NANOVESIKEL BERASASKAN SURFAKTAN ASID AMINO NATRIUM N-LAUROYLSARKOSINAT SEBAGAI PEMBAWA PEMEKA SINARAN HIDROGEN PEROKSIDA DAN APLIKASINYA KE ATAS SEL KARSINOMA PAYUDARA MDA-MB-231

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PENGAKUAN

Saya akui karya ini adalah hasil kerja saya sendiri kecuali nukilan dan ringkasan yang tiap-tiap satunya telah saya jelaskan sumbernya.

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ABSTRAK

Agen pemeka sinaran khususnya hidrogen peroksida (H_2O_2) berkepekatan rendah telah digunakan pada peringkat klinikal dalam meningkatkan keberkesanan terapi sinaran terhadap kanser payudara. Walaupun penggunaan agen ini telah meningkatkan kepekaan sel kanser payudara terhadap sinaran, namun kaedah penyampaian langsung agen secara suntikan *intratumoral* menyebabkan pesakit mengalami kesan sampingan seperti pengerasan tisu, keradangan dan kesakitan di kawasan suntikan. Justeru, objektif utama kajian ini adalah untuk mengkaji sistem penyampaian ubat (DDS) alternatif khususnya nanovesikel berasaskan surfaktan asid amino natrium N-lauroylsarkosinat (SNLS) sebagai pembawa H_2O_2 bagi mengurangkan kesan ketoksikan agen melalui pengkapsulan agen dalam teras akueus sistem dwilapisan nanovesikel. Kompleks nanovesikel-hidrogen peroksida (NVs-H) disintesis melalui kaedah pemuatan pasif agen H_2O_2 secara sinergi dengan himpunan kendiri surfaktan utama SNLS dan dekanol pada nisbah molar optima surfaktan iaitu 1:1.73 dalam 92 wt% larutan H_2O_2 berkepekatan 0.0003 - 3% v/v. Proses sintesis disusuli dengan kaedah penyemperitan (*extrusion*) dalam mengecilkan dan menghomogenkan saiz NVs-H serta proses penulenan menggunakan kaedah ultrapenurasan emparan. Pencirian menggunakan mikroskop cahaya berkutub (PLM), teknik serakan cahaya dinamik (DLS), mikroskop transmisi elektron (TEM), spektroskopi inframerah jelmaan Fourier (FTIR) dan spektrofotometer ultra-lembayung nampak (UV-Vis) dijalankan untuk mengkaji sifat fizikal dan kimia NVs-H yang disintesis. Imej mikroskopik PLM dan TEM menunjukkan bahawa agen H_2O_2 pada kepekatan 0.0003 - 3% v/v tidak membantut pembentukan mahupun menyebabkan perubahan morfologi sfera nanovesikel. Berdasarkan pencirian DLS, kompleks NVs-H mempunyai saiz purata yang seiring dengan saiz prasyarat untuk penyetempatan dalam tumor iaitu saiz lebih kecil daripada 150 nm. NVs-H turut berkeadaan homogen dan mempunyai kestabilan yang tinggi berlandaskan nilai indeks poliserakan (PDI) yang lebih kecil daripada 0.3 serta nilai magnitud potensi zeta yang lebih besar daripada -50 mV. Berdasarkan pencirian FTIR, konformasi molekular NVs-H menunjukkan bahawa ia mempunyai susunan struktur yang lebih teratur berdasarkan anjakan rantaian alkil surfaktan kepada nombor gelombang yang lebih kecil. Anjakan ini menandakan bahawa dwilapisan nanovesikel mempunyai penghalang yang efisien dalam mengkapsulkan agen. Pencirian UV-Vis mengesahkan pengkapsulan agen H_2O_2 dengan nilai peratusan kecekapan pengkapsulan (EE%) bersamaan dengan ~ 30%. Kajian secara *in vitro* ke atas sel kanser payudara MDA-MB-231 menunjukkan bahawa NVs-H bersifat tidak toksik. NVs-H turut telah memekakan sel kanser terhadap sinaran gama serta berupaya dalam mencapai *lethal dose* (LD50) pada dos sinaran yang bersamaan dengan 2, 6, dan 10 Gy. Seiring dengan ini, prinsip keselamatan sinaran *as low as reasonably achievable* (ALARA) dapat dicapai melalui rawatan sel kanser dengan NVs-H sebelum penyinaran gama. Hasil daripada kajian ini menunjukkan bahawa sistem nanovesikel berasaskan surfaktan asid amino SNLS mempunyai potensi sebagai pembawa pemeka sinaran H_2O_2, lantas berpotensi untuk mengatasi masalah kesan sampingan yang dialami oleh pesakit klinikal ketika terapi sinaran di samping mengurangkan jumlah dos sinaran yang diterima oleh pesakit ketika rawatan.

NANOVESICLE COMPOSED OF SODIUM N-LAUROYLSARCOSINATE AMINO ACID SURFACTANT AS HYDROGEN PEROXIDE RADIATION SENSITIZER CARRIER AND ITS APPLICATION ON BREAST CARCINOMA CELL LINE MDA-MB-231

ABSTRACT

Radiation sensitizer agent, specifically hydrogen peroxide (H_2O_2) of low concentration, has been employed in clinical regimens to enhance the radiation treatment outcome on breast cancer. Even though utilisation of this novel agent has effectively increased breast cancer cell sensitivity towards radiation, the agent direct delivery method via intratumoral injection causes patients to experience side effects such as tissue induration, inflammation and local pain at the injection site. Hence, the main objective of this study is to investigate an alternative drug delivery system (DDS), respectively nanovesicle composed of sodium N-lauroylsarcosinate (SNLS) amino acid surfactant as a H_2O_2 carrier to reduce agent toxicity effect through agent encapsulation in the nanovesicle bilayer core system. Nanovesicle-hydrogen peroxide (NVs-H) complex was synthesized through passive H_2O_2 agent loading synergistically with the self-assembly of the main surfactant SNLS and decanol at optimum surfactant molar ratio of 1:1.73 in 92 wt% H_2O_2 solution of 0.0003 - 3% v/v concentration. The synthesis process was complemented with an extrusion method to reduce and homogenize the NVs-H size with subsequent purification process via the centrifugal ultrafiltration method. Characterisation using polarized light microscope (PLM), dynamic light scattering (DLS) technique, transmission electron microscopy (TEM), Fourier transform infrared spectroscopy (FTIR) and ultraviolet-visible spectrophotometer (UV-Vis) were conducted to study the physical and chemical properties of synthesized NVs-H. PLM and TEM microscopic images deduced that the presence of H_2O_2 agent at 0.0003 - 3% v/v concentration neither hampers the formation nor induces changes to the spherical morphology of nanovesicle. Based on DLS characterization, the synthesized NVs-H complex had an average size in tandem with tumour localization prerequisite size of below 150 nm. The NVs-H was also at a homogenized state and had high stability per polydispersity index (PDI) value of lower than 0.3 and zeta potential magnitude value of higher than -50 mV, respectively. Based on FTIR characterization, the molecular conformation of the NVs-H complex illustrates that it has a more ordered structure based on the shift of the surfactant alkyl chain to a lower wavenumber value. The shift denotes that the nanovesicle bilayer had a more efficient barrier in the encapsulation of the agent. The UV-Vis characterization affirmed the encapsulation of H_2O_2 agent with an encapsulation efficiency percentage (EE%) value equivalent to ~ 30%. Furthermore, an investigation via *in vitro* studies on breast cancer line MDA-MB-231 also demonstrates that the NVs-H was non-toxic. NVs-H has also sensitized cancer cells towards gamma radiation whereby lethal dose (LD50) was achieved at absorbed radiation dose of 2, 6, and 10 Gy. In conjunction with this, the radiation safety principle, as low as reasonably achievable (ALARA) could be achieved through the treatment of cancer cells with NVs-H prior to gamma irradiation. The findings of this study envisage that nanovesicles composed of amino acid SNLS surfactant have the potential as a H_2O_2 radiation sensitizer carrier, hence could overcome the agent side effects currently faced by patients during radiation therapy while reducing radiation dose received by patients during treatment.

KANDUNGAN

Halaman

SENARAI JADUAL

SENARAI ILUSTRASI

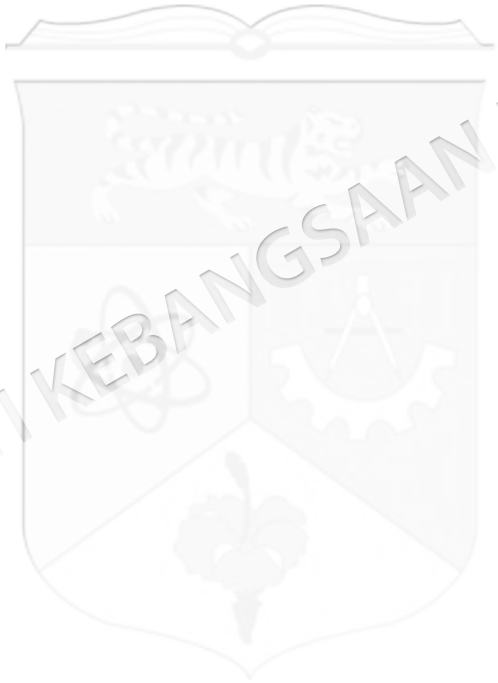
No. Gambar **Halaman**

SENARAI TATANAMA

ALAF	Pusat Pengurusan Makmal Alami dan Fizikal
ALARA	*As Low As Reasonably Achievable*
ANOVA	Ujian Analisis Varians
BaO	Barium Oksida
C_3H_8O	Isopropanol
CH_3COOH	Asid Asetik
CPC	*N-cetylpyridinium chloride*
CPP	Parameter Pemampatan Kritikal
CSC	Sel Stem Kanser
CTCAE	*Common Terminology Criteria for Adverse Events*
DDS	Sistem Penyampaian Ubat
DI	Air Ternyahion
DMEM	*Dulbecco's Minimum Essential Medium*
DMSO	*Dimethyl Sulfoxide*
DNA	Asid Deoksiribonukleik
DPC	*Dodecylpyridinium chloride*
DSB	Pemutusan Jalur Gandaan Dua
EE%	Peratusan Kecekapan Pengkapsulan
EMT	Peralihan Epitelium-Mesenchymal
EPR	*Enhanced Permeability and Retention*
ETC	Rantaian Pengangkutan Elektron
FDA	*U.S. Food and Drug Administration*
FTIR	Spektroskopi Inframerah Jelmaan Fourier
H_2O_2	Hidrogen Peroksida
HDI	Indeks Pembangunan Manusia

HNO_3	Asid Nitrik
HSD	*Honestly Significant Difference*
ICRP	*International Commission on Radiologic Protection*
LD	*Lethal Dose*
LET	Tenaga Perpindahan Linear
MSSG	*Monosodium N-stearoyl-L-glutamate*
MTT	*Microculture* Tetrazolium
NDDS	Sistem Penyampaian Ubat Nano
$(NH_4)_2MoO_4$	Ammonium Molibdat
NVs-AA	Nanovesikel Berasaskan Surfaktan Asid Amino
NVs-AA.Ex	Nanovesikel Berasaskan Surfaktan Asid Amino selepas Proses Penyemperitan
NVs-AA.Ex.UF	Nanovesikel Berasaskan Surfaktan Asid Amino selepas Proses Penyemperitan-Ultrapenurasan Emparan
NVs-H	Nanovesikel-Hidrogen Peroksida
NVs-H.Ex.UF	Nanovesikel-Hidrogen Peroksida selepas Proses Penyemperitan-Ultrapenurasan Emparan
O_2	Oksigen
OD	Ketumpatan Optik
OER	Nisbah Peningkatan Oksigen
PBS	Pengimbal Fosfat
PC	Polikarbonat
PDI	Indeks Poliserakan
PES	Polieter Sulfon
PLM	Mikroskop Cahaya Berkutub
RCF	Daya Relatif Emparan
ROS	Spesies Oksigen Reaktif
SNLS	Natrium N-lauroylsarkosinat

SOD	Superoksida Dismutase
SSB	Pemutusan Jalur Tunggal
TEM	Mikroskop Transmisi Elektron
TLD	Dosimeter Pendarkilau Haba
TME	Persekitaran Mikro Tumor
UKM	Universiti Kebangsaan Malaysia
UV-VIS	Spektrofotometer Ultra-lembayung Nampak
WHO	*World Health Organization*



SENARAI SIMBOL

a_o	Keluasan permukaan bahagian hidrofilik surfaktan
A_o	Aktiviti awal radionuklid
A_t	Aktiviti semasa radionuklid
D_f	Dos terserap
DNA•	Radikal asid deoksiribonukleik
DNA-OO•	Peroksil asid deoksiribonukleik
e^-	Elektron
Fe^{2+}	Ion ferus
Fe^{3+}	Ion ferik
G (Fe^{3+})	Bilangan ion ferik
H^+	Radikal hidrogen
H_2O^+	Air terion
H_3O^+	Radikal hidronium
I_3^-	Ion Triiodida
l	Panjang lintasan optik
l_c	Panjang bahagian hidrofobik surfaktan
M	Kemolaran
$O_2^{\bullet-}$	Anion superoksida
OH•	Radikal hidroksil
OO	Peroksida
t	Hari semasa penyinaran
$t_{1/2}$	Setengah hayat radioaktif
v	Isipadu
W_i	Nilai penyerapan agen kawalan
W_t	Nilai penyerapan agen yang terkapsul

ε	Pemalar serapan linear molar
λ	Pemalar reputan
ρ	Nilai ketumpatan larutan

BAB I

PENDAHULUAN

1.1 LATAR BELAKANG KAJIAN

Kanser merupakan salah satu punca utama kematian di peringkat global. Berdasarkan laporan *World Health Organization* (WHO), statistik terkini menunjukkan bahawa kanser menyebabkan 9.7 juta kematian pada tahun 2022 (Bray et al. 2024; WHO 2024a) dan angka ini dijangka akan meningkat kepada 25 juta menjelang tahun 2040 (Sung et al. 2021; WHO 2024b). Selain daripada mempunyai jumlah kes insiden yang tertinggi, kanser payudara merupakan salah satu jenis kanser utama yang menyumbang kepada statistik kematian ini serta menjadi punca utama kematian di kalangan wanita (Bray et al. 2024; WHO 2024c). Secara tidak langsung, seiring dengan penekanan terhadap ujian saringan awal dalam membasmi kanser payudara, statistik ini turut menggambarkan perlunya penekanan terhadap pelaksanaan kaedah rawatan yang efektif untuk meningkatkan kelangsungan hidup pesakit yang menghidap kanser payudara.

Terapi sinaran yang dikenali sebagai radioterapi adalah salah satu rawatan adjuvan yang dipraktikan secara klinkal dalam merawat kanser. Sinaran mengion seperti sinar gama, sinar-X dan alur elektron yang mempunyai nilai tenaga perpindahan linear (LET) rendah lazimnya digunakan dalam kaedah rawatan kanser ini (Bast et al. 2023; Wang et al. 2019). Spesies oksigen reaktif (ROS) khususnya radikal hidroksil yang terhasil daripada kesan secara tidak langsung sinaran mengion ini dengan molekul air intrasel dan ektrasel mendominasi dua per tiga kerbekesanan terapi sinaran (Cadet, Angelov & Wagner 2022; Hall & Giaccia 2018). Radikal bebas ini menyebabkan kerosakan sel kanser melalui tindak balas dengan asid deoksiribonukleik (DNA) yang merupakan komponen sel kritikal yang utama (Mavragani et al. 2019). Namun untuk mengaruh kematian sel kanser, kerosakan DNA ini perlu dikekalkan melalui proses

tindak balas dengan molekul oksigen yang dikenali sebagai proses hipotesis pengekalan oksigen (*oxygen fixiation hypothesis*) (Hall & Giaccia 2018; Zhu et al. 2021). Ini menunjukkan bahawa oksigen merupakan unsur genting bagi keberkesanan terapi sinaran dalam merawat kanser. Secara tidak langsung, ini dapat menjelaskan sifat tumor pepejal (*solid tumor*) seperti kanser payudara yang lazimnya rintang terhadap sinaran disebabkan oleh keadaan hipoksia iaitu keadaan kekurangan oksigen di dalam dan di persekitaran tumor. Walaupun 50% kes kanser dirawat menggunakan terapi sinaran, namun hipoksia merupakan salah satu cabaran dalam merawat kanser secara efektif disebabkan oleh kerintangan sel terhadap sinaran apabila kekurangan oksigen (Gilreath et al. 2021; Rakotomalala et al. 2021). Selain itu, sifat kerintangan tumor terhadap sinaran turut disebabkan oleh kandungan enzim antioksidan yang lebih aktif pada tumor pepejal. Enzim antioksidan ini berperanan dalam memulihkan kerosakan DNA (Merlin et al. 2022; Wang et al. 2019) serta menghapus radikal bebas (Chen et al. 2021; Jiang, Wang & De Ridder 2018; Wang et al. 2019).

Kerintangan sel kanser terhadap sinaran dapat di atasi melalui penggunaan pemeka sinaran yang merupakan agen farmakologi. Pemeka sinaran ini berperanan dalam meningkatkan keberkesanan terapi sinaran dengan meningkatkan kepekaan sel kanser terhadap sinaran (Gong et al. 2021; Wang et al. 2018). Pelbagai kajian berkenaan pemeka sinaran telah dikaji sejak lima puluh tahun dahulu (Moulder 2019). Namun sedemikian, pemeka sinaran hidrogen peroksida (H_2O_2) mempunyai ciri mutlak dalam menyahaktifkan enzim antioksidan di samping mengoksigenkan kembali sel kanser yang hipoksik (Akima et al. 2016; Koga et al. 2022; Ogawa 2016). Selain daripada itu, H_2O_2 yang memainkan peranan penting dalam proses selular secara asasnya boleh menyebabkan tekanan oksidatif dan mengaruh sifat kesitotoksikan pada kepekatan suprafisiologi iaitu kepekatan melebihi yang terkandung dalam badan secara semulajadi (Andrés et al. 2022; Nimalasena et al. 2020). Selain daripada sifat pro-oksidan H_2O_2 ini, keupayaan agen ini dalam mempengaruhi laluan isyarat berkaitan dengan kerintangan sinaran (*radioresistance-associated signalling pathway*) serta mengaruh penghasilan ROS intraselular dalam meningkatkan pemutusan ikatan ganda dua DNA (Adachi et al. 2022; Oike et al. 2021; Sies 2017) diekploitasi dalam merawat kanser seiring dengan terapi sinaran.

1.2 PERMASALAHAN KAJIAN

Kajian terdahulu (Oike et al. 2021; Shiba et al. 2022) telah menunjukkan keupayaan H_2O_2 berkepekatan rendah dalam memainkan peranan sebagai agen pemeka sinaran yang berkesan apabila diaplikasikan menggunakan *gauze bolus* ke atas tumor payudara superfisial yang rintang terhadap sinaran di peringkat klinikal. Walau bagaimanapun, suntikan secara langsung agen ini ke dalam tumor yang tidak superfisial menyebabkan kesakitan di kawasan suntikan. Selain itu, embolisme oksigen intra arteri turut mempunyai kebarangkalian untuk berlaku (Tokuhiro et al. 2010). Penambahan agen sekunder natrium *hyaluronate* telah mengurangkan kesan sampingan tersebut, di mana pesakit hanya mengalami kesakitan (Nimalasena et al. 2020; Obata et al. 2022) serta keradangan (Aoyama et al. 2017b) sederhana di kawasan suntikan. Namun begitu, penggunaan agen anestetik khususnya lidocaine serta lignocaine telah digunakan secara tambahan dalam rawatan tersebut untuk mengurangkan kesakitan pada kawasan suntikan agen yang disampaikan secara penyuntikan *intratumoral*.

Justeru sebagai penyelesaian bagi mengurangkan ketoksikan atau kesan sampingan ubat ke kawasan sekeliling sasaran, sistem penyampaian ubat nano (NDDS) digunakan dalam membawa ubat ke kawasan sasaran (Gao et al. 2023; Gupta et al. 2019). Salah satu NDDS efisien yang telah dikaji dan dibangunkan adalah sistem nanovesikel. Nanovesikel yang terdiri daripada struktur membran dwilapisan yang melingkungi ruang teras akueus berupaya untuk membawa ubat yang bersifat hidrofobik di dalam membran dwilapisan vesikel dan ubat yang bersifat hidrofilik di teras akueus (Ge et al. 2019; Rideau et al. 2018). Dalam konteks rawatan kanser, selain daripada keupayaan dalam mengurangkan ketoksikan ubat ke kawasan selain sasaran, sistem nanovesikel ini turut dapat meningkatkan penyerapan serta internalisasi ubat di kawasan tumor (Ansari et al. 2023). Kajian terdahulu yang telah mengkaji pengkapsulan agen H_2O_2 dalam sistem nanovesikel adalah terhad, secara khususnya, kajian terdahulu hanya mengkaji pengkapsulan agen H_2O_2 dalam nanovesikel yang berasaskan lipid (Song et al. 2018). Nanovesikel tersebut telah disintesis melalui kaedah sintesis penghidratan filem nipis tiga langkah disusuli dengan penyemperitan (*extrusion*). Pengkapsulan agen H_2O_2 dalam sistem lipid yang disintesis ini telah mengurangkan ketoksikan agen seiring dengan meningkatkan kepekaan tumor terhadap sinaran.

Selain daripada lipid yang konvensional, surfaktan berasaskan asid amino turut mempunyai potensi sebagai bahan asas sistem penyampaian ubat (DDS) alternatif dalam membawa agen H_2O_2. Surfaktan berasaskan asid amino memiliki kelebihan seperti tidak bersifat toksik, diperoleh daripada sumber boleh diperbaharui, kestabilan yang tinggi serta sifat bioserasian dan biodegradasi yang baik (Borkowski et al. 2023; Guo et al. 2022; Tripathy et al. 2018). Kajian terdahulu (Chican et al. 2020; Lanigan 2001) turut mendapati bahawa surfaktan asid amino khususnya natrium N-lauroylsarkosinat (SNLS) adalah stabil dalam H_2O_2 dan begitu juga sebaliknya. Seiring dengan ini, kajian oleh Akter et al. (2011) telah menunjukkan bahawa nanovesikel berasaskan surfaktan asid amino SNLS yang dihasilkan melalui himpunan kendiri surfaktan dalam media akueus mempunyai ciri-ciri DDS yang baik dari segi kestablian yang tinggi.

Rentetan itu, dalam kajian ini nanovesikel berasaskan surfaktan asid amino SNLS telah dikaji sebagai DDS alternatif dalam mengurangkan ketoksikan agen H_2O_2 melalui pengkapsulan agen dalam teras akueus sistem dwilapisan nanovesikel. Sistem ini dinamakan sebagai kompleks nanovesikel-hidrogen peroksida (NVs-H). Selain itu, keupayaan sistem ini dalam meningkatkan kepekaan sel kanser payudara manusia khususnya sel kanser MDA-MB-231 terhadap sinaran gama turut dikaji.

Novelti kajian ini secara prinsipnya menerokai dan menyelesaikan permasalahan melalui pengkapsulan agen H_2O_2 dalam nanovesikel yang dibentuk melalui himpunan kendiri surfaktan asid amino SNLS serta penggunaan kaedah sintesis satu langkah disusuli dengan proses penyemperitan (*extrusion*) dan penulenan yang mampu menghasilkan NDDS yang berkesan sebagai pembawa pemeka sinaran. Kompleks NVs-H disintesis melalui kaedah pemuatan pasif agen H_2O_2 secara sinergi dengan himpunan kendiri surfaktan utama SNLS dan dekanol pada nisbah molar optima surfaktan iaitu 1:1.73 dalam 92 wt% larutan H_2O_2 berkepekatan 0.0003 - 3% v/v. Proses sintesis disusuli dengan kaedah penyemperitan dalam mengecilkan dan menghomogenkan saiz NVs-H serta proses penulenan menggunakan kaedah ultrapenurasan emparan. Pencirian menggunakan mikroskop cahaya berkutub (PLM), teknik serakan cahaya dinamik (DLS), mikroskop transmisi elektron (TEM), spektroskopi inframerah jelmaan Fourier (FTIR) dan spektrofotometer ultra-lembayung

nampak (UV-Vis) dijalankan untuk mengkaji sifat fizikal dan kimia NVs-H yang disintesis. Manakala kajian *in vitro* khususnya asai *microculture* tetrazolium (MTT *assay*) digunakan dalam mengkaji sifat kesitotoksikan serta sifat pemekaan sinaran NVs-H ke atas sel kanser payudara MDA-MB-231.

1.3 OBJEKTIF KAJIAN

Kajian ini terdiri daripada beberapa objektif yang memenuhi tujuan utama kajian iaitu mengkaji nanovesikel berasaskan surfaktan asid amino SNLS sebagai sistem penyampaian ubat alternatif dalam mengurangkan ketoksikan agen H_2O_2 serta meningkatkan kepekaan sel kanser payudara terhadap sinaran melalui pengkapsulan agen dalam teras akueus sistem dwilapisan nanovesikel. Objektif-objektif khusus kajian yang turut mewakili fasa kajian adalah seperti berikut:

1. Mensintesis dan mencirikan nanovesikel berasaskan surfaktan asid amino SNLS
2. Mensintesis dan mencirikan kompleks NVs-H
3. Menentukan sifat kesitotoksikan kompleks NVs-H ke atas sel kanser payudara
4. Menentukan sifat pemekaan sinaran kompleks NVs-H ke atas sel kanser payudara

Objektif pertama kajian ini adalah mensintesis dan mencirikan nanovesikel berasaskan surfaktan asid amino SNLS. Pada fasa kajian ini, tumpuan diberikan kepada kaedah optimum khususnya proses penyemperitan-ultrapenurasan emparan sebagai kaedah susulan dalam mensintesis vesikel yang bersaiz nano, homogen dan stabil. Pembentukan DDS ini difahami berlandaskan ciri fizikal dan kimia nanovesikel khususnya sifat anisotropik, saiz purata nanovesikel, taburan saiz nanovesikel, indeks poliserakan (PDI) sistem, nilai potensi zeta, morfologi dan konformasi molekular sistem. Hasil pencirian pada fasa ini turut dijadikan sebagai piawai untuk fasa kajian seterusnya iaitu fasa mensintesis kompleks NVs-H.

Mensintesis dan mencirikan kompleks NVs-H merupakan objektif kedua kajian ini. Keupayaan nanovesikel berasaskan surfaktan asid amino SNLS yang disintesis

dalam membawa dan mengkapsul agen H_2O_2 dikenal pasti dalam fasa kajian ini seiring dengan kesan agen H_2O_2 ke atas sistem nanovesikel yang disintesis. Secara tidak langsung, kebolehan mensintesis serta menghasilkan semula nanovesikel melalui kaedah penyemperitan-ultrapenurasan emparan yang dikaji dalam fasa pertama kajian turut dikaji dalam mensintesis kompleks NVs-H pada fasa ini. Keupayaan sistem ini dalam membawa H_2O_2 dikaji berdasarkan sifat anisotropik, saiz purata nanovesikel, taburan saiz nanovesikel, PDI sistem, nilai potensi zeta, morfologi dan konformasi molekular sistem serta peratusan kecekapan pengkapsulan (EE%) agen.

Objektif ketiga kajian ini adalah menentukan sifat kesitotoksikan kompleks NVs-H ke atas sel kanser payudara. Sifat kesitotoksikan kompleks NVs-H terhadap kemandirian sel kanser payudara MDA-MB-231 ditentukan dalam fasa ini berdasarkan kajian secara *in vitro*. Kesan pengkapsulan agen H_2O_2 dalam kompleks nanovesikel yang disintesis turut dikaji melalui perbandingan dengan kesan kesitotoksikan agen H_2O_2 sahaja ke atas sel kanser payudara tersebut. Ini memberi pengetahuan asas mengenai sifat kesitotoksikan NVs-H serta keupayaan sistem yang disintesis dalam mengurangkan ketoksikan agen yang dikapsul.

Menentukan sifat pemekaan sinaran kompleks NVs-H ke atas sel kanser payudara merupakan objektif keempat dan terakhir kajian ini. Sifat pemekaan sinaran kompleks NVs-H terhadap kemandirian sel kanser payudara MDA-MB-231 turut ditentukan berdasarkan kajian secara *in vitro*. Tujuan fasa ini adalah untuk mengetahui kesan kompleks NVs-H dalam memekakan sel kanser payudara terhadap sinaran gama. Ini memberi gambaran mengenai keupayaan sistem dalam memekakan sel kanser payudara terhadap sinaran.

1.4 SKOP PENYELIDIKAN

Kajian ini adalah berlandaskan pembentukan struktur nanovesikel melalui sifat himpunan kendiri surfaktan asid amino SNLS dalam larutan akueus H_2O_2 serta kaedah penyemperitan dan penulenan dalam mensintesis NVs-H. Seiring dengan itu, kajian ini tertumpu kepada keupayaan kompleks yang disintesis dalam mengurangkan kesitotoksikan agen H_2O_2 yang dikapsul serta keupayaan sistem ini dalam memekakan sel kanser terhadap sinaran gama. Pencirian sifat fizikal dan kimia kompleks

nanovesikel yang disintesis adalah berlandaskan pencirian menggunakan PLM, teknik DLS, TEM, FTIR dan UV-Vis.

Pembentukan nanovesikel melalui himpunan kendiri surfaktan dalam larutan akueus pada nisbah molar campuran surfaktan optima dikenal pasti berdasarkan pembentukan imej silang Maltese di bawah PLM. Kesan H_2O_2 ke atas pembentukan nanovesikel turut dikaji berdasarkan imej silang Maltese yang terhasil di bawah PLM. Manakala saiz purata nanovesikel, taburan saiz nanovesikel, PDI, nilai potensi zeta dan kestabilan sistem yang disintesis ditentukan berdasarkan pencirian menggunakan teknik DLS. Penentuan kaedah yang optima iaitu kaedah penyemperitan disusuli dengan penulenan dalam mensintesis vesikel yang bersaiz nano, homogen dan stabil turut dikaji menggunakan teknik DLS. Selanjutnya, TEM digunakan untuk mengkaji morfologi nanovesikel yang disintesis serta kesan H_2O_2 ke atas morfologi sistem. Manakala FTIR digunakan untuk mengkaji konformasi molekular nanovesikel yang disintesis serta kesan H_2O_2 ke atas membran dwilapisan sistem. Pengkapsulan serta EE% agen H_2O_2 dalam kompleks nanovesikel yang disintesis dikenal pasti menggunakan UV-Vis. Kajian *in vitro* khususnya asai MTT digunakan dalam mengkaji sifat kesitotoksikan serta sifat pemekaan sinaran kompleks NVs-H yang disintesis berdasarkan kemandirian sel kanser payudara MDA-MB-231.

1.5 STRUKTUR DAN KERANGKA TESIS

Tesis ini terdiri daripada tujuh bab utama iaitu bab pendahuluan, bab kajian kepustakaan, bab metodologi kajian, bab hasil kajian fasa satu, bab hasil kajian fasa kedua, bab hasil kajian fasa ketiga dan fasa keempat serta bab kesimpulan. Latar belakang kajian, permasalahan kajian, objektif kajian dan skop kajian dihuraikan dalam Bab I. Manakala kajian kepustakaan yang diulaskan dalam Bab II menghuraikan lima topik utama iaitu kanser, terapi sinaran, pemeka sinaran, hidrogen peroksida, sistem penyampaian ubat nano dan vesikel sebagai sistem penyampaian ubat nano.

Bab III menghuraikan metodologi kajian yang terdiri daripada empat fasa yang merujuk kepada objektif kajian. Empat fasa metodologi kajian ini terdiri daripada fasa sintesis NVs-AA, fasa sintesis kompleks NVs-H, fasa kajian kesitotoksikan secara *in vitro* dan fasa kajian pemekaan sinaran secara *in vitro*. Bahan dan kaedah kajian

dihuraikan secara terperinci dalam bab ini berserta dengan instrumentasi pencirian yang digunakan dalam kajian.

Hasil kajian yang merujuk kepada objektif dan kaedah kajian dihuraikan dalam Bab IV, V dan VI. Hasil kajian dibincangkan berdasarkan hasil pencirian menggunakan PLM, teknik DLS, TEM, FTIR dan UV-Vis serta kajian secara *in vitro* berlandaskan asai MTT.

Keseluruhan dapatan kajian disimpulkan dalam bab terakhir iaitu Bab VII. Bab kesimpulan ini turut membincangkan cadangan kajian masa depan.

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