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FUNCTIONALIZED GRAPHENE OXIDE LOADED WITH PROTOCATECHUIC ACID FOR PASSIVE AND ACTIVE DELIVERY SYSTEMS

KALAIVANI BUSKARAN

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By

KALAIVANI BUSKARAN

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Chair : Professor Sharida Fakurazi, PhD
Faculty : Institute of Bioscience

Cancer presents as one of the biggest health threat in the world. Chemotherapeutic agents which are commonly used to treat cancer are lacking in its specificity, resulting in harming and injuring healthy tissues in trivial treatment efficacy. To overcome these obstacles, considerable efforts have been made in ensuring effective cancer therapy particularly utilizing nanotechnology. Recent studies have shown that functionalized graphene oxide (GO) as nanocarrier with biocompatible polymers lead to higher loading efficacy and better stability with lower cellular toxicity.

This study is aimed to explore and investigate cellular uptake of passive and active targeting of functionalized graphene oxide coated with folic acid nanocomposite for cancer therapy. The nanodrug delivery system was designed with an anticancer compound like protocatechuic acid (PCA) and chlorogenic acid (CA) on functionalized graphene oxide conjugated polyethylene glycol as the nanocarrier (GOP) and coated with folic acid for targeting cancer cells. The physicochemical parameters such as size, morphology, drug encapsulation and drug release profile of these compounds were thoroughly characterized.

The nanocarrier and nanocomposites were screened against normal and cancer cells using MTT assay for 72 h within the tested range of concentration and duration. Graphene oxide conjugated with polyethylene gycol, loaded with protocatechuic acid and coated with folic acid (GOP-PCA-FA) showed the optimum IC50 value at lowest concentration of 18.89 µg/mL towards HepG2 cells after 72 h of treatment. Besides, folate receptor coated nanocomposite were found to be highly expressed in HepG2 cells compared to HT29 cells.

The nanocomposite explored as a promising nanodelivery strategy by enhancing the cellular uptake and localization of nanocomposite to improve therapeutic efficacies. Transmission electron microscope (TEM) was utilize to observe the nanocomposites cellular uptake and morphological changes which occurred by post treatment on HepG2 cell from 24 h to 72 h. Fluorescein isothiocyanate (FITC) was conjugated to GOP-PCA-FA which confirms the intracellular localization and accumulation into cell at 48 h later.

Subsequent anticancer toxicity acitivies were evaluated among pristine protocatechuic acid, GOP-PCA (passive target) and GOP-PCA-FA (active target) drug delivery. All the experiments were conducted at IC50 value of pristine protocatechuic acid (38 µg/mL) on HepG2 cells. The cell migration of HepG2 treated nanocomposites shows significant cell exclusion zone. Clonogenic assay was carried out to examine the colony forming ability of treated cells on potential chronic toxicity. Lactate dehydrogenase assay shows dose-dependent manner severity on membrane integrity of HepG2 cells.

The Annexin V/PI flow cytometry analysis showed that nanocomposites induces late apoptosis in HepG2 cells. Following the intervention of nanocomposites, the cell cycle arrest was ascertained at G2/M phase. Mitochondrial membrane potentials were evaluated to determine the extent of mitochondrial disruption including changes in membrane potential caused by nanocomposites. The level of free radical species production was significantly increased in nanocomposites treated HepG2 cells.

The proteomic profiling array exposed the pro-apoptotic proteins such as BAD, BAX, pro-caspase-3, cytochrome-c, p21 and p53 were upregulated and anti-apoptotic proteins Bcl-2, Bcl-xL and HSP70 were downregulated upon GOP-PCA-FA treatment in HepG2 cells. This data was confirmed by conducting RT-qPCR in identifying the changes in gene expression of HepG2 cells.

In conclusion, GOP-PCA-FA nanocomposite treated HepG2 cells exhibit less toxicity, better cellular uptake and localization with significant anticancer activity compared to pristine protocatechiuc acid or GOP-PCA nanocomposite due to the utilization of active targeting drug delivery system.

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FUNGSIONALISASI GRAPHENE OKSIDA MEMUAT DENGAN ASID PROTOKATEKUIK BAGI SISTEM PENYAMPAIAN UBATAN SECARA PASIF DAN AKTIF

Oleh

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Fakulti : Institut Biosains

Kanser merupakan salah satu ancaman kesihatan terbesar di dunia. Ejen kemoterapi yang biasa digunakan untuk merawat kanser adalah kurang spesifik terhadap sel-sel kanser. Untuk mengatasi masalah ini, pelbagai usaha telah diambil terutamanya dalam memastikan terapi kanser yang berkesan dan penjimatan kos dengan menggunakan teknologi nano. Kebelakangan ini kajian menunjukkan bahawa penyampaian ubatan graphene oksida (GO) yang berkonjugat dengan polimer memberikan keberkesanan muatan yang lebih tinggi dan kestabilan yang lebih baik di samping penurunan ketoksikan selular.

Tujuan kajian ini adalah untuk meneroka dan menyiasat aktiviti pengambilan ubatan oleh selular melalui penyampaian ubatan melalui kaedah sasaran pasif dan aktif oleh nanokomposit untuk terapi kanser. Sistem penyampaian ubat terkawal nanokomposit direkabentuk dengan asid protokatekuik (PCA) dan asid klorogenik (CA) dan menggunakan graphene oksida-polietilena glikol yang berfungsi sebagai nanovektor (GOP) yang disaluti dengan asid folik bagi penyampaian ubatan kaedah aktif kepada sel-sel kanser. Ciri-ciri fizikokimia seperti saiz, morfologi, kapasiti muatan dadah dan profil pembebasan dadah terkawal bagi sebatian ini telah dicirikan dengan teliti.

Nanovektor dan nanokomposit telah disaringkan mengunakan sel-sel normal dan sel-sel kanser menggunakan eksperimen MTT dirawat untuk 72 jam dalam pelbagai kepekatan. Graphene oksida yang berkojugasi dengan polietilena glikol yang dimuatkan dengan asid protokatekuik dan bersaluti dengan asid folik (GOP-PCA-FA) menunjukkan optitum IC50 dengan sitotoksisiti terendah terhadap sel HepG2 iaitu sebanyak 18.89 µg/mL

selepas dirawat selama 72 jam. Sel-sel HepG2 didapati mempunyai reseptor folik yang tinggi berbanding dengan sel-sel HT29. Malah, ia membantu dalam penyampaian ubatan melalui kaedah penyampaian aktif.

Nanokomposit dieksplorasi sebagai strategi penyampaian ubatan yang baik kerana ia meningkatkan pengambilan dan pengkumpulan molekul biologi dalam sel bagi tujuan meningkatkan kesan terapi. Mikroskop elektron penghantaran (TEM) digunakan untuk mengkaji pengambilan dan perubahan morfologi yang berlaku setelah dirawat dengan nanokomposit at HepG2 sel dari 24 jam hing 72 jam. Fluorescein isothiocyanate (FITC) dikonjukasikan dengan GOP-PCA-FA nanokomposit untuk memastikan pengambilan dan pengumpulan selular diperhatikan pada 24 jam dan 48 jam.

Ketoksikan antikanser berikutnya dinilai dengan mengunakan asid protokatekuik, GOP-PCA (sasaran pasif) dan GOP-PCA-FA (sasaran aktif) untuk penyampaian ubatan terkawal. Kesemua eksperimen dijalankan menggunakan nilai IC50 asid protokatekuik (38 μg/mL) atas sel-sel HepG2. Penghijrahan sel-sel HepG2 yang dirawat dengan nanokomposit menunjuk ujian zon pengecualian sel yang signifikasi. Ujian klonogenik dijalankan untuk mengkaji keupayaan pembentukan koloni sel setelah dirawat untuk ketoksikan potensi kronik. Eksperimen laktat dehidrogenase menunjukan kecederaan dan kerosakan liputan luar membran sel dengan keberkesanan.

Analisis sitometri aliran menggunakan Annexin V/PI menunjukkan bahawa nanokomposit menginduksikan apoptotik lewat pada sel-sel HepG2. Berikutan rawatan nanokomposit juga menunjukkan bahawa gangguan kitaran sel wujud pada fasa G2/M. Potensi membran mitokondria dinilai untuk menentukan sejauh mana gangguan potensi membran mitokondria berlaku setelah dirawat dengan nanokomposit. Tahap penghasilan spesis radikal bebas telah meningkat dengan ketara dalam sel-sel HepG2 delepas dirawat dengan nanokomposit.

Susunan profiling proteomik mendedahkan penghalisan protein pro-apoptotik iaitu BAD, BAX, pro-caspase-3, cytochrome-c, p21 and p53 telah bertambah dan protein anti-apoptotik Bcl-2, Bcl-xL and HSP70 telah berkurang selepas dirawat oleh GOP-PCA-FA dalam sel-sel HepG2. Akhirnya, RT-qPCR dijalankan untuk mengenal pasti perubahan dalam ekspresi gen dalam HepG2 sel.

Kesimpulannya, nanokomposit GOP-PCA-FA yang digunakan untuk merawat sel-sel HepG2 menunjukkan sitotoksisiti terendah, pengambilan and pengumpulan selular dan aktiviti antikanser yang signifikan berbanding dengan asid protokatekuik atau GOP-PCA nanokomposit dengan penggunaan sistem penyampaian ubatan terkawal yang aktif.

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Declaration by graduate student

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LIST OF ABBREVIATIONS

GO	Graphene oxide
HCC	Human hepatocellular carcinoma
RFA	Radiofrequency ablation
TACE	Transarterial chemoembolization
PCA	Protocatechuic acid
CA	Chlorogenic acid
GOP	Graphene oxide coated with PEG
GOP-PCA	Graphene oxide coated PEG and loaded with protocatechuic acid
GOP-PCACA	Graphene oxide coated PEG and loaded with protocatechuic acid+ chlorogenic acid
GOP-PCA-FA	Graphene oxide coated PEG and loaded with protocatechuic acid tagged with folic acid
GOP-PCACA-FA	Graphene oxide coated PEG and loaded with protocatechuic acid+ chlorogenic acid tagged with folic acid
Gr	Graphite
WHO	World Health Organization
°C	Degree Celsius
g	gram
µL	microliter
mL	millilitre
mg	milligram
min	minute
sec	seconds
h	hours
mm	millimetre
mM	milimolar
%	Percentage
rpm	Rotation per minute
kV	Kilo Volt
mA	Miliampere

nm	nanometer
cm^2	Centimetre square
NIH 3T3	Human fibroblast cell
HepG2	Human hepatocellular carcinoma
HT29	Human colorectal adenocarcinoma
MCF-7	Human Breast cancer cell
PEG	Polyethylene glycol
FA	Folic acid
FITC	Fluorescein isothiocyanate
DAPI	4',6-diamidino-2-phenylindole
HR-TEM	High Reselution Transmission electron microscope
UV/vis	Ultraviolet/visible spectroscopy
RPMI	Roswell Park Memorial Institute
FBS	Fetal Bovine Serum
CO^2	Carbon dioxide
EDTA	Ethylenediaminetetraacetic acid
MTT	(3-(4, 5 Dimethylthiazol 2-yl)-2,5-Diphenyltetrazolium Bromide)
DMSO	dimethylsulfoxide
PBS	Phosphate Buffer solution
SDS-PAGE	Sodium dodecyl sulfate-polyacrylamide gel electrophoresis
APS	Ammonium persulfate
TEMED	Tetramethylethylenediamine
H_2O	Water
HCl	Hydrogen Chloride
V	Volt
β-actin	Beta actin
PVDF	Polyvinylidene difluoride
BSA	Bovine Serum Albumin
IC_{50}	Inhibitory concentration at fifty percentage
LDH	Lactate dehydrogenase
PI	Propidium Iodide
DNA	Deoxyribonucleic acid

ΔΨm	Membrane potential permeability
DCFH-DA	Dichloro-dihydro-fluorescein diacetate
ROS	Reactive oxygen species
RNA	Ribonucleic acid
RT	Room temperature
PCR	Polymerase Chain Reaction
qPCR	Real time Polymerase Chain Reaction
C	Carbon
H	Hydrogen
O	Oxygen
ND	Not determined
FR	Folate receptors
ANOVA	Analysis of variance
SD	Standard deviation
PS	Phosphatidylserine
S	Synthesis
CCCP	Carbonyl cyanide m-chlorophenyl hydrazone
H_2O_2	Hydrogen peroxide
rRNA	Ribosomal ribonucleic acid
RIN	RNA Integrity Number
GAPDH	Glyceraldehyde-3-phosphate dehydrogenase
RES	reticuloendothelial system
XRD	X-ray diffraction
FTIR	Fourier transformed infrared spectroscopic
DLS	Dynamic light scattering
HPLC	High performance liquid chromatography
HSP	Heat shock proteins
TfR	Transferrin receptor
EGFR	Epidermal growth factor receptor
SODs	Superoxide dismutases
TUNEL	TdT-mediated dUTP nick-end labeling

CHAPTER 1

INTRODUCTION

1.1 Background

Cancer is known as the second leading cause of death worldwide which was accountable for 9.6 million deaths in 2018. Globally, nearly 1 in 6 deaths is due to cancer (WHO, 2018). It has been reported by International Agency for Research on Cancer (IARC) by 2030, the global burden is predicted to extend to 21.7 million new cancer cases and 13 million cancer deaths due to unhealthy lifestyle and ageing of the population. Nearly 70% of cancer deaths occur in low and middle-income countries. One-third of deaths from cancer is due to high body mass index, low fruit and vegetable intake, tobacco and alcohol uses and lack of exercise. According to WHO the most common cancers that cause leading mortalities rate are from lung carcinoma (1.69 million), Liver cancer (788, 000), Colorectal carcinoma (774,000), Stomach cancer (754,000) and Breast cancer (571,000) (WHO, 2017). Besides, advancement in diagnosis, treatment and prevention of cancer, this disease is still responsible for about 26,395 deaths with 43, 837 new cases per year in Malaysia (GLOBALCAN, 2018). These strongly suggest the need of evaluation of early diagnosis, comprehensive treatment and wide range of management of cancer patients are crucial for curbing this killer disease.

The current available cancer treatments are surgical removal of tumour, chemotherapy and radiation therapy (Hussein et al. 2011). Chemotherapy drugs that are commercially available in healthcare to constraint and eradicate cancer were shown to be highly successful and at the same time the treatment strategy imposes side effects towards healthy cells. Higher concentrations and repeated doses, are needed to maintain effective curative level in cancer treatment. Patients are imposed to higher drug concentrations experiences from high frequency of side effects (Zhang et al. 2005). A contemporaneous treatment strategy consists of chemotherapy and radiation expose the cancer patient to various adverse effects besides its known efficacy. Most patients experience adverse effects such as damage cells in the digestive tract, kidney, heart, bladder, reproductive system, mouth and hair follicles. While there are some percentage of patients will experience disintegration of bone marrow and collapsing of the nervous system. There are patients also exposed to infection caused by the deficiency of white blood cells. Although, the side effects may disappear quickly, but certain symptoms might take months or even years to eradicate completely. There are some that last a lifetime, causes long-term damage to the heart, lungs, kidneys, or reproductive organs and may cause suspended effects such as reoccurring cancer (American Cancer Society, 2018).

This lead to demand an effective drug delivery system for cancer therapy. Nanotechnology has made massive impact through advances in drug delivery system. The principle objective of a novel drug delivery system is to ensure the drug payload is transported and distributed to the desired disease tissue, with the required dose to achieve its optimal therapeutic plasma concentration. Hence, this improved the outcome of pharmacotherapy (Babu, Praveen, and Ajayaghosh 2014). Precipitous development in the field of nanomedicine has ensued in multiple productive synthesis and characterization of various nanomaterial for drug delivery system (Bhattacharyya et al. 2011). The distinctive physical properties of nanomaterial includes surface functionality, biocompatibility, sustained release abilities and wide bioavailability, making the material extremely appropriate for an extensive range of medical applications (Jain 2008).

1.2 Problem Statement

Liver cancer is listed as the fifth commonest cancer, which is responsible for 9.1% of all cancer deaths globally (Ferlay et al. 2013). Due to its assertive nature and poor survival rate, it remains an important public health issue worldwide (Altekruse, McGlynn, and Reichman 2009). Hepatocellular carcinoma (HCC) or hepatoma known as a primary malignant neoplasm derived from hepatocytes, accounting for about 75–90% of all liver cancer (Ferlay et al. 2013). American Cancer Society's estimated there were about 40,710 (29,200 in men and 11,510 in women) new cases of HCC and intrahepatic bile duct cancer were diagnosed and about 28,920 people (19,610 men and 9,310 women) died due to this cancer (Siegel et al. 2017). The epidemiology of HCC for the regions with the highest incidence are Asia–Pacific (East Asia and Southeast Asia), Central and Western Africa, where about 85% of the cases reported (GLOBOCAN, 2012).

In Malaysia, the physiognomies and clinical presentation of HCC were common among the Chinese followed by the Malays and Indians. This is the second most common cancer in the digestive tract following colorectal carcinoma among Malaysian men with the male: female ratio of 3.4:1 between age 54-69 years (Goh et al. 2015). The prognosis of hepatocellular carcinoma has suggested that patients with small, resectable tumour with no cirrhosis or other critical health problems are likely to survive longer if their cancers are discarded with overall of 5-year survival is over 50%. Whereas people with initial-stage liver cancers who have undergone liver transplant, the 5-year survival rate is in the range of 60% to 70% (Farinati et al. 2016).

Treatment for HCC depends on the accessibility of local expertise and resources. Current available treatment in Malaysia are surgery, radiofrequency ablation (RFA), transarterial chemoembolization (TACE), systemic chemotherapy and palliative care. The RFA and TACE are commonly used with the accessibility of a dedicated interventional hepatobiliary radiology team. However, both procedures remain expensive

(Goh et al. 2015). In systemic circulation chemotherapy drugs used is not based on local accumulation at the diseased site but rather depends on the distribution of drug in the body which makes the drug to cross several barriers and reach both healthy and diseased tissue. As a result, high drug concentration is used for better treatment which is therapeutically effective at certain body compartment. In this procedures along with tumour cells, healthy tissue or organs are harmed which give rise to unwanted side effects (Torchilin 2011).

Current problems with chemotherapy in treating cancer beside toxic to healthy tissues, they are also possessing low specificity, rapid in drug clearance and biodegradation, low therapeutic index and limited targeting (Sinha et al. 2006). Additionally, cancer chemoresistance, which is accountable for most failure cases in cancer therapy, is a phenomenon in which cancer cells that are initially suppressed by an anticancer drug develop resistance towards the particular drug. For this reason, novel drug delivery systems with better targeting ability are needed for cancer prevention, suppression of adverse side effects and pain management associated with cancer chemotherapy (Shapira et al. 2011).

1.3 Justification

Drug targeting system has gain attention due to their ability in transport and release drugs at the targeted site over a long period of time which enhance drug activity and prevent drug accumulation in healthy tissue thus avoid wastage of drug and reduce side effects. In passive targeting, the prepared drug nanocarrier complex circulates through the bloodstream and it's driven to the targeted site by enhance permeation retention (EPR) effect or utilizing influenced properties like pH, temperature, molecular site and shape. Whereas, in active targeting, moieties, such as antibodies and peptides are coated to nanocarrier drug delivery system allow them to anchor to the receptor structures expressed at the targeted site. Therefore, it is desirable to develop a chemotherapeutic drug that can either passively or actively target cancerous cells, thereby reducing adverse side effects while improving therapeutic efficacy.

Graphene oxide (GO) is consider as a promising nanomaterial for drug delivery and has enticed significant attention from researchers globally for its high biocompatibility, low cytotoxicity, enabled endocytosis, large specific surface area available for drugs entrapment, and enhanced bioavailability at the targeted site (Yang et al. 2013). Hence, the aim of this study is to investigate the efficacy of GO-based nano drug delivery system including cellular uptake, localization, transport and eventually toxicity of the nanocarrier and nanocomposites system. The observation made from the project will enable to decide on the potentiality of the nanomaterial in delivering anticancer biocompound into the cells.
Phenolic compounds like protocatechuic acid (3, 4-dihydroxybenzoic acid,

PCA) (Kakkar and Bais 2014) and chlorogenic acid (CA) are well known for its properties to induce caspase-mediated apoptosis activity and enhance the cytotoxicity effect on various cancer cell lines. This phenolic compounds are mainly responsible for apoptosis, scavenging of radicals, antioxidant, and pro-oxidant characteristics of the antitumor activities (Bordwell et al. 1991; Tanaka, Tanaka, and Tanaka 2011). However, this possesses major challenges including *in vivo* instability, poor bioavailability, and poor solubility, poor absorption, lack of specific delivery, and tonic effectiveness (Jahangirian et al. 2017).

Therefore, using nanodrug delivery systems for targeting specific body parts could solve this critical issue. Nanodrug delivery system has its potential advantages such as the possibility to modify properties like solubility, drug release profiles, diffusivity, bioavailability and immunogenicity (Mirza and Siddiqui 2014). This, can consequently leads to the improvement and development of convenient administration routes, lower toxicity, fewer side effects, improved biodistribution and extended drug life cycle. So the development of functionalized graphene oxide nanocarrier loaded phenolic compound for passive and active targeting were used for the drug delivery system as an alternative way for anticancer treatment.

1.4 Hypotheses

Nanodelivery system (graphene oxide conjugated PEG with folic acid coated) is anticipated to enhance cellular drug transport/uptake through the membrane with improving delivery of the anticancer biocompound (protocatechuic acid or chlorogenic acid) through active targeting on cancer cells as compared to passive targeted nanocomposite or native form (pure compound).

1.5 General Objective

To determine the efficacy of functionalized graphene oxide loaded with protocatechuic acid nanocomposite drug delivery system for passive and active receptor targeting in human hepatocellular carcinoma.

1.5.1 Specific Objectives

1 To synthesize and characterize physicochemical properties of functionalized graphene oxide (GO), polymer (PEG) and folic acid (FA) loaded protocatechuic acid (PCA) and chlorogenic acid (CA) nanocomposites.

2 To measure and screen the cytotoxicity activity of functionalized graphene oxide (GO), GO polymer, GOP nanocomposites loaded with protocatechuic acid (PCA) and chlorogenic acid (CA) with or without folic acid (FA) against normal and cancer cell lines.

3 To investigate and observe the localization, ultra-morphological changes and cellular uptake of GOP-PCA and GOP-PCA-FA nanocomposites on human hepatocellular carcinoma HepG2 cell line.

4 To analyse the anti-cancer cell cytotoxicity of GOP-PCA and GOP-PCA-FA nanocomposites on human hepatocellular carcinoma HepG2 cell line.

5 To evaluate and screen the cytotoxic and apoptosis-inducing pathway of GOP-PCA-FA nanocomposite human hepatocellular carcinoma HepG2 cell line.

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