HYALURONIC ACID/CHITOSAN-COATED POLY (LACTIC-CO-GLYCOLIC ACID) NANOPARTICLES TO DELIVER PACLITAXEL AND TEMOZOLOMIDE FOR ORAL CANCER CELLS

By

MESRATI MALAK HASSN ALI

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

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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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Faculty : Biotechnology and Biomolecular Sciences

Oral cancer has a poor survival rate despite comprehensive therapy. Conventional therapies may eliminate most of the tumour mass cells; however, they are leaving behind the oral cancer stem cells (OCSCs). Among these cells, an aggressive group capable of tumour initiating, self-renewal, invasion and metastasis resulting in tumour relapse and resistance, overexpressing the cancer stem cell (CSC) biomarker, cluster of differentiation 44 (CD44). Therefore, the discovery of a treatment strategy to enhance chemotherapeutic efficiency against oral cancer cells, mainly $CD44^{+}$cells, is imperative. This study aims to synthesise and characterise hyaluronic acid/chitosan-coated poly (lactic-co-glycolic acid) nanoparticles and assess their effectiveness in delivering PTX and TMZ to oral cancer cells in terms of cell inhibition and apoptosis. This study also focused on assessing the coordinated administration of PTX and TMZ and whether they exhibit significant synergistic cell inhibition effects with reduced introduced drug concentration if co-delivered simultaneously. Additionally, to determine the potentially involved mechanisms by which the formulated drug-loaded nano-carrier induced cell apoptosis. Dynamic light scattering (DLS), high resolution-transmission electron microscopy (HR-TEM), field emission-scanning electron microscopy (FE-SEM), and Fourier transform infrared spectroscopy (FT-IR) were used to characterise the nanoparticles. Results of DLS show that the nanoparticles were successfully synthesised and had a promising nano-sized diameter of 260.40±11.54 nm, a positive zeta potential of +14.31±1.37 mV and a homogeneous distribution proven by a low polydispersity index value of 0.15±0.03. HR-TEM and FE-SEM results confirmed that nanoparticles are uniformed and spherical in structure with a size smaller than 100 nm. FT-IR spectra confirmed that polylactic-co-glycolic acid, chitosan and hyaluronic acid are all involved in nanoparticle formation. XTT assay manifested that PTX and TMZ, as well as their combination (PTX:TMZ), have inhibited the proliferation of CAL-27 oral cancer cell line with the half maximal inhibitory concentration of 4nM, 1000µM and 2nM:300µM respectively. XTT assay and xCELLigence real-time cell analysis revealed that compared to free drugs, the single-loaded drug and the co-loaded one induced more

cytotoxicity. PTX and TMZ showed a considerable synergistic inhibitory effect on CAL-27 cells. This effect was discovered to be more significant when the drugs were encapsulated in the nanoparticles. To examine the signs of cell death and cell cycle alteration induced by the drug-loaded nanoparticles, Annexin V-FITC assay and cell cycle arrest assay were performed. Both were followed by flow cytometry analysis. Apoptosis analysis verified that all drug-loaded nanoparticle groups demonstrated significantly higher apoptosis rates than their relative free drug groups. Cell cycle analysis indicated that free and loaded PTX resulted in causing the highest G2-phase arrest rates of 17.69% and 22.45% of cells, respectively. Treatment with free or loaded TMZ arrested higher cell proportion at S-phase, and the combination drug treatment groups showed the highest S-phase arrest rates among all groups. In order to determine the reactive oxygen species (ROS) levels induced by the treatment, a dihydroethidium assay was performed. Cells treated with single and dual PTX and TMZ possessed higher ROS levels than non-treated cells, and nanoparticles retained and modestly improved ROS levels induction. JC-1 assay revealed that loaded PTX and TMZ caused more vital green staining within the mitochondria than the free drugs did, indicating more mitochondrial collapse. The combination drug groups, especially the loaded drugs, exhibited more downward trend in the mitochondrial potential membrane than single drugs. Additionally, from an mRNA gene expression study, loaded single or dual drugs resulted in more upregulation in genes expression associated with DNA damage, mitochondrial collapse, cell apoptosis and MAPK signalling pathways. In conclusion, established nanoparticles could be considered a potential candidate for oral cancer therapy in the near future since they could deliver and improve the efficacy of single and dual drugs against oral cancer cells and induce cell cycle alteration and intrinsic mitochondrial-mediated apoptosis. In contrast, without drugs, it did not exert toxicity effects on the cells.

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

ZARAH NANO POLI (ASID LACTIK-KO-GLIKOLIK) YANG DISALUTI ASID HIALURONIK/KITOSAN UNTUK MENGHANTAR PACLITAXEL DAN TEMOZOLOMIDE KEPADA SEL-SEL KANSER MULUT

Oleh

MESRATI MALAK HASSN ALI

Disember 2022

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Kanser mulut mempunyai kadar kelangsungan hidup yang lemah walaupun dengan terapi yang komprehensif. Terapi-terapi konvensional boleh menghapuskan kebanyakan sel jisim tumor; bagaimanapun, ia meninggalkan sel stem kanser mulut ("*oral cancer stem cells*"-OCSC). Di antara sel-sel ini, kumpulan agresif ini mampu memulakan tumor, memperbaharui diri, menyebabkan pencerobohan dan metastasis di mana ia mengakibatkan tumor berulang dan ketahanan, dan mengekspresikan biomarker sel stem kanser ("*cancer stem cells*"-CSC), kelompok pembezaan 44 ("*cluster of differentiation 44*"-CD44) secara berlebihan. Oleh itu, penemuan strategi rawatan untuk meningkatkan kecekapan kemoterapi terhadap sel kanser mulut, terutamanya sel $CD44^+$, adalah penting. Kajian ini bertujuan untuk mensintesis dan mencirikan zarah nano poli (asid laktik-ko-glikolik) yang disaluti asid hialuronik/kitosan dan menilai keberkesanannya dalam menghantar PTX dan TMZ kepada sel-sel kanser mulut dari segi perencatan sel dan apoptosis. Kajian ini juga memberi tumpuan kepada menilai penghantaran PTX dan TMZ yang diselaraskan dan sama ada mereka menunjukkan kesan perencatan sel sinergistik yang ketara dengan pengurangan kepekatan ubat yang dihantar secara bersama. Di samping itu, mekanisme yang terlibat di mana penghantar nano yang dirumuskan dan dimuatkan ubat mendorong kepada apoptosis sel juga ditentukan. Penyerakan cahaya dinamik ("*Dynamic light scattering*"-DLS), transmisi mikroskop elektron beresolusi tinggi ("*high resolution-transmission electron microscopy*"-HR-TEM), pengimbasan mikroskop elektron pelepasan medan ("*field emission-scanning electron microscopy*"-FE-SEM), dan spektroskopi inframerah transformasi Fourier ("*Fourier transform infrared spectroscopy*"-FT-IR) digunakan untuk mencirikan zarah-zarah nano. Keputusan DLS menunjukkan bahawa zarah-zarah nano berjaya disintesis dan mempunyai diameter bersaiz nano yang baik iaitu 260.40±11.54 nm, potensi zeta bernilai positif +14.31±1.37 mV dan taburan homogen dibuktikan dengan nilai indeks polidispersiti yang rendah 0.15±0.03. Keputusan HR-TEM dan FE-SEM mengesahkan bahawa zarah-zarah nano ini adalah seragam dan berstruktur sfera dengan saiz lebih kecil daripada 100 nm. Spektrum FT-IR mengesahkan bahawa asid polilaktik-ko-

glikolik, kitosan dan asid hialuronik semuanya terlibat dalam pembentukan zarah nano. Ujian XTT menunjukkan bahawa PTX dan TMZ, serta gabungan mereka (PTX:TMZ), telah menghalang percambahan garis sel kanser mulut CAL-27 dengan separuh kepekatan perencatan maksimum (IC50) masing-masing 4nM, 1000μM dan 2nM:300μM. Ujian XTT dan analisis sel masa nyata xCELLigence mendedahkan bahawa berbanding ubat sahaja, ubat muatan tunggal dan ubat muatan bersama menyebabkan lebih banyak sitotoksisiti. PTX dan TMZ menunjukkan kesan perencatan sinergistik yang besar pada sel CAL-27. Kesan ini didapati lebih ketara apabila ubat-ubatan tersebut dikapsulkan dalam zarah nano. Untuk mengkaji tanda-tanda kematian sel dan perubahan kitaran sel yang disebabkan oleh zarah nano yang dimuatkan ubat, ujian Annexin V-FITC dan ujian penangkapan kitaran sel telah dilakukan. Kedua-duanya diikuti oleh analisis sitometri aliran. Analisis apoptosis mengesahkan bahawa semua kumpulan zarah-zarah nano yang dimuatkan ubat menunjukkan kadar apoptosis yang jauh lebih tinggi daripada kumpulan ubat bebas relatif mereka. Analisis kitaran sel menunjukkan bahawa PTX sahaja dan yang dimuatkan menyebabkan kadar penangkapan fasa G2 tertinggi masing-masing sebanyak 17.69% dan 22.45% sel. Rawatan dengan TMZ sahaja atau yang dimuatkan pada penghantar nano menahan perkadaran sel yang lebih tinggi pada fasa S, dan kumpulan rawatan ubat gabungan menunjukkan kadar penahanan fasa S tertinggi dalam kalangan semua kumpulan. Untuk menentukan tahap spesis oksigen reaktif ("*reactive oxygen species*"-ROS) yang disebabkan oleh rawatan, ujian "*dihydroethidium*" telah dilakukan. Sel yang dirawat dengan PTX dan TMZ tunggal dan secara bersama mempunyai tahap ROS yang lebih tinggi daripada sel yang tidak dirawat, dan zarah-zarah nano mengekalkan dan meningkatkan induksi tahap ROS secara sederhana. Ujian JC-1 mendedahkan bahawa PTX dan TMZ yang dimuatkan menyebabkan pewarnaan hijau yang lebih tinggi dalam mitokondria daripada ubat bebas, menunjukkan lebih banyak penguraian mitokondria. Kumpulan ubat gabungan, terutamanya ubat yang dimuatkan pada penghantar nano, menunjukkan lebih banyak penurunan dalam potensi membran mitokondria daripada ubat tunggal. Selain itu, daripada kajian ekspresi gen mRNA, ubat tunggal atau gabungan yang dimuatkan menghasilkan lebih banyak ekspresi gen yang dikaitkan dengan kerosakan DNA, penguraian mitokondria, apoptosis sel, dan laluan isyarat MAPK. Kesimpulannya, zarah-zarah nano yang dihasilkan boleh dianggap sebagai berpotensi untuk terapi kanser mulut dalam masa terdekat kerana ia boleh menghantar dan meningkatkan keberkesanan penggunaan ubat terhadap sel-sel kanser mulut dan mendorong perubahan kitaran sel dan apoptosis perantaraan mitokondria intrinsik. Sebaliknya, tanpa ubat, ia tidak memberikan kesan ketoksikan pada sel.

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This thesis was submitted to the Senate of the Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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ATM	Ataxia telangiectasia mutated
ANOVA	One-way analysis of variance
ATCC	American type culture collection
CD44	Cluster of differentiation 44
CDI	Co-efficient of drug interaction
cDNA	Complementary DNA
CGM	Complete growth medium
Chk2	Checkpoint kinase 2
CI	Cell index
CP	Cisplatin
CS	Chitosan
CSC	Cancer stem cell
CSCs	Cancer stem cells
DCM	Dichloromethane
ddH2O	Double-distilled water
DEX	Dexamethasone
DFS	Disease-free survival
DHE	Dihydroethidium
DLS	Dynamic light scattering
DMEM	Dulbecco's Modified Eagle's medium
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
DOX	Doxorubicin
DSBs	Double-strand breaks

DSS	Disease-specific survival
DTX	Docetaxel
ECM	Extracellular matrix
EMT	Epithelial-to-mesenchymal transition
EPR	Permeability and retention effect
ERK	Extracellular signal regulated kinase
FBS	Fetal bovine serum
FDA	Food and drug administration
FE-SEM	Field emission-scanning electron microscopy
FITC	Fluorescein isothiocyanate
FT-IR	Fourier transform-infrared spectroscopy
5-FU	Fluorouracil
GSCs	Glioma stem cells
GSH	Glutathione
HA	Hyaluronic acid
HR-TEM	High resolution-transmission electron microscopy
IC50	Half-maximal inhibitory concentration
ID-CD44	Intracellular domain of CD44
JNK	c-Jun N-terminal Kinase
MAPKs	Mitogen-activated protein kinases
MDR1	Multi-drug resistance protein 1
MET	Mesenchymal-to-epithelial transition
MTX	Methotrexate
MW	Molecular weight
MWCO	Molecular weight cut off

NAOH	Sodium hydroxide
NCI	Normalized cell index
NPs	Nanoparticles
OCSCs	Oral cancer stem cells
OS	Overall survival
OSCC	Oral squamous cell carcinoma
PBS	Phosphate buffer saline
PDI	Polydispersity index
PEG	Polyethylene glycol
PFS	Progression free survival
PGA	Polyglycolic acid
PI	Propidium iodide
PLA	Polylactic acid
PLGA	Poly-lactic-glycolic acid
p38 MAPK	p38 mitogen-activated protein kinase
PMMA	Polymethyl methacrylate
PS	Phosphatidylserine
PTX	Paclitaxel
RGR	Relative growth rate
ROS	Reactive oxygen species
RPM	Revolutions per minute
SD	Standard deviation
SEM	Scanning electron microscopy
siRNA	Small interfering RNA
TEM	Transmission electron microscopy

TMZ	Temozolomide
TNF	Tumour necrosis factor
$\Delta\psi m$	Mitochondrial membrane potential

CHAPTER 1

INTRODUCTION

1.1 Background

Globally, cancer of oral cavity is recognized as one of the most 10 common cancers (Saranath, 2021). Several reports revealed that it is the sixth most common human malignancy in the world (Farah *et al*., 2014, Sawant *et al*., 2016, Kashyap *et al*., 2018, Dhanuthai *et al*., 2018). The anatomical parts of the oral cavity that might be affected by cancer are: upper and lower lips, tongue, buccal mucosa, floor of the mouth, upper and lower gingiva (gum), hard and soft palate, retromolar trigone, upper and lower alveolar ridge (Montero *et al*., 2015, Giammarile *et al*., 2019, Kerker *et al*., 2019) (Figure 1.1). The lip is the most common site affected by oral cancer, often in light-skinned older men. Inside the mouth, the tongue is the highest-risk site for cancer and is often aggressive. After the tongue comes the floor of the mouth and the soft palate. Involvement of the gums and cheeks is also joint, especially in countries with specific habits such as chewing betel nut or tobacco (Khani Jeihooni and Jafari, 2022).

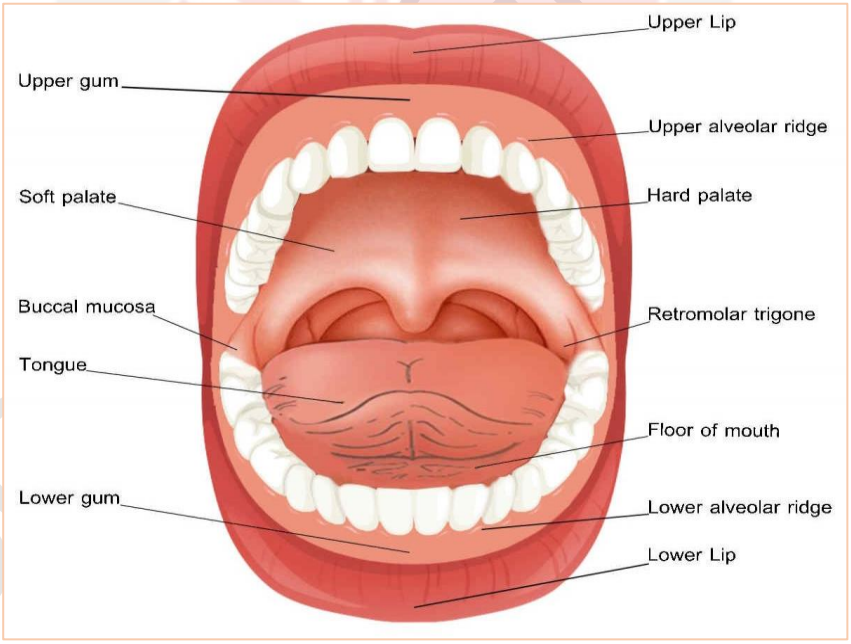

Figure 1.1 : The anatomical parts of the mouth affected by oral cancer

1.1.1 Oral cancer epidemiology

Epidemiological studies show that oral cancer is a growing serious problem in several countries and that its incidence and mortality varies in different parts of the world (Jeihooni *et al*., 2019). According to the global cancer observatory (GLOBACON) 2012, cancer of the oral cavity accounted for 300,000 new cases and 145,000 deaths annually worldwide (Ferlay *et al*., 2015, Gupta *et al*., 2016). As time progresses, there is an increase in the number of incidence and mortality caused by this cancer. Based on the GLOBOCAN 2018, worldwide, 354,864 and 177,384 of new cases and deaths occurred respectively (Bray *et al*., 2018). An updated report using GLOBOCAN 2020 revealed 377,713 of oral cancer new cases and 177,757 deaths yearly worldwide (Sung *et al*., 2021).

Internationally, middle aged and older people are most likely to be affected by oral cancer. Incidence and mortality are higher in men in comparison with women because there are less risk factors involved in women than in men (Tiyuri *et al*., 2017), and amongst females, it is reported to be the highest among Asian women while the lowest among African women (Sarode *et al*., 2020). South and southeast Asia, Melanesia (New Guinea) as well as some countries in Europe suffer from the highest prevalence of oral cancer (Ghantous and Elnaaj, 2017, Sung *et al*., 2021), while lower rates have been reported from west Africa and east Asia (Tiyuri *et al*., 2017). Reports from GLOBOCAN 2012 showed an annual 17,276 new cases of oral cancer in the African population, while recordings of GLOBOCAN 2018 reported decrease of occurrence with an incidence rate of 13,613 new cases. Its occurrence is comparatively low in western Pacific region contributing to only 0.91% of all the diagnosed cancer cases. However, with changes in lifestyle behaviors, lately, a change in this scenario is observed with an increase in the reported new cases of oral cancer in developed countries as well (Sarode *et al*., 2020). A significant rise in oral cancer occurrence has been shown in several countries in Europe such as in Germany (Ghantous and Elnaaj, 2017). Amongst the northern European countries, the highest oral cancer incidence corresponds to Denmark (Sarode *et al*., 2020). India, Srilanka, Pakistan and Bangladesh have the commonest occurrences of oral cancer which accounts almost one-third of all global new cases of cancers (Gupta *et al*., 2016).

Compared to other south Asian countries, Malaysia observes moderately lower cases of oral cancer. This occurrence varies between the different ethnical groups because of different social and cultural risk factors, such as the chewing habit of betel and areca nuts. Most cases are observed in indigenous groups and Indians. Gender also plays a determinant of oral cancer in Malaysia. It was reported that it tends to affect women more than men, which contradicts the global data that it affects men more than women. For instance, in the Indian group, it is the third most malignancy in Indian women and the sixth most common cancer in Indian men. Because of the low 5-year survival rate of less than 20% in Malaysia, oral cancer is considered a major national health problem (Sitheeque *et al*., 2014). In a more recent study in Malaysia, oral cancer showed a 5-year survival of 50% after treatment with surgery and radiotherapy. Most patients were male with a mean age of 48 years, and tongue cancer was the most commonly involved part of the oral cavity. Notwithstanding the accessibility of oral cavity parts for visual examination alongside well-defined diagnostic characteristics for oral cancers, most

cases were diagnosed at an advanced stage at the time of diagnosis. This may be attributed to the lack of awareness and knowledge regarding the signs and symptoms of oral cancer (Ahmad *et al*., 2021).

According to GLOBACON 2020 and statistical data obtained from HPV and cancer information centre, 742 patients are annually diagnosed with oral cancer in Malaysia. 377 of the new cases are men, while 365 are women. The mortality rate for oral cancer includes 403 deaths; 223 are from men, while 180 are from women. Figures 1.2 and 1.3 show the annual incidence and mortality among all ages of men and women in Malaysia, respectively.

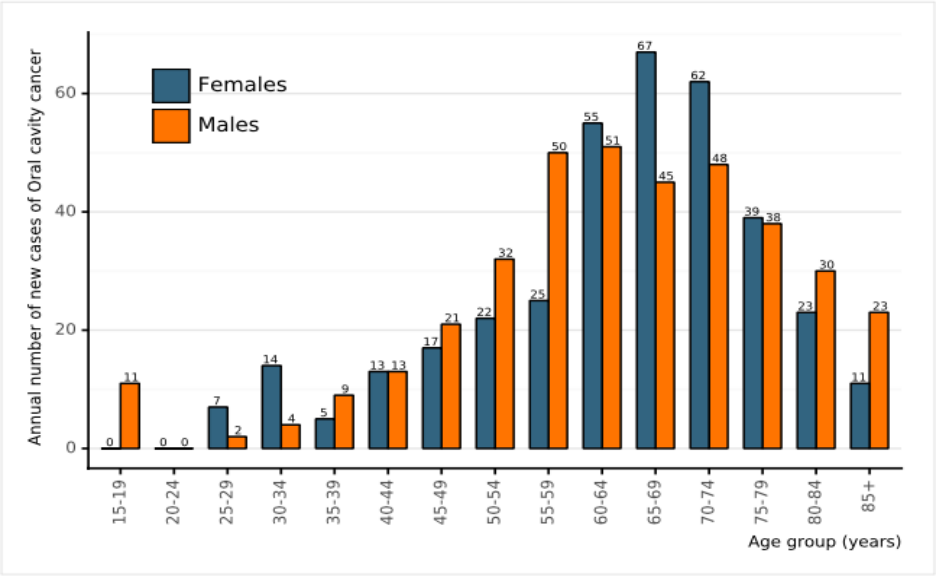

Figure 1.2 : Annual number of new cases in men and women among all ages of oral cancer in Malaysia (2020). 742 patients are annually diagnosed with oral cancer in Malaysia. 377 of them are men, while 365 are women. Data sources: Ferlay *et al*., 2021. GLOBACON 2020. HPV and cancer information center. Available from: https://hpvcentre.net.

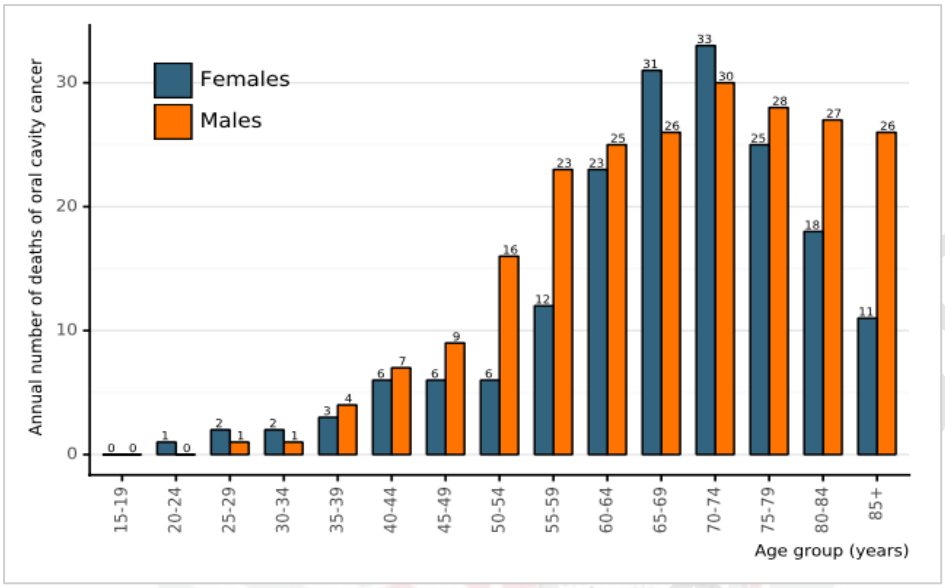

Figure 1.3 : Annual number of deaths in men and women among all ages of oral cancer in Malaysia (2020). The mortality rate for oral cancer includes 403 deaths; 223 are from men, while 180 are from women. Data sources: Ferlay *et al*., 2021. GLOBACON 2020. HPV and cancer information center. Available from: https://hpvcentre.net.

According to the American Cancer Society, and based on incidence data were collected from surveillance epidemiology and end results (SEER) program, the national program of cancer registries and the north American association of central cancer registries and mortality data were collected by the national center for health statistics, in the United States, 32,670 patients are annually diagnosed with oral cavity cancers in 2017 and 6650 patients die from this disease (Siegel *et al*., 2017). Based on data collected by the same sources, incidence continued to increase in the United States. By 2020, 53,260 are annually diagnosed with oral cancer with mortality rate of 10,750 deaths. Occurrences of this disorder in men is found to be twice as often as in women with lower survival rates for black patients than for whites (Siegel *et al*., 2020).

1.1.2 Risk factors

Tobacco smoking, alcohol consumption and betel quid chewing, which is common in south and southeast Asia as well as between people from south Asian origin across the world, are the most well-known risk factors for oral cancer. Smokeless tobacco, consumed as chewed tobacco or as a powdered snuff, found to increase the risk of oral cancer occurrence in comparison with smoked cigarette. Amongst smokers who never drink alcohol, there is a two-fold risk estimate for oral cancer which increases with regularity and duration of smoking. Similarly, a two-fold risk was found for alcohol consumption among those who never smoke, but only in the heavier alcohol drinkers. The supreme risk was observed in those who both smoking and drinking alcohol heavily,

with a five-fold increased risk (Conway *et al*., 2018). Oral cancer found to be caused primarily by areca nut chewing in southeast Asia and that the chronic arecoline, a major areca nut alkaloid, exposure induces malignant phenotype by the acquisition of cancer stemness and oncogenicity in-vitro and in-vivo (Wang *et al*., 2016). In addition, disturbance in oral microflora, for instance, Fusobacterium (enriched) and Streptococcus (decreased), causes production of carcinogenic substances (e.g. nitrosamine), inflammatory responses and direct proliferative effects on cellular signalling in oral epithelium, all of which may dictate the development of oral cancer. Other than the two most differential types of microflora mentioned above, Prevotella, Capnocytophaga and Peptostreptococcus are also detected as oral cancer associated biomarkers (Su *et al*., 2020).

1.1.3 Current treatments

Oral cancers are traditionally treated with: surgery, radiotherapy, and chemotherapy. Surgery is the backbone of the treatment and treatment strengthening by way of adjuvant radiation and/or chemotherapy is often necessary for those with advanced tumour stages. Figure 1.4 shows the main current therapies for oral cancers.

1.1.3.1 Surgery

Primary surgical resection and either sentinel node biopsy procedure or selective neck dissection is the ideal modality of treatment for patients with resectable oral cancers (Bozec *et al*., 2019). In a randomized trial of total of 119 patients comparing surgery versus concurrent radio and chemotherapy in patients with locally advanced oral cancers, DSS was significantly superior for those who underwent surgery (Iyer *et al*., 2015). Surgical resection of oral cancers with clear surgical margins is the key factor to prevent recurrence and to avoid the demand for adjuvant treatment or re-resection. There is frequently an inconsistency observed between the margins of the tumour that determined clinically when it is being resected, intraoperatively, and the histopathological results after the specimen has been resected. This phenomenon occurs post tumour resection and histopathological processing named margin shrinkage. Achieving clear surgical margin is critical for successful complete removal of a tumour resulting in decrease the risk of local and locoregional recurrences as well as the need for adjuvant treatment or re-resection after primary surgery (Shah, 2018, Burns and Gorina Faz, 2021). Consequently, recurrences in many patients with oral cancer whom primarily treated with surgery have been reported to occur among local, locoregional, and regional sites making these patients candidates for adjuvant radio or chemotherapy following surgical salvage (Hamoir *et al*., 2018).

Early stage of oral cancer has usually favourable prognosis outcomes. However, recurrences may occur in 30–35% of patients, and about 20% will finally die by the disease (Ivaldi *et al*., 2019). Matsuura *et al*., 2018 reported a series of 46 patients with oral cancer mainly treated by surgery alone or followed by radio or chemotherapy who underwent surgical salvage for local or locoregional cancer recurrences. Salvage surgery is considered as the best option for controlling the recurrences from oral cancers, mostly in previously irradiated tumours as reirradiation resulted in poor overall survival (OS)

rate with severe complications with those survivors due to the dose and toxicity. Similarly chemotherapeutic drugs resulted in no significant impact on survival in patients with recurrence tumours. Even when submitted to surgical salvage, patients with recurrent oral cancer are commonly have a poor prognosis (Agra *et al.*, 2006). In addition, besides distorted facial appearance, which can cause psychological pain and social isolation, surgery may also result in significant dysfunction in talking, swallowing, sensory impairment and chronic pain (Valdez and Brennan, 2018).

1.1.3.2 Radiotherapy

Although surgery is the recommended treatment for oral cancer treatment, radiotherapy plays a critical role in the treatment either exclusively in the early stage cancers or combined with surgery and/or chemotherapy in advances or unresectable cancers (Cabrera-Rodriguez, 2016). Nevertheless, national and international treatment guidelines do not recommend radiotherapy postoperatively in the early oral cancer, and highlight unaccompanied surgery as the standard modality treatment (Ivaldi *et al*., 2019). Surgical procedure is more flexible and easier to execute, yet despite excellent surgical management, local and locoregional recurrences have expanded the role of radiotherapy (Kirthi Koushik and Charith Alva, 2022), which may be introduced using two techniques: external beam radiotherapy or brachytherapy (Cabrera-Rodriguez, 2016). Radiation such as X-rays, gamma rays and particle therapy like protons delivered from a distance away from the body is called external radiation. On the other hand, delivery of such radiation types in close proximity to or within the target tissue is known as brachytherapy. These forms of radiation are considered to have the capability to generate ions in the cells it passes through, by removing the electrons from atoms.

Radiation is effectual only on dividing cells. Amongst the 5 phases that each cell goes through during division; G0, G1, S, G2 and M, G2 and M phases are the most radiosensitive while S phase is the most radioresistant one. Besides the long-term radiation illness that affects quality of the patient's life in those whom receiving radiation as a single modality of treatment, the survival rate is not very encouraging (Kirthi Koushik and Charith Alva, 2022). Several neighborhood organs like the skin, masticatory apparatus, salivary glands, dentition and jaws receive significant doses of radiation during treatment resulting in moderate to severe adverse effects. Acute effects such as mucositis dermatitis and hyposalivation, and chronic effects such as xerostomia and trismus (Basu *et al*., 2012). With its capacity to give high doses to cancerous tissues and very low dose to the nearby areas, brachytherapy considered the most ideal radiotherapy. Nonetheless, it is also implicated with acute complications such as infection, haemorrhage, airway compromise and sialadenitis. Other complications such as soft tissue necrosis, telangiectasia and rarely osteoradionecrosis may occur due to long-term exposure (Kirthi Koushik and Charith Alva, 2022).

Cancer stem cells (CSCs) have been confirmed to be in a quiescent or dormant state in most established tumours, with their innate radioresistance helping them survive more easily when exposed to radiation (Olivares-Urbano *et al*., 2020). As mentioned earlier, only active proliferative cells are qualified for efficient chemotherapy and radiotherapy of tumours, and any quiescent or senescent cells including CSCs can be resistant to such

therapies. Radiotherapy found to be able of not only causing dormant CSCs population to be awakened, enter the cell cycle and initiate proliferation and differentiation but also induce them to acquire malignant phenotypes and carcinogenic metabolism which plays significant role in tumour relapse and metastasis. In addition, radiation can also awaken cancer cells with the potential of stemness, returning them to CSCs phenotype with stemness related markers expressions (Liu *et al*., 2020).

1.1.3.3 Chemotherapy

Besides surgery and radiotherapy, chemotherapy, alone or in combinations, is the third conventional treatment strategy for patients with oral cancer. The common chemotherapeutic drugs utilize to treat oral cancers are cisplatin (CP) (Kirave *et al*., 2020), docetaxel (DTX) (Cui *et al*., 2020), paclitaxel (PTX) (Song *et al*., 2019), fluorouracil (5-FU) (Patel and Dalwadi, 2020) and methotrexate (MTX) (Jin *et al*., 2018). Although the gold standard treatment for oral cancer is the complete surgical removal, chemotherapy alone or combined with radiotherapy is occasionally considered when surgery is not possible due to many reasons including patients' comorbidities or their refusal of undergoing resection surgery (Bennardo *et al*., 2021). Nevertheless, advanced oral cancers are biologically very aggressive and the patients are generally responding poorly to chemotherapy (Robert *et al*., 2018).

Chemoresistance is a major difficulty to efficient treatment and is correlated with poor prognosis in patients with oral cancer (Suenaga *et al*., 2019). The most important reason of such resistant is CSCs that are substantially resistant to standard chemotherapy. Moreover, anti-cancer agents result in a significant enrichment of these CSCs (Zhang *et al*., 2010). Additionally, in oral cancer, epithelial-to-mesenchymal transition (EMT)-activated transcription factors such as Snail, ZEB and TWIST can trigger different molecular signal pathways such as NF-κB, TGF-β and PI3K/AKT resulting in a peritumoural extracellular environment supports cancer cells survival and evasion of the immune system and subsequently up-regulate drug resistance (Sha *et al*., 2021).

Chemotherapeutic drugs such as CP, 5-FU and DTX when followed by surgery in comparison with surgery alone or surgery combined with adjuvant radiotherapy helped in decreasing the number of patients who required to undergo mandibular preservation and/or radiation therapy, however, they failed to provide any survival improvement (Licitra *et al*., 2003, Zhong *et al*., 2013). The oral route is the superior approach to administrate chemotherapies to the body. Though, oral administration is limited due to high toxicity, low permeability and bioavailability and poor water solubility of the administrated drugs. Similarly, when intravenously administered, anti-cancer drugs show non-specific distribution within the body, simply cause greater damages to healthy tissues with severe side effects such as nausea, vomiting, infections, hair loss, and diarrhea in patients with oral cancers (Zhao *et al*., 2020, Zhang *et al*., 2020).

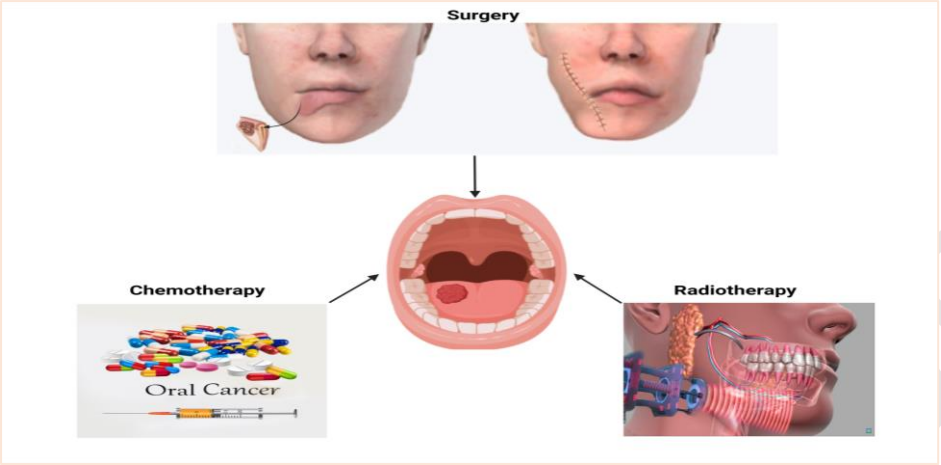

Figure 1.4 : Conventional treatments of oral cancers. Oral cancers are traditionally treated with: surgery, radiotherapy, and chemotherapy. Surgery is the backbone of the treatment and treatment strengthening by way of adjuvant radiation and/or chemotherapy is often necessary.

1.2 Problem statement

Due to unclear tumour margins, surgery results in increase the risk of recurrences (Shah, 2018, Burns and Gorina Faz, 2021). Besides, surgery causes distorted facial appearance, chronic pain and major dysfunctions (Valdez and Brennan, 2018). Following radiotherapy, several neighborhood organs receive significant doses of radiation causing severe adverse effects such as mucositis, infection, haemorrhage, sialadenitis, dermatitis, trismus and osteoradionecrosis (Kirthi Koushik and Charith Alva, 2022). Patients with oral cancer are generally responding poorly to chemotherapy, mainly due chemoresistance, resulting in poor prognosis in these patients (Suenaga *et al*., 2019). Chemotherapies are also limited due to high toxicity, low bioavailability, poor solubility and non-specificity leading to severe side effects such as nausea, vomiting, infections, hair loss, and diarrhea in patients with oral cancers (Zhang *et al*., 2020).

PTX has wide range activity against head and neck cancers including oral cancer singularly or in combination with other drugs (Bharadwaj *et al*., 2019, Sawatani *et al*., 2020). It functions by interaction with and stabilization of microtubules and subsequently inhibits mitosis and cellular growth (Riestra-Ayora *et al.*, 2021). PTX can also induce significant reactive oxygen species (ROS) production-mediated cell proliferation inhibition, apoptosis and cell cycle arrest in several cancer types (Jiang *et al*., 2019, Chien *et al*., 2021). However, its low solubility and poor permeability reduce its absorption when administrated orally. On the other hand, when administrated intravenously, it distributes extensively in the body causing severe side effects such as liver dysfunction hypersensitivity, neurotoxicity, bone marrow suppression, and nephrotoxicity reactions (Choi, 2002, Singla *et al*., 2002, Nakakaji *et al*., 2018). Temozolomide (TMZ), the standard and the food and drug administration (FDA)

approved drug for treatment of glioblastoma, is a deoxyribonucleic acid (DNA) alkylating agent that exerts its cytotoxicity by methylation of DNA at the O^6 or N^7 position of guanine residue, which leads eventually to induction of DNA double-strand breaks (DSBs), which in turn prompts cell death (Xie *et al.*, 2016). TMZ also can up-regulate ROS levels in different cancer cells and this ROS production influenced cell viability inhibition, DNA damage, apoptosis and cell cycle arrest (Lin *et al.*, 2012, Song *et al.*, 2016). Although TMZ is an efficient drug in cancer treatment, it is complicated with drug resistance and some predictable side effects such as skin rash, blurred vision, diarrhea, nausea, anorexia, dizziness, hair loss, insomnia and headache (Chamberlain, 2010, Tai *et al.*, 2021).

Oral cancer stem cells (OCSCs) are a small sub-population of cells, nonetheless are capable of tumour initiating, self-renewal, invasion and metastasis resulting in tumour relapse and resistance (Lin *et al.*, 2017). One group of these cells is cells that overexpressing the cancer stem cell (CSC) biomarker, cluster of differentiation 44 (CD44). These cells acquire several CSCs characters, all of which contributing to tumour cell migration, invasion, metastasis as well as treatment resistance (Hassn Mesrati *et al.*, 2021). Conventional therapies including surgery, radiotherapy and chemotherapy can eliminate the majority of cells in the bulk tumour mass, however they are leaving behind the CSCs (Shibata and Hoque, 2019). Chemotherapy and radiotherapy are only effective against dividing cells. CSCs are usually in quiescent status and therefore are resistant to such therapies. Furthermore, conventional therapies can cause dormant CSCs to be awaken, enter the cell cycle and initiate proliferation and differentiation (Liu *et al.*, 2020). (Figure 1.5).

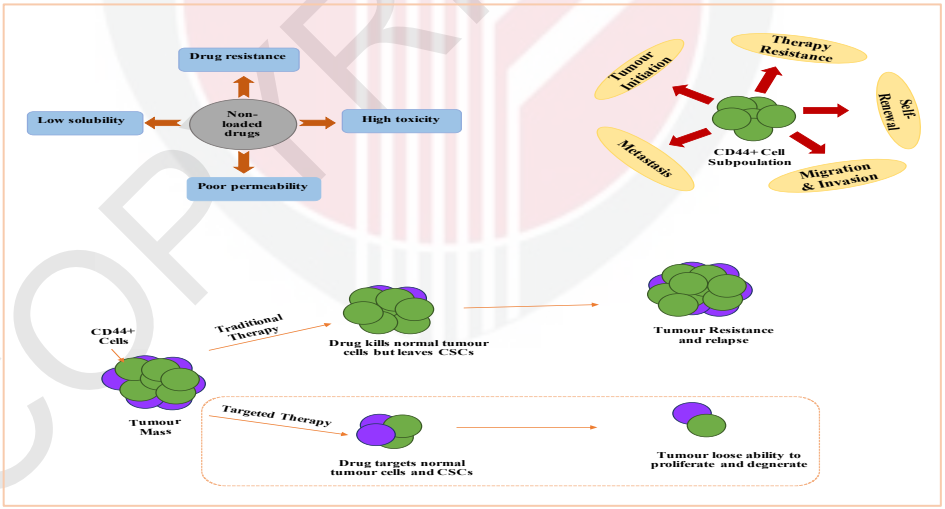

Figure 1.5 : Summarized scheme for the problem statement. Sub-population of cells, $CD44^+$cells, acquire several CSCs characters including tumour initiating, self-renewal capability, invasion, metastasis and tumour resistance. This group of cells cannot be eliminated by conventional treatments. Chemotherapeutic drugs are limited by their high toxicity, poor solubility and permeability and trigger drug resistance. Establishment of

targeted drug delivery system that can target both, normal cancer cells and CSCs is imperative.

1.3 Research objectives

1.3.1 General objective

To develop drug-loaded delivery nano-system to enhance chemotherapeutic efficiency against oral cancer cells in terms of cell inhibition and apoptosis.

1.3.2 Specific objective statements

1- To determine the CSC biomarker, CD44, percentage on the surface of the human oral cancer cell line (CAL-27).

2- To synthetize and characterize hyaluronic acid/chitosan-coated poly-lactic-glycolic acid nanoparticles (HA/CS-coated PLGA NPs).

3- To examine the single and synergic anti-tumour effect of free and loaded PTX and TMZ on the growth of oral cancer cells.

4- To examine the single and synergic anti-tumour effect of free and loaded PTX and TMZ in enhancing oral cancer cell apoptosis, cell cycle arrest and possible associated mechanisms.

5- To examine the potential relevant signalling pathways by which the treatment induced cell apoptosis.

1.4 Research hypothesis

Poly-lactic-glycolic acid (PLGA) NPs coated by hyaluronic acid (HA)/chitosan (CS) complex is postulated to effectively target oral cancer cells that overexpress CD44 ($CD44^+$cells) through HA-selective binding to this biomarker. Figure 1.6 shows hypothetical scheme of the established nano-carrier drug delivery system formation. HA and its probable interaction with CD44 will improve PTX and TMZ accumulation in these tumour cells resulting in enhanced cell inhibition which will eventually lead to cell apoptosis. As they have different mechanisms of action, it is also hypothesized that the coordinated administration of PTX and TMZ will exhibit significant synergistic cell inhibition effect with reduction in introduced drug concentration if co-delivered simultaneously (Figure 1.7). Induced cell death predicted to be mediated by increased ROS levels and associated with mitochondrial collapse, Cytochrome c release and caspase-3 expression. Further involved mechanisms and pathways such as induction of ataxia telangiectasia mutated (ATM) expression, whose activity is augmented by DNA damage, and mitogen-activated protein kinase (MAPKs) signalling pathways including c-Jun N-terminal Kinase (c-Jun/JNK), extracellular regulated kinase (ERK) and p38 mitogen-activated protein kinase (p38 MAPK) will be elucidated (Figure 1.8).

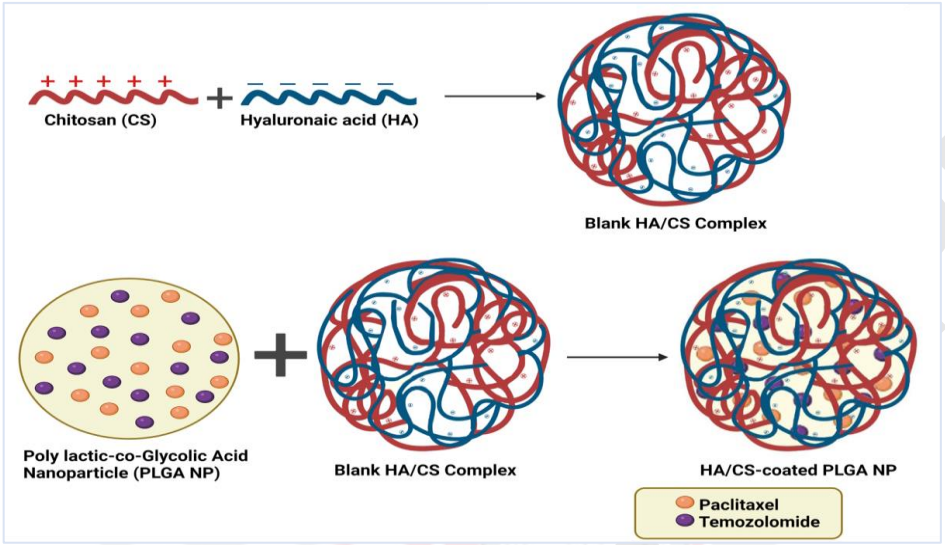

Figure 1.6 : Hypothetical scheme of the established nano-carrier formation. Three biocompatible, biodegradable and non-toxic polymers including, poly-lactic-glycolic acid (PLGA) coated with chitosan (CS), and hyaluronic acid (HA) will be developing into a new nanoparticulate drug delivery system to deliver PTX and TMZ to oral cancer cells.

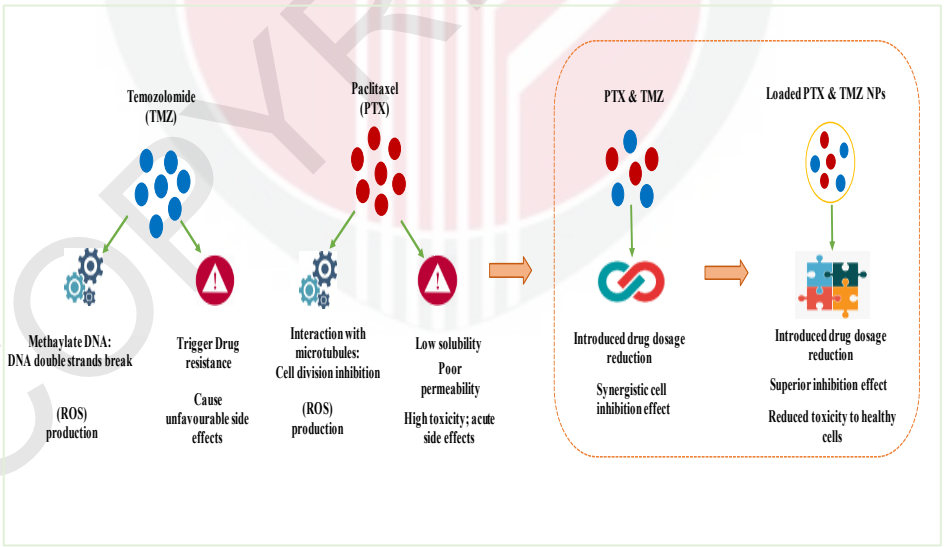

Figure 1.7 : Mechanism of drug candidates and hypothetical synergistic effect. As they have different mechanisms of action, co-delivered PTX and TMZ are hypothesized to result in superior chemotherapy efficiency against oral cancer cells in terms of cell inhibition.

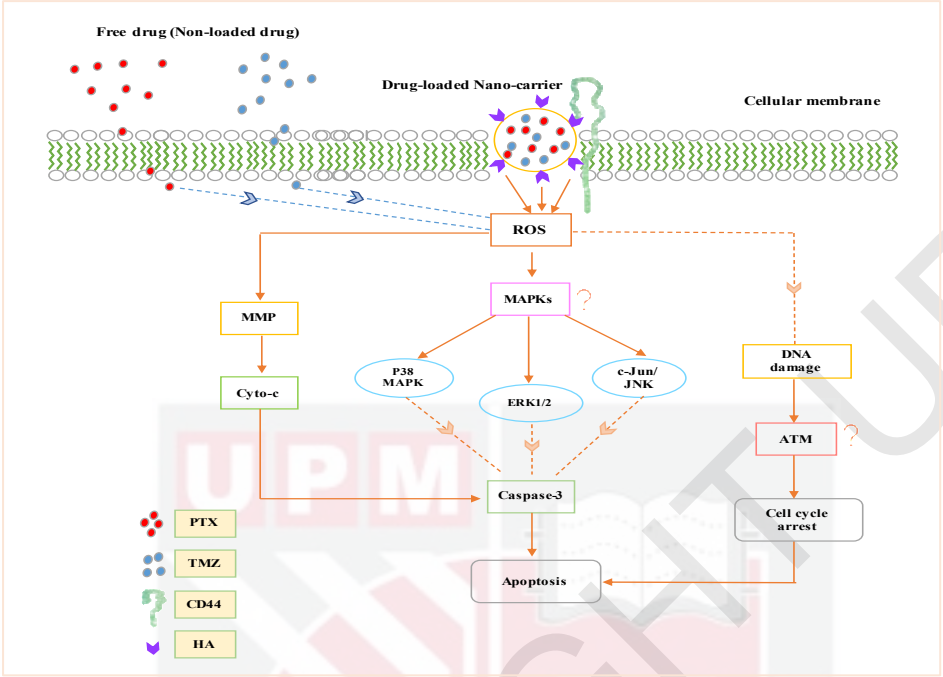

Figure 1.8 : Hypothetical mechanism of potential apoptosis-mediated relevant signaling pathways. The drug loaded nano-carrier is postulated to effectively target oral cancer cells that overexpress CD44. Several mechanisms and pathways such as induction of mitochondrial collapse, DNA damage and MAPKs signalling are hypothesized to be involved in cell apoptosis.

1.5 Limitation of study

One limitation of this study is the absence of an animal model use to confirm the anti-cancer effect of the novel nano-carrier drug delivery system in in-situ tumour. In addition, the involved molecular anti-cancer mechanisms were superficially investigated and need to be deeper investigated. For instance, the inhibition of ROS can confirm its mediation of cell death. Furthermore, inhibition of specific genes can confirm the involvement of the hypothesized signalling pathways in cell death. Besides, these pathways need to be more explored at protein and phosphorylated protein level. Further research is also needed to determine the effect of the drug loaded nano-carrier on other cancer cell lines and other cancers besides oral cancer.

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