Anti-oxidative and pro-oxidative effects of curcuminoids on cellular senescence in aging and cancer

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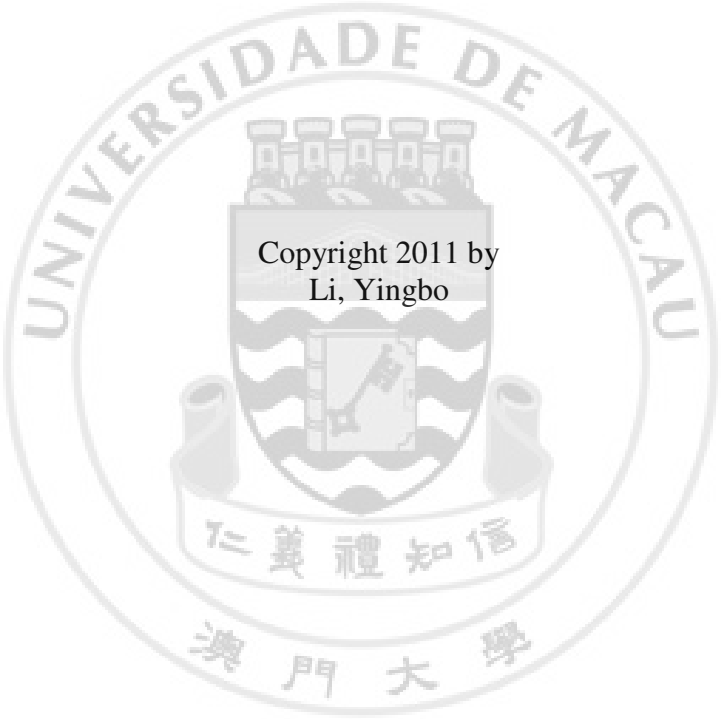

Acknowledgements

My deepest gratitude goes first and foremost to my supervisor Prof. Yi-tao Wang who has given me guidance and support throughout the course of my work. I am deeply grateful to my co-supervisor Prof. Simon Ming-Yuen Lee for the constant enlightenment, encouragement and support in my study. I would also like to express my deeply gratitude to Dr. Pui-Man Hoi for her valued suggestion and incredible patience during my whole project.

Also, I would like to express my gratitude to Dr. Qing-Wen Zhang who provides me with isolated components. I wish to thank Prof. Shao-ping Li, Dr. Ru Yan, Dr. Yuan-jia Hu, Dr. Xiu-ping Chen, Dr. Ying Zheng and Dr. Li-Jen Cheng for their help and encouragement. I wish to thank Dr. Jing-jian Lu, Dr. Mei-wan Chen and Dr. Ming-qing Huang, Dr. Rui Wang from Weill medical college of Cornell University, for the comments and assistance on my thesis completion.

Moreover, I would like to acknowledge and thank the ICMS colleagues, Dr. Jian-li Gao, Zai-jun Zhang, Guo-zhen Cui, Zhang-feng Zhong, Guo-sheng Wu, Wen Tan, Shang Li, Zhu-qing Lin and Jiao-lin Bao, for the supports and helps throughout the

project; Xiao-jia Chen, Jia Guan, Guang Hu, Kun Feng and Zheng-ming Qian for the help and encouragement.

The current study was supported by the University of Macau (Project No. RG084/07-08S/WYT/ICMS) and the Macao Science and Technology Development Fund (No. 029/2007/A2).

Finally, I would like to thank for my family for their full supports and intensive care.

Abstract

Curcuminoids, the major active components of *Curcuma longa* (薑黃), attract increasing interest due to their favourable therapeutic effects with low toxicity. Notably, curcuminoids exert a wide spectrum of benefits in disease conditions that are closely related to functional declines with age, such as cardiovascular diseases, neurodegenerative diseases and cancer. In addition, recent studies demonstrated that curcuminoids extend lifespan in model organisms. Hence, curcuminoids represent promising candidates for the promotion of healthy aging. In this study, the systematic beneficial effects of curcuminoids in regard to aging and aging-related disorders were explored. This study focused on the effects of curcuminoids on the regulation of redox homeostasis in different cell types including normal and cancer cells that might help to reflect comparable underlying mechanisms in aging, cardiovascular diseases and cancers. Major achievements of this study are summarized as follows:

（1） The protective and anti-aging effects of curcuminoids against *t*-BHP-induced oxidative damage in human WI38 fibroblasts have been demonstrated for the first time. Curcuminoid prevented *t*-BHP-caused senescence-like phenomenon in fibroblasts and is thought to interfere with senescence-related pathways.

（2） The action mechanism of curcuminoids might be related to the concept of hormesis, which proposes that mild stress could result in hormetic response with beneficial effects such as anti-aging. It is interesting to point out that while the *t*-BHP-stimulated ROS generation in WI38 fibroblasts could almost be prevented completely by longer pretreatment (48 h) of curcuminoids, a shorter pretreatment (90

min) had an opposite effect and increased the cellular ROS level rapidly. Thus, it is postulated that short duration of curcuminoid pretreatment might act as a hormetic stress which could enhance the rescue of oxidative damage later on.

（3） The activation of SIRT1 by curcuminoids in WI38 fibroblasts has been reported for the first time in this study. SIRT1 has been proved to be the principal mediator of caloric restriction (CR) to extend lifespan. Curcuminoids could increase both the translational and transcriptional levels of SIRT1. Whereas, inhibition on SIRT1 by pharmacological or genetic approaches attenuated the benefit of curcuminoids. These observations might imply that curcuminoids could mediate improvements in disorders through regulatory systems related to CR such as maintaining glucose homeostasis and insulin sensitivity via the stimulation of SIRT1.

（4） Pretreatments (48 h) of various concentrations of curcuminoids increased the cell viability of *t*-BHP-stimulated endothelial cells (HUVECs), and significantly prevented the morphological damages induced by *t*-BHP including the loss of cell attachment, cell shrinkage, nucleus pycnosis and apoptotic body formation. ERK1/2 and PI3K/Akt signaling pathways were shown to be involved in the protective mechanisms of curcuminoids against *t*-BHP-induced damage in HUVECs.

（5） It is suggested that the pro-oxidant action played an important role in the mechanism of the anti-cancer properties of curcuminoids in MCF-7 cells. The results showed that oxidative stress stimulated by curcuminoids may induce cellular senescence in cancer cells, which may add a novel facet in the anti-cancer actions of curcuminoids.

（6） The present study highlighted that curcuminoids could exert differential effects on the regulation of redox system in different cell types. In normal fibroblasts and endothelial cells, the pretreatments of curcuminoids protected them from oxidative insults, either by enhancing oxidative defense systems or by regulating relevant signaling pathways. On the other hand, in malignant MCF-7 breast cancer cells, curcuminoids suppressed cancer cell growth probably by increasing oxidative stress and subsequently enhancing cellular senescence.

In summary, the present study has provided evidence for the systematic beneficial effects of curcuminoids in aging, disease states and cancer. The results added further evidence of the importance of free radicals in the process of aging and related-disorders. Therefore, the regulation of redox homeostasis might provide an efficienct approach to maintain healthy aging.

Table of contents

List of Figures and Tables

List of Abbreviations

AMPK	5' adenosine monophosphate-activated protein kinase
BME	Basal medium Eagle
CR	Caloric restriction
Cur1	Curcumin
Cur2	Demethoxycurcumin
Cur3	Bisdemethoxycurcumin
CVD	Cardiovascular diseases
DAF-FM	4-amino-5-methylamino-2', 7'- difluorescein
DAPI	4'-6-Diamidino-2-phenylindole
DMSO	Dimethyl sulfoxide
ECGS	Endothelial cell growth supplement
ELISA	Enzyme-linked immunosorbent assay
eNOS	Endothelial nitric oxide synthase
ER	Endoplasmic reticulum
ERK 1/2	Extracellular-signal-regulated kinases 1/2
F12 medium	Ham's F12 medium
FACS analysis	Fluorescence-activated cell sorting analysis
FBS	Fetal bovine serum
FCS	Fetal calf serum
H_2DCF-DA	2', 7'-dichlorodihydrofluorescein diacetate
HDF	Human diploid fibroblasts
HO-1	Heme oxygenase-1
HUVECs	Human umbilical vein endothelial cells
LDH	Lactate dehydrogenase
IGF-1	Insulin-like growth factor-1
iNOS	inducible nitric oxide synthase

MAPK	Mitogen-activated protein kinase
MMP	Mitochondrial membrane potential
mtDNA	Mitochondrial Deoxyribonucleic acid
MTT	3-(4, 5-dimethyl-2-thiazolyl)-2, 5-diphenyl tetrazolium bromide
NAC	N-acetyl-cysteine
NAD	Nicotinamide adenine dinucleotide
NAM	Nicotinamide
NO	Nitric oxide
NOS	Nitric oxide synthase
oxLDL	Oxidized low-density lipoprotein
PBS	Phosphate Buffered Saline
PBST	Phosphate Buffered Saline Tween-20
PD	Population doublings
PI	Propidium iodide
PI3K	Phosphatidylinositol 3-kinase
PMSF	Phenylmethylsulfonyl fluoride
Rb	Retinoblastoma protein
Res	Resveratrol
ROS	Reactive oxygen species
RPE cells	Retinal pigmented epithelial cells
SAHF	Senescence-associated beta-heterochromatic foci
SA β-gal	Senescence-associated β-galactosidase
SIPS	Stress-induced premature senescence
siRNA	Short interfering ribonucleic acid
Sir2	Silent information regulator 2 gene
SIRT1/Sir2	Silent mating type information regulation 2 homolog
SOD	Superoxide dismutase
t-BHP	*tert*-butyl hydroperoxide

TF	Thrombin-induced tissue factor
TNF-α	Tumor necrosis factor-α
VEGF	Vascular endothelial growth factor
X-gal	5-bromo-4-chloro-3-indolyl -β-D-galactopyranoside