



**Magnetite – Hydroxyapatite Nanoparticles
Functionalized with Catechin for the Potential
Treatment of Cancer**

by

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LIST OF ABBREVIATIONS

ANN	Artificial neural network
ATP	Adenosine triphosphate
BP	Backpropagation
CaP	Calcium phosphate
CaPO ₄	Calcium orthophosphate
CNT	Carbon nanotube
CS	Chitosan
DI	Deionized water
DNA	Deoxyribonucleic acid
DOX	Doxorubicin
EDXRF	Energy dispersive X-ray fluorescence
FAP	Fluorapatite
FDA	Food and Drug Administration
FESEM	Field emission scanning electron
FTIR	Fourier transform infrared spectroscopy
FWHM	Full-width at half maximum
HAp	Hydroxyapatite
HMLP	Hybrid multilayered perceptron
MSE	Mean square error
MIPPy	Molecularly imprinted polypyrrole
MRI	Magnetic resonance imaging
MWCNT	Multiwall carbon nanotube
Nano-MH	Magnetite-hydroxyapatite nanoparticle
Nano-MHC	Magnetite-hydroxyapatite-catechin nanoparticle
NdFeB	Neodymium iron boron magnet
NIR	Near-infrared radiation
NLS	Nuclear localization sequence
NPC	Nuclear pore complex
RES	Reticuloendothelial system
RNA	Ribonucleic acid
RSM	Response surface methodology

PdI	Polydispersity index
PEG	Polyethylene glycol
PLA	Poly lactide
PVD	Pulsed plasma deposition
NaOH	Sodium hydroxide
TEM	Transmission electron microscope
UV	Ultraviolet
UV-Vis	Ultraviolet-visible
VSM	Vibrating sample magnetometer
XRD	X-ray diffraction

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LIST OF SYMBOLS

Abs	Absorbance
k_1	Adsorption rate constant for pseudo-first-order
k_2	Adsorption rate constant for pseudo-second-order
q_e	Amount of adsorbate adsorbed per unit mass of adsorbent at equilibrium
q_t	Amount of adsorbate adsorbed per unit mass of adsorbent at time, t
a.u.	Arbitrary units
θ	Angle
Å	Angstrom
H	Applied magnetic field strength
b	Bias
Ca	Calcium
Ca^{2+}	Calcium ions
$q_{e,cal}$	Calculated adsorption capacity values
CO_3^{2-}	Carbonate ions
cm	centimeter
H_C	Coercive field
C_e	Concentration of adsorbate at equilibrium
Q_0	Constant reflecting a maximum monolayer adsorption
R^2	Correlation coefficient
T_C	Curie temperature
Fe^{2+}	Divalent iron
°C	degree Celcius
emu	electromagnetic unit
E	Energy
E_B	Energy barrier
$q_{e,exp}$	Experimental adsorption capacity values
K_F	Freundlich constant
1/n	Freundlich intensity parameter
g	gram
H	Hydrogen

OH	Hydroxyl group
Fe	Iron
pI	Isoelectric point
K	Kelvin
kDa	kilodaltons
b	Langmuir constant
L	liter
$\gamma\text{-Fe}_2\text{O}_3$	Maghemite
μ_B	magnetic moment per unit molecule
M_S	Magnetic saturation
Fe_3O_4	Magnetite
M	Magnetization
m	meter
μg	microgram
μm	micrometer
mbar	millibar
mg	milligram
mL	milliliter
mV	millivolt
min	minutes
nm	nanometer
x	Neural network input
\hat{y}	Neural network output
O	Oxide
%	percentage
PO_4^{3-}	Phosphate ions
P	Phosphorus
π	pi
M_R	Remnant magnetization
rpm	revolution per minute
R_L	Separation factor
T	Tesla
t	time

$F(\cdot)$	Transfer function
Fe^{3+}	Trivalent iron
V	Volume
H_2O	Water
wt %	weight percent
w_j	Weight vector

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Pemfungsian Nanopartikel Magnetit – Hidrosiapatit dengan Katekin yang Berpotensi untuk Merawat Kanser

ABSTRAK

Penggunaan flavonoid bioaktif dari tumbuhan herba adalah strategi baru untuk merawat kanser dalam mengatasi banyak kesan toksik daripada ubat kemoterapi. Namun, pengedaran sebatian flavonoid yang tidak spesifik menghadkan dos terapeutik dalam sel-sel kanser. Kebelakangan ini, nanopartikel mempunyai tarikan yang besar dalam bertindak sebagai pembawa bersaiz nano yang meningkatkan kepekatan ubat-ubatan di tempat yang dikehendaki. Kajian ini mengenengahkan nanopembawa yang sesuai untuk penghantaran flavonoid katekin. Struktur yang berskala nano yang terdiri daripada teras magnet magnetit nanopartikel dan salutan hidroksiapatit pelbagai fungsi telah dikembangkan sebagai nanopembawa. Adalah diketahui bahawa keberkesanan pengangkutan nanopembawa ini dipengaruhi oleh saiznya. Oleh itu, nanopartikel magnetit yang disediakan menggunakan kaedah pemendakan-bersama diselidiki berdasarkan kesan keadaan pemprosesan yang berbeza ke arah saiz akhir. Pengeluaran magnetit dilakukan dengan mengubah kadar pengacau, suhu reaksi dan larutan pH. Di samping itu, rangkaian saraf yang dinamakan rangkaian Hibrid Pelbilang Lapisan Perseptron (HMLP) digunakan untuk memodelkan dan meramalkan parameter pemprosesan yang optimum untuk menghasilkan saiz nanopartikel magnetit yang terkecil. HMLP meramal parameter pemprosesan optimum tersebut adalah pada kadar kacau 725rpm, suhu 60°C dan pH12.15 dengan saiz ramalan 8.81nm. Kajian eksperimen sebenar kemudian menunjukkan bahawa pengeluaran magnetit pada parameter yang diramalkan memberikan saiz 8.69nm yang memperlihatkan ralat yang sangat kecil sebanyak 1.36%. Selepas itu, magnetit terkecil yang diperolehi disaluti dengan lapisan salutan HAp melalui proses sol-gel cepat. Tujuan salutan lapisan HAp adalah mengelakkan masalah aglomerasi timbul daripada magnetit yang terdedah, meningkatkan profil keselamatan nanopartikel dan meningkatkan keberkesanan pengangkutan katekin. Penggabungan HAp ke permukaan magnetit menyebabkan perubahan morfologi permukaan serta sifat magnetnya. Telah diperhatikan bahawa struktur teras-salutan terbentuk dengan zarah yang dihasilkan mempunyai diameter 48.26nm. Selain itu, berdasarkan analisis struktur, lapisan HAp menunjukkan ketulenan fasa yang tinggi dengan komposisi fasa hampir sama dengan tulang manusia semulajadi. Walau bagaimanapun, nilai ketepuan magnet didapati lebih kecil daripada magnetit yang terdedah. Ini disebabkan oleh lapisan HAp yang bersifat diamagnet. Untuk menyiasat sifat penjerapan nanokomposit, katekin, sebatian flavonoid yang paling banyak terdapat di daun *Ficus deltoidea* dipilih sebagai agen terapeutik. Kajian penjerapan dijalankan dalam siri eksperimen kelompok. Kajian isoterma penjerapan menunjukkan data penjerapan yang paling sesuai adalah mengikuti model Langmuir dengan menunjukkan penjerapan ekalapis katekin ke permukaan nanokomposit secara homogen. Tambahan pula, kajian kinetik penjerapan telah menunjukkan hubungan yang baik dengan kinetik pseudo-taraf-kedua yang menunjukkan bahawa kadar penjerapan katekin adalah melalui pengaturan kadar kimia. Akhirnya, kajian *in vitro* dari magnetit-HAp-katekin nanokomposit dilakukan pada sel kanser payudara. Ketoksikan selular dari nanopartikel

dipengaruhi dengan ketara oleh pendedahan medan magnet yang berterusan. Namun, pengambilan selular di bawah medan magnet adalah terhad kerana magnet mencetuskan gumpalan nano-MHC pada permukaan sel.

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MAGNETITE – HYDROXYAPATITE NANOPARTICLES FUNCTIONALIZED WITH CATECHIN FOR THE POTENTIAL TREATMENT OF CANCER

ABSTRACT

The use of bioactive flavonoids from herbal plant is an emerging strategy for treating cancer in overcoming myriad of toxic effects from chemotherapeutic drugs. However, the non-specific distribution of flavonoid compounds limits the therapeutic dose within cancer cells. In recent years, nanoparticles have a great interest in acting as nanocarriers to increase the concentration of drugs at the desired site. This thesis present on the development of suitable nanocarriers for catechin flavonoid delivery. A nanoscale structure composed of magnetic core of magnetite nanoparticles and multifunctional hydroxyapatite (HAp) shell were developed as a nanocarrier. It is known that the effectiveness of nanocarrier transportation is mainly governed by their size. In view of this argument, magnetite nanoparticles that were prepared using co-precipitation method were studied based on the effects of different processing conditions towards the final size. The production of magnetite were carried out by varying the stirring rate, temperature of reaction and pH of solution. In addition, a neural network named Hybrid Multi-Layered Perceptron Network (HMLP) was used to model and predict the optimum processing condition that yield smallest size of magnetite nanoparticles. It was found that the optimum processing parameters to yield smallest size of magnetite predicted by HMLP are at stirring rate of 725rpm, temperature of 60°C and pH of 12.15 with predicted size of 8.81nm. The real experimental study then revealed that magnetite production at the predicted parameters give a size of 8.69nm, which was a very small error of 1.36%. Subsequently, that smallest magnetite obtained were introduced with HAp coating layer via rapid sol-gel route. The aim of HAp coating layer were to avoid agglomeration issue arises from bare magnetite, enhancing the safety profile of nanoparticles and improving the efficacy of catechin transportation. Incorporation of HAp onto magnetite surfaces resulted in changes in the surface morphology as well as their magnetism properties. It was observed that a core-shell structure was formed with the resulting particles having an average diameter of 48.26nm. In addition, based on structural analyses, HAp layer demonstrated a high phase purity with the phase composition close to the naturally-occurring human bones. However, the magnetic saturation value were found to be slightly decrease than that of bare magnetite which due to the diamagnetic HAp layer. In order to investigate the adsorption properties of the nanocomposites, catechin, a most abundant flavonoid compound present in *Ficus deltoidea* leaf was selected as a therapeutic agent and adsorbate. The adsorption studies were conducted in a series of batch experiments. The adsorption isotherm studies showed that the data were best fitted to a Langmuir model indicating a monolayer adsorption of catechin onto homogenous nanocomposites surfaces had taken place. Furthermore, the adsorption kinetic studies has demonstrated a good correlation with pseudo-second-order kinetics suggesting that the rate of catechin adsorption were chemically rate controlling. Finally, *in vitro* studies of magnetite-HAp-catechin nanocomposites (nano-MHC) were performed on breast cancer cell. Cellular toxicity of nanoparticles was significantly affected by constant magnetic field exposure.

However, cellular uptake under the present of magnetic field was limited due to magnetically-induced nano-MHC aggregates on the cell surfaces.

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CHAPTER 1: INTRODUCTION

1.1 Introduction

The field of nanotechnology is fast becoming a popular topic than most other branches in its history. Nanotechnology has already permeated virtually every sector in view of its potential to revolutionize every field in which it is exploited. Encompassing the development of man-made particles in the 1-100 nanometer size range, made it appealing to researchers, particularly their unique capabilities at a nano level. Intriguing phenomena and extraordinary properties at nano range size could bridge the gaps and overcome the shortcomings of particular fields. It could make human lives more secure, improved human healthcare, managed limited resources with maximum efficiency and provide a better environment.

In the fields of medicine and biology, nanoparticles has since come up with very significant advances in these disciplines. A lot of nanoparticles have firmly entered the realm of diseases diagnosis, targeted therapy, biomarker mapping and molecular imaging. These nanotechnological innovations and their applications, termed as “nanomedicines” draw in information from physics, chemistry, engineering and biology, cooperating together to develop novel treatment and diagnosing modalities. In regards to their nano size, it is possible to deliver the drugs into the hardly accessible areas. They can travel through the blood vessels and permeate into the cell membranes to deliver drugs in proper amounts (Puri & Ganguly, 2014). Furthermore, these smaller particles also have a large surface area-to-volume ratio that allow more drugs to be conjugated per particle (R. Singh & Lillard, 2009). Thus, it can reduce the cost and dosage required for the treatment.