### TABLE OF CONTENTS

		Page
ACKNOWI	LEDGMENTS	iii
ABSTRAC	Γ (IN ENGLISH)	iv
ABSTRAC'	Γ (IN THAI)	vi
TABLE OF	CONTENTS	viii
LIST OF T	ABLES	xii
LIST OF F	IGURES	xiii
LIST OF A	BBREVIATIONS	XV
CHAPTER		
I	GENERAL INTRODUCTION	1
	Discovery of polyphenols	1
	Health benefits of polyphenols particularly quercetin and its	2
	glycoside derivatives in cancer treatments	
	Antioxidant might protect against carcinogenesis	3
	Quercetin known as antioxidant and anticancer molecule	5
	Quercetin action in normal cells	8
	Antioxidant ability of quercetin in cancer cell systems	10
	Inhibition of NF-κB and AP-1 oxidation	12
	Anticancer action of intact molecule of quercetin	19
	Determination of apoptosis against cancer cells	22
	Decrease in the ROS; and alteration of $\Delta \psi_m$ of cancer cells	23

	3.2 Binding studies of quercetin, quercetrin and rutin	46
	with BSA	
	DISCUSSION	51
	CONCLUSION	52
	ACKNOWLEDGEMENT	52
	REFERENCES	52
III	QUERCETIN, QUERCETRIN EXCEPT RUTIN	56
	POTENTIALLY INCREASED PIRARUBICIN	
	CYTOTOXICITY BY NON-COMPETITIVELY INHIBITING	
	THE P-GLYCOPROTEIN AND MRP1 FUNCTION IN LIVING	
	K562/adr AND GLC4/adr CELLS	
	INTRODUCTION	58
	MATERIALS AND METHODS	60
	Cell lines, cell culture and cytotoxicity assay	60
	Kinetics of membrane protein transporter-mediated efflux of	61
	THP	
	RESULTS	61
	Cytotoxicity of quercetin, quercetrin and rutin	61
	Quercetin, quercetrin and rutin enhanced cytotoxicity of	62
	pirarubicin against K562/adr and GLC4/adr cells	
	Effects of quercetin, quercetrin and rutin on the P-	63
	glycoprotein- and MRP1-mediated efflux of THP	

	Determination of the plasma memorane 1 -glycoprotein- and	03
	MRP1-mediated efflux of pirarubicin	
	Direct measurements of P-glycoprotein- and MRP1-mediated	65
	efflux of pirarubicin out of cells in presence of quercetin,	
	quercetrin and rutin	
	DISCUSSION	70
	CONCIUSION	71
	ACKNOWLEDGEMENT	71
	REFERENCES	71
IV	DISCUSSIONS AND CONCLUSIONS	74
	REFERENCES	79
	CURRICULUM VITAE	81

## ลิขสิทธิ์มหาวิทยาลัยเชียงใหม่ Copyright<sup>©</sup> by Chiang Mai University All rights reserved

### LIST OF TABLES

Table		Page
CHAPTER	ษ ผมถูนตุ	
1	Summary of studies on the inhibiting effect of quercetin	7
	on cell proliferation.	
CHAPTER	RII (S)	
1	IC <sub>50</sub> of quercetin and its glycoside derivatives	48
	against K562 and GLC4 cells.	
2	The FRET and BSA-molecule complexation	53
	parameters measured by using FRET	
CHAPTER	еш	
1	IC <sub>50</sub> values of quercetin and its glycoside derivatives,	65
	pirarubicin for K562 and GLC4 cell lines.	
2	MDR reversing efficacy (α) of quercetin, quercetrin	65
	and rutin in K562/adr and GLC4/adr cells	

## **LIST OF FIGURES**

Figure			Page
CHAP	TER	D WHEIRING	
	1	Chemical structures of flavonols; quercetin, quercitrin and rutin	3
	2	Intrinsic apoptosis pathway carried out by a multistage chain	8
		of reactions in which ROS act as triggers.	
	3	Kinetics of DHCF-DA oxidation in cell	9
	4	Reaction of quercetin with hydrogenperoxide (1)	11
		and with hydroxyl radical (2)	
	5	Activation of NF-κB pathway in cells	13
	6	Fluorescence micrograph of cells and enumeration of NF-κB	14
		activated cells induced by various stimuli.	
	7	K562 and K562/Adr cells show qualitative and quantitative	15
		differences in NF-κB and AP1 DNA binding profiles.	
	8	Siamois polyphenols and withasteroids inhibit endogenous	18
		NF- <b>k</b> B dependent transcription in K562 and K562/Adr cells.	
	9	Chemical structure of catechin, eriodictyol, apigenin,	20
		kaempferol, quercetin, WP 279, WP 280 and WP283.	
СНАР	TER	<u>Ignts</u> reserve	
	1	The partition of quercetin, quercetrin and rutin into K562,	44
		K562/adr, GLC4 and GLC4/adr cells at the indicated	

	incubation time.	
2	The emission spectra of BSA and absorption spectra of	47
	quercetin measured in the HEPES-Na <sup>+</sup> buffered solution pH 4	
	and pH 7.3.	
3	The absorption spectra of quercetrin and rutin.	47
4	FRET analysis of BSA-Quercetin complex as a function of the	49
	quercetin concentration.	
CHAPTER	· III	
5021	Chemical structure of quercetin, quercetrin and rutin.	59
2	Typical kinetics of pirarubicin uptake in K562 and deprived-	64
	energy K562/adr cells.	
3	Conceptual model of cellular distribution and MDR	65
	transporters mediated efflux of pirarubicin in GLC4/adr cells	
4	Kinetics of pirarubicin uptake in deprived-energy GLC4/adr	66
	cells	
5	Typical kinetics of pirarubicin uptake in deprived-energy	67
	K562/adr (a) and GLC4/adr (b) cells	
65	Inhibition of P-glycoprotein-mediated efflux of pirarubicin by	68
	quercetin (a), quercetrin (b) and rutin (c).	
7	Inhibition of MRP1-mediated efflux of pirarubicin by	69
	quercetin (a), quercetrin (b) and rutin (c).	

#### **ABBREVIATIONS**

BSA, HSA Bovine serum albumin, Human serum albumin

FRET Fluorescence resonance energy transfer

ATP adenosine triphosphate

MDR Multidrug resistance

Trp tryptophan

NBDs nucleotide binding domain

MRP Multidrug resistance protein

EpRE Electrophile Responsive Element

PCMCB Laboratory of Physical Chemistry, Molecular and cellular

Biology (ams.cmu.ac.th)

NF-κB nuclear factor kappa-light-chain-enhancer of activated B

cells

AP-1 activator protein 1

ANT adenine nucleotide translocator

ATP Adenosine triphosphate

ROS Reactive oxygen species

DHCF-DA Dichlorodihydrofluorescein diacetate

cGy Centi-gray

 $\Delta \Psi_{\rm m}$  Potential different on mitochondria membrane

OHEC Office of the Higher Education Commission

 $J_{(\lambda)}$  spectral overlap integral

K<sub>D</sub> macroscopic binding constant

k<sub>d</sub> microscopic binding constant



# ลิขสิทธิ์มหาวิทยาลัยเชียงใหม่ Copyright<sup>©</sup> by Chiang Mai University All rights reserved