



**UNIVERSITI PUTRA MALAYSIA**

***ANTINOCICEPTIVE ACTIVITY OF A SYNTHETIC CURCUMINOID  
ANALOGUE, 5-(3, 4-DIHYDROXYPHENYL)-3-HYDROXY-1-(2-  
HYDROXYPHENYL) PENTA-2,4-DIEN-1-ONE IN MICE***

**NUR NADHIRAH BINTI KAMARUDIN**

**FPV 2019 1**



**ANTINOCICEPTIVE ACTIVITY OF A SYNTHETIC CURCUMINOID  
ANALOGUE, 5-(3, 4-DIHYDROXYPHENYL)-3-HYDROXY-1-(2-  
HYDROXYPHENYL) PENTA-2,4-DIEN-1-ONE IN MICE**

By

**NUR NADHIRAH BINTI KAMARUDIN**

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

**March 2019**

All materials contained within the thesis, including without limitation text, logos, icons, photographs and all other artwork, is copyright material of Universiti Putra Malaysia unless otherwise stated. Use may be made of any material contained within the thesis for non-commercial purposes from the copyright holder. Commercial use of material may only be made with the express, prior, written permission of Universiti Putra Malaysia.

Copyright © Universiti Putra Malaysia



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

**ANTINOCICEPTIVE ACTIVITY OF A SYNTHETIC CURCUMINOID  
ANALOGUE, 5-(3,4-DIHYDROXYPHENYL)-3-HYDROXY-1-(2-  
HYDROXYPHENYL)PENTA-2,4-DIEN-1-ONE IN MICE**

By

**NUR NADHIRAH BINTI KAMARUDIN**

**March 2019**

**Chair : Wan Mastura Shaik Mohamed Mossadeq, PhD**  
**Faculty : Veterinary Medicine**

Curcuminoids, including curcumin, are low in bioavailability and solubility, limiting their usage in bioassays and therapeutic interventions. Hence, curcuminoid analogues with better bioavailability and solubility were synthesized. This study was designed to evaluate the antinociceptive activities of a synthetic curcuminoid analogue, 5-(3,4-dihydroxyphenyl)-3-hydroxy-1-(2-hydroxyphenyl)penta-2,4-dien-1-one (DHHPD) via the mouse models of induced nociception. Adult male ICR mice were administered with DHPPD (0.1, 0.3, 1 and 3mg/kg) intraperitoneally (i.p.) 30 min prior to 0.8% acetic acid injection (i.p.), and the frequencies of abdominal constrictions were recorded. Separately, mice which received DHHPD at the same doses were subjected to the hot plate test and the response latency recorded. The response of DHHPD-treated mouse to 2.5% formalin (i.p.) was recorded at 5 min interval over a period of 30 min. Possible involvements of the opioidergic, vanilloid and glutamatergic systems were evaluated through the hot plate test, capsaicin- and glutamate-induced paw licking tests, respectively. The sedative effect of DHHPD was determined through the Rotarod test. Results showed that DHHPD (0.1, 0.3, 1 and 3mg/kg, i.p.) significantly ( $p<0.0001$ ) inhibited the abdominal constrictions by 45.9, 74.9, 90.7 and 97.3%, respectively, indicating a possible pain modulating activity at the peripheral level. Additionally, DHHPD at 1 and 3mg/kg (i.p.) significantly prolonged ( $p<0.05$ ) the response latency of mice on the hot plate, suggesting its centrally-mediated activity. DHHPD (0.1, 0.3, 1 and 3 mg/kg, i.p.) also significantly inhibited ( $p<0.05$ ) the paw licking behaviour during the neurogenic/early and inflammatory/late phases of the formalin test, thus confirming its pain modulating activity at the central and peripheral levels. The central antinociceptive activity produced by DHHPD was not antagonized by naloxone, indicating a non-involvement of the opioidergic system. Additionally, DHHPD at 0.1, 0.3, 1 and 3 mg/kg (i.p.) significantly ( $p<0.05$ ) inhibited the capsaicin- and glutamate-induced paw licking behaviour, suggesting involvement of the vanilloid and glutamatergic systems in DHHPD-induced analgesia. Furthermore, DHHPD (0.1,

0.3, 1 and 3 mg/kg, i.p.) did not induce any sedative effects, abnormal behaviour or mortality in mice. In conclusion, DHHPD (1 and 3 mg/kg, i.p.) exerted significant ( $p<0.05$ ) antinociceptive activities at the central and peripheral levels possibly through the vanilloid and glutamatergic systems.



Abstrak thesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

**ANTINOSISEPTIF AKTIVITI ANALOG CURCUMINOID SINTETIK, 5-(3,4-DIHYDROXYPHENYL)-3-HYDROXY-1-(2-HYDROXYPHENYL)PENTA-2,4-DIEN-1-ONE PADA MENCIT**

Oleh

**NUR NADHIRAH BINTI KAMARUDIN**

**Mac 2019**

**Pengerusi : Wan Mastura Shaik Mohamed Mossadeq, PhD**  
**Fakulti : Perubatan Veterinar**

Curcuminoids, termasuk curcumin, mempunyai bioavailabiliti dan keterlarutan rendah yang menghadkan penggunaannya dalam bioasai dan intervensi terapeutik. Maka, analog curcuminoid dengan bioavailabiliti dan kelarutan yang lebih baik telah disintesis. Kajian ini dijalankan untuk menilai aktiviti antinosiseptif analog curcuminoid sintetik, 5-(3,4-dihydroxyphenyl)-3-hydroxy-1-(2-hydroxyphenyl) penta-2,4-dien-1-one (DHHPD) menggunakan model nosiseptif teraruh pada mencit. Mencit jantan ICR dewasa disuntik dengan DHHPD (0.1, 0.3, 1 dan 3mg/kg) secara intraperitoneal (i.p.) 30 minit sebelum suntikan 0.8% asid asetik (i.p.), dan kekerapan konstriksi abdomen direkod. Secara berasingan, mencit yang menerima DHHPD pada dos yang sama menjalani ujian plat panas dan latensi tindak-balas terhasil direkod. Respons mencit yang dirawat dengan DHHPD terhadap 2.5% formalin (i.p.) direkodkan pada selang 5 minit dalam tempoh 30 minit. Kemungkinan penglibatan sistem opioidergik, vanilloid dan glutamatergik masing-masing dinilai melalui ujian plat panas dan ujian penjilatan kaki yang dicetuskan oleh capsaicin dan glutamat. Kesan sedatif DHHPD ditentukan melalui ujian Rotarod. Keputusan menunjukkan bahawa DHHPD (0.1, 0.3, 1 dan 3mg/kg, i.p.) dengan ketara ( $p < 0.0001$ ) menghalang konstriksi abdomen sebanyak 45.9, 74.9, 90.7 dan 97.3%, menunjukkan kemungkinan aktiviti modulasi rasa sakit di peringkat periferi. Di samping itu, DHHPD pada 1 dan 3mg/kg (i.p.) secara ketara ( $p < 0.05$ ) memanjangkan latensi tindak balas mencit di atas plat panas, mencadangkan aktiviti DHHPD secara berpusat. DHHPD (0.1, 0.3, 1 dan 3 mg/kg, i.p.) secara ketara ( $p < 0.05$ ) menghalang tingkah laku menjilat kaki semasa fasa neurogenik/awal dan keradangan/lewat dalam ujian formalin, justeru mengesahkan aktiviti antinosiseptif di peringkat pusat dan periferi. Aktiviti antinosiseptif pusat yang dihasilkan oleh DHHPD tidak diterbalikkan oleh naloxone, menunjukkan ketidaklibatan sistem opioidergik. Di samping itu, DHHPD pada 0.1, 0.3, 1 dan 3 mg/kg (i.p.) dengan ketara ( $p < 0.05$ ) menghalang tingkah laku menjilat kaki yang dicetus oleh capsaicin dan glutamat, mencadangkan penglibatan sistem vanilloid dan

glutamatergik dalam analgesia yang disebabkan oleh DHHPD. Tambahan pula, DHHPD (0.1, 0.3, 1 dan 3 mg/kg, i.p.) tidak menyebabkan sebarang kesan sedatif, kelakuan tidak normal atau kematian pada mencit. Kesimpulannya, DHHPD (1 dan 3 mg/kg, i.p.) menghasilkan aktiviti antinosiseptif yang ketara ( $p < 0.05$ ) di peringkat pusat dan periferi kemungkinan melalui sistem vanilloid dan glutamatergik.



## ACKNOWLEDGEMENTS

Alhamdulillah and praise to Allah for giving me the chance to pursue my study and giving me the strength and courage that I needed to go through my postgraduate study and finally graduate.

Firstly, I would like to thank Dr Wan Mastura Shaik Mohamed Mossadeq, my supervisor, and Prof. Dr Mohd Roslan Sulaiman, my co-supervisor. Thank you for always being there for me and supervising me throughout my Master's program.

Next, to my team members; Nadia Hisamuddin, Rasyidah Ryta Ayumi Mohd Rasol and Madihah Abdul Talib, thank you for always being there for me and helping me throughout the experiments.

To all staff and students of the Physiology Laboratory of the Faculty of Veterinary Medicine, especially Kak Ros, thank you for helping me. To all staff and students of the Physiology Laboratory of the Faculty of Medicine and Health Sciences especially Ong Hui Ming, Ahmad Farhan Ahmad Azmi, Kak Yati and Kak Ngah, thank you for helping me throughout the experiments, day by day as well as Dr. Faridah Abas and Dr Sze Wei Leong. To each and every person in Universiti Putra Malaysia that I have met throughout my study for over 2 and a half years-Thank you for helping me directly or indirectly.

Last but not least, to my mother, Norlizah binti Yamaludin who have always trusted me to further my study and supporting me all the time. Thank you Ma, I love you. Thank you to my sisters: Kak Bilah, Nora, Ina and Maya, who are always ready to listen to my concerns and giving me good solutions and advice. Thank you. Kak Yah loves you all.

Nur Nadhirah Binti Kamarudin



This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

**Wan Mastura Shaik Mohamed Mossadeq, PhD**

Senior Lecturer  
Faculty of Veterinary Medicine  
Universiti Putra Malaysia  
(Chairman)

**Mohd Roslan Sulaiman, PhD**

Professor  
Faculty of Medicine and Health Sciences  
Universiti Putra Malaysia  
(Member)

---

**ROBIAH BINTI YUNUS, PhD**

Professor and Dean  
School of Graduate Studies  
Universiti Putra Malaysia

Date:

## 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.: Nur Nadhirah Binti Kamarudin (GS45786)

## 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

Dr. Wan Mastura Shaik Mohamed Mossadeq

Signature: \_\_\_\_\_

Name of Member of  
Supervisory Committee

Prof. Dr. Mohd Roslan Sulaiman

## TABLE OF CONTENTS

	<b>Page</b>
<b>ABSTRACT</b>	i
<b>ABSTRAK</b>	iii
<b>ACKNOWLEDGEMENTS</b>	v
<b>APPROVAL</b>	vi
<b>DECLARATION</b>	viii
<b>LIST OF TABLES</b>	xii
<b>LIST OF FIGURES</b>	xiii
<b>LIST OF ABBREVIATIONS</b>	xiv
<b>CHAPTER</b>	
<b>1 INTRODUCTION</b>	<b>1</b>
<b>2 LITERATURE REVIEW</b>	<b>4</b>
2.1 Pain and nociception	4
2.2 Pain: Induction, transmission and interpretation	5
2.3 Analgesia and antinociception	8
2.4 Analgesics	8
2.5 Non-narcotic analgesics	8
2.6 Non-steroidal anti-inflammatory drugs	9
2.7 NSAIDs: Mechanism of action and side effects	9
2.8 Narcotic analgesics	12
2.9 Opioids	12
2.10 Pain and the vanilloid system	13
2.11 Pain and the glutamatergic system	14
2.12 Alternatives to conventional analgesics	14
2.13 <i>Curcuma longa</i>	15
2.14 Chemical constituents of <i>Curcuma longa</i>	17
2.15 Analogues of curcumin	19
2.16 Synthetic curcuminoid analogues: Bioactivities	19
<b>3 MATERIALS AND METHODS</b>	<b>21</b>
3.1 Synthesis of 5-(3,4-dihydroxyphenyl)-3-hydroxy-1-(2-hydroxyphenyl)penta-2,4-dien-1-one	21
3.2 Animals	21
3.3 Drugs and chemicals	21
3.4 Preliminary/pilot study	22
3.5 Acute toxicity test	22
3.6 Acetic acid-induced writhing test	22
3.7 Hot-plate test	23
3.8 Formalin-induced paw licking test	23
3.9 DHHPD-induced analgesia: Mechanism of	23

	action	
	3.9.1 The involvement of the opioidergic system in DHHPD-induced analgesia	23
	3.9.2 The involvement of the vanilloid system in DHHPD-induced analgesia	24
	3.9.3 The involvement of glutamatergic system in DHHPD-induced analgesia	24
	3.10 The Rotarod test	24
	3.11 Statistical analysis	25
<b>4</b>	<b>RESULTS</b>	26
	4.1 Acute toxicity test	26
	4.2 Acetic-acid induced writhing test	26
	4.3 Hot-plate test	29
	4.4 Formalin-induced paw licking test	31
	4.5 DHHPD-induced analgesia: Mechanism of action	33
	4.5.1 The involvement of the opioidergic system in DHHPD-induced analgesia	33
	4.5.2 The involvement of vanilloid system in DHHPD-induced analgesia	33
	4.5.3 The involvement of glutamatergic system in DHHPD-induced analgesia	35
	4.6 The Rotarod	37
<b>5</b>	<b>DISCUSSION</b>	39
<b>6</b>	<b>SUMMARY, CONCLUSION AND RECOMMENDATIONS FOR FUTURE RESEARCH</b>	46
	<b>REFERENCES</b>	47
	<b>APPENDICES</b>	55
	<b>BIODATA OF STUDENT</b>	74
	<b>LIST OF PUBLICATIONS</b>	75

## LIST OF TABLES

<b>Table</b>		<b>Page</b>
1	Taxonomic hierarchy of <i>Curcuma longa</i>	16
2	Summary of the effect of DHPD on mice behaviours and mortalities in the acute toxicity test	26
3	Summary of the effect of DHPD on the physical characteristics of mice vital organs in the acute toxicity study	27
4	Effect of DHPD against the hot-plate test in mice	30



## LIST OF FIGURES

Figure		Page
1	The spinal and supraspinal pathways of pain	7
2	The mechanism of action of NSAIDs	11
3	(a) <i>C. longa</i> plant (b) <i>C. longa</i> rhizome (c) <i>C. longa</i> powder (d) DHHPD powder	16
4	The chemical structure of curcuminoids: curcumin, demethoxycurcumin and bisdemethoxycurcumin	18
5	The chemical structure of 5-(3,4-dihydroxyphenyl)-3-hydroxy-1-(2-hydroxyphenyl)penta-2,4-dien-1-one (DHHPD)	21
6	The effect of DHHPD against the acetic acid-induced abdominal constriction test	28
7	The effect of DHHPD against the formalin-induced paw licking test (A: Early phase, B: Late phase)	32
8	The effect of DHHPD against the capsaicin-induced paw licking test	34
9	The effect of DHHPD against the glutamate-induced paw licking test	36
10	The effect of DHHPD against the Rotarod test	38

## LIST OF ABBREVIATIONS

3,5DHPG	(S)-3,5-Dihydroxyphenylglycine
AIDS	Acquired immune deficiency syndrome
AMPA	$\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ASA	Acetylsalicylic acid/Aspirin
BBr <sub>3</sub>	Boron tribromide
BC	Before Christ
BDMC	Bisdemethoxycurcumin
BHMBC	2,6-bis-(4-hydroxy-3-methoxybenzylidene)cyclohexane
BHMC	2,6-bis-(4-hydroxy-3-methoxybenzylidene)cyclohexanone
cGMP	Cyclic Guanosine Monophosphate
C-NMR	Carbon-13 Nuclear Magnetic Resonance
CNS	Central nervous system
CO <sub>2</sub>	Carbon dioxide
COX	Cyclooxygenase
DHHPD	5-(3,4-dihydroxyphenyl)-3-hydroxy-1-(2-hydroxyphenyl)penta-2,4-dien-1-one
DMC	Demethoxycurcumin
DMSO	Dimethyl sulfoxide
DRG	Dorsal root ganglion
EA	Ethyl acetate
GABA	Gamma-aminobutyric acid
GTP	Guanosine triphosphate
HCl	Hydrochloric acid
H-NMR	Hydrogen Nuclear Magnetic Resonance
HPLC	High performance liquid chromatography
IACUC	Institutional Animal Care and Use Committee
IFN	Interferon
iGluRs	Ionotropic glutamate receptors



KA	Kainate
LOX	Lipoxygenase
LPS	Lipopolysaccharide
mGluRs	Metabotropic glutamate receptors
MOR	Morphine
MPEP	2-Methyl-6-(phenylethynyl)pyridine
MTEP	3-[(2-Methyl-4-thiazolyl)ethynyl]pyridine
NMDA	N-methyl-D-aspartate
NO	Nitric oxide
NSAIDs	Non-steroidal anti-inflammatory drugs
PNS	Peripheral nervous system
POCl <sub>3</sub>	Phosphoryl chloride
ROS	Reactive oxygen species
TG	Terminal ganglion
TRPV1	Transient Receptor Potential Vanilloid 1

## CHAPTER 1

### INTRODUCTION

The quality of a person's life may be affected by pain, often resulting in increased medical bills and expenses (Zhang et al., 2014). Pain is described as sensations or emotional encounters that are associated with possible or impending tissue destruction (Basbaum et al., 2010; Merskey & Bogduk, 1994). Before the definition of pain was coined by modern physiologist, pain is explained in terms of magical and religious ways. Prior to modern medicine, pain was described as a condition which resulted from the intrusion of dangerous spirits into the body thus causing an unpleasant and distressful experience. Thus, in the past, people often depend on magical spells, religious therapies and rituals to reduce or eliminate pain altogether (Perl, 2011).

Today, pain management strategies typically depend on non-steroidal anti-inflammatory drugs (NSAIDs), steroidal anti-inflammatory drugs and opiates. Even though these drugs have been used widely to relieve pain, their use are usually accompanied with adverse effects such as gastrointestinal ulcer (Honey et al., 2012), respiratory depression (Zhang et al., 2014), and haemorrhage (Deghrigue et al., 2015).

Therefore, the use of natural products as an alternative to the present drugs minus the side effects is warranted. For over 7000 years, various extracts of plants had been used as analgesics (Grant, 2006). Rhizomes from the Zingiberaceae family such as *Zingiber zerumbet* (pinecone) have been used by the Chinese, Malays, Indians and Hawaiians as an alternative medication for cuts, pyrexia, bruises and inflammation (Yob et al., 2011). In addition, *Boesenbergia pandurata* or fingerroot, has been used by Indonesians to treat inflammation, fungal infection and vaginal infections (Chahyadi et al., 2014).

Aside from pinecone and fingerroot, turmeric or *Curcuma longa* has been identified as another Zingiberaceae rhizome with medicinal properties. Turmeric has been used since the Ayuverdic era to treat cough, diabetic wounds, rheumatism and sinusitis (Suloon et al., 2011; Ammon et al., 1992).

In modern medicine, turmeric has been used to treat cancer, dermatitis, AIDS and cholesterolaemia (Suloon et al., 2011; Azuine & Bhide, 1992; Ammon & Wahl, 1991; Kuttan et al., 1985). According to Suloon et al. (2011), turmeric contains essential oils, curcuminoids, starch and oleoresin. Its essential oil was reported to produce anti-inflammatory (Arora et al., 1971), anti-hepatotoxic (Kiso et al., 1983), anti-bacterial (Singh et al., 2002), antioxidant (Singh et al., 2008) and anti-

platelet (Prakash et al., 2011) activities. In addition, its curcuminoids have demonstrated significant antioxidant, analgesic and anti-inflammatory activities (Anand et al., 2008). However, the use of curcuminoids in medicine and research is limited due to their poor bioavailability and instability under physiological conditions (Liang et al., 2009). Therefore, analogues of curcuminoids with better bioavailability and pharmacokinetic profiles were synthesized to overcome these limitations. For instance, a new synthetic analogue of curcuminoid known as 2,6-bis-(4-hydroxy-3-methoxybenzylidene) cyclohexanone (abbrev. BHMC), has been reported to possess central and peripheral antinociceptive activities (Ming-Tatt et al., 2012), indicating that the synthetic analogues of curcuminoids could be as beneficial as the natural analogues of curcuminoids in reducing pain. The efficiency of these synthetic analogues in reducing certain adverse biological activities is attributed to their structural conformation such as the presence of certain functional groups, which allows these compounds to be more soluble in water, remain in the circulation for a longer time and hence, provide a better absorption rate into the tissues or cells affected. Moreover, several synthetic curcuminoid analogues including 5-(3,4-dihydroxyphenyl)-3-hydroxy-1-(2-hydroxyphenyl)penta-2,4-dien-1-one (DHHPD) or Compound 97, had been shown to induce good nitric oxide (NO) inhibition activity in the IFN- $\gamma$ /LPS-stimulated RAW 264.7 macrophages (Leong et al., 2014). The absorption, distribution, metabolism, excretion and toxicity analysis (ADMET) and, toxicity prediction of compounds using computer-aided technology (TOPKAT) conducted on DHHPD in the same study indicated that this compound has high aqueous solubility, non-hepatotoxic, possess good human intestinal absorption (HIA) activities, no skin-sensitizing effect or has any ocular irritating properties, and has low blood-brain barrier activities. Furthermore, the presence of a hydroxyl group on both of its aromatic rings renders it more soluble than other natural or synthetic diarylpentanoids. The *in vivo* effects of DHHPD was however, not explored. The current study evaluates the analgesic activity of a newly designed synthetic analogue of curcuminoid, referred to as 5-(3,4-dihydroxyphenyl)-3-hydroxy-1-(2-hydroxyphenyl)penta-2,4-dien-1-one.

### **1.1 Objectives of the study**

The objectives of this research were:

1. To determine the acute toxicity effects of DHHPD in mice
2. To evaluate the peripheral and central antinociceptive activities of DHHPD using the mouse models of induced nociception
3. To determine the participation of opioidergic, vanilloid and glutamatergic systems in DHHPD-induced analgesia
4. To determine the sedative effect of DHHPD in mice

### **1.2 Hypotheses of the study**

The null hypotheses for this study include:

1. DHHPD does not exert acute toxicity effects in mice

2. DHHPD exerts peripheral and central antinociceptive activities in the mouse models of induced nociception
3. The opioidergic, vanilloid and glutamatergic systems participate in DHHPD-induced analgesia
4. DHHPD does not exert a sedative effect in mice

### 1.3 Significance of study

Natural and synthetic curcuminoids have been proven to exhibit good antinociceptive and anti-inflammatory properties *in vivo* and *in vitro*. However, synthetic curcuminoids with better pharmacokinetic profiles such as good solubility and bioavailability may assist in the healing process of the trauma-inflicted tissues through better absorption rate, distribution, metabolism and excretion. Furthermore, DHHPD has been proven to exert anti-inflammatory activity *in vitro*. Therefore, knowledge regarding the synthetic curcuminoid's *in vivo* and *in vitro* pharmacological activities may be used by scientists to further enhance the beneficial activity of the compound, either by enhancing its activities or inhibiting/modulating specific pain pathways, consequently reducing or even eliminating pain altogether. Lastly, turmeric and curcumin are cheap sources of analgesic and anti-inflammatory agents, and can be found in the tropics all year round. Hence, the cost of manufacturing new analgesic drugs from this rhizome may be further reduced due their abundant supply and affordable price.

## REFERENCES

- Ahmad Wani, T., Kumar, D., Prasad, R., Verma, P. K., Sardar, K. K., Tandan, S. K., & Kumar, D. (2012). Analgesic activity of the ethanolic extract of *Shorea robusta* resin in experimental animals. *Indian Journal of Pharmacology*, 44(4), 493–499.
- Ahsan, H., Parveen, N., Khan, N., & Hadi, S. (1999). Pro-oxidant, anti-oxidant and cleavage activities on DNA of curcumin and its derivatives demethoxycurcumin and bisdemethoxycurcumin. *Chemico-Biological Interactions*, 121, 161–175.
- Ali Hammad, Y., Atalla, S., & Alabdrubalnabi, Z. (2012). Efficacy and side effects of small versus large bolus size morphine patient controlled analgesia combined with paracetamol. *Egyptian Journal of Anaesthesia*, 28(1), 79–82.
- Ammon, H., & Wahl, M. (1991). Pharmacology of *Curcuma longa*. *Planta Medica*, 57(1), 1–7.
- Ammon, H. P. T., Anazodo, M. I., Safayhi, H., Dhawan, B. N., & Srimal, R. C. (1992). Curcumin: a potent inhibitor of leukotriene B4 formation in rat peritoneal polymorphonuclear neutrophils (PMNL). *Planta Medica*, 58(2), 226–226.
- Anand, P., Thomas, S. G., Kunnumakkara, A. B., Sundaram, C., Harikumar, K. B., Sung, B., Tharakan, S. T., Misra, K., Priyasarsini, I. K., Rajasekharan, K.N. & Aggarwal, B. B. (2008). Biological activities of curcumin and its analogues (Congeners) made by man and Mother Nature. *Biochemical Pharmacology*, 76(11), 1590–1611.
- Anto, R., George, J., Babu, K., Rajasekharan, K., & Kuttan, R. (1996). Antimutagenic and anticarcinogenic activity of natural and synthetic curcuminoids. *Mutation Research*, 370, 127–131.
- Antony, B., Benny, M., & Rao, S. B. (2005). Enhancing the absorption of curcuminoids. *Journal of Spices India*, 76, 23–26.
- Arora, R. B., Kapoor, V., Basu, N., & Jain, A. P. (1971). Anti-inflammatory studies on *Curcuma longa* (turmeric). *The Indian Journal of Medical Research*, 59(8), 1289–1295.
- Audette, J. F., & Bailey, A. (2008). *Integrative Pain Medicine: The Science and Practice of Complementary and Alternative Medicine in Pain Management*. Totowa, NJ: Humana Press.
- Azmi, F., Leong, S. W., Abas, F., Ming, O. H., Perimal, E. K., Akira, A., Israf, D.A., & Sulaiman, M. R. (2016). Antinociceptive effect of 2-benzoyl-6-(3,4-dihydroxybenzylidene)cyclohexen-1-ol on nociception induced models in mice. *Journal of Pharmacological and Toxicological Investigations*, 2(1), 1–9.
- Azuine, M. A., & Bhide, S. V. (1992). Chemopreventive effect of turmeric against stomach and skin tumors induced by chemical carcinogens in Swiss mice. *Nutrition and Cancer*, 17(1), 77–83.
- Basbaum, A. I., Bautista, D. M., Scherrer, G., & Julius, D. (2010). Cellular and molecular mechanisms of pain. *Cell*, 139(2), 267–284.
- Bastos, G. N. T., Santos, A. R. S., Ferreira, V. M. M., Costa, A. M. R., Bispo, C. I., Silveira, A. J. A., & Do Nascimento, J. L. M. (2006). Antinociceptive effect of the aqueous extract obtained from roots of *Physalis angulata* L. on mice. *Journal of Ethnopharmacology*, 103(2), 241–245.
- Bavry, A. A., Khaliq, A., Gong, Y., Handberg, E. M., Cooper-DeHoff, R. M., & Pepine, C. J. (2011). Harmful effects of NSAIDs among patients with hypertension and coronary artery disease. *The American Journal of Medicine*, 124(7), 614–620.

- Beirith, A., Santos, A. R. S., & Calixto, J. B. (2002). Mechanisms underlying the nociception and paw oedema caused by injection of glutamate into the mouse paw. *Brain Research*, 924(2), 219–228.
- Beirith, A., Santos, A. R. S., Rodrigues, A. L. S., Creczynski-Pasa, T. B., & Calixto, J. B. (1998). Spinal and supraspinal antinociceptive action of dipyrone in formalin, capsaicin and glutamate tests. Study of the mechanism of action. *European Journal of Pharmacology*, 345(3), 233–245.
- Berry, P. H., Covington, E. C., Dahl, J. L., Katz, J. A., & Miaskowski, C. (2001). *Pain: Current Understanding of Assessment, Management, and Treatments*. America: American Pain Society.
- Bleakman, D., Alt, A., & Nisenbaum, E. S. (2006). Glutamate receptors and pain. *Seminars in Cell & Developmental Biology*, 17(5), 592–604.
- Botting, R. M. (2010). Vane's discovery of the mechanism of action of aspirin changed our understanding of its clinical pharmacology. *Pharmacological Reports*, 62(3), 518–525.
- Calabrese, V., Mancuso, C., Calvani, M., Rizzarelli, E., Butterfield, D. A., Maria, A., & Stella, G. (2007). Nitric oxide in the central nervous system: neuroprotection versus neurotoxicity. *Nature Reviews Neuroscience*, 8(October), 766–775.
- Capone, M. L., Tacconelli, S., Rodriguez, L. G., & Patrignani, P. (2010). NSAIDs and cardiovascular disease: transducing human pharmacology results into clinical read-outs in the general population. *Pharmacological Reports*, 62(3), 530–535.
- Caterina, M., Schumacher, M., Timinaga, M., & Rosen, T. (1997). The capsaicin receptor: a heat-activated ion channel in the pathway. *Nature Reviews Neuroscience*, 389(October), 816–824.
- Caterina, M. J., Leffler, A., Malmberg, A. B., Martin, W. J., Trafton, J., Petersen-Zeit, K. R., Koltzenburg, M., Basbaum, A. I., & Julius, D. (2000). Impaired nociception and pain sensation in mice lacking the capsaicin receptor. *Science*, 288(5464), 306–313.
- Cauffield, J. S. (2012). The Psychosocial Aspects of Complementary and Alternative Medicine. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, 20(11), 1289–1294.
- Chahyadi, A., Hartati, R., & Wirasutisna, K. R. (2014). *Boesenbergia pandurata* roxb., an indonesian medicinal plant: Phytochemistry, biological activity, plant biotechnology. *Procedia Chemistry*, 13, 13–37.
- Chandrasekharan, N. V., Dai, H., Roos, K. L. T., Evanson, N. K., Tomsik, J., Elton, T. S., & Simmons, D. L. (2002). COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: Cloning, structure, and expression. *Proceedings of the National Academy of Sciences*, 99(21), 13926–13931.
- Cheung, C. K., Wyman, J. F. & Halcon, L. L. (2007). Use of complementary and alternative therapies in community-dwelling older adults. *Journal of Alternative and Complementary Medicine*, 13(9), 997–1006.
- Conney, A., Lysz, T., Ferraro, T., Abidi, T., Manchand, P., Laskin, J., & Huang, M. T. (1991). Inhibitory effect of curcumin and some related dietary compounds on tumor promotion and arachidonic acid metabolism in mouse skin. *Advances in Enzyme Regulation*, 31, 385–396.
- Couto, V. M., Vilela, F. C., Dias, D. F., Santos, M. H., Soncini, R., Nascimento, C. G. O., & Giusti-paiva, A. (2011). Antinociceptive effect of extract of *Emilia sonchifolia* in mice. *Journal of Ethnopharmacology*, 134(2011), 348–353.



- Dalal, S., & Melzack, R. (1998). Potentiation of Opioid Analgesia by Psychostimulant Drugs : A Review. *Journal of Pain and Symptom Management*, 16(4), 245–253.
- Dawkins, M. S. (1980). *Animal suffering: The science of animal welfare*. London, UK: Chapman and Hall.
- Deghrigue, M., Festa, C., Ghribi, L., D'Auria, M. V., De Marino, S., Ben Jannet, H., & Bouraoui, A. (2015). Anti-inflammatory and analgesic activities with gastroprotective effect of semi-purified fractions and isolation of pure compounds from Mediterranean gorgonian *Eunicella singularis*. *Asian Pacific Journal of Tropical Medicine*, 8(8), 606–611.
- De Sousa, D. P. (2011). Analgesic-like activity of essential oils constituents. *Molecules*, 16(3), 2233–2252.
- Farouk, L., Laroubi, A., Aboufatima, R., Benharref, A., & Chait, A. (2008). Evaluation of the analgesic effect of alkaloid extract of *Peganum harmala* L.: Possible mechanisms involved. *Journal of Ethnopharmacology*, 115, 449–454.
- Fattori, V., Hohmann, M., Rossaneis, A., Pinho-Ribeiro, F., & Verri, W. (2016). Capsaicin: Current Understanding of Its Mechanisms and Therapy of Pain and Other Pre-Clinical and Clinical Uses. *Molecules*, 21(844), 1-33.
- Flagg, A., McGreevy, K., & Williams, K. (2012). Spinal cord stimulation in the treatment of cancer-related pain: Back to the origins. *Current Pain and Headache Reports*, 16(4), 343–349.
- Garcia, M., Fernandez, M., Alvarez, A., & Saenz, M. (2004). Antinociceptive and anti-inflammatory effect of the aqueous extract from leaves of *Pimenta racemosa* var. *ozua* (Mirtaceae). *Journal of Ethnopharmacology*, 91(1), 69–73.
- Gebhart, G. F., Basbaum, A. I., Bird, S. J., Flecknell, P., Goodly, L., Karas, A. Z., Soriano, S. G. (2009). *Recognition and Alleviation of Pain and Distress in Laboratory Animals*. Washington: The National Academies Press.
- Goel, A., Kunnumakkara, A. B., & Aggarwal, B. B. (2008). Curcumin as “Curecumin”: From kitchen to clinic. *Biochemical Pharmacology*, 75(4), 787–809.
- Gonzalez-Trujano, M., Pena, E., Martinez, A., Moreno, J., Guevara-Fefer, P., Deciga-Campos, M., & Lopez-Moreno, F. (2007). Evaluation of the antinociceptive effect of *Rosmarinus officinalis* L. using three different experimental models in rodents. *Journal of Ethnopharmacology*, 111, 476–482.
- Graham, G. G., Davies, M. J., Day, R. O., Mohamudally, A., & Scott, K. F. (2013). The modern pharmacology of paracetamol: Therapeutic actions, mechanism of action, metabolism, toxicity and recent pharmacological findings. *Inflammopharmacology*, 21(3), 201–232.
- Grant, D. (2006). *Pain Management in Small Animals*. Philadelphia, USA: Elsevier.
- Guilhon, C. C., Rahayu, I., Wahab, A., Boylan, F., & Fernandes, P. D. (2015). Central Antinociceptive and Mechanism of Action of *Pereskia bleo* Kunth Leaves Crude Extract , Fractions , and Isolated Compounds. *Evidence-Based Complementary and Alternative Medicine*, 2015, 1–12.
- Hajhashemi, V., Ghannadi, A., & Pezeshkian, S. K. (2002). Antinociceptive and anti-inflammatory effects of *Satureja hortensis* L. extracts and essential oil. *Journal of Ethnopharmacology*, 82(2–3), 83–87.
- Hitner, H., & Nagle, B. (2002). *Basic Pharmacology*. New York, USA: Glencoe/McGraw-Hill Education.
- Honey, Thareja, S., Kumar, M., & Sinha, V. R. (2012). Self-organizing molecular field analysis of NSAIDs: assessment of pharmacokinetic and physicochemical

- properties using 3D-QSPkR approach. *European Journal of Medicinal Chemistry*, 53, 76–82.
- Hong, J., Bose, M., Ju, J., Ryu, J. H., Chen, X., Sang, S., & Yang, C. S. (2004). Modulation of arachidonic acid metabolism by curcumin and related  $\beta$ -diketone derivatives: Effects on cytosolic phospholipase A2, cyclooxygenases and 5-lipoxygenase. *Carcinogenesis*, 25(9), 1671–1679.
- Hossain, C. F., Al-Amin, M., Rahman, K. M. M., Sarker, A., Alam, M. M., Chowdhury, M. H., & Sultana, G. N. N. (2015). Analgesic principle from *Curcuma amada*. *Journal of Ethnopharmacology*, 163, 273–277.
- Hughes, Miller, & Briar. (2007). *Nervous System*. Scotland: Mosby Elsevier.
- Ismail, N., Ming-Tatt, L., Lajis, N., Akhtar, M., Akira, A., Perimal, E., Israf, D.A., & Sulaiman, M. (2016). Antinociceptive effect of 3-(2,3-Dimethoxyphenyl)-1-(5-methylfuran-2-yl)prop-2-en-1-one in mice models of induced nociception. *Molecules*, 21(1077), 1–16.
- Jantan, I., Rafi, I. A. A., & Jalil, J. (2005). Platelet-activating factor (PAF) receptor-binding antagonist activity of Malaysian medicinal plants. *Phytomedicine: International Journal of Phytotherapy and Phytopharmacology*, 12(1–2), 88–92.
- Jurenka, J. S. (2009). Anti-inflammatory properties of Curcumin, a major constituent of *Curcuma longa*: A review of preclinical and clinical research. *Alternative Medicine Review*, 14(2), 142–153.
- Katzung, B. G. (2005). *Basic and Clinical Pharmacology*. Connecticut, USA: Appleton and Lange.
- Khatun, A., Imam, M., & Rana, M. (2015). Antinociceptive effect of methanol extract of leaves of *Persicaria hydropiper* in mice. *BMC Complementary and Alternative Medicine*, 15(63), 1–8.
- Kiso, Y., Suzuki, Y., Watanabe, N., Oshima, Y., & Hikino, H. (1983). Antihepatotoxic Principles of *Curcuma longa* Rhizomes. *Planta Medica*, 49(11), 185–187.
- Kumar, M., Shete, A., & Akbar, Z. (2010). A Review on Analgesic: From Natural Sources. *International Journal of Pharmaceutical & Biological Archives*, 1(2), 95–100.
- Kuttan, R., Bhanumathy, P., Nirmala, K., & George, M. C. (1985). Potential anticancer activity of turmeric (*Curcuma longa*). *Cancer Letters*, 29(2), 197–202.
- Lebovitz, E. E., Keller, J. M., Kominsky, H., Kaszas, K., Maric, D., & Iadarola, M. J. (2012). Positive allosteric modulation of TRPV1 as a novel analgesic mechanism. *Molecular Pain*, 8(70), 1–14.
- Lee, K. H., Farida, F. H., Syahida, A., Abas, F., Shaari, K., Israf, D. A., & Lajis, N. H. (2009). Synthesis and biological evaluation of curcumin-like diarylpentanoid analogues for anti-inflammatory, antioxidant and anti-tyrosinase activities. *European Journal of Medicinal Chemistry*, 44(8), 3195–3200.
- Leong, S. W., Mohd Faudzi, S. M., Abas, F., Mohd Aluwi, M. F. F., Rullah, K., Wai, L. K., Abdul Bahari, M. N., Ahmad, S., Tham, C. L., Shaari, K., & Lajis, N. H. (2014). Synthesis and sar study of diarylpentanoid analogues as new anti-inflammatory agents. *Molecules*, 19(10), 16058–16081.
- Li, J.-X., Zhang, Y., & Winter, J. C. (2011). Morphine-induced antinociception in the rat: Supra-additive interactions with imidazoline I2 receptor ligands. *European Journal of Pharmacology*, 669(1), 59–65.
- Liang, G., Shao, L., Wang, Y., Zhao, C., Chu, Y., Xiao, J., Zhao, Y., Li, X., & Yang, S. (2009). Exploration and synthesis of curcumin analogues with improved structural stability both in vitro and in vivo as cytotoxic agents. *Bioorganic & Medicinal Chemistry*, 17, 2623–2631.



- Mallet, C., Eschalier, A., & Daulhac, L. (2017). Paracetamol: Update on its Analgesic Mechanism of Action, *In Pain Relief - From Analgesics to Alternative Therapies* (pp. 207–224). Clermont-Ferrand, France : IntechOpen.
- Marks, J., & Ogbru, O. (2015). Non-steroidal anti-inflammatory drugs. Retrieved 28 July 2017 from [https://www.medicinenet.com/nonsteroidal\\_antiinflammatory\\_drugs/article.htm](https://www.medicinenet.com/nonsteroidal_antiinflammatory_drugs/article.htm)
- Meeks, N. M., Glass, J. S., & Carroll, B. T. (2015). Chronic pain management in dermatology. *Journal of the American Academy of Dermatology*, 73(4), 563–573.
- Merskey, H., & Bogduk, N. (1994). *Classification of chronic pain : Descriptions of chronic pain syndromes and definition of pain terms*. Seattle: International Association for the Study of Pain (IASP).
- Milind, P., & Monu, Y. (2013). Laboratory models for screening analgesics. *International Research Journal of Pharmacy*, 4(1), 15–19.
- Millan, M. J. (1999). The induction of pain: An integrative review. *Progress in Neurobiology*, 57(1), 1–164.
- Ming-Tatt, L., Khalivulla, S. I., Akhtar, M. N., Mohamad, A. S., Perimal, E. K., Khalid, M. H., Akira, A., Lajis, N., Israf, D. A., & Sulaiman, M. R. (2012). Antinociceptive activity of a synthetic curcuminoid analogue, 2,6-bis-(4-hydroxy-3-methoxybenzylidene)cyclohexanone, on nociception-induced models in mice. *Basic and Clinical Pharmacology and Toxicology*, 110(3), 275–282.
- Mohamad, A. S., Akhtar, M. N., Zakaria, Z. A., Perimal, E. K., Khalid, S., Mohd, P. A., Khalis, M.H., Israf, D.A., Lajis, N.H., & Sulaiman, M. R. (2010). Antinociceptive activity of a synthetic chalcone, flavokawin B on chemical and thermal models of nociception in mice. *European Journal of Pharmacology*, 647(1–3), 103–109.
- Mohankumar, S., & McFarlane, J. R. (2011). An aqueous extract of *Curcuma longa* (turmeric) rhizomes stimulates insulin release and mimics insulin action on tissues involved in glucose homeostasis in vitro. *Phytotherapy Research*, 25, 396–401.
- Moniruzzaman, M., & Imam, M. Z. (2014). Evaluation of antinociceptive effect of methanolic extract of leaves of *Crataeva nurvala* Buch.-Ham. *BMC Complementary and Alternative Medicine*, 14(1), 354.
- Nawaz, A., Khan, G. M., Hussain, A., Ahmad, A., & Khan, A. (2011). Curcumin : a natural product of biological. *Gomal University Journal of Research*, 27(1), 07–14.
- Nichols, C., Youssef, D., Harris, R., & Jha, A. (2006). Microwave- assisted synthesis of curcumin analogs. *Archive for Organic Chemistry*, 13, 64–72.
- Nucci-Martins, C., Martins, D. F., Nascimento, L. F., Venzke, D., Oliveira, A. S., Frederico, M. J. S., Silva, F. R. M. B., Brighente, I. M. C., Pizzolatti, M.G., & Santos, A. R. S. (2015). Ameliorative potential of standardized fruit extract of *Pterodon pubescens* Benth on neuropathic pain in mice: Evidence for the mechanisms of action. *Journal of Ethnopharmacology*, 175, 273–286.
- Ong, H. M., Mohamad, A. S., Makhtar, N., Khalid, M. H., Khalid, S., Perimal, E. K., Mastuki, S. N., Zakaria, Z. A., Lajis, N., Israf, D. A., & Sulaiman, M. R. (2011). Antinociceptive activity of methanolic extract of *Acmella uliginosa* (Sw.) Cass. *Journal of Ethnopharmacology*, 133(1), 227–233.
- Osikowicz, M., Mika, J., & Przewlocka, B. (2013). The glutamatergic system as a target for neuropathic pain relief. *Experimental Physiology*, 98(2), 372–384.
- Ossipov, M. H., Dussor, G. O., & Porreca, F. (2010). Central modulation of pain. *The Journal of Clinical Investigation*, 120(11), 3779–3787.

- Page, G., Khidir, F. A. L., Pain, S., Barrier, L., Fauconneau, B., Guillard, O., Alain, P., & Hugon, J. (2006). Group I metabotropic glutamate receptors activate the p70S6 kinase via both mammalian target of rapamycin (mTOR) and extracellular signal-regulated kinase (ERK 1/2) signaling pathways in rat striatal and hippocampal synaptoneuroosomes. *Neurochemistry International*, 49(4), 413–421.
- Park, H. J., & Moon, D. E. (2010). Pharmacologic management of chronic pain. *The Korean Journal of Pain*, 23(2), 99–108.
- Perl, E. R. (2011). Pain mechanisms: A commentary on concepts and issues. *Progress in Neurobiology*, 94(1), 20–38.
- Piazuelo, E., & Lanas, A. (2015). NSAIDs and gastrointestinal cancer. *Prostaglandins & Other Lipid Mediators*, 120, 91–96.
- Prakash, P., Misra, A., Surin, W. R., Jain, M., Bhatta, R. S., Pal, R., Raj, K., Barthwal, M. K., & Dikshit, M. (2011). Anti-platelet effects of Curcuma oil in experimental models of myocardial ischemia-reperfusion and thrombosis. *Thrombosis Research*, 127(2), 111–118.
- Rang, H. P., Dale, M. M., Ritter, J. M., Flower, R. J., & Henderson, G. (2012). Rang and Dale's Pharmacology (7th ed.). Edinburgh: Elsevier/Churchill Livingstone.
- Revathy, S., Elumalai, S., Benny, M., & Antony, B. (2011). Isolation, purification and identification of curcuminoids from turmeric (*Curcuma longa* L.) by column chromatography. *Journal of Experimental Sciences*, 2(7), 21–25.
- Rousseaux, C. G. (2008). A review of glutamate receptors II: Pathophysiology and pathology. *Journal of Toxicologic Pathology*, 21(3), 133–173.
- Ruby, A., Kuttan, G., Babu, K., Rajasekharan, K., & Kuttan, R. (1995). Anti-tumour and antioxidant activity of natural curcuminoids. *Cancer Letters*, 94, 79–83.
- Russo, P., Frustaci, A., Bufalo, A. Del, Fini, M., & Cesario, A. (2013). From traditional European medicine to discovery of new Drug candidates for the treatment of Dementia and Alzheimer's disease: Acetylcholinesterase Inhibitors. *Current Medicinal Chemistry*, 20, 976–983.
- Sani, M. H. M., Zakaria, Z. A., Balan, T., Teh, L. K., & Salleh, M. Z. (2012). Antinociceptive activity of methanol extract of *Muntingia calabura* leaves and the mechanisms of action involved. *Evidence-Based Complementary and Alternative Medicine*, 2012, 1–10.
- Serpell, M. (2006). Anatomy, physiology and pharmacology of pain. *Surgery (Oxford)*, 24, 350–353.
- Sharma, O. (1976). Antioxidant activity of curcumin and related compounds. *Biochemical Pharmacology*, 25, 1811–1812.
- Shishodia, S., Sethi, G., & Aggarwal, B. B. (2005). Curcumin: Getting back to the roots. *Annals of the New York Academy of Sciences*, 1056, 206–217.
- Shrishail, D., Harish, H., Ravichandra, H., Tulsianand, G., & Shruthi, S. D. (2013). Turmeric: Nature's precious medicine. *Asian Journal of Pharmaceutical and Clinical Research*, 6(3), 10–16.
- Siew, T., Pippen, R., Yusof, R., Rahman, N. A., Ibrahim, H., Khalid, N., & Malaya, U. (2006). Screening of selected Zingiberaceae extracts for dengue-2 virus protease inhibitory activities. *Sunway Academic Journal* 3, 7, 1–7.
- Singh, G., Kapoor, I. P. S., Singh, P., de Heluani, C. S., de Lampasona, M. P., & Catalan, C. A. N. (2008). Chemistry, antioxidant and antimicrobial investigations on essential oil and oleoresins of *Zingiber officinale*. *Food and Chemical Toxicology*, 46(10), 3295–3302.

- Singh, G., Singh, O. P., & Maurya, S. (2002). Chemical and biocidal investigations on essential oils of some Indian Curcuma species. *Progress in Crystal Growth and Characterization of Materials*, 45(1), 75–81.
- Smith, H. S. (2012). Opioids and chronic neuropathic pain. *Pain Physician*, 15(July), ES93-ES110.
- Sneddon, L. U., Elwood, R. W., Adamo, S. A., & Leach, M. C. (2014). Defining and Assessing Animal Pain. *Animal Studies Repository*, 97, 201–212.
- Steeds, C. E. (2013). The anatomy and physiology of pain. *Surgery (United Kingdom)*, 31(2), 49–53.
- Story, G. (2006). The emerging role of TRP Channels in mechanisms of temperature and pain sensation. *Current Neuropharmacology*, 4(3), 183–196.
- Sulaiman, M. R., Hussain, M. K., Zakaria, Z. A., Somchit, M. N., Moin, S., Mohamad, A. S., & Israf, D. A. (2008). Evaluation of the antinociceptive activity of *Ficus deltoidea* aqueous extract. *Fitoterapia*, 79(7–8), 557–561.
- Sulaiman, M. R., Perimal, E. K., Zakaria, Z. A., Mokhtar, F., Akhtar, M. N., Lajis, N. H., & Israf, D. A. (2009a). Preliminary analysis of the antinociceptive activity of zerumbone. *Fitoterapia*, 80(4), 230–232.
- Sulaiman, M. R., Tengku Mohamad, T. A. T., Shaik Mossadeq, W. M., Moin, S., Yusof, M., Mokhtar, A. F., Zakaria, Z. A., Israf, D. A. & Lajis, N. (2009b). Antinociceptive Activity of the Essential Oil of Zingiber zerumbet. *Planta Medica*, 76, 107–112.
- Suloon, J., Sulaiman, M. R., Azlina, N., Bakar, A., Adilah, N., Ismail, N. I., Lee, M. T., Kamaldin, M. N., Mohamad, A. S., Lajis, N., Israf, D. A., & Akhtar, N. (2011). Antinociceptive activity of *Curcuma longa* essential oil. *Universiti Malaysia Terengganu Annual Symposium, 2011*, 555–560.
- Süntar, I., Akkol, E. K., Nahar, L., & Sarker, S. D. (2012). Wound healing and antioxidant properties: do they coexist in plants? *Free Radicals and Antioxidants*, 2(2), 1–7.
- Swieboda, P., Filip, R., Prystupa, A., & Drozd, M. (2013). Assessment of pain: types, mechanism and treatment. *Annals of Agricultural and Environmental Medicine*, 1(1), 2–7.
- Takayama, Y., Uta, D., Furue, H., & Tominaga, M. (2015). Pain-enhancing mechanism through interaction between TRPV1 and anoctamin 1 in sensory neurons. *Proceedings of the National Academy of Sciences*, 112(16), 5213–5218.
- Tasleem, F., Azhar, I., Ali, S. N., Perveen, S., & Mahmood, Z. A. (2014). Analgesic and anti-inflammatory activities of *Piper nigrum* L. *Asian Pacific Journal of Tropical Medicine*, 7S1(Suppl 1), S461–S468.
- Trang, T., Al-Hasani, R., Salvemini, D., Salter, M. W., Gutstein, H., & Cahill, C. M. (2015). Pain and poppies: The good, the bad, and the ugly of opioid analgesics. *Journal of Neuroscience*, 35(41), 13879–13888.
- Ullman-Cullere, M. & Foltz. (1999). Body condition scoring: a rapid and accurate method for assessing health status in mice. *Laboratory Animal Science*, 49(3): 319-323.
- Vane, J. R., & Botting, R. M. (2003). The mechanism of action of aspirin. *Thrombosis Research*, 110(5–6), 255–258.
- Vasudevan, M., Gunnam, K. K., & Parle, M. (2007). Antinociceptive and anti-inflammatory effects of *Thespesia populnea* bark extract. *The Journal of Ethnopharmacology*, 109(2007), 264–270.

- Viana, A. F., Heckler, A. P., Fenner, R., & Rates, S. M. K. (2003). Antinociceptive activity of *Hypericum caprifoliatum* and *Hypericum polyanthemum* (Guttiferae). *Brazilian Journal of Medical and Biological Research*, 36(5), 631–634.
- Wojdyło, A., Oszmiński, J., & Czemerys, R. (2007). Antioxidant activity and phenolic compounds in 32 selected herbs. *Food Chemistry*, 105, 940–949.
- Woode, E., Amoh-Barimah, A. K., Abotsi, W. K. M., Ainooson, G. K., & Owusu, G. (2012). Analgesic effects of stem bark extracts of *Trichilia monadelpha* (Thonn.). *Indian Journal of Pharmacology*, 44(6), 765–773.
- Yob, N. J., Jofrry, S. M., Affandi, M. M. R. M. M., Teh, L. K., Salleh, M. Z., & Zakaria, Z. A. (2011). *Zingiber zerumbet* ( L . ) Smith : A review of its ethnomedicinal, chemical , and pharmacological uses. *Evidence-Based Complementary and Alternative Medicine*, 2011, 1–12.
- Youssef, D., Nichols, C., Cameron, T., Balzarini, J., De Clercq, E., & Jha, A. (2007). Design, synthesis, and cytostatic activity of novel cyclic curcumin analogues. *Bioorganic & Medicinal Chemistry Letters*, 17, 5624–5629.
- Zhang, Y., Wang, C., Wang, L., Parks, G. S., Zhang, X., Guo, Z., Ke, Y., Li, K., Kim, M. K., Vo, B., Borrelli, E., Ge, G., Yang, L., Wang, Z., Garcia-Fuster, M. J., Luo, Z. D., Liang, X., & Civelli, O. (2014). A novel analgesic isolated from a traditional Chinese medicine. *Current Biology*, 24(2), 117–123.
- Zhao, X., Xu, Y., Zhao, Q., Chen, C. R., Liu, A. M., & Huang, Z. L. (2012). Curcumin exerts antinociceptive effects in a mouse model of neuropathic pain: Descending monoamine system and opioid receptors are differentially involved. *Neuropharmacology*, 62(2), 843–854.