(1), 184. https://doi.org/10.1186/s12891-016-1038-3

Vardhan, P. V., & Shukla, L. I. (2017). Gamma irradiation of medicinally important plants and the enhancement of secondary metabolite production. *International Journal of Radiation Biology, 93*(9), 967-979. https://doi.org/10.1080/09553002.2017.1344788

Végh, E., Kerekes, G., Pusztai, A., Hamar, A., Szamosi, S., Váncsa, A., et al. (2020). Effects of 1-year anti-TNF-α therapy on vascular function in rheumatoid arthritis and ankylosing spondylitis. *Rheumatology International, 40*(3), 427-436. https://doi.org/10.1007/s00296-019-04497-0

Venkatesha, S. H., Dudics, S., Astry, B., & Moudgil, K. D. (2016). Control of autoimmune inflammation by celastrol, a natural triterpenoid. *Fems Pathogens and Disease, 74*(6), ftw059. https://doi.org/10.1093/femspd/ftw059

Venkatesha, S. H., Yu, H., Rajaiah, R., Tong, L., & Moudgil, K. D. (2011). Celastrus-derived celastrol suppresses autoimmune arthritis by modulating antigen-induced cellular and humoral effector responses. *Journal of Biological chemistry, 286*(17), 15138-15146. DOI 10.1074/jbc.M111.226365

Verdura, S., Cuyàs, E., Llorach-Parés, L., Pérez-Sánchez, A., Micol, V., Nonell-Canals, A., et al. (2018). Silibinin is a direct inhibitor of STAT3. *Food and Chemical Toxicology, 116*, 161-172. https://doi.org/10.1016/j.fct.2018.04.028

Vernes, J. M., & Meng, Y. G. (2015). Detection and quantification of VEGF isoforms by ELISA. In *VEGF Signaling* (pp. 25-37). Humana Press, New York, NY. https://doi.org/10.1007/978-1-4939-2917-7_2

Voskuhl R. (2011). Sex differences in autoimmune diseases. *Biology of Sex Differences, 2*(1), 1. https://doi.org/10.1186/2042-6410-2-1

Vostrý M. (2010). Multiplex Immunoassays: Chips and Beads. *The Electronic Journal of The International Federation of Clinical Chemistry and Laboratory Medicine, 20*(4), 162–165.

Waksman, B. H. (2002). Immune regulation in adjuvant disease and other arthritis models: relevance to pathogenesis of chronic arthritis. *Scandinavian Journal of Immunology, 56*(1), 12-34. https://doi.org/10.1046/j.1365-3083.2002.01106.x

Walgraeve, C., Demeestere, K., De Wispelaere, P., Dewulf, J., Lintelmann, J., Fischer, K., et al. (2012). Selective accurate-mass-based analysis of 11 oxy-PAHs on atmospheric particulate matter by pressurized liquid extraction followed by high-performance liquid chromatography and magnetic sector mass spectrometry. *Analytical and Bioanalytical Chemistry, 402*(4), 1697-1711. DOI 10.1007/s00216-011-5568-0

Walker, E. H. (1939). Concerning *Ardisia crispa* (Thunb.) A. DC. and *A. crenata* Sims, confused species of Myrsinaceae from eastern Asia. *Journal of the Washington Academy of Sciences, 29*(6), 256-261.

Walker, J. G., & Smith, M. D. (2005). The Jak-STAT pathway in rheumatoid arthritis. *The Journal of Rheumatology, 32*(9), 1650-1653. http://www.jrheum.org/content/32/9/1650.citation

Wang, B., Ma, L., Tao, X., & Lipsky, P. E. (2004). Triptolide, an active component of the Chinese herbal remedy *Tripterygium wilfordii* Hook F, inhibits production of nitric oxide by decreasing inducible nitric oxide synthase gene transcription. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology, 50*(9), 2995-3003. DOI 10.1002/art.20459

Wang, G., Qian, P., Jackson, F. R., Qian, G., & Wu, G. (2008). Sequential activation of JAKs, STATs and xanthine dehydrogenase/oxidase by hypoxia in lung microvascular endothelial cells. *The International Journal of Biochemistry & Cell Biology, 40*(3), 461-470. https://doi.org/10.1016/j.biocel.2007.08.008

Wang, H. L., Jiang, Q., Feng, X. H., Zhang, H. D., Ge, L., Luo, C. G., et al. (2016). *Tripterygium wilfordii* Hook F versus conventional synthetic disease-modifying anti-rheumatic drugs as monotherapy for rheumatoid arthritis: a systematic review and network meta-analysis. *BMC Complementary and Alternative Medicine, 16*(1), 215. https://doi.org/10.1186/s12906-016-1194-x

Wang, H., Cong, F., Guan, J., Xiao, L., Zhu, Y., Lian, Y., ... & Guo, P. (2019). Establishment of xMAP for the simultaneous detection of antibodies to Newcastle disease virus and avian influenza virus. *Poultry Science, 98*(3), 1494-1499. https://doi.org/10.3382/ps/pey510

Wang, J., & Zhao, Q. (2019). Kaempferitrin inhibits proliferation, induces apoptosis, and ameliorates inflammation in human rheumatoid arthritis fibroblast-like synoviocytes. *Phytotherapy Research, 33*(6), 1726-1735. DOI: 10.1002/ptr.6364

Wang, J., Chen, N., Fang, L., Feng, Z., Li, G., Mucelli, A., et al. (2018). A systematic review about the efficacy and safety of *Tripterygium wilfordii* Hook. f. preparations used for the management of rheumatoid arthritis. *Evidence-Based Complementary and Alternative Medicine, 2018*. https://doi.org/10.1155/2018/1567463

Wang, L., Ding, Y., Guo, X., & Zhao, Q. (2015). Role and mechanism of vascular cell adhesion molecule-1 in the development of rheumatoid arthritis. *Experimental and Therapeutic Medicine, 10*(3), 1229-1233. https://doi.org/10.3892/etm.2015.2635

Wang, M., Wu, J., Guo, Y., Chang, X., & Cheng, T. (2017). The tripartite motif-containing protein 3 on the proliferation and cytokine secretion of rheumatoid arthritis fibroblast-like synoviocytes. *Molecular Medicine Reports, 15*(4), 1607-1612. https://doi.org/10.3892/mmr.2017.6164

Wang, Q., Ye, C., Sun, S., Li, R., Shi, X., Wang, S., et al. (2019). Curcumin attenuates collagen-induced rat arthritis via anti-inflammatory and apoptotic effects. *International Immunopharmacology, 72*, 292-300. https://doi.org/10.1016/j.intimp.2019.04.027

Wang, S., Liang, S., Zhao, X., He, Y., & Qi, Y. (2017). Propofol inhibits cell proliferation and invasion in rheumatoid arthritis fibroblast-like synoviocytes via the nuclear factor-κB pathway. *American Journal of Translational Research, 9*(5), 2429–2436.

Wang, Y., Da, G., Li, H., & Zheng, Y. (2013). Avastin exhibits therapeutic effects on collagen-induced arthritis in rat model. *Inflammation, 36*(6), 1460-1467. DOI: 10.1007/s10753-013-9687-y

Wang, Z., Chen, Z., Yang, S., Wang, Y., Huang, Z., Gao, J., et al. (2014). Berberine ameliorates collagen-induced arthritis in rats associated with anti-inflammatory and anti-angiogenic effects. *Inflammation, 37*(5), 1789-1798. DOI:10.1007/s10753-014-9909-y

Wang, Z., Dabrosin, C., Yin, X., Fuster, M. M., Arreola, A., Rathmell, W. K., et al. (2015). Broad targeting of angiogenesis for cancer prevention and therapy. In *Seminars in Cancer Biology* (Vol. 35, pp. S224-S243). Academic Press. https://doi.org/10.1016/j.semcancer.2015.01.001

Waritani, T., Chang, J., McKinney, B., & Terato, K. (2017). An ELISA protocol to improve the accuracy and reliability of serological antibody assays. *MethodsX, 4*, 153-165. https://doi.org/10.1016/j.mex.2017.03.002

Watanabe, S., Toyama, T., Sato, T., Suzuki, M., Morozumi, A., Sakagami, H., et al. (2019). Kampo therapies and the use of herbal medicines in the dentistry in Japan. *Medicines, 6*(1), 34. doi:10.3390/medicines6010034

Wee, P., & Wang, Z. (2017). Epidermal growth factor receptor cell proliferation signaling pathways. *Cancers, 9*(5), 52. doi:10.3390/cancers9050052

Weinberg, M. A. (2016). RES-529: a PI3K/AKT/mTOR pathway inhibitor that dissociates the mTORC1 and mTORC2 complexes. *Anti-cancer Drugs, 27*(6), 475-487. doi: 10.1097/CAD.0000000000000354

Weis, S. M., & Cheresh, D. A. (2011). Tumor angiogenesis: molecular pathways and therapeutic targets. *Nature Medicine, 17*(11), 1359-1370. doi:10.1038/nm.2537

Wen Jun, L., Foong, C. P., & Abd Hamid, R. (2019). *Ardisia crispa* root hexane fraction suppressed angiogenesis in human umbilical vein endothelial cells (HUVECs) and *in vivo* zebrafish embryo model. *Biomedicine &*

Pharmacotherapy, 118, 109221. https://doi.org/10.1016/j.biopha.2019.109221

Westra, J., Molema, G., & Kallenberg, C. G. M. (2010). Hypoxia-inducible factor-1 as regulator of angiogenesis in rheumatoid arthritis-therapeutic implications. *Current Medicinal Chemistry, 17*(3), 254-263. https://doi.org/10.2174/092986710790149783

Wijekoon, H. S., Kim, S., Bwalya, E. C., Fang, J., Aoshima, K., Hosoya, K., et al. (2019). Anti-arthritic effect of pentosan polysulfate in rats with collagen-induced arthritis. *Research in Veterinary Science, 122*, 179-185. https://doi.org/10.1016/j.rvsc.2018.11.028

Winthrop, K. L., Park, S. H., Gul, A., Cardiel, M. H., Gomez-Reino, J. J., Tanaka, Y., et al. (2016). Tuberculosis and other opportunistic infections in tofacitinib-treated patients with rheumatoid arthritis. *Annals of The Rheumatic Diseases, 75*(6), 1133-1138. doi:10.1136/annrheumdis-2015-207319

Woods, J. M., Mogollon, A., Amin, M. A., Martinez, R. J., & Koch, A. E. (2003). The role of COX-2 in angiogenesis and rheumatoid arthritis. *Experimental and Molecular Pathology, 74*(3), 282-290. https://doi.org/10.1016/S0014-4800(03)00019-4

Wooley, P. H., Luthra, H. S., Griffiths, M. M., Stuart, J. M., Huse, A., & David, C. S. (1985). Type II collagen-induced arthritis in mice. IV. Variations in immunogenetic regulation provide evidence for multiple arthritogenic epitopes on the collagen molecule. *The Journal of Immunology, 135*(4), 2443-2451.

World Health Organization. Chronic diseases and health promotion, 2020. Retrieved 15 October 2020 from https://www.who.int/chp/topics/rheumatic/en/

Wu, C. J., Sundararajan, V., Sheu, B. C., Huang, R. Y. J., & Wei, L. H. (2020). Activation of stat3 and stat5 signaling in epithelial ovarian cancer progression: mechanism and therapeutic opportunity. *Cancers, 12*(1), 24. doi:10.3390/cancers12010024

Wu, M., Ma, L., Cong, F., Zhu, Y., Xu, F., Lian, Y., et al. (2019). High-throughput Luminex xMAP assay for simultaneous detection of antibodies against rabbit hemorrhagic disease virus, Sendai virus and rabbit rotavirus. *Archives of Virology, 164*(6), 1639-1646. https://doi.org/10.1007/s00705-019-04226-9

Wu, X., Long, L., Liu, J., Zhang, J., Wu, T., Chen, X., ... & Lv, T. Z. (2017). Gambogic acid suppresses inflammation in rheumatoid arthritis rats via PI3K/Akt/mTOR signaling pathway. *Molecular Medicine Reports, 16*(5), 7112-7118. https://doi.org/10.3892/mmr.2017.7459

Xu, F., Na, L., Li, Y., & Chen, L. (2020). Roles of the PI3K/AKT/mTOR signalling pathways in neurodegenerative diseases and tumours. *Cell & Bioscience, 10*, 1-12. https://doi.org/10.1186/s13578-020-00416-0

Xu, S., Xiao, Y., Zeng, S., Zou, Y., Qiu, Q., Huang, M., et al. (2018). Piperlongumine inhibits the proliferation, migration and invasion of fibroblast-like synoviocytes from patients with rheumatoid arthritis. *Inflammation Research, 67*(3), 233-243. DOI:10.1007/s00011-017-1112-9

Xu, Z., Wu, G., Wei, X., Chen, X., Wang, Y., & Chen, L. (2013). Celastrol induced DNA damage, cell cycle arrest, and apoptosis in human rheumatoid fibroblast-like synovial cells. *The American Journal of Chinese Medicine, 41*(03), 615-628. https://doi.org/10.1142/S0192415X13500432

Yamagishi, Y., Igarashi, M., Suzuki, A., Suguro, S., Hirano, S. I., & Nagaoka, I. (2012). Evaluation of the effect of methionine and glucosamine on adjuvant arthritis in rats. *Experimental and Therapeutic Medicine, 4*(4), 640-644. https://doi.org/10.3892/etm.2012.668

Yang, C. M., Chen, Y. W., Chi, P. L., Lin, C. C., & Hsiao, L. D. (2017). Resveratrol inhibits BK-induced COX-2 transcription by suppressing acetylation of AP-1 and NF-κB in human rheumatoid arthritis synovial fibroblasts. *Biochemical Pharmacology, 132*, 77-91. https://doi.org/10.1016/j.bcp.2017.03.003

Yang, H. L., Korivi, M., Lin, M. W., Chen, S. C., Chou, C. W., & Hseu, Y. C. (2015). Anti-angiogenic properties of coenzyme Q0 through downregulation of MMP-9/NF-κB and upregulation of HO-1 signaling in TNF-α-activated human endothelial cells. *Biochemical Pharmacology, 98*(1), 144-156. https://doi.org/10.1016/j.bcp.2015.09.003

Yang, M., Xiao, C., Wu, Q., Niu, M., Yao, Q., Li, K., et al. (2010). Anti-inflammatory effect of Sanshuibaihu decoction may be associated with nuclear factor-κB and p38 MAPKα in collagen-induced arthritis in rat. *Journal of Ethnopharmacology, 127*(2), 264-273. https://doi.org/10.1016/j.jep.2009.11.010

Yang, S., Jiang, S., Wang, Y., Tu, S., Wang, Z., & Chen, Z. (2016). Interleukin 34 upregulation contributes to the increment of MicroRNA 21 expression through STAT3 activation associated with disease activity in rheumatoid arthritis. *The Journal of Rheumatology, 43*(7), 1312-1319. https://doi.org/10.3899/jrheum.151253

Yang, X., & Friedl, A. (2015) A Positive feedback loop between prolactin and stat5 promotes angiogenesis. In: *Diakonova, PhD M. (eds) Recent Advances in Prolactin Research. Advances in Experimental Medicine and Biology, 846*, 265-280. Springer, Cham. https://doi.org/10.1007/978-3-319-12114-7_12

Yang, X., Qiao, D., Meyer, K., & Friedl, A. (2009). Signal transducers and activators of transcription mediate fibroblast growth factor–induced vascular endothelial morphogenesis. *Cancer Research, 69*(4), 1668-1677. DOI: 10.1158/0008-5472.CAN-07-6385

Yao, Y., Jiang, C. S., Sun, N., Li, W. Q., Niu, Y., Han, H. Q., et al. (2017). Tamaractam, a new bioactive Lactam from *Tamarix ramosissima*, induces apoptosis in rheumatoid arthritis fibroblast-like synoviocytes. *Molecules,* 22(1), 96. https://doi.org/10.3390/molecules22010096

Yeo, L., Adlard, N., Biehl, M., Juarez, M., Smallie, T., Snow, M., et al. (2016). Expression of chemokines CXCL4 and CXCL7 by synovial macrophages defines an early stage of rheumatoid arthritis. *Annals of The Rheumatic Diseases, 75*(4), 763-771. doi:10.1136/annrheumdis-2014-206921

Yeong, L. T. (2014). *In vitro and in vivo studies of chemopreventive effects of bioactive fractions from Ardisia crispa (thunb.) on skin tumour promotion.* (Unpublished doctoral dissertation). Universiti Putra Malaysia, Malaysia.

Yeong, L. T., Abdul Hamid, R., Saiful Yazan, L., Khaza'ai, H., & Awang Hamsin, D. E. Z. (2014). Synergistic action of compounds isolated from the hexane extract of *Ardisia crispa* root against tumour-promoting effect, *in vitro*. *Natural Product Research, 28*(22), 2026-2030. https://doi.org/10.1080/14786419.2014.917415

Yeong, L. T., Hamid, R. A., Yazan, L. S., & Khaza'ai, H. (2013). Isolation of a quinone-rich fraction from *Ardisia crispa* roots and its attenuating effects on murine skin tumorigenesis. *Asian Pacific Journal of Cancer Prevention, 14*, 2301-2305. http://dx.doi.org/10.7314/APJCP.2013.14.4.2301

Yeong, L. T., Hamid, R. A., Yazan, L. S., Khaza'ai, H., & Mohtarrudin, N. (2015). Low dose triterpene-quinone fraction from *Ardisia crispa* root precludes chemical-induced mouse skin tumor promotion. *BMC Complementary and Alternative Medicine, 15*(1), 431. https://doi.org/10.1186/s12906-015-0954-3

Yi, T., Cho, S. G., Yi, Z., Pang, X., Rodriguez, M., Wang, Y., et al. (2008). Thymoquinone inhibits tumor angiogenesis and tumor growth through suppressing AKT and extracellular signal-regulated kinase signaling pathways. *Molecular Cancer Therapeutics, 7*(7), 1789-1796. doi:10.1158/1535-7163.MCT-08-0124

Yin, H., Zhang, F., Yu, M., Cheng, H., Lin, J., Gao, Y., et al. (2005). Beta-endorphin ameliorates synovial cell hyperfunction in the collagen-induced arthritis rat model by specific downregulation of NF-kappa B activity. *Neuroendocrinology, 81*(1), 10-18. DOI: 10.1159/000084828

Yu, C., Yang, C., Song, S., Yu, Z., Zhou, X., & Wu, J. (2018). Development of a sensitive Luminex xMAP-based microsphere immunoassay for specific detection of Iris yellow spot virus. *Virology Journal, 15*(1), 62. https://doi.org/10.1186/s12985-018-0952-4

Yuan, H., Ma, Q., Ye, L., & Piao, G. (2016). The traditional medicine and modern medicine from natural products. *Molecules, 21*(5), 559. doi:10.3390/molecules21050559

Yue, M., Xia, Y., Shi, C., Guan, C., Li, Y., Liu, R., et al. (2017). Berberine ameliorates collagen-induced arthritis in rats by suppressing Th17 cell responses via inducing cortistatin in the gut. *The Federation of European Biochemical Societies Journal, 284*(17), 2786-2801. doi:10.1111/febs.14147

Zahidah, A. F., Faizah, O., Aqilah, K. N., & Anna, K. T. (2012). Curcumin as an anti-arthritic agent in collagen-induced arthritic Sprague-Dawley rats. *Sains Malaysiana, 41*(5), 591-595.

Zampeli, E., Vlachoyiannopoulos, P. G., & Tzioufas, A. G. (2015). Treatment of rheumatoid arthritis: unraveling the conundrum. *Journal of Autoimmunity, 65*, 1-18. https://doi.org/10.1016/j.jaut.2015.10.003

Zeng, N., Tong, B., Zhang, X., Dou, Y., Wu, X., Xia, Y., et al. (2015). Antiarthritis effect of morin is associated with inhibition of synovial angiogensis. *Drug Development Research, 76*(8), 463-473. DOI: 10.1002/ddr.21282

Zhai, K. F., Duan, H., Luo, L., Cao, W. G., Han, F. K., Shan, L. L., et al. (2017). Protective effects of paeonol on inflammatory response in IL-1β-induced human fibroblast-like synoviocytes and rheumatoid arthritis progression via modulating NF-κB pathway. *Inflammopharmacology, 25*(5), 523-532. DOI 10.1007/s10787-017-0385-5

Zhang N, Hu J-M, Zhou J, & Zhao Y-X. (2010). Chemical Constituents of *Ardisia crispa* (Thunb.) A. DC. *Natural Product Research and Development, 22*:587–589. 593.

Zhang, H., Watanabe, R., Berry, G. J., Tian, L., Goronzy, J. J., & Weyand, C. M. (2018). Inhibition of JAK-STAT signaling suppresses pathogenic immune responses in medium and large vessel vasculitis. *Circulation, 137*(18), 1934-1948. DOI: 10.1161/CIRCULATIONAHA.117.030423

Zhang, Q., Liu, J., Zhang, M., Wei, S., Li, R., Gao, Y., et al. (2019). Apoptosis induction of fibroblast-like synoviocytes is an important molecular-mechanism for herbal medicine along with its active components in treating rheumatoid arthritis. *Biomolecules, 9*(12), 795. doi:10.3390/biom9120795

Zhang, Q., Peng, W., Wei, S., Wei, D., Li, R., Liu, J., et al. (2019). Guizhi-Shaoyao-Zhimu decoction possesses anti-arthritic effects on type II

collagen-induced arthritis in rats via suppression of inflammatory reactions, inhibition of invasion & migration and induction of apoptosis in synovial fibroblasts. *Biomedicine & Pharmacotherapy, 118,* 109367. https://doi.org/10.1016/j.biopha.2019.109367

Zhang, W., & Liu, H. T. (2002). MAPK signal pathways in the regulation of cell proliferation in mammalian cells. *Cell Research, 12*(1), 9-18. https://doi.org/10.1038/sj.cr.7290105

Zhang, W., Li, F., & Gao, W. (2017). *Tripterygium wilfordii* inhibiting angiogenesis for rheumatoid arthritis treatment. *Journal of the National Medical Association, 109*(2), 142-148. DOI:10.1016/j.jnma.2017.02.007

Zhang, Y., & Zhang, B. (2016). Trichostatin A, an inhibitor of histone deacetylase, inhibits the viability and invasiveness of hypoxic rheumatoid arthritis fibroblast-like synoviocytes via PI3K/Akt signaling. *Journal of Biochemical and Molecular Toxicology, 30*(4), 163-169. DOI 10.1002/jbt.21774

Zhang, Z., Yao, L., Yang, J., Wang, Z., & Du, G. (2018). PI3K/Akt and HIF-1 signaling pathway in hypoxia-ischemia. *Molecular Medicine Reports, 18*(4), 3547-3554. https://doi.org/10.3892/mmr.2018.9375

Zhao, F., Hu, Y., Chong, C., Lu, M., Chen, L., Kan, W., et al. (2014). Ardisiphenol D, a resorcinol derivative identified from *Ardisia brevicaulis*, exerts antitumor effect through inducing apoptosis in human non-small-cell lung cancer A549 cells. *Pharmaceutical Biology, 52*(7), 797-803. https://doi.org/10.3109/13880209.2013.869231

Zhao, J., Liu, T., Xu, F., You, S., Xu, F., Li, C., et al. (2016). Anti-arthritic effects of total flavonoids from *Juniperus sabina* on Complete Freund's Adjuvant induced arthritis in rats. *Pharmacognosy Magazine, 12*(47), 178–183. https://doi.org/10.4103/0973-1296.186346

Zhao, M., Yang, B., Wang, J., Li, B., & Jiang, Y. (2006). Identification of the major flavonoids from pericarp tissues of lychee fruit in relation to their antioxidant activities. *Food Chemistry, 98*(3), 539-544. https://doi.org/10.1016/j.foodchem.2005.06.028

Zhao, O., Du, Y., Ban, D. M., & Wei, W. L. (2013). Study on bioactive components of *Ardisia crispa* (Thunb.) DC. of Miao Nationality Herba (Ⅰ). *Hubei Agricultural Sciences, 2013*(19), 45.

Zheng, Z., Sun, Y., Liu, Z., Zhang, M., Li, C., & Cai, H. (2015). The effect of curcumin and its nanoformulation on adjuvant-induced arthritis in rats. *Drug Design, Development and Therapy, 9*, 4931–4942. https://doi.org/10.2147/DDDT.S90147

Zhou, H., Wong, Y. F., Wang, J., Cai, X., & Liu, L. (2008). Sinomenine ameliorates arthritis via MMPs, TIMPs, and cytokines in rats.

Biochemical and Biophysical Research Communications, 376(2), 352-357. https://doi.org/10.1016/j.bbrc.2008.08.153

Zhou, J. J., Xie, G., & Yan, X. (2011). Encyclopedia of Molecular Structures, Pharmacological Activities, Natural Sources and Applications Traditional Chinese Medicines *3*, 47. Isolated Compounds HM.

Zhou, J., Yu, Y., Yang, X., Wang, Y., Song, Y., Wang, Q., et al. (2019). Berberine attenuates arthritis in adjuvant-induced arthritic rats associated with regulating polarization of macrophages through AMPK/NF-κB pathway. *European journal of Pharmacology, 852*, 179-188. https://doi.org/10.1016/j.ejphar.2019.02.036

Zhou, M., Qin, S., Chu, Y., Wang, F., Chen, L., & Lu, Y. (2014). Immunolocalization of MMP-2 and MMP-9 in human rheumatoid synovium. *International Journal of Clinical and Experimental Pathology, 7*(6), 3048–3056.

Zhou, Y. Z., Zhao, L. D., Chen, H., Zhang, Y., Wang, D. F., Huang, L. F., et al. (2018). Comparison of the impact of *Tripterygium wilfordii* Hook F and Methotrexate treatment on radiological progression in active rheumatoid arthritis: 2-year follow up of a randomized, non-blinded, controlled study. *Arthritis Research & Therapy, 20*(1), 70. https://doi.org/10.1186/s13075-018-1563-6

Zhu, D., Zhao, J., Lou, A., Huang, Q., OuYang, Q., Zhu, J., et al. (2019). Transforming growth factor β1 promotes fibroblast-like synoviocytes migration and invasion via TGF-β1/Smad signaling in rheumatoid arthritis. *Molecular and Cellular Biochemistry, 459*(1-2), 141-150. https://doi.org/10.1007/s11010-019-03557-0

Zhu, J. J., Wang, Z. Q., Bi, L. Q., & Liu, G. F. (2018). Role of lentivirus-mediated overexpression of SOCS3 in proliferation and apoptosis of fibroblasts-like synoviocytes in Lewis rats with adjuvant-induced rheumatoid arthritis. *International Journal of Clinical and Experimental Pathology, 11*(2), 981.

Zhu, M., Yuan, K., Lu, Q., Zhu, Q., Zhang, S., Li, X., et al. (2019). Emodin ameliorates rheumatoid arthritis by promoting neutrophil apoptosis and inhibiting neutrophil extracellular trap formation. *Molecular Immunology, 112*, 188-197. https://doi.org/10.1016/j.molimm.2019.05.010

Zimmermann, T., Kunisch, E., Pfeiffer, R., Hirth, A., Stahl, H. D., Sack, U., et al. (2000). Isolation and characterization of rheumatoid arthritis synovial fibroblasts from primary culture—primary culture cells markedly differ from fourth-passage cells. *Arthritis Research & Therapy, 3*(1), 72. https://doi.org/10.1186/ar142

Zou, L., Zhang, G., Liu, L., Chen, C., Cao, X., & Cai, J. (2016). Relationship between PI3K pathway and angiogenesis in CIA rat synovium. *American Journal of Translational Research, 8*(7), 3141–3147.