UNIVERSITI PUTRA MALAYSIA

COCKLE SHELL-DERIVED NANO CARRIER FOR ARA-C IN THE TREATMENT OF ACUTE MYELOID LEUKAEMIA

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By

MUSTAFA SADDAM GHAJI

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

June 2018

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DEDICATIONS

To

My Dear Parents,

Mr. Saddam Ghaji

Mrs. Sbeha Abod

To

My brothers and sisters

To

My Marvellous Family

In Recognition of their Worth, Love, and Respect

Abstract of thesis presented to the senate of Universiti Putra Malaysia in fulfilment of the requirements for the degree of Doctor of Philosophy

COCKLE SHELL-DERIVED NANO CARRIER FOR ARA-C IN THE TREATMENT OF ACUTE MYELOID LEUKAEMIA

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June 2018

Chairman : Professor Md Zuki bin Abu Bakar, PhD
Faculty : Veterinary Medicine

Leukemia is a cancerous disease of bone marrow and blood in which acute form progresses more rapidly than the chronic form. The major therapeutic approaches of different cancer types are limited to conventional chemotherapy such as (Ara-C) which suffers less specific, high toxicity and short half-life, multidrug resistance and selectivity, narrow therapeutic index and significant increases in high dose distribution to healthy cells or tissues. Targeting anticancer drug delivery system has the potential to overcome these significant drawbacks by improving chemotherapy drug efficacy, specific tumor targeting, enhance accumulation in tumor tissues or cells and minimize the systemic toxicity. Nanoparticles as drug delivery system enable unique approaches to cancer treatment. Over the last two decades, a large number of nanoparticle delivery systems have been developed for cancer therapy including organic and inorganic materials. Cockle shells (*Anadara granosa*) are found to be a rich natural resource for calcium carbonate aragonite. In this study, the cockle shell-derived calcium carbonate aragonite nanoparticles (CCANPs) were used as a carrier for Cytarabine (Ara-C) as a unique approach for cancer treatment. Nanoparticles were spherical-shaped when CCANPs was synthesized using the combination of chemical and mechanical method. The morphology and compositions of the products were characterized by Field Emission Scanning Electron Microscope (FE-SEM), Transmission Electron Microscope (TEM), Energy Dispersive X-ray (EDX), X-Ray Diffraction (XRD), Fourier Transform Infra-Red (FT-IR) and zeta potential. The anti-leukemia drug (Ara-C) was loaded into CCANPs. The spectrophotometer was used with a wavelength UV-invisible, to estimate the amount of loading and release profile of Ara-C. The results showed that the drugs (Ara-C) could be efficiently loaded into the CCANPs, and furthermore, the fast and sustained release of Ara-C was observed from the nanocarriers at pH 4.8 and slow release at pH 7.4, which shows pH-dependent properties. The nanoparticles were used as a carrier against HL-60 human leukemia cells (*in vitro* study) and for cancer therapy in a murine xenograft model (SCID mice) (*in vivo* study). The *in vitro* evaluation showed IC_{50} values upon

72 hours of treatment with pure Ara-C was 5μg/mL, and Ara-C loaded CCANPs was 2.5μg/mL. Apoptosis was demonstrated by Cell Counting Reagent (SF), Flow Cytometry (FCM), Methylene blue (MB) and Fluorescent Microscope (FM) where apparently cellular uptake of Ara-C/CCANPs through endocytosis indicating a dose and time-dependent response relationship. Morphological observations by SEM revealed microvilli disappearance, cell shrinkage, membrane blebbing and the formation of apoptotic bodies, which confirmed both Ara-C and half dose of Ara-C/CCANPs induced apoptosis of HL-60 cells. In brief, Ara-C loaded CCANPs are more effective than pure Ara-C to human leukemia (HL-60) cells. *In vivo* study revealed that CCANPs nanocarrier significantly enhances the effects of Ara-C on AML through blood smear, bone marrow smear and histopathological survey for vital organs (heart, liver, lung, spleen and kidney) for severe combined immunodeficient (SCID) mice. The pharmacokinetic study showing significant effect between pure Ara-C 50mg/kg group, 100mg/kg CCANPs loaded with 50mg/kg Ara-C and half dose of loaded drug (25/50 mg/kg), the rate of release of the drug in the plasma was slow in the two groups of the drug-loaded compared to the pure drug. The study revealed a new biodegradable, biocompatible, non-toxic to health and pH-sensitive, CCANPs with a feasible promising potential for targeted delivery carriers of antitumor drugs. The results established strong evidence that CCANPs has excellent properties that make it an ideal candidate for biological drug delivery systems.

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

PEMBAWA NANO BERASASKAN KULIT KERANG UNTUK ARA-C DALAM RAWATAN LEUKIMIA MYELOID AKUT

Oleh

MUSTAFA SADDAM GHAJI

Jun 2018

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Leukemia adalah penyakit kanser sumsum tulang dan darah dimana bentuk akut merebak lebih pantas dari bentuk kronik. Pendekatan rawatan utama untuk jenis kanser yang berlainan adalah terhad kepada kemoterapi seperti (Ara-C) konvensional yang kurang spesifik, tinggi toksisiti dan berjangka hayat yang pendek, bersifat memilih dan rintangan drug pelbagai, indeks terapeutik yang sempit dan peningkatan pengedaran dos yang tinggi kepada sel atau tisu yang sihat. Sistem penyampaian drug antikanser yang disasarkan berpotensi untuk mengatasi permasalahan ini dengan meningkatkan keberkesanan drug kemoterapi, sasaran tumor yang spesifik, meningkatkan pengumpulan drug pada tisu atau sel tumor dan mengurangkan toksisiti sistemik. Nanopartikel sebagai sistem penyampaian drug memungkinkan pendekatan unik kepada rawatan kanser. Selama dua dekad yang lalu, sebahagian besar sistem penyampaian nanopartikel untuk terapi kanser telah dicipta termasuk penggunaan bahan organik dan bukan organik. Kulit kerang (*Anadara granosa*) merupakan sumber aragonit kalsium karbonat yang tinggi. Di dalam kajian ini, nanopartikel aragonit kalsium karbonat dari kulit kerang (CCANPs) digunakan sebagai pengangkut untuk Cytarabine (Ara-C) sebagai pendekatan unik rawatan kanser. Nanopartikel yang terhasil daripada gabungan kaedah mekanikal dan kimia adalah berbentuk sfera. Morfologi dan komposisi CCANPs telah dikenalpasti melalui Mikroskop Pengimbasan Pelepasan Medan (FE-SEM), Mikrsokop Transmisi Elektron (TEM), X-ray Penyerak Tenaga (EDX), Transformasi Fourier Spektroskopi Infra Merah (FTIR) dan Potensi Zeta. Drug anti-leukemia (Ara-C) telah dimuatkan ke dalam CCANPs. Spektrofotometer dengan gelombang bebas ultra-ungu telah digunakan untuk menilai jumlah muatan dan profil pelepasan Ara-C. Keputusan menunjukkan drug Ara-C boleh dimuatkan secara berkesan ke dalam CCANPs dan sebagai tambahan, pelepasan Ara-C daripada pengangkut nano adalah pantas dan berterusan pada pH 4.8 dan perlahan pada pH 7.4, di mana ini menunjukkan sifat kecenderungannya terhadap pH. Pengangkut nanotelah digunakan sebagai pengangkut melawan sel leukemia manusia HL-60 (kajian *in-vitro*) dan rawatan kanser menggunakan model xenograf mencit

(CISD) (di dalam kajian *in-vivo*). Penilaian *in-vitro* menunjukkan nilai IC_{50} selepas rawatan selama 72 jam dengan Ara-C adalah 5 µg/ml dan Ara-C/CCANPs adalah 2.5 µg/ml. Proses apoptosis telah ditunjukkan melalui reagen Pengiraan Sel (SF), Sitometer Aliran (FCM), Methylene Biru (MB) dan Mikroskopi Flouresens (FM) di mana telah jelas pengambilan selular Ara-C/CCANPs ialah melalui endositosis yang menunjukkan perhubungan respon dos dan masa. Pemerhatian morfologi melalui SEM menunjukkan kehilangan mikrovili, pengecutan sel, pembengkakan membran dan pembentukan jasad apoptosis yang mengesahkan kedua-dua Ara-C dan Ara-C/CCANPs separa dos berjaya menghasilkan apoptosis ke atas HL-60. Secara ringkas, ARA-C/CCANPs adalah lebih sitotoksik dari Ara-C ke atas sel leukemia HL-60. Kajian *in-vivo* menunjukkan pengangkut nano CCANPs berjaya meningkatkan ($P<0.05$) kesan Ara-C ke atas Myeloid Leukemia Akut melalui calitan darah, dan sumsum tulang serta kajian histopatologi pada organ-organ utama (jantung, hati, limpa dan buah pinggang) dalam mencit berdefisit keimunan gabungan teruk (SCID). Kajian farmakokinetik menunjukkan perbezaan ketara di antara kumpulan Ara-C 50 mg/kg, kumpulan Ara-C/CCANPs 50/100 mg/kg dan separuh dos Ara-C/CCANPs 25/50mg/kg. Kadar pelepasan drug ke dalam plasma adalah perlahan di dalam dua kumpulan drug-termuat (Ara-C/CCANPs) dibandingkan dengan drug yang asli (Ara-C). Kajian ini mendedahkan bahawa CCANPs adalah biodegradabel, bioerasi, sensitif-pH dan kurang toksik yang berpotensi sebagai pembawa nano untuk drug anti-kanser yang disasarkan. Hasil kajian menunjukkan bahawa CCANPs telah terbukti mempunyai sifat yang cemerlang dan merupakan calon bahan yang sesuai digunakan untuk sistem pengangkutan drug biologi.

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I certify that a Thesis Examination Committee has met on 7 June 2018 to conduct the final examination of Mustafa Saddam Ghaji on his thesis entitled "Cockle Shell-Derived Nano Carrier for Ara-C in the Treatment of Acute Myeloid Leukemia" 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.

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LIST OF ABBREVIATIONS

AML	Acute myeloid leukemia
ALL	Acute lymphoid leukemia
CML	Chronic Myeloid Leukemia
CLL	Chronic Lymphoid Leukemia
Ara-C	Cytarabine
EDX	Equipped dispersive x-ray
DL	Drug loaded
LE	Loading efficiency
FESEM	Field emission scanning electron microscopy
FTIR	Fourier transformed infrared
CCANPs	Calcium Carbonate Aragonite nanoparticles
Ara-C/CCANPs	Cytarabine-loaded Calcium Carbonate nanoparticles
NP	Nanoparticle
PBS	Phosphate Buffer Saline
SEM	Scanning electron microscopy
TEM	Transmission electron microscopy
XRD	X-ray diffraction
Nm	Nano meter
Mg/m^2	Milligram per square meter
mL	Milliliter
µ	Micro meter
Kg	Kilogram
nM	Nano Molar

µg/mL	Microgram per Milliliter
h	Hour (s)
IC_{50}	Lethal concentration, 50%
SCID mice	Severe combined immunodeficient mice
CO_2	Carbon dioxide
AO	Acridine Orange
ATCC	American Type Culture Collection
FBS	Fetal bovine serum
Min	Minute
Rpm	Revolution per minute
PI	Propidium iodide
UV	Ultraviolet
%	Percentage
DNA	Deoxyribonucleic acid
HD	High dose
LD	Low dosage
BM	Bone marrow
PSD	Particle size distributions
MTD	Maximally tolerated dose
ID	Intermediate dose
MTCs	Metastatic tumour cells

CHAPTER 1

INTRODUCTION

1.1 General Background

Cancers develop from an uncontrolled growth of body cells and can develop from any part of the body. Any tissue from any part of the body can become cancerous provided the necessary factors needed for its propagation are in place (Folkman, 1996). Leukemia is a cancerous condition which primarily affects the blood and bone marrow. In the case of acute myeloid leukemia (AML), it develops from the bone marrow and in most cases, spread to the blood system. AML can also migrate from the bone marrow to the spleen, the central nervous system, the liver, the testicles, and the lymph nodes (Valent *et al.*, 2007). The global rate of leukemia cases in 2012 was put at 4,000,000, resulting in 3,000,000 deaths. A large number of people in the USA (around 24,500, made up of 14,300 males and 10,200 females) were predicted to die from leukemia-related conditions in 2017 (Siegel *et al.*, 2017). AML is the commonest form of adult leukemia, which despite the intimidating statistics regarding its associated mortality and morbidity, the treatment options is still unsuccessful in its management. Chemotherapy, which aims at killing the dividing cells over time to restore the normal blood count of normal cells, has been the only option for AML management; but, chemotherapy is a highly toxic procedure which lacks specificity. Nano-carriers are a new method of improving the specificity of chemotherapeutic agents and reducing their toxicity level. Based on this, cockle shell (*Anadara granosa*)-derived calcium carbonate aragonite nanoparticles (CCANPs) was produced and used as a drug carrier in this study. The size of nanoparticles (NPs) was within the transitional zone between the corresponding bulk materials and the individual atoms or molecules. This helps to alter the material's physicochemical properties and present a chance to increase the uptake capability and interaction with biological tissues. In the living cells, the combination of these events can have an adverse impact biologically, which otherwise, would not have been possible with the same material in a larger form (Moore, 2006). Calcium and its derivatives are the most vital components of teeth and bone, in fact, the osseous tissues of bone are primarily composed of inorganic calcium-derived composite materials (Bandyopadhyay-Ghosh, 2008). Calcium carbonate ($CaCO_3$) is the commonest calcium derivative with the longest history of applications in various fields, such as in the plastics, paper, paint, food, inks, and pharmaceutical industries (Biradar *et al.*, 2011). In the modern times, $CaCO_3$ has attracted medical attention owing to its high applicability. It is a cost-effective, safe, biocompatible, resorptive, accessible, and osteoconductive material (Biradar *et al.*, 2011). Owing to its pH sensitivity and relatively slow degradation, it can be used as an agent for the controlled release of active substances such as drugs to maintain their tolerable serum concentration and for targeted delivery over time (Qian *et al.*, 2011). This study focused on the synthesis, characterization, and application of CCANPs as an agent for the *in vivo* and *in vitro* controlled release of Ara-C to targeted cancer tissues.

1.2 Problem Statements

Acute leukemia is an aggressive form of cancer that requires immediate treatment. AML multimodal chemotherapy is used to re-establish and normalize blood and bone marrow cell numbers and morphology. Ara-C is a traditional chemotherapeutic agent for the management of all types of leukemia (Gökbuget *et al.*, 2011). It is similar to most cancer chemotherapies which target the S-phase of cell division (healthy and cancer cells). The strategy requires a prolonged period of cell exposure to highly toxic concentrations of the agents for cancer treatment (Gökbuget *et al.*, 2011; Hamada *et al.*, 2002). However, the activity of Ara-C is decreased by its rapid deamination to the biologically-inactive metabolite, uracil (Hamada *et al.*, 2002). This rapid deamination led to a search for effective formulations of Ara-C that cannot be deaminated, but still, exhibit better pharmacokinetic parameters and protection for Ara-C. The chemical therapies for AML are often limited in their use by high systemic toxicity and low specificity. Drug delivery through carrier systems is presumed to avoid their side effects through a controlled biodistribution. These carriers can contribute towards the control of leukemia metastasis. A new natural approach at nano-scale needs to be developed which ensures an efficient and enhanced drug delivery for AML treatment.

1.3 Hypothesis

i. CCANPs is a biocompatible and non-toxic to normal cells in normal pH.
ii. CCANPs can be used as nano-carrier in the management of AML.
iii. CCANPs reduce effective dose of Ara-C into half.
iv. CCANPs loaded Ara-C has therapeutic effects on reduced metastasis HL-60 human cells to other organs.

1.4 Research Question

i. What is the *in vitro* drug release profile and biocompatibility of CCANPs loaded Ara-C?
ii. How safe is CCANPs loaded Ara-C on the biological system *in vivo*?
iii. How effective CCANPs loaded Ara-C in the treatment Acute Myeloid leukaemia?
iv. How CCANPs loaded Ara-C can reduce metastasis AML in other body organs?
v. How CCANPs loaded Ara-C can reduce the dose of Ara-C?

1.5 Objectives of the Study

1.5.1 Main Objective

This study was conducted with the aim of investigating the effectiveness of CCANPs loaded Ara-C in the treatment of AML.

1.5.2 Specific Objectives

i. To synthesise and characterize CCANPs, and evaluate the *in-vitro* release profile of CCANPs loaded Ara-C.
ii. To determine the CCANPs loaded Ara-C in the treatment HL-60 human cells *in vitro*.
iii. To determine the pharmacokinetic of CCANPs loaded Ara-C *in vivo*.
iv. To evaluate the effectiveness of CCANPs loaded Ara-C in the treatment of AML in SCID mice-induced AML *in vivo*.

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