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CURCUMIN ENCAPSULATED CHITOSAN NANOPARTICLES AS ANTIVIRAL THERAPY AGAINST FELINE INFECTIOUS PERITONITIS

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By

NG SHING WEI

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

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This thesis is dedicated to my beloved parents and siblings for their love, encouragement and endless support

and

affectionate thanks to my supervisors and friends.

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

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Feline infectious peritonitis (FIP) is a fatal immune-mediated disease caused by coronavirus known as feline infectious peritonitis virus (FIPV). The occurrence of FIP is greatly affecting cat populations worldwide especially kittens and immunocompromised cats. To date, there is no effective vaccine or antiviral treatment against this deadly disease. Curcumin is a natural polyphenol compound extracted from *Curcuma longa*, which is renowned for its wide spectrum of biological and pharmacological activities in profound diseases and disorders. However, poor bioavailability of curcumin has limited its own potential as an effective therapeutic agent. The oral bioavailability can be enhanced with polymeric nanoparticles as a delivery system for curcumin. The main objective of this study was to evaluate the therapeutic effects of synthesized chitosan-based curcumin nanoparticles for FIP *in vitro* and *in vivo*. Curcumin encapsulated chitosan (Cur-CS) nanoparticles were prepared via ionic-gelation method and the physicochemical properties of nanoparticles were characterized. The Cur-CS nanoparticles were found in size approximately 330 nm with positive surface charges of 42.1 ± 3.0 mV. A sustained release of curcumin for 24 hours was observed. Moreover, enhanced cellular uptake of curcumin was observed in cells treated with Cur-CS nanoparticles compared to curcumin. The nanoparticles were stored at 4ºC for up to one month without changes in physical properties. The cell cytotoxicity, antiviral and anti-inflammatory activities of curcumin and Cur-CS nanoparticles were evaluated in Crandell Reese feline kidney (CrFK) cells. Cur-CS nanoparticles showed reduced cytotoxicity compared to curcumin. The viral inhibitory effects of Cur-CS nanoparticles were significantly greater than curcumin in FIPV-infected cells where increased cellular protection percentage in co-inoculation treatment and significant reduction in viral copy number were detected. Cur-CS nanoparticles also exhibited enhanced anti-inflammatory activities compared to curcumin in virus-infected cells. Pharmacokinetic study and clinicopathologic evaluation of curcumin and Cur-CS nanoparticles were determined in clinically healthy cats. The oral bioavailability of curcumin was improved when delivered via chitosan nanoparticles where higher plasma curcumin concentrations

were noted in cats administered with Cur-CS nanoparticles, with a relative bioavailability of 301% compared to curcumin. Furthermore, the clinicopathologic evaluation results indicated no significant toxicological effect in body weights, urinalysis, haematology and serum biochemistry parameters in cats administered with 100 mg/kg of chitosan nanoparticles, 100 mg/kg of curcumin and 100 mg/kg of Cur-CS nanoparticles, either once daily or twice daily, for 28 days. The antiviral and anti-inflammatory effects of Cur-CS nanoparticles were further evaluated in FIP diagnosed cats. A total of 22 cats that fulfilled the criteria were recruited, however, only nine cats were sustained for data analysis. Out of the nine cats, two cats were successfully completed the 28 days clinical study and returned to the owners. The efficacy of Cur-CS nanoparticles was studied upon comparison among before and after treatments. The viral inhibitory effect of Cur-CS nanoparticle was evidenced by the reduced viral titre in macrophages in ascites. In addition, combination treatment of prednisolone and Cur-CS nanoparticles showed enhanced anti-inflammatory effects in FIP diagnosed cats compared to prednisolone and Cur-CS nanoparticles alone. However, the results also showed there were no significant effects of Cur-CS nanoparticles on survival time, the quality of life or any clinical or laboratory parameter in cats diagnosed with FIP. In conclusion, Cur-CS nanoparticles showed antiviral and anti-inflammatory effects in FIPV infection and further investigation will be necessary to scrutinize the possibility of a combination of curcumin and other agents as an effective FIP treatment.

Keywords: Feline infectious peritonitis, curcumin, curcumin encapsulated chitosan nanoparticles, antiviral, anti-inflammatory

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

NANOPARTIKEL KITOSAN BERKANDUNG KURKUMIN SEBAGAI TERAPI ANTIVIRUS UNTUK PERITONITIS BERJANGKIT FELIN

Oleh

NG SHING WEI

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Pengerusi : Profesor Abdul Rahman Omar, PhD
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Peritonitis berjangkit felin (FIP) merupakan salah satu penyakit maut akibat tindak balas sistem imun yang disebabkan oleh coronavirus, iaitu virus peritonitis berjangkit felin (FIPV). Kemunculan FIP amat mempengaruhi populasi kucing di seluruh dunia terutamanya anak kucing dan kucing imunokompromi. Sehingga kini, tiada vaksin ataupun rawatan antivirus yang berkesan untuk mengawal penyakit maut ini. Kurkumin merupakan sebatian polifenol semulajadi yang diekstrak daripada *Curcuma longa*, terkenal dengan pelbagai aktiviti biologi dan farmakologi terhadap penyakit yang berbeza. Walau bagaimanapun, kurkumin yang kekurangan bioavailabiliti telah menyekat potensinya sebagai agen terapeutik yang bermanfaat. Bioavailabiliti oral boleh dipertingkatkan dengan menggunakan nanopartikel polimer sebagai sistem penghantaran untuk kurkumin. Objektif utama kajian ini adalah untuk menilai kesan-kesan terapeutik nanopartikel kurkumin berasaskan kitosan yang dihasilkan untuk rawatan FIP dalam *in vitro* dan *in vivo*. Nanopartikel kitosan berkandung kurkumin (Cur-CS) dihasilkan melalui kaedah ionik-gelation dan sifat-sifat fizikokimia nanopartikel telah dicirikan. Nanopartikel Cur-CS didapati dalam saiz kira-kira 330 nm dengan caj permukaan positif sebanyak 42.1 ± 3.0 mV. Pelepasan kurkumin yang terkawal dalam nanopartikel Cur-CS selama 24 jam telah diperhatikan. Selain itu, peningkatan dalam pengambilan kurkumin selular juga telah diperhatikan dalam sel yang inkubasi dengan nanopartikel Cur-CS berbanding dengan kurkumin sahaja. Nanopartikel didapati bahawa boleh disimpan pada suhu 4ºC selama satu bulan tanpa perubahan pada sifat fizikalnya. Kajian ini diteruskan dengan perbandingan aktiviti sitotoksis sel, aktiviti antivirus dan anti-radang antara kurkumin dan nanopartikel Cur-CS terhadap sel Crandell Resse feline kidney (CrFK). Nanopartikel Cur-CS menunjukkan kesan sitotosik yang lebih rendah berbanding dengan kurkumin terhadap sel CrFK. Selain itu, keputusan juga menunjukkan nanopartikel Cur-CS lebih berupaya untuk menghalang replikasi virus dalam sel CrFK jangkitan FIPV, di mana peningkatan dalam peratusan perlindungan selular dan pengurangan dalam bilangan salinan genom virus telah dicatatkan dalam sel jangkitan virus yang diinkubasi dengan nanopartikel Cur-CS. Nanopartikel Cur-CS juga mempamerkan aktiviti anti-radang

yang lebih berkesan berbanding dengan kurkumin. Kajian farmakokinetik dan penilaian parameter klinikopatologi berdasarkan kesan kurkumin dan nanopartikel Cur-CS terhadap kucing sihat telah diljalankan. Peningkatan bioavailabiliti oral kurkumin telah ditunjukkan apabila kurkumin dihantar melalui nanopartikel kitosan dimana kucing yang diberi nanopartikel Cur-CS menunjukkan kepekatan kurkumin dalam plasma yang lebih tinggi dengan nilai bioavailabiliti relatif sebanyak 301% berbanding dengan kurkumin. Tambahan pula, keputusan penilaian klinikopatologi mendedahkan bahawa tiada kesan toksikologi yang ketara didapati di berat badan, urinalisis, hematologi dan parameter biokimia serum dalam kucing yang diberi 100 mg/kg kitosan nanopartikel, 100 mg/kg kurkumin dan 100 mg/kg nanopartikel Cur-CS, sama ada sekali sehari atau dua kali sehari yang selama 28 hari. Penilaian aktiviti antivirus dan anti-radang nanopartikel Cur-CS juga dijalankan secara lanjut dalam kucing yang menghidap FIP. Sebanyak 22 ekor kucing yang memenuhi kriteria telah dimasukkan untuk kajian ini. Namun demikan, hanya sembilan kucing dapat diambilkira untuk analisis data. Daripada sembilan ekor kucing, dua ekor kucing telah berjaya melengkapkan kajian klinikal yang selama 28 hari ini dan telah dikembalikan kepada pemiliknya. Perbandingan keberkesanan nanopartikel Cur-CS antara sebelum dan selepas rawatan telah dikajikan. Keupayaan nanopartikel Cur-CS untuk menghalang replikasi virus telah dibuktikan bahawa pengurangan bilangan salinan genom virus dicatatkan dalam makrofaj dari asites. Rawatan kombinasi yang terdiri daripada prednisolone dan nanopartikel Cur-CS menunjukkan kesan anti-radang yang lebih tinggi berbanding dengan kucing yang diberi prednisolone ataupun nanopartikel Cur-CS sahaja. Walau bagaimanapun, keputusan kajian ini telah menunjukkan ketidakberkesanan nanopartikel Cur-CS dalam perlanjutan masa hidup, memperbaiki kualiti hidup ataupun membawa perubahan dalam parameter klinilopatologi pada kucing yang menghidap FIP. Kesimpulannya, nanopartikel Cur-CS menunjukkan keupayaan dalam aktiviti antivirus dan anti-radang terhadap jangkitan FIPV dan penyiasatan lanjutan amat diperlukan untuk meneliti potensi rawatan kombinasi antara kurkumin dan agen lain sebagai rawatan FIP yang berkesan.

Kata kunci: Peritonis berjangkit felin, kurkumin, nanopartikel chitosan berkandung kurkumin, antivirus, anti-radang

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A:G	Albumin-globulin
ADE	Antibody-dependent enhancement
AGP	α1-acid glycoprotein
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
APP	Acute phase protein
AST	Aspartate aminotransferase
ATCC	American Tissue Culture Collection
AUC	Area under curve
b.i.d	Two dosing per day
BUN	Blood urea nitrogen
CC_{50}	50% cytotoxic concentration
CCV	Canine coronavirus
cDNA	Complementary DNA
C_{max}	Maximum plasma concentration
CMI	Cell-mediated immunity
CNS	Central nervous system
COX-2	Cyclooxygenase-2
CPE	Cytopathic effect
CrFK	Crandell-Resse Feline Kidney
CsA	Cyclosporin A
CSF	Cerebrospinal fluid
Cur-CS	Curcumin encapsulated chitosan
DLS	Dynamic light scattering
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DPBS	Dulbecco's phosphate buffered saline
DSH	Domestic short-haired
DV-II	Dengue virus type II
E	Envelope
EC_{50}	50% effective concentration
EV-71	Enterovirus 71
F	Relative bioavailability
fAPN	Feline aminopeptidase
Fas	Fas ligand (CD95L) [Source: HGNC Symbol; Acc:11920]
FCoV	Feline coronavirus
Fcwf-4	Felis catus whole fetus
FECV	Feline enteric coronavirus
FeLV	Feline leukaemia virus
FIP	Feline infectious peritonitis

FIPV	Feline infectious peritonitis virus
FIV	Feline immunodeficiency virus
Flt-3L	FMS-like tyrosine kinase 3 ligand
GGT	Gamma-glutamyl transferase
GM-CSF	Granulocyte-macrophage colony-stimulating factor [Source: HGNC Symbol; Acc:2434]
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HCV-229E	Human coronavirus 229E
HIV	Human immunodeficiency virus
Hp	Haptoglobin
hpi	Hours post-infection
HPLC	High-performance liquid chromatography
HSV-1	Herpes simplex virus-1
IACUC	Institutional Animal Care and Use Committee
IBV	Infectious bronchitis virus
IFNγ	Interferon, Gamma [Source: HGNC Symbol; Acc:5438]
IL	Interleukin
IL-10	Interleukin 10 [Source: HGNC Symbol; Acc:5962]
IL-12(p40)	Interleukin 12 [Source: HGNC Symbol; Acc:5970]
IL-13	Interleukin 13 [Source: HGNC Symbol; Acc:5973]
IL-18	Interleukin 18 [Source: HGNC Symbol; Acc:5986]
IL-1β	Interleukin 1, Beta [Source: HGNC Symbol; Acc:5992]
IL-2	Interleukin 2 [Source: HGNC Symbol; Acc:6001]
IL-4	Interleukin 4 [Source: HGNC Symbol; Acc:6014]
IL-6	Interleukin 6 [Source: HGNC Symbol; Acc:6018]
IL-8	Interleukin 8 [Source: HGNC Symbol; Acc:6025]
IMPDH	Inosine monophosphate dehydrogenase
iNOS	Inducible nitric oxide synthase
JEV	Japanese encephalitis virus
KC	C-X-C motif ligand 1 (CXCL1) [Source: HGNC Symbol; Acc:4602]
kg	Kilogram
M	Membrane
MAPK p38	Mitogen-activated protein kinases p38
MCHC	Mean corpuscular haemoglobin concentration
MCP-1	Monocyte chemotactic protein 1[Source: HGNC Symbol; Acc:10618]
MCV	Mean corpuscular volume
MEM	Minimum essential media
mg	Milligram
MHV	Mouse hepatitis virus
MILLIPLEX	Immunology bead-based multiplex assay
mL	Millilitre

MRI	Magnetic resonance imaging
mRNA	Messenger RNA
MTT	3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide
mV	Millivolt
MX1	MX Dynamin-Like GTPase 1 [Source: HGNC Symbol; Acc:7532]
NaOH	Sodium hydroxide
NEAA	Non-essential amino acid
NF-kB	Nuclear factor kappa-B
ng	Nanogram
NK	Natural killer
nm	Nanometre
OD	Optical density
ORF	Open reading frame
PBMC	Peripheral blood mononuclear cell
PBS	Phosphate buffered saline
PCL	Poly(Ɛ-caprolactone)
PCR	Polymerase chain reaction
PCV	Packed cell volume
PDGF-BB	Platelet-derived growth factor subunit B [Source: HGNC Symbol; Acc:8800]
pg	picogram
PLA	Polylactic acid
PLGA	Poly(lactide-co-glycolide)
ppm	Part per million
qPCR	Quantitative real-time polymerase chain reaction
RANTES	C-C motif ligand 5[Source: HGNC Symbol; Acc:10632]
RBC	Red blood cell
RNA	Ribonucleic acid
rpm	Revolutions per minute
RSAD2	Radical S-Adenosyl Methionine Domain Containing 2 [Source: HGNC Symbol; Acc:30908]
RSV	Respiratory syncytial virus
RT-PCR	Reverse transcriptase polymerase chain reaction
RVFV	Rift valley fever virus
S	Spike
SAA	Serum amyloid A
SARS	Severe acute respiratory syndrome
SARS-CoV	Severe acute respiratory syndrome coronavirus
SCF	Stem cell factor [Source: HGNC Symbol; Acc:6343]
SD	Standard deviation
SDF-1	Stromal cell-derived factor 1 [Source: HGNC Symbol; Acc:10672]
Seg. neutrophils	Segmented neutrophils

s.i.d	Single dosing per day
SPF	Specific pathogen free
$TCID_{50}$	Tissue culture infective dose 50
TGEV	Transmissible gastroenteritis virus
TEM	Transmission electron microscope
T_{max}	Time to reach maximum plasma concentration
TNFα	Tumor necrosis factor alpha [Source: HGNC Symbol; Acc:11892]
TPGS	d-α-Tocopheryl polyethylene glycol 1000 succinate
TPP	Tripolyphosphate
UPM	Universiti Putra Malaysia
UPS	Ubiquitin-proteasome system
UTR	Untranslated region
UV	Ultraviolet
UV-Vis	Ultraviolet-visible
UVH-UPM	University Veterinary Hospital-Universiti Putra Malaysia
VEGF	Vascular endothelial growth factor
v/v	Volume per volume
WBC	White blood cell
w/v	Weight per volume
x *g*	Gravity force
µg	Microgram
µL	Microlitre
µM	Micromole

CHAPTER 1

INTRODUCTION

Feline infectious peritonitis (FIP) is a complex immune-mediated viral disease caused by feline infectious peritonitis virus (FIPV), a virulent biotype of feline coronavirus (FCoV). FCoV is classified under the same family with severe acute respiratory syndrome coronavirus (SARS-CoV), namely *Coronaviridae*. FIP is not only recognized in cat populations, but also in domestic ferret and wild felids (Stephenson et al., 2013; Garner et al., 2008). The seroprevalence study of FCoV revealed 90% of cats in catteries and 50% of single-cat households had been infected by FCoV, and among those FCoV-infected cats, approximately 5% developed FIP (Hartmann, 2005).

Clinical manifestation of FIP can be categorized into two forms; non-effusive form which frequently involved abnormalities in the ocular and central nervous system (CNS), and effusive form evident from the distended abdomen with yellow-tinged effusion (Pedersen, 2014a). A definite FIP diagnosis is made upon gross post-mortem examination and histopathology. Several organs including kidneys, intestine, spleen, liver, and CNS were affected during FIPV infection, lesions accompanied necrosis and pyogenic granulomatous inflammation was visible in the infected organs. In histopathology, localized infiltration of inflammatory cells associated with the destruction of tissues structure was noted in the infected areas (Pedersen, 2009).

FIP shares common features with Dengue virus, where the virus infects immune cells facilitated by antibody-dependent enhancement, induced overwhelming immune responses and cytokine productions that highly engaged in the pathogenesis of the diseases. Macrophages and monocytes act as a major role in the pathogenesis of FIP. Production of pro-inflammatory cytokines by infected macrophages or monocytes promote the humoral immunity where antibodies further enhance the uptake and replication of FIPV and eventually contribute to type III hypersensitivity reactions (Arthus hypersensitivity reactions) (Pedersen, 2014a). Most of the infected cats eventually succumbed to FIP due to the uncontrollable inflammatory responses.

A large number of experimental and clinical studies have investigated the prospective treatment for FIP, but most were to no avail (Hartmann and Ritz, 2008). Nevertheless, studies in recent years have shown a few potential treatments for FIP. Legendre et al. (2017) claimed polyprenyl immunostimulant significantly improved the survival time of FIP diagnosed cats, strictly for non-effusive form FIP. Another study proposed the use of 3CLpro inhibitors inhibited the replication FIPV, thus reversal progression of FIP was achievable. Promising results were demonstrated *in vitro*, in experimental cats and in FIP diagnosed cats, yet these treatments induced side effects to the cats and most of relapses cases were no longer responsive to the treatment (Pedersen et al., 2017; Kim et al., 2016; Kim et al., 2015).

Curcumin is a polyphenolic compound, derived from *Curcuma longa,* exhibits a broad spectrum of biological and pharmacological activities such as anti-bacterial, anti-angiogenic, anti-inflammatory and antiviral properties (Gupta et al., 2013). Accumulated evidence has demonstrated the efficacy of curcumin against numerous prominent health ailments including rheumatoid arthritis, Alzheimer's disease and human cancers (Goozee et al., 2016; Chandran and Goel, 2012; Maheshwari et al., 2006). It is a solid fact that curcumin expressed high therapeutic value as evident from numbers of successful preclinical and clinical studies (Goozee et al., 2016; Hatcher et al., 2008). The benefits of curcumin not only extend to humans health but also in veterinary medicine and poultry industry (Rajput et al., 2013; Leray et al., 2011).

Albeit curcumin displays extraordinary biological activities which benefits humans and animals, poor absorption, rapid metabolism and rapid systemic clearance are the major factors curtails the bioavailability of curcumin (Liu et al., 2016). Countless efforts had been made to improve the bioavailability of curcumin by incorporating different delivery methods and formulations together with nanoscales delivery system (Rachmawati, 2013; Anand et al., 2007). Numerous studies demonstrated curcumin encapsulated polymeric nanoparticles possessed enhanced cellular uptake, improved bioavailability, reduced cytotoxicity effects and prolonged release kinetic profiles (Khdair et al., 2016; Khalil et al., 2013; Gou et al., 2011).

Among the available polymeric nanoparticles, chitosan nanoparticles are one of the favourable oral delivery systems for curcumin due to its mucoadhesion property (Luo et al., 2015). Other than that, chitosan nanoparticles are biodegradable, biocompatible, exhibit better stability and can be easily prepared via simple methods. Several published papers reported the efficacy of chitosan nanoparticles in the delivery of poor bioavailability and hydrophobic drugs. Cyclosporin A (CsA), a highly lipophilic, poorly absorbable drug, which was encapsulated in chitosan nanoparticles resulted in higher relative bioavailability compared to other delivery systems (El-Shabouri, 2002). Another study had shown curcumin bounded chitosan nanoparticles could serve as an efficacious anti-malarial drug with enhanced chemical stability and oral bioavailability (Akhtar et al., 2012).

The bioavailability of curcumin can be improved with the use of chitosan nanoparticles as a delivery agent while pertaining the antiviral properties, and this curcumin delivery system is potential to be an antiviral agent against FIPV infection. Hence, the main objective of this study is to evaluate the therapeutic effects of synthesized chitosan-based curcumin nanoparticles against FIPV infection *in vitro* and *in vivo*.

The specific objectives were:

1. To synthesize and characterize the physicochemical properties of chitosan-based curcumin nanoparticles prepared via ionic-gelation technique
2. To determine the antiviral and anti-inflammatory activities of curcumin and curcumin encapsulated chitosan (Cur-CS) nanoparticles in FIPV-infected cells
3. To determine the pharmacokinetic profile of curcumin and Cur-CS nanoparticles in healthy cats

4. To evaluate the clinicopathologic parameters on the effects of chitosan nanoparticles, curcumin and Cur-CS nanoparticles in healthy cats
5. To evaluate the antiviral and anti-inflammatory effects of Cur-CS nanoparticles in cats diagnosed with FIP

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