UNIVERSITI PUTRA MALAYSIA

CHARACTERIZATION, HISTOLOGICAL EVALUATION AND EFFICACY OF DOCETAXEL-LOADED COCKLE SHELLDERIVED CaCO3 NANOPARTICLES IN VITRO AND IN VIVO

NAHIDAH IBRAHIM HAMMADI

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By

NAHIDAH IBRAHIM HAMMADI

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

March 2018

DEDICATION

This Thesis is dedicated to

My Beloved Mother Kifayia and My late father Ibrahim

My beloved Husband Mohammed

My Lovely Sons and doughter Abdulrahman, Humamm and Jana

My Lovely Parents and Siblings

All My Kind Hearted Teachers, Lecturers and Friends

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirements for the degree of Doctor of Philosophy

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Chairman : Profesor Md Zuki Abu Bakar, PhD
Faculty : Veterinary Medicine

Breast cancer is one of the most widely researched cancers worldwide. Currently, therapeutic options aimed at reducing its metastasis have a limitation of toxicity to the patient. Cockle shell-derived calcium carbonate aragonite nanoparticles ($CSCaCO_3NP$) have shown promising potentials as a slow drug releasing compound in cancer chemotherapy. This study explores $CSCaCO_3NP$ as a delivery system aimed at enhancing docetaxel (DTX) release in breast cancer. Furthermore, this study also evaluated the *in vitro* cytotoxicity of DTX-loaded $CSCaCO_3NP$ against 4T1 cell line, and *in vivo* toxicity evaluation of $CSCaCO_3NP$, and the effect of DTX-loaded $CSCaCO_3NP$ in 4T1 cancer-bearing Balb/C mice.

The nano-anticancer formulation (DTX-$CSCaCO_3NP$) was characterized by various physico-chemical characterizations. The *in vitro* cytotoxicity evaluation was achieved using different bioassay parameters. The pharmacokinetic study was estimated. The *in vivo* mice acute and sub-chronic toxicity studies were conducted for 14 days. In the therapeutic study, mice were subcutaneously inoculated with 5×10^5 4T1 cells in the right mammary fat pad. Tumor treatment commenced in two stages, the early and late stages. Mice were grouped into 3 treatment groups of DTX (10 mg/kg), DTX-$CSCaCO_3NP$ (10 mg/kg) and DTX-$CSCaCO_3NP$ (5 mg/kg). The positive and negative control groups were also included.

Characterization results revealed that DTX-$CSCaCO_3NP$ synthesis was excellent, and had a sustained release at pH 7.4. TEM results showed nanoparticles sizes of 42 nm. The XRD patterns revealed strong crystallizations and pure aragonite particles formulation, while FTIR showed entrapment between the drug and nanoparticles. The

DTX-CS$CaCO_3$NP had comparable ($p>0.05$) cytotoxicity effects as DTX against MCF-7 and 4T1 cells. Fluorescence and apoptosis assay showed higher ($p<0.05$) number of apoptotic cells in both DTX and DTX-CS$CaCO_3$NP groups. SEM showed the presence of cellular blebbing, while TEM showed nuclear fragmentation, apoptosis and vacuolation. In *in vivo* toxicity analysis, no significant sign was observed and no mortality was recorded in both study periods. Tumor volume, organ weights, tumour inhibition rates and metastatic cells were significantly ($p<0.05$) lower in the DTX-CS$CaCO_3$NP (10 mg/kg) group.

In conclusion, the results showed that the formulated DTX-CS$CaCO_3$NP released DTX slower at pH 7.4. It was also observed that DTX-CS$CaCO_3$NP has similar anticancer effects on MCF-7 and 4T1 cells as DTX and since it has a slow release, CS$CaCO_3$NP is a promising delivery system for DTX in the 4T1 induced breast cancer model. Hence, DTX-CS$CaCO_3$NP (10 mg/kg) showed high efficacy against breast cancer metastasis.

Keywords: Breast cancer, docetaxel, cockle shell nanoparticles, drug delivery system, Balb C/Mice

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

PENCIRIAN, PENILAIAN HISTOLOGI DAN KEBERKESANAN NANOZARAH $CaCO_3$-BERASAL KULIT KERANG BERMUATAN-DOCETAXEL *IN VITRO* DAN *IN VIVO*

Oleh

NAHIDAH IBRAHIM HAMMADI

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Kanser payudara adalah salah satu daripada kanser yang paling meluas dikaji di seluruh dunia. Pada masa ini, pilihan terapeutik yang bertujuan untuk mengurangkan metastasisnya mempunyai batasan ketoksikan kepada pesakit. Nanozarah kalsium karbonat aragonit yang berasal dari kulit kerang ($CSCaCO_3NP$) telah menunjukkan potensi yang mempunyai harapan sebagai sebatian yang melepaskan ubat dengan perlahan dalam kemoterapi kanser. Kajian ini menyelidik $CSCaCO_3NP$ sebagai suatu sistem penyampaian yang bertujuan untuk meningkatkan pelepasan docetaxel (DTX) dalam kanser payudara. Tambahan pula, kajian ini juga menilai ketoksikan sel in *vitro* $CSCaCO_3NP$ bermuatan-DTX terhadap turunan sel 4T1, dan penilaian ketoksikan *in vivo* CSCaCO3NP, serta kesan $CSCaCO_3NP$ bermuatan-DTX dalam tikus BALB/C pembawa-kanser 4T1.

Perumusan nano-antikanser (DTX-$CSCaCO_3NP$) dicirikan oleh pelbagai pencirian fizikal-kimia. Penilaian ketoksikan sel *in vitro* telah dicapai menggunakan parameter biocerakin berbeza. Kajian farmakokinetik telah dianggarkan. Kajian ketoksikan tikus akut dan sub-kronik *in vivo* telah dijalankan selama 14 hari. Dalam kajian terapeutik, tikus telah diinokulasi secara subkutaneus dengan 5×10^5 sel 4T1 ke dalam pad lemak kelenjar mama kanan. Rawatan tumor bermula dengan dua peringkat iaitu peringkat awal dan lewat. Tikus dibahagikan kepada 3 kumpulan rawatan iaitu DTX (10 mg/kg), DTX-$CSCaCO_3NP$ (10 mg/kg) dan DTX-$CSCaCO_3NP$ (5 mg/kg). Kumpulan kawalan positif dan negatif turut dimasukkan.

Hasil pencirian menunjukkan bahawa sintesis DTX-CS$CaCO_3$NP sangat baik, dan mempunyai pelepasan yang berterusan pada pH 7.4. Keputusan TEM menunjukkan saiz nanozarah 42 nm. Corak XRD menunjukkan penghabluran yang kuat dan rumusan zarah aragonit tulen, manakala FTIR menunjukkan pemerangkapan antara ubat dan nanozarah. DTX-CS$CaCO_3$NP mempunyai kesan ketoksikan sel ($p>0.05$) yang serupa dengan DTX terhadap sel-sel MCF-7 dan 4T1. Asai pendarfluor dan apoptosis menunjukkan bilangan sel apoptosis yang lebih tinggi ($p<0.05$) dalam kedua-dua kumpulan DTX dan DTX-CS$CaCO_3$NP. SEM menunjukkan kehadiran penempekan sel, manakala TEM menunjukkan pemecahan nuklear, apoptosis dan kelompangan. Dalam analisis ketoksikan *in vivo*, tiada tanda-tanda ketara diperhatikan dan tiada kematian dicatatkan pada kedua-dua tempoh ujian. Isipadu tumor, berat organ, kadar penyekatan tumor dan sel-sel metastasis lebih rendah secara signifikan ($p<0.05$) dalam kumpulan DTX-CS$CaCO_3$NP (10 mg/kg).

Sebagai kesimpulan , keputusan menunjukkan bahawa DTX-CS$CaCO_3$NP yang dirumuskan melepaskan DTX lebih perlahan pada pH 7.4. Juga diperhatikan bahawa DTX-CS$CaCO_3$NP mempunyai kesan antikanser yang sama ke atas sel-sel MCF-7 dan 4T1 seperti DTX dan oleh kerana ia mempunyai pelepasan yang perlahan, CS$CaCO_3$NP adalah sistem penghantaran yang berpotensi untuk DTX bagi model kanser payudara yang disebabkan oleh 4T1. DTX-CS$CaCO_3$NP (10 mg/kg) menunjukkan keberkesanan yang tinggi terhadap metastasis kanser payudara.

Kata kunci: Kanser payudara, docetaxel, partikel nano kulit kerang, sistem pengangkutan drug, mencit Balb/c

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I certify that a Thesis Examination Committee has met on 8 March 2018 to conduct the final examination of Nahidah Ibrahim Hammadi on her thesis entitled "Characterization, Histological Evaluation and Efficacy of Docetaxel-Loaded Cockle Shell-Derived $CaCO_3$ Nanoparticles *In Vitro* and *In Vivo*" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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

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LIST OF ABBREVIATIONS

ANP	Aragonite nanoparticles
BET	Brunauer-Emmett-Teller
$CSCaCO_3$	Cockle shell-derived calcium carbonate
$CSCaCO_3NP$	Cockle shell-derived calcium carbonate nanoparticle
DMSO	Dimethylsulfoxide
DTX-$CaCO_3NP$	Docetaxel-loaded cockle shell-derived calcium carbonate nanoparticle
DTX	Docetaxel
EDX	Equipped dispersive x-ray
EE	Encapsulation efficiency
EPR	Enhanced permeabilty and retention
FESEM	Field emission scanning electron microscopy
FTIR	Fourier transformed infrared
hEGF	human Epithelial growth factor
MTT	3-[4, 5- dimethylthiazol-2-yl]-3, 5-diphenyl tetrazolium bromide dye.
NP	Nanoparticle
PBS	Phosphate Buffer Saline
PC	Positive control
PK	Pharmcokinetic
RPMI	Rosewell Park Memorial Institute medium
SEM	Scanning electron microscopy
TEM	Transmission electron microscopy
VANP	Vancomycin Aragonite Nanoparticles

XRD	X-ray diffraction
nm	Nanometer
mg/m^2	Milligram per square meter
mL	Mililiter
µ	Micrometer
kg	kilogram
nM	NanoMolar
µg/mL	Microgram per Mililiter
hr	Hour(s)
IC_{50}	Half-maximal inhibitory concentration

CHAPTER 1

INTRODUCTION

1.1 Study Background

Over the years, cancer has globally become a revered condition among people worldwide. Annually, the growing number of newly identified cancer cases throughout the world is alarming (Siegel *et al*., 2013). Malignant neoplasm is an extensive group of diseases produced by unregulated cell growth in the body mostly due to functional failure of tumor suppressor genes (Gomathi & Thangaraj, 2010). Cancer initiates when cells in a part of the body start to grow out of control (DeSantis *et al*., 2014). Factors such as food, water, air, chemicals and sunlight have been attributed to primary causes of cancer in humans.

Breast cancer is the most common invasive cancer that affects women worldwide. It is the number one cause of morbidity and mortality among women worldwide, and the second highest cause of cancer fatality only next to lung cancer (Sanna *et al*., 2011b). Developments in early breast cancer discovery methods have improved frequency, but mortality has progressively declined. The epidemiology of breast cancer, comprising mostly of reproductive, genetic, and environmental risk factors has led to a more informed patient investigation and assisted in screening and management practices (Ban & Godellas, 2014). Breast cancer is a complex and heterogeneous disease which has a common complication of metastasis to various body organs (Holliday & Speirs, 2011). Chemotherapy and surgery have several drawbacks including physical pain, increased degeneration and lower survival rate. There are currently several chemotherapeutic agents that have been shown to exhibit significant anti-tumorigenic effect against breast cancer; among these are the taxanes which include docetaxel and paclitaxel.

Docetaxel (DTX), a member of the taxane family is a hydrophobic model drug that has become an anticancer drug with an approved clinical effectiveness against breast cancer as well as lung, ovary and prostate cancers (Oh *et al*., 2016). Docetaxel is compromised by its hydrophobic and lipophilic nature. It is a clinically well-established antimitotic chemotherapeutic medication that works by interfering with cell division (Baker *et al*., 2006; Anna, 2014). DTX stimulates the formation of microtubules from tubulin which inhibits microtubules assembly and suppresses tumor cell growth (Yuan *et al*., 2014). A limitation of docetaxel is the serious side effects exhibited in patients such as allergic reactions, neurotoxicity, nephrotoxicity, decreased white blood cell counts and increased level of liver enzymes (Clarke & Rivory, 1999). Since its toxicity is of paramount concern, research has focused on developing more efficient delivery methods aimed at reducing its toxicity. To this end, several kinds of nanoparticles have been developed as drug delivery system in order to improve the intracellular absorption of DTX in solid tumors while avoiding toxicity

to the normal tissue by applying the 'enhanced permeability and retention effect' (EPR effect) (Maeda *et al.*, 2000).

Recently, spherically shaped calcium carbonate nanocrystals have been utilized as a novel delivery for drugs and bioactive proteins with a remarkably persistent release and high stability (Kamba *et al.*, 2013a; Isa *et al.*, 2016; Saidykhan *et al.*, 2016; Fu *et al.*, 2017; Jaji *et al.*, 2017; Syairah *et al.*, 2017). Calcium carbonate ($CaCO_3$) is one of the most abundant minerals in nature, and it has three polymorphs; calcite, aragonite and vaterite. In recent years, researchers have investigated a variety of approaches using biogenic calcium carbonate as a promising drug delivery system due to its safety, biodegradability and pH sensitivity. Similarly, evidenced-based research has shown that calcium carbonate based nanoparticles, especially spherical nanoparticles are a good candidate for anticancer drug delivery and bioactive proteins (Islam *et al.*, 2011).

1.2 Problem Statements

Breast cancer is distinctive among the potentially dangerous malignancies due to the wide difference between the high incidence of histological changes evident as cancer and the much lower prevalence of clinical disease(Abu *et al.*, 2014b). Despite initial androgen chemotherapy, growth and progression are evident in approximately all patients. Common treatment of breast cancer such as surgery, hormone therapy, radiation therapy and chemotherapy are still not able to effectively remedy this disease. Chemotherapeutic agents are distributed non-specifically around the body, and they affect both cancerous and normal cells, thus limiting the dose that reaches the tumor while causing excessive toxicities (Wang *et al.*, 2008).

Current treatments against cancer are to a large extent hampered by the difficulties of poor water-solubility, non-specific delivery and poor bio distribution of drugs, inability to avoid biological barriers, and the lack of an effective modality for treatment monitoring(Lyseng-Williamson & Fenton, 2005). Nowadays, the treatment of hormone-refractory breast cancer depends mainly on docetaxel-based chemotherapy. However, the application of DTX is limited by its hydrophobic nature and non-selective toxicity, as well as induction of hypersensitivity reaction and multidrug resistance (Rabinow, 2004; Porter *et al.*, 2007).

1.3 Significance of the Study

In recent years, nanotechnology, exemplified through design of novel drug delivery systems, has tremendously contributed to the diagnosis, prevention, and treatment of various diseases and ailments. The adoption of nanotechnology in cancer therapeutics has shown promising resolve to amend limitations of conventional treatments, which include poor drug bioavailability, nonspecific systemic drug distribution, insufficient concentration of drug at the tumor site and inability to monitor therapeutic responses in real time. The preparation of a cockle shell-derived calcium carbonate aragonite

nanoparticle-based delivery system to incorporate water-insoluble molecules may further enhance the success seen with DTX.

The strategy for the design of such carrier will be based on the use of BS12 realization of chemical reaction and formation of nanoparticles. The use of $CaCO_3$ aragonite nanoparticles for drug delivery in the management of breast cancer is yet to be reported. It is highly expected that the use of nanoparticle-based drug delivery system improves delivery of anticancer agents and metabolites to cancerous organs.

1.4 Hypothesis

This research hypothesizes that cockle shell-derived $CaCO_3$ aragonite nanoparticles ($CSCaCO_3NP$) can be loaded with hydrophobic DTX to be used as a safe and non-toxic nanocarrier and induces apoptosis and necrosis in *vitro a*nd in *vivo*.

1.5 Objectives

1.5.1 General Objective

The main aim of the study was to evaluate the anticancer efficacy and histological changes of breast cancer in mouse model treated with Docetaxel-loaded cockle shells-derived $CaCO_3$ aragonite nanoparticles (DTX-$CSCaCO_3NP$).

1.5.2 Specific Objectives

The specific objectives of the study were:

i. To prepare, characterize and evaluate the drug loading capacity, encapsulation efficiency of cockle shells-derived $CaCO_3$ aragonite nanoparticles ($CSCaCO_3NP$).
ii. To evaluate the anticancer efficacy of DTX-$CSCaCO_3NP$ using cell line *in vitro*.
iii. To evaluate toxicity of Cockle Shells-derived Aragonite Calcium Carbonate Nanoparticles (CSCaCO3NP) in *vivo*.
iv. To assess the histological changes in the organs of breast cancer mouse model treated with DTX-$CSCaCO_3NP$.

REFERENCES

Abercrombie, M., & Ambrose, E. (1962). The surface properties of cancer cells: a review. *Cancer Research,* 22(5): 525-548.

Abhilash, 2010). Potential applications of Nanoparticles. *International Journal of Pharma and Bio Sciences,* 5(1*):* 1-12.

Abu, N., Akhtar, M. N., Yeap, S. K., Lim, K. L., Ho, W. Y., Zulfadli, A. J., . . . Alitheen, N. B. (2014). Flavokawain A induces apoptosis in MCF-7 and MDA-MB231 and inhibits the metastatic process in vitro. *PloS one,* 9(10): e105244.

Aguilar F, Dusemund B, Galtier P, Gilbert J, Gott DM, Grilli S, Gürtler R, König J, Lambré C, Larsen J-C, Leblanc J-C, *et al*., (2011). Scientific opinion on re-evaluation of calcium carbonate (E170) as a food additive. *European Food Safety Authority (EFSA) Journal* 9(7):231854.

Ajani, J. A. (2006). Chemotherapy for advanced gastric or gastroesophageal cancer: defining the contributions of docetaxel. *Expert Opinion on Pharmacotherapy*. 7(12): 1627-1631.

Al Dhaheri, Y., Attoub, S., Ramadan, G., Arafat, K., Bajbouj, K., Karuvantevida, N., Iratni,R.(2014). Carnosol induces ROS-mediated beclin1-independent autophagy and apoptosis in triple negative breast cancer. *Nanomedicine & Biotherapeutic Discovery*, 9(10): 630-45.

American Cancer Society. (2013).*Types of breast cancer*. Retrieved from: www.cancer.org/cancer/breastcancer/detailedguide/breast-cancer-breast-cancer-types.

Anna Azvolinsky (2014). Docetaxel with ADT Improves Survival for Metastatic *Prostate Cancer Patients.* Casreport, 2014

Assi, M.A, M. N. M. Hezmee, Y. Abba, M. Y. Sabri, A. W. Haron, F. H. Baiee, and M. A. Rajion (2017). Effect of Nigella sativa pre-treatment on sub-chronic lead acetate induced hematological and biochemical alterations. J. *Comput. Theor. Nanosci.* 14(3): 2752–2758

Awang-Hazmi, A., Zuki, A., Noordin, M., Jalila, A., & Norimah, Y. (2007). Mineral Composition of the Cockle (Anadara granosa) Shells of West Coast of Peninsular Malaysia and It Potential as Biomaterial for Use in Bone Repair. *Journal of Animal and Veterinary Advances,* 6*: 591-594.*

Baker, S. D., Sparreboom, A., & Verweij, J. (2006). Clinical pharmacokinetics of docetaxel. *Clinical pharmacokinetics,* 45(3): 235-252.

Ban, K. A., & Godellas, C. V. (2014). Epidemiology of breast cancer. *Surgical oncology clinics of North America,* 23(3): 409-422.

Benga, G. and Holmes, R. P. (1984). Interactions between components in biological membranes and their implications for membrane function. *Progress in Biophysics and Molecular Biology* 43(6):195–257.

Berliner, Janice L & Fay, Angela Musial (2007). Risk assessment and genetic counseling for hereditary breast and ovarian cancer: recommendations of the National Society of Genetic Counselors. *Journal of genetic counseling*, 16(3): 241-260.

Beruto, D., & Giordani, M. (1993). Calcite and aragonite formation from aqueous calcium hydrogencarbonate solutions: effect of induced electromagnetic field on the activity of CaCO 3 nuclei precursors. *Journal of the Chemical Society, Faraday Transactions,* 89(14): 2457-2461.

Biosciences, B. D. (2011). *Detection of Apoptosis Using the BD Annexin V FITC Assay on the BD FACSVerse™ System* (pp.1-12).

Biradar S, Ravichandran P, Gopikrishnan R, *et al* (2011). Calcium carbonate nanoparticles: Synthesis, characterization and biocompatibility nanosci and nanotechnology. *Nanosci Nanotechnol*, 11(4):6868-74.

Bissery, M.-C. (1995). Preclinical pharmacology of docetaxel. *European journal of cancer*, 31: 1-6.

Bleiweiss, I. J. (2013, December 19). *Pathology of breast cancer.* Retrieved from the Up to Date website: http://www.uptodate.com/contents/*pathology-of-breast-cance*r.

Bloom, H. J. G. and Richardson, W. W. (1957). *British Journal of Cancer* 11: 359.

Boulaiz, H., Alvarez, P. J., Ramirez, A., Marchal, J. A., Prados, J., Rodríguez-Serrano, F. Aranega, A.(2011). Nanomedicine: application areas and development prospects. *International journal of molecular sciences,* 12(5): 3303-3321.

Bradshaw-Pierce, E. L., Steinhauer, C. A., Raben, D., & Gustafson, D. L. (2008). Pharmacokinetic-directed dosing of vandetanib and docetaxel in a mouse model of human squamous cell carcinoma. *Molecular cancer therapeutics*, 7(9): 3006-3017.

Brigger, I., Dubernet, C., & Couvreur, P. (2012). Nanoparticles in cancer therapy and diagnosis. *Advanced drug delivery reviews*, 64: 24-36.

Brunsvig, P. F., Andersen, A., Aamdal, S., Kristensen, V. and Olsen, H. (2007). Pharmacokinetic analysis of two different docetaxel dose levels in patients with non-small cell lung cancer treated with docetaxel as monotherapy or with concurrent radiotherapy. *BMC cancer*, 7(1): 197--206.

Burstein, H. J., Manola, J., Younger, J., Parker, L. M., Bunnell, C. A., Scheib, R., Shulman, L. N. (2000). Docetaxel administered on a weekly basis for metastatic breast cancer. Journal of *Clinical Oncology*, 18(6): 1212-1219.

Butler, P., Mitchell, A. and Ellis, H. (2007). *Applied Radiological Anatomy for Medical Students (*PP 1-165). Cambridge University Press. Amazon.com.

Buzea, Cristina, Pacheco, Ivan I, Robbie, Kevin (2007). Nanomaterials and nanoparticles: Sources and toxicity. *Biointerphases*, 2(4):7-71.

Bwatanglang, I. B., Mohammad, F., Yusof, N. A., Abdullah, J., Alitheen, N. B., Hussein, M. Z., & Yeap, S. K. (2016a). In vivo tumor targeting and anti-tumor effects of 5-fluororacil loaded, folic acid targeted quantum dot system. J*ournal of colloid and interface science*, 480: 146-158.

Bwatanglang, I. B., Mohammad, F., Yusof, N. A., Abdullah, J., Hussein, M. Z., Alitheen, N. B., & Abu, N. (2016b). Folic acid targeted Mn: ZnS quantum dots for theranostic applications of cancer cell imaging and therapy. *International journal of nanomedicine*, 11: 413.

Bwatanglang IB, Mohammad F, Yusof NA, *et al* ;(2017). Histological analysis of anti-cancer drug loaded, targeted Mn: ZnS quantum dots in metastatic lesions of 4T1 challenged mice, *J. Mater Sci Mater Med;* 28(9):138.

Carlsson, G., Ekelund, L., Stigsson, L., & Hafstroem, L. (1982). Vascularization and tumour volume estimations of solitary liver tumours in rats. Paper presented at the *Annales Chirurgiae et Gynaecologiae*, 72(4):187-191.

CCA *(Calcium Carbonate Association)* (2005). Skin & eye irritation studies performed on calcium carbonate, Summary report, December 2005, Calcium Carbonate Association– Europe A.I.S.B.L. Member of IMA-Europe: 1–2.

Cho, K., Wang, X., Nie, S., & Shin, D. M. (2008). Therapeutic nanoparticles for drug delivery in cancer. *Clinical cancer research*, 14(5): 1310-1316.

Choi, S.-J., & Choy, J.-H. (2011). Layered double hydroxide nanoparticles as target-specific delivery carriers: uptake mechanism and toxicity. *Nanomedicine*, 6(5): 803-814.

Chu, K. S., Hasan, W., Rawal, S., Walsh, M. D., Enlow, E. M., Luft, J. C., Zamboni, W. C. (2013). Plasma, tumor and tissue pharmacokinetics of Docetaxel delivered via nanoparticles of different sizes and shapes in mice bearing SKOV-3 human ovarian carcinoma xenograft. Nanomedicine: *Nanotechnology, Biology and Medicine*, 9(5): 686-693.

Chuba, P. J., Hamre, M. R., Yap, J., Severson, R. K., Lucas, D., Shamsa, F., & Aref, A. (2005). Bilateral risk for subsequent breast cancer after lobular carcinoma-in-situ: Analysis of surveillance, epidemiology, and end results data. *Journal of Clinical Oncology*, 23(24): 5534-5541.

Clarke, S. J., & Rivory, L. P. (1999). Clinical pharmacokinetics of docetaxel. *Clinical pharmacokinetics*, 36(2): 99-114.

Coelho S. C., Pereira M. C., & Coelho M. A. N. (2012). Delivery of biomolecules by functionalized inorganic nanoparticles. *Bioengineering*, 3(1):1-6.

Collins, Jerr Rubinstein, Larry Pickeral, Oxana Steinberg, Seth M (2007). Phase 0 clinical trials in cancer drug development: from FDA guidance to clinical practice. *Molecular Interventions*,7(6): 325-334.

Collins, L. C., & Schnitt, S. J. (2014). Pathology of benign breast disorders. In J. Harris, M. E. Lippman, M. Morrow, & C. K. Osborne (Eds.), *Diseases of the breast*, 5th edition (pp 71-88). Philadelphia, PA: Wolters Kluwer Health.

Corben, A. D., & Brogi, E. (2014). Ductal Carcinoma in situ and other intraductal lesions: Pathology, immunohistochemistry, and molecular alterations. In J. Harris, M. E. Lippman, M. Morrow, & C. K. Osborne (Eds.), *Diseases of the breast,* 5th edition PA (pp. 309-323.) Wolters Kluwer Health., Philadelphia

Danhier, F., Feron, O., & Préat, V. (2010). To exploit the tumor microenvironment: passive and active tumor targeting of nanocarriers for anti-cancer drug delivery. *Journal of Controlled Release*, 148(2): 135-146.

Das, S., Banerjee, R., & Bellare, J. (2005). Aspirin loaded albumin nanoparticles by coacervation: implications in drug delivery. *Trends Biomater Artif Organs*, 18(2): 203-212.

De Smet, L., Ceelen, W., Remon, J. P., & Vervaet, C. (2013). Optimization of drug delivery systems for intraperitoneal therapy to extend the residence time of the chemotherapeuticagent.*The Scientific World Journal:* pages 1-7

De Souza Garcia, C. M., de Araújo, M. R., Lopes, M. T. P., Ferreira, M. A. N. D., & Cassali,G. D. (2014). Morphological and Immunophenotipical Characterization of Murine Mammary Carcinoma 4t1. *Braz J Vet Pathol*, 7(3): 158-165.

De Santis, C. E., Lin, C. C., Mariotto, A. B., Siegel, R. L., Stein, K. D., Kramer, J. L., Alteri, R., Robbins, A. S., & Jemal, A. (2014). Cancer treatment and survivorship statistics, 2014. CA: *a cancer journal for clinicians*, 64(4):252-271.

Dhakar, R. C. (2012). From formulation variables to drug entrapment efficiency of microspheres: A technical review. *Journal of Drug Delivery and Therapeutics*, 2(6): 128-133.

Diaz, M. R., & Vivas-Mejia, P. E. (2013). Nanoparticles as Drug Delivery Systems in Cancer Medicine: Emphasis on RNAi-Containing. *Nanoliposomes. Pharmaceuticals,* 6(11):1361-1380.

Dillon, D., Guidi, A. J., & Schnitt, S. J.(2014). Pathology of invasive breast cancer. In J. Harris, M. E. Lippman, M. Morrow, & C. K. Osborne (Eds.), *Diseases of the breast*, 5th edition (pp 381-410). Philadelphia, PA: Wolters Kluwer Health.

Dizaj, S. M., Barzegar-Jalali, M., Zarrintan, M. H., Adibkia, K., & Lotfipour, F. (2015). Calcium carbonate nanoparticles; potential in bone and tooth disorders. *Pharmaceutical Sciences*, 20 (1): 175-18.

Dobrovolskaia, M. A., & McNeil, S. E. (2007). Immunological properties of engineered nanomaterials. *Nature nanotechnology*, 2(8): 469-478.

Dobrzynska P. (2013). *Properties, applications, and manufacture*. Retrieved from http://global.britannica.com/EBchecked/topic/1109065/nanoparticle.

Dołowy, K. (1984). Bioelectrochemistry of cell surface. *Progress in Surface Science* 15(3):245–368.

Du, N., Song, L.-P., Li, X.-S., Wang, L., Wan, L., Ma, H.-Y., & Zhao, H. (2015). Novel pH-sensitive nanoformulated docetaxel as a potential therapeutic strategy for thetreatment ofcholangiocarcinoma. *Journal of Nanobiotechnology*, 13(1): pages 1-17.

Elmore, S. (2007). Apoptosis: a review of programmed cell death. *Toxicologic Pathology*, 35: 495-516.

Emerich, Dwaine F (2003). Nanotechnology and medicine. *Expert Opinion on Biological Therapy* 3(4):655-663.

Engels, F., Sparreboom, A., Mathot, R., & Verweij, J. (2005). Potential for improvement of docetaxel-based chemotherapy: a pharmacological review. *British journal of cancer*, 93(2): 173-177.

Fang, G., Tang, B., Liu, Z., Gou, J., Zhang, Y., Xu, H., & Tang, X. (2014). Novel hydrophobin-coated docetaxel nanoparticles for intravenous delivery: in vitro characteristics and in vivo performance. *Eur J Pharm* Sci, 18(6): 1-9.

Fang, J., Nakamura, H., & Maeda, H. (2011). The EPR effect: unique features of tumor blood vessels for drug delivery, factors involved, and limitations and augmentation of the effect. *Advanced drug delivery reviews*, 63(3): 136-151.

Fantozzi, A., & Christofori, G. (2006). Mouse models of breast cancer metastasis. *Breast Cancer Res*, 8(4): 212.

Fay, F. and Scott, C. J. (2011). Antibody-targeted Nanoparticles for Cancer Therapy. *Immunotherapy* 3(3): 381-394.

Feng, L., Wu, H., Ma, P., Mumper, R. J., & Benhabbour, S. R. (2011). Development and optimization of oil-filled lipid nanoparticles containing docetaxel conjugates designed to control the drug release rate in vitro and in vivo. *International journal of nanomedicine*, 6(1): 2545-56.

Ferlay, J., Shin, H. R., Bray, F., Forman, D., Mathers, C., & Parkin, D. M. (2010). Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *International journal of cancer*, 127(12): 2893-2917.

Ferlini, C., Scambia, G., Distefano, M., Filippini, P., Isola, G., Riva, A., & Mancuso, S. (1997). Synergistic antiproliferative activity of tamoxifen and docetaxel on three oestrogen receptor-negative cancer cell lines is mediated by the induction of apoptosis. *British journal of cancer*, 75(6): 884.

Fu, W., Mohd Noor, M. H., Yusof, L. M., Ibrahim, T. A. T., Keong, Y. S., Jaji, A. Z., & Zakaria, M. Z. A. B. (2017). In vitro evaluation of a novel pH sensitive drug delivery system based cockle shell-derived aragonite nanoparticles against osteosarcoma. *Journal of Experimental Nanoscience*, 12(1): 166-187.

Fujiwara, K., Armstrong, D., Morgan, M., & Markman, M. (2007). Principles and practice of intraperitoneal chemotherapy for ovarian cancer. International *Journal of Gynecological Cancer*, 17(1): 1-20.

Gao, Y., Chen, L., Gu, W., Xi, Y., Lin, L., & Li, Y. (2008). Targeted nanoassembly loaded with docetaxel improves intracellular drug delivery and efficacy in murine breast cancer model. *Molecular pharmaceutics*, 5(6): 1044-1054.

Giordano, Sharon H, Buzdar, Aman U, Smith, Terry L *et al*., (2004). Is breast cancer survival improving?. *Journal Cancer*, 100(1): 44-52.

Gomathi, M., and Thangaraj, P. (2010). A computer aided diagnosis system for lung cancer detection using support vector machine. *American Journal of Applied Sciences*, 7: 1532-1538.

Gong, C., Yang, B., Qian, Z., Zhao, X., Wu, Q., Qi, X., Wang, Y., Guo, G., Kan, B., & Luo, F. (2012). Improving intraperitoneal chemotherapeutic effect and preventing postsurgical adhesions simultaneously with biodegradable micelles. Nanomedicine: Nanotechnology, *Biology and Medicine*, 8(6): 963-973.

Govers, M., & Van der Meet, R. (1993). Effects of dietary calcium and phosphate on the intestinal interactions between calcium, phosphate, fatty acids, and bile acids. *Gut*, 34(3):365-370.

Group, E. B. C. T. C. (2005). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *The Lancet*, 365(9472):1687-1717.

Guarneri, V., & Conte, P. F. (2004). The curability of breast cancer and the treatment of advanced disease. *European journal of nuclear medicine and molecular imaging*, 31(1): S149-S161.

Gueritte-Voegelein, F., Guenard, D., Lavelle, F., Le Goff, M. T., Mangatal, L., & Potier, P. (1991). Relationships between the structure of taxol analogs and their antimitotic activity. *Journal of medicinal chemistry*, 34(3):992-998.

Guptha, A. (2015). Nano Drug delivery system - A mini review. Research & Reviews: *Journal of Pharmaceutics and Nanotechnology* 3(2): 126-144.

Häcker, G. (2000). The morphology of apoptosis. *Cell and Tissue Research*, 30(1):5-17.

Haagensen, C. D. (1933). Grading in breast cancer. *American Journal of Cancer.*19 (2): pages 1-45.

Hammadi, I. N., Abba, Y., Hezmee, M. N. M., Razak, I. S. A., Jaji, A. Z., Isa, T., Mahmood, S. K., & Zakaria, M. Z. A. B. (2017a). Formulation of a Sustained Release Docetaxel Loaded Cockle Shell-Derived Calcium Carbonate Nanoparticles against Breast Cancer. *Pharmaceutical Research.* 34:1193–1203.

Harush-Frenkel, O., Debotton, N., Benita, S., & Altschuler, Y. (2007). Targeting of nanoparticles to the clathrin-mediated endocytic pathway. *Biochemical and biophysical research communications*, 353(1): 26-32.

Haughland, R. (2002). Handbook of Fluorescent Compounds and Research Products, *Molecular Probes* (pp. 20–35).

Heaney, R. P., & Nordin, B. (2002). Calcium effects on phosphorus absorption: implications for the prevention and co-therapy of osteoporosis. *Journal of the American College of Nutrition*, 21(3): 239-244.

Heaney RP (2002). Ethnicity, bone status, and calcium requirement. *Nutr Res* 22(2):153–178.

Hegdekar, C. N. (2010). Nanotechnology and the theranostic approach for the future management of cancer and the ethics of nanomedicine. *Research paper based on pathology lectures at Medlink:* Pages 1-18.

Hennighausen L, Robinson GW :(1998). Think globally, act locally: the making of a mouse mammary gland. *Genes Dev,* 12:

Hernández-Vargas, H., Palacios, J., & Moreno-Bueno, G. (2007a). Molecular profiling of docetaxel cytotoxicity in breast cancer cells: uncoupling of aberrant mitosis and apoptosis. *Oncogene*, 26(20):2902-2913.

Hernández-Vargas, H., Palacios, J., & Moreno-Bueno, G. (2007b). Telling cells how to die: docetaxel therapy in cancer cell lines. *Cell Cycle*, 6(7): 780-783.

Hill, B. T., Whelan, R. D., Shellard, S. A., McClean, S., & Hosking, L. K. (1994). Differential cytotoxic effects of docetaxel in a range of mammalian tumor cell lines and certain drug resistant sublinesin vitro. *Investigational new drugs*, 12(3):169-182.

Huh, A. J., & Kwon, Y. J. (2011). Nanoantibiotics": a new paradigm for treating infectious diseases using nanomaterials in the antibiotics resistant era. *Journal of Controlled Release*, 156(2): 128-145.

Holliday, D. L., & Speirs, V. (2011). Choosing the right cell line for breast cancer research. *Breast Cancer Res*, 13(4): 215.

Honary S, Zahir F (2013). Effect of zeta potential on the properties of nano-drug delivery systems – a review (part 2). *Trop J Pharm Res*.; 12: 265–273.

Hondroulis, Evangelia Zhang, Rui Zhang, Chengxiao Chen, Chunying Ino, Kosuke Matsue, Tomokazu Li, Chen-Zhong (2014). Immuno nanoparticles integrated electrical control of targeted cancer cell development using whole cell bioelectronic device. *Theranostics.* 4(9): 919–930.

Howlader, N., Noone, A. M., Krapacho, M., Garshell, J., Neyman, N., Altekruse, S. F…Cronin, K. A. (Eds).SEER Cancer Statistics Review, 1975-2010, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975-2010.

Hoy, N. Y., & Metcalfe, P. (2013). Complications following breast cancer therapy in the adult spina bifida population: A case report. *Canadian Urological Association Journal*, 7: 11-12.

Hu Z, Deng Y, Sun Q. (2004). Synthesis of precipitated calcium carbonate nanoparticles using a two-membrane system. *Colloid J*; 66:745-50 *Cancer Res,* 13(4): 215.

Hu, Q., Rijcken, C. J., Bansal, R., Hennink, W. E., Storm, G., & Prakash, J. (2015). Complete regression of breast tumour with a single dose of docetaxel-entrapped core-cross-linked polymeric micelles. *Biomaterials*, 53: 370-378.

Ibrahima, Y., & Agrahari, V. (2015). Developing docetaxel-loaded nanocapsules: Apromising approach for cancer therapy. *Cancer Cell & Microenvironment,* DOI: http://dx.doi.org/10.14800/ccm.689.

Isa, T., Zakaria, Z. A. B., Rukayadi, Y., Mohd Hezmee, M. N., Jaji, A. Z., Imam, M. U., Hammadi, N. I., & Mahmood, S. K. (2016). Antibacterial Activity of Ciprofloxacin-Encapsulated Cockle Shells Calcium Carbonate (Aragonite) Nanoparticles and Its Biocompatability in Macrophage J774A. 1. *International journal of molecular sciences*, 17(5): 713.

Islam, K NBakar, M Z B AAli, M EHussein, M Z BNoordin, M MLoqman, MMiah, GWahid, H, *et al*. (2013). A novel method for the synthesis of calcium carbonate (aragonite) nanoparticles from cockle shells. *Powder Technology*, 235(3):70-75.

Islam, K NBakar, M Z B ANoordin, M MHussein, M Z BRahman, N S B A andAli, M E (2011). Characterization of calcium carbonate and its polymorphs from cockle shells (Anadara granosa). *Powder Technology*, 213 (1): 188-191.

Islam, K. N., Zuki, A., Ali, M., Hussein, M. Z. B., Noordin, M., Loqman, M., Hamid, S. B. A. (2012). Facile synthesis of calcium carbonate nanoparticles from cockleshells.*Journal of Nanomaterials*, 16(1): 262–271.

Jain, Rakesh K , Martin, John D, Stylianopoulos, Triantafyllos (2014). The role of mechanical forces in tumor growth and therapy. *Annual review of biomedical engineering*, 16, 321-346.

Jaji, A. Z., Bakar, M. Z. B. A., Mahmud, R., Loqman, M. Y., Hezmee, M. N. M., Isa, T., Wenliang, F., & Hammadi, N. I. (2017). Synthesis, characterization, and cytocompatibility of potential cockle shell aragonite nanocrystals for osteoporosis therapy and hormonal delivery. *Nanotechnology, Science and Applications*, 10: 1-23.

Jirát, J., Košata, B., Jenkins, A., & McNaught, A. (2009). IUPAC: Research Triagle Park: NC. *Journal for Clinicians*, 63: 1-19.

Kamba AS, Ismail M, Ibrahim TAT, Zakaria ZAB (2014a). Biocompatibility of bio based calcium carbonate nanocrystals aragonite polymorph on NIH 3T3 fibroblast cell line. *African J Tradit Complement Altern Med*; 11(4):31-38.

Kamba, A. S., Ismail, M., Ibrahim, T. A. T., & Zakaria, Z. A. B. (2013a). Synthesis and characterisation of calcium carbonate aragonite nanocrystals from cockle shellpowder (Anadaragranosa).*JournalofNanomaterials:* 1-6.

Kamba, S AIsmail, MTengku Ibrahim, T A andZakaria, Z a B (2013b). A pH-sensitive, biobased calcium carbonate aragonite nanocrystal as a novel anticancerdelivery system. *BioMed research international*, 1: 1-10.

Kamba, S. A., Ismail, M., Hussein-Al-Ali, S. H., Ibrahim, T. A. T., & Zakaria, Z. A. B. (2013c). In vitro delivery and controlled release of doxorubicin for targeting osteosarcoma bone cancer. *Molecules*, 18(9): 10580-10598.

Kamba, S. A., Ismail, M., Tengku Ibrahim, T. A., Zakaria, Z. A. B., & Hassan Gusau, L. (2014b). In Vitro Ultrastructural Changes of MCF-7 for Metastasise Bone Cancer and Induction of Apoptosis via Mitochondrial Cytochrome C Released by CaCO 3/Dox Nanocrystals. *BioMed research international*: 1-14.

Kerr, J.F.R., Wyllie A.H. and Currie A.R. (1972). Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. *British Journal of Cancer*, 26(4):239-57.

Keun sang Oh, Kyungim Kim, Byeong Deok Yoon hye Jin lee Dal Yong Park *et al*., (2016). Docetaxel-loaded multilayer nanoparticles with nanodroplets for cancer therapy. *International Journal of Nanomedicine*, 11: 1077–1087.

Kim, B. J., Min, K. H., Hwang, G. H., Lee, H. J., Jeong, S. Y., Kim, E.-C., & Lee, S. C. (2015). Calcium carbonate-mineralized polymer nanoparticles for pH-responsive robust nanocarriers of docetaxel. *Macromolecular Research*, 23(1): 111-117.

King, T. A., & Reis-Filho, J. S. (2014). *Lobular carcinoma in situ: biology and management. Diseases of the breast. 5th edition,* (PP.1-33) Philadelphia: Lippincott Williams & Wilkins.

Kloth, J. S., Hamberg, P., Mendelaar, P. A., Dulfer, R. R., van der Holt, B., Eechoute, K., Wiemer, E. A., Kruit, W. H., Sleijfer, S., & Mathijssen, R. H. (2016). Macrocytosis as a potential parameter associated with survival after tyrosine kinase inhibitor treatment. *European Journal of Cancer*, 56: 101-106.

Kodumudi, K. N., Woan, K., Gilvary, D. L., Sahakian, E., Wei, S., & Djeu, J. Y. (2010). A novel chemoimmunomodulating property of docetaxel: suppression of myeloid-derived suppressor cells in tumor bearers. *Clinical Cancer Research*, 16(18): 4583-4594.

Koletzko B, Saris W, Flynn A, *et al* (2003). Report of the scientific committee on food on the revision of essential requirements of infant formulae and follow-on formulae. Sci Comm Food Eur Comm Heal Consum Prot Dir Brussels.

Kong, F., Zhang, H., Zhang, X., Liu, D., Chen, D., Zhang, W., Zhang, L., Santos, H. A., & Hai, M. (2016). Biodegradable Photothermal and pH Responsive Calcium Carbonate@ Phospholipid@ Acetalated Dextran Hybrid Platform for Advancing Biomedical Applications. *Advanced Functional Materials*, 26(34): 6158-6169.

Koopae N, M., Khoshayand, M. R., Mostafavi, S. H., Amini, M., Khorramizadeh, M. R., Jeddi Tehrani, M. Dinarvand, R. (2014). Docetaxel loaded PEG-PLGA nanoparticles: optimized. *Iran J Pharm Res*. 2014 summer; 13(3):819-33

Kouroussis, C., Agelaki, S., Mavroudis, D., Souglakos, J., Kakolyris, S., Kalbakis, K., Samonis, G. (2000). A dose escalation study of weekly docetaxel in patients with advanced solid tumors. *Cancer chemotherapy and pharmacology*, 46(6): 488-492.

Kumar, P. S., Ramya, C., Jayakumar, R., & Lakshmanan, V.-K. (2013). Drug delivery and tissue engineering applications of biocompatible pectin–chitin/nano $CaCO_3$ composite scaffolds. *Colloids and Surfaces B: Biointerfaces*, 106(6):109-116.

Kura, A. U., Hussein, M. Z., Fakurazi, S., & Arulselvan, P. (2014). Layered double hydroxide nanocomposite for drug delivery systems; bio-distribution, toxicity and drug activity enhancement.*Chemistry Central Journal*, 8(1): 1-8:

Kura, A. U., Saifullah, B., Cheah, P.-S., Hussein, M. Z., Azmi, N., & Fakurazi, S. (2015). Acute oral toxicity and biodistribution study of zinc-aluminium-levodopa nanocomposite. *Nanoscale research letters*, 10(1): 1-11.

Kurosaka, K., Takahashi M., Watanabe N. and Kobayashi Y. (2003). Silent cleanup of very early apoptotic cells by macrophages. *The Journal of Immunology*, 171(9) : 4672-4679.

Lauby-Secretan, Béatrice, Scoccianti, Chiara, Loomis, Dana, Benbrahim-Tallaa, Lamia *et al.*, (2015). Breast-cancer screening—viewpoint of the IARC Working Group. *New England Journal of Medicine*, 374(24): 2353-2358.

Lee, J.-A., Kim, M.-K., Kim, H.-M., Lee, J. K., Jeong, J., Kim, Y.-R., Oh, J.-M., & Choi, S.-J. (2015). The fate of calcium carbonate nanoparticles administered by oral route: absorption and their interaction with biological matrices. *International Journal of Nanomedicine*, 10(1): 2273-2293.

Li, Y., Jin, M., Shao, S., Huang, W., Yang, F., Chen, W., Zhang, S., Xia, G., & Gao, Z. (2014). Small-sized polymeric micelles incorporating docetaxel suppress distant metastases in the clinically-relevant 4T1 mouse breast cancer model. *BMC Cancer*, 14(1): 329.

Liang, C.-C., Park, A. Y., & Guan, J.-L. (2007). In vitro scratch assay: a convenient and inexpensive method for analysis of cell migration in vitro. *Nature Protocols*, 2(2):329-333.

Liu, Z., Chen, K., Davis, C., Sherlock, S., Cao, Q., Chen, X., & Dai, H. (2008). Drug delivery with carbon nanotubes for in vivo cancer treatment. *Cancer research*, 68(16): 6652-6660.

Lu, J., Huang, Y., Zhao, W., Marquez, R. T., Meng, X., Li, J., Gao, X., Venkataramanan, R., Wang, Z., & Li, S. (2013). PEG-derivatized embelin as a nanomicellar carrier for delivery of paclitaxel to breast and prostate cancers. *Biomaterials*, 34(5):1591-1600.

Lu, Y., Li, Y., & Wu, W. (2016). Injected nanocrystals for targeted drug delivery. *Acta Pharmaceutica Sinic*a *B*, *6*(2): 106-113.

Lundqvist, M., Stigler, J., Elia, G., Lynch, I., Cedervall, T., & Dawson, K. A. (2008). Nanoparticle size and surface properties determine the protein corona with possible implications for biological impacts. *Proceedings of the National Academy of Sciences*, 105(38): 14265-14270.

Lyseng-Williamson, K. A., & Fenton, C. (2005). Docetaxel. Drugs, 65(17): 2513-2531.

Maeda, H., Sawa, T., & Konno, T. (2001). Mechanism of tumor-targeted delivery of macromolecular drugs, including the EPR effect in solid tumor and clinical overview of the prototype polymeric drug SMANCS. *Journal of controlled release*, 74(1): 47-61.

Maeda, H., Wu, J., Sawa, T., Matsumura, Y., & Hori, K. (2000). Tumor vascular permeability and the EPR effect in macromolecular therapeutics: a review. *Journal of controlled release*, 65(1): 271-284.

Manolova V, Flace A, Bauer M, Schwarz K, Saudan P, Bachmann MF (2008). Nanoparticles target distinct dendritic cell populations according to their size. *Eur J Immunol* 38(5):1404–1413.

Maleki Dizaj, S., Barzegar-Jalali, M., Zarrintan, M. H., Adibkia, K., & Lotfipour, F. (2015). Calcium carbonate nanoparticles as cancer drug delivery system. *Expert opinion on drug delivery*, 12(10):1649-1660.

Mao, Z., Ma, L., GAO, C., & Shen, J. (2005). Preformed microcapsules for loading and sustained release of ciprofloxacin hydrochloride. *Journal of controlled release*, 104(1):193-202.

Marchettini, P., Stuart, A. O., Mohamed, F., Yoo, D., & Sugarbaker, P. H. (2002). Docetaxel: pharmacokinetics and tissue levels after intraperitoneal and intravenous administration in a rat model.*Cancer chemotherapy and pharmacology*, 49(6): 499-503.

Markman, Janet L, Rekechenetskiy, Arthur, Holler, Eggehard, Ljubimova, Julia Y (2013). Nanomedicine therapeutic approaches to overcome cancer drug resistance. *Advanced drug delivery reviews*, 65(13): 1866-1879.

McRae Page, S., Henchey, E., Chen, X., Schneider, S., & Emrick, T. (2014). Efficacy of polyMPC–DOX prodrugs in 4T1 tumor-bearing mice. *Molecular pharmaceutics*, 11(5): 1715-1720.

Miller, M. L., Andringa, A., Dixon, K., & Carty, M. P. (2002). Insights into UV-induced apoptosis: ultrastructure, trichrome stain and spectral imaging. *Micron*, 33(2):157-166.

Mohamad, N. E., Abu, N., Rahman, H. S., Ky, H., Ho, W. Y., Lim, K. L., How, C. W., Rasedee, A., Alitheen, N. B., & Yeap, S. K. (2015). Nanostructured lipid carrier improved in vivo anti-tumor and immunomodulatory effect of Zerumbone in 4T1 challenged mice. *RSC Advances*, 5(28): 22066-22074.

Mohamed, M., Yusup, S., & Maitra, S. (2012). Decomposition study of calcium carbonate in cockle shell. *Journal of Engineering Science and Technology*, 7(1): 1-10.

Moore, M. A., Tajima, K., Anh, P., Aydemir, G., Basu, P. S., Bhurgri, Y., Mosavi-Jarrahi, A. (2003). Grand challenges in global health and the practical prevention program? Asian focus on cancer prevention in females of the developing world. Asian Pacific J*ournal of Cancer Prevention*, 4(2): 153-165.

Montero, A., Fossella, F., Hortobagyi, G., & Valero, V. (2005). Docetaxel for treatment of solid tumours: a systematic review of clinical data. *The lancet oncology*, 6(4): 229-239.

Morse, D. L., Gray, H., Payne, C. M., & Gillies, R. J. (2005). Docetaxel induces cell death through mitotic catastrophe in human breast cancer cells. *Molecular cancer therapeutics*, 4(10), 1495-1504.

Morse, J. W., & Mackenzie, F. T. (1990). *Geochemistry of sedimentary carbonates Elsevier*. Amsterdam-Oxford-NewYork.

Morse, David L, Raghunand, Natarajan, Sadarangani, Pooja, Murthi, Shiva, Job, Constantin *et al*., (2007). Response of choline metabolites to docetaxel therapy is quantified in vivo by localized 31P MRS of human breast cancer xenografts and in vitro by high- resolution 31P NMR spectroscopy of cell extracts. *Magnetic resonance in medicine*, 58(2):270-280.

Mosmann Tim (1983). Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays. *Journal of immunological methods*, 65 (1-2): 55-63.

Mullins, John J &Mullins, Linda J (2004). Insights from the rat genome sequence. *Genome biology*, 5(5):221.

Murakami, M., Ernsting, M. J., Undzys, E., Holwell, N., Foltz, W. D., & Li, S.-D. (2013). Docetaxel Conjugate Nanoparticles That Target α-Smooth Muscle Actin–Expressing Stromal Cells Suppress Breast Cancer Metastasis. *Cancer research*, 73(15): 4862-4871.

Nagda, C., Chotai, N., Patel, S., Soni, T., & Patel, U. (2008). Preparation and in vitro evaluation of bioadhesive microparticulate system. *International Journal of Pharmaceutical Sciences and Nanotechnology*, 1(3): 257-266.

Natarajan, J. V., Nugraha, C., Ng, X. W., & Venkatraman, S. (2014). Sustained-release from nanocarriers: a review. *Journal of Controlled Release*, 193: 122-138. doi: http://dx.doi.org/10.1016/j.jconrel.2014.05.029.

Norsa'adah, Bachok, Rahmah, Mohd Amin, Rampal, Krishna Gopal, Knight, Aishah (2005). Understanding barriers to Malaysian women with breast cancer seeking help. *Asian Pacific Journal of Cancer Prevention*, 13(8): 3723-3730.

Oh, K. S., Kim, K., Yoon, B. D., Lee, H. J., Park, D. Y., Kim, E.-y., Lee, K., Seo, J. H., & Yuk, S. H. (2016). Docetaxel-loaded multilayer nanoparticles with nanodroplets for cancer therapy. *International Journal of Nanomedicine*, 11: 1077.

Ojima, Iwao, Zuniga, Edison S, Berger, William T, Seitz, Joshua D (2012). Tumor-targeting drug delivery of new-generation toxoids. *Future medicinal chemistry*, 4(1): 33-50.

Ouyang, L., Shi, Z., Zhao, S., Wang, F. T., Zhou, T. T., Liu, B., & Bao, J. K. (2012). Programmed cell death pathways in cancer: a review of apoptosis, autophagy and programmed necrosis. *Cell proliferation*, 45(6):487-498.

Page, S. M., Henchey, E., Chen, X., Schneider, S., & Emrick, T. (2014). Efficacy of polyMPC–DOX prodrugs in4T1 tumor-bearing mice.*Molecular pharmaceutics*, 11(5): 1715-1720.

Pang, L. Y., Cervantes-Arias, A., Else, R. W., & Argyle, D. J. (2011). Canine mammary cancer stem cells are radio-and chemo-resistant and exhibit an epithelial-mesenchymal transition phenotype. *Cancers*, 3(2):1744-1762.

Parkin, D. M., Bray, F., Ferlay, J., & Pisani, P. (2005). Global cancer statistics, 2002. *CA: a cancer journal for clinicians*, 55(2): 74-108.

Pasanna, AA Ram, S Fecht, HJ (2013). Consecutive magnetic and magnetocaloric transitions in herringbone nanostructured Heusler Mn50Ni41Sn9 alloy. *Journal of Nanoscience and Nanotechnology*, 13(8). 5351-5359.

Peacock, M. (2010). Calcium metabolism in health and disease. *Clinical Journal of the American Society of Nephrology*, 5(1):23-30.

Pettan-Brewer, C., Goh, J., & Ladiges, W. C. (2014). An immunohistochemical approach for monitoring effects of exercise on tumor stromal cells in old mice. *Pathobiology of aging & age related diseases*, 4: 1-10.

Porter, C. J., Trevaskis, N. L., & Charman, W. N. (2007). Lipids and lipid-based formulations: optimizing the oral delivery of lipophilic drugs. *Nature reviews. Drug discovery*, 6(3): 231.

Putz, Mihai V (2011). *Quantum and optical dynamics of matter for nanotechnology*. IGI Global. (pp227-5456).

Qin, Y.-Y., Li, H., Guo, X.-J., Ye, X.-F., Wei, X., Zhou, Y.-H., Zhang, X.-J., Wang, C., Qian, W., & Lu, J. (2011). Adjuvant chemotherapy, with or without taxanes, in early or operable breast cancer: a meta-analysis of 19 randomized trials with 30698 patients. *PLoS One*, 6(11):e26946.

Rabinow, B. E. (2004). Nanosuspensions in drug delivery. Nature reviews. *Drug discovery*, 3(9):785-96.

Radwan, E. M., Abdullah, R., Al-Qubaisi, M. S., El Zowalaty, M. E., Naadja, S. E., Alitheen, N. B., & Omar, A. R. (2016). Effect of recombinant human erythropoietin and doxorubicin in combination on the proliferation of MCF-7 and MDA-MB231 breast cancer cells. *Molecular medicine reports*, 13(5):3945-3952.

Rahman, H. S., Rasedee, A., Othman, H. H., Chartrand, M. S., Namvar, F., Yeap, S. K.Anasamy,T.(2014). Acute toxicity study of zerumbone-loaded nanostructured lipid carrier on BALB/c mice model.*BioMed research international*, 34(3): 1-15.

Rai, Mahendra, Yadav, Alka, Gade, Aniket (2009). Silver nanoparticles as a new generation of antimicrobials. *Biotechnology advances*, 27(1): 76-83.

Rakha, E. A., Reis-Filho, J. S., Baehner, F., Dabbs, D. J., Decker, T., Eusebi, V., Fox, S. B., Ichihara, S., Jacquemier, J., & Lakhani, S. R. (2010). Breast cancer prognostic classification in the molecular era: the role of histological grade. *Breast Cancer Res*, 12(4): 207.

Rampersad, Sephra N (2012). Multiple applications of Alamar Blue as an indicator of metabolic function and cellular health in cell viability bioassays. *Jornal sonsors,* 12(9): 12347-12360.

Rawat, M., Singh, D., Saraf, S., & Saraf, S. (2006). Nanocarriers: promising vehicle for bioactive drugs. *Biological and Pharmaceutical Bulletin*, 29(9): 1790-1798.

Redelman, D., & Hunter, K. W. (2007). The mouse mammary carcinoma 4T1: characterization of the cellular landscape of primary tumours and metastatic tumour foci. *International journal of experimental pathology*, 88(5): 351-360.

Riggio, Cristina, Pagni, Eleonora, Raffa, Vittoria, Cuschieri, Alfred (2011). Nano-oncology: clinical application for cancer therapy and future perspectives. *Journal of Nanomaterials,* http://dx.doi.org/10.1155/2011/164506.

Rivera-Rodríguez, G., Alonso, M., & Torres, D. (2013). Poly-L-asparagine nanocapsules as anticancer drug delivery vehicles. *European Journal of Pharmaceutics and Biopharmaceutics*, 85(3):481-487.

Rodriguez-Blanco, J. D., Shaw, S., & Benning, L. G. (2011). The kinetics and mechanisms of amorphous calcium carbonate (ACC) crystallization to calcite, via vaterite. *Nanoscale*, 3(1): 265-271.

Saidykhan, L., Bakar, M. Z. B. A., Rukayadi, Y., Kura, A. U., & Latifah, S. Y. (2016). Development of nanoantibiotic delivery system using cockle shell-derived aragonite nanoparticles for treatment of osteomyelitis. *International journal of nanomedicine*, 11:661.

SafePharma Laboratories, (2008). *Calcium carbonate: acute oral toxicity in the rat-fixed dose method.* Unpublished study report provided by CCAEurope.April 2011.

Saifullah, B. a. M. Z. H. (2015). Inorganic nanolayers: structure, preparation, and biomedical applications. *International Journal Journal of nanomedicine* IJNM, 10, 24. Doi: http://dx.doi.org/10.2147/IJN.S72330

Sakamoto, K., Schmidt, J. W., & Wagner, K.-U. (2015). Mouse Models of Breast Cancer. Mouse Models of Cancer: *Methods and Protocols,* 1267*:47-71*

Salmaso, Stefano, Bersani, Sara, Semenzato, Alessandra, Caliceti, Paolo. Nanotechnologies in protein delivery, *Journal of nanoscience and nanotechnology*, 6(1):2736-2753.

Sánchez-Moreno, P., Boulaiz, H., Ortega-Vinuesa, J. L., Peula-García, J. M., & Aránega, A. (2012). Novel drug delivery system based on docetaxel-loaded nanocapsules as a therapeutic strategy against breast cancer cells. *International journal of molecular sciences*, 13(4): 4906-4919.

Sanna, V., Roggio, A. M., Posadino, A. M., Cossu, A., Marceddu, S., Mariani, A., Alzari, V., Uzzau, S., Pintus, G., & Sechi, M. (2011). Novel docetaxel-loaded nanoparticles based on poly (lactide-co-caprolactone) and poly (lactide-co-glycolide-co-caprolactone) for prostate cancer treatment: formulation, characterization, and cytotoxicity studies. *Nanoscale research letters*, 6(1):1-9.

Saraya &Rokbaa (2016). Preparation of Vaterite Calcium Carbonate in the Form of Spherical Nano-size Particles with the Aid of Polycarboxylate Superplasticizer as a Capping Agent. *American Journal of Nanomaterials*, 4(2): 44-51.

Savill John & Fadok (2000). Corpse clearance defines the meaning of cell death. *Journal of Nature*, 407: 784-788.

Seyfried, Thomas N & Huysentruyt, Leanne C (2013). On the origin of cancer metastasis. *Critical reviews in oncogenesis*, 18 (2):43.

Sheetal, M. (2013). A Simple Ultraviolet Spectrophotometric Method for the Estimation of Docetaxel in Bulk Drug and Formulation. *Asian Journal of Pharmaceutical Analysis*, 3(2): 48-52.

Shi, H., Li, L., Zhang, L., Wang, T., Wang, C., Zhu, D., & Su, Z. (2015). Designed preparation of polyacrylic acid/calcium carbonate nanoparticles with high doxorubicin payload for liver cancer chemotherapy. *Cryst Eng Comm*, 17(26): 4768-4773.

Shimada, T., Nomura, M., Yokogawa, K., Endo, Y., Sasaki, T., Miyamoto, K. i., & Yonemura, Y. (2005). Pharmacokinetic advantage of intraperitoneal injection of docetaxel in the treatment for peritoneal dissemination of cancer in mice. *Journal of Pharmacy and Pharmacology*, 57(2),:177-181.

Shukla, R., Bansal, V., Chaudhary, M., Basu, A., Bhonde, R. R., & Sastry, M. (2005). Biocompatibility of gold nanoparticles and their endocytotic fate inside the cellular compartment: a microscopic overview. *Langmuir*, 21(23): 10644-10654.

Siegel R. , Naishadham D., Jemal A (2013). *Cancer Statistics*, 2013. CA: A cancer

Siegel, E. T., Kim, H.-G., Nishimoto, H. K., & Layman, L. C. (2013). The molecular basis of impaired follicle-stimulating hormone action: evidence from human mutations and mouse models. *Reproductive Sciences*, 20(3): 211-233.

Singh, S. K., Banala, V. T., Gupta, G. K., Verma, A., Shukla, R., Pawar, V. K., Tripathi, P., & Mishra, P. R. (2015). Development of docetaxel nanocapsules for improving in vitro cytotoxicity and cellular uptake in MCF-7 cells. *Drug development and industrial pharmacy*, 41(11): 1759-1768.

Śliwka, Lidia., Wiktorska., Katarzyna ., Suchocki, Piotr. Milczarek, Małgorzata *et al.*, (2016). The comparison of MTT and CVS assays for the assessment of anticancer agent interactions. *Journal PloS one*, 11(5): e0155772.

Som A, Raliya R, Tian L, *et al*. (2016). Monodispersed calcium carbonate nanoparticles modulate local pH and inhibit tumor growth in vivo. *Nanoscale.* 8:12639-12647.

Soundrapandian, C., Basu, D., SA, B., & Datta, S. (2011). Local drug delivery system for the treatment of osteomyelitis: In vitro evaluation. *Drug Development and Industrial Pharmacy*, 37(5): 538–46.

Svenskaya, Y., Parakhonskiy, B., Haase, A., Atkin, V., Lukyanets, E., Gorin, D., & Antolini, R. (2013). Anticancer drug delivery system based on calcium carbonate particles loaded with a photosensitizer. *Biophysical Chemistry*, 182: 11-15.

Syairah Liyana Mohd Abd Ghafar, Mohd Zobir Hussein, and Zuki Abu Bakar Zakaria (2017). Synthesis and Characterization of Cockle Shell-Based Calcium Carbonate Aragonite Polymorp Nanoparticles with Surface Functionalization, *Hindawi Journal of Nanoparticles*, 10:12.

Tan, Q., Liu, X., Fu, X., Li, Q., Dou, J., & Zhai, G. (2012). Current development in nanoformulations of docetaxel. *Expert opinion on drug delivery*, 9(8): 975-990.

Tao, K., Fang, M., Alroy, J., & Sahagian, G. G. (2008). Imagable 4T1 model for the study of late stage breast cancer. *BMC Cancer*, 8(1): 228.

Tenzer, S., Docter, D., Rosfa, S., Wlodarski, A., Kuharev, J. R., Rekik, A., Knauer, S. K., Bantz, C., Nawroth, T., & Bier, C. (2011). Nanoparticle size is a critical physicochemical determinant of the human blood plasma corona:a comprehensive quantitative proteomic analysis. *ACS Nano*, 5(9): 7155-7167.

Tran, T. H., Ramasamy, T., Choi, J. Y., Nguyen, H. T., Pham, T. T., Jeong, J.-H., Ku, S. K., Choi, H.-G., Yong, C. S., & Kim, J. O. (2015). Tumor-targeting, pH-sensitive nanoparticles for docetaxel delivery to drug-resistant cancer cells. *International journal of nanomedicine*, 10: 5249.

Trebuňová, M., Laputková, G., Géci, I., Andrašina, I., & Sabo, J. (2013). Enhancement of docetaxel-treated MCF-7 cell death by 900-MHz radiation. *Central European Journal of Biology*, 8(4): 357-365.

Trebunova, M., Laputkova, G., Slaba, E., Lacjakova, K., & Verebova, A. (2012). Effects of docetaxel, doxorubicin and cyclophosphamide on human breast cancer cell line MCF-7. *Anticancer research*, 32(7): 2849-2854.

Udofot, O., Affram, K., Smith, T., Tshabe, B., Krishnan, S., Sachdeva, M., & Agyare, E. (2016). Pharmacokinetic, biodistribution and therapeutic efficacy of 5-fluorouracil-loaded pH-sensitive PEGylated liposomal nanoparticles in HCT-116 tumor bearing mouse. *Journal of nature and science*, 2(1):171.

Ueno, Y., Futagawa, H., Takagi, Y., Ueno, A., & Mizushima, Y. (2005). Drug-incorporating calcium carbonate nanoparticles for a new delivery system. *Journal of Controlled Release*, 103(1): 93-98.

Ulukaya, E., Acilan, C., Ari, F., Ikitimur, E., & Yilmaz, Y. (2011). A glance at the methods for detection of apoptosis qualitatively and quantitatively. Turk. J. *Bioch*, 36: 261-269.

Van Zee, K. J., White, J., Morrow, M., & Harris, J. (2014). Ductal carcinoma in situ and microinvasive carcinoma. In J. Harris, M. E. Lippman, M. Morrow, & C. K. Osborne (Eds.), *Diseases of the breast*, 5th edition (pp 337-359). Philadelphia, PA: Wolters Kluwer Health

Verma, S., Lavasani, S., Mackey, J., Pritchard, K., Clemons, M., Dent, S., Latreille, J., Lemieux, J., Provencher, L., & Verma, S. (2010). Optimizing the management of HER2-positive early breast cancer: the clinical reality. *Current Oncology*, 17(4): 20–33.

Vogel, Victor G, Costantino, Joseph P, Wickerham, D Lawrence, Cronin, Walter M, Cecchini, Reena S, Atkins, *et al*., (2006). Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. *Journal Jama*, 295(23): 2727-2741.

Wang, X., Du, Y., & Luo, J. (2008). Biopolymer/montmorillonite nanocomposite: preparation, drug-controlled release property and cytotoxicity. *Nanotechnology*, 19(6): 065707.

Wang, C., Chen, Y.G., Gao, J.L., Lyu, G.Y., Su, J., Zhang, Q.I., Ji, X., Yan, J.Z., Qiu, Q.L., Zhang, Y.L. and Li, L.Z. (2015). Low local blood perfusion, high white blood cell and high platelet count are associated with primary tumor growth and lung metastasis in a 4T1 mouse breast cancer metastasis model. *Oncology letters*, 10(2): 754-760.

Wang, J., Chen, J.-S., Zong, J.-Y., Zhao, D., Li, F., Zhuo, R.-X., & Cheng, S.-X. (2010a). Calcium carbonate/carboxymethyl chitosan hybrid microspheres and nanospheres for drug delivery. *The Journal of Physical Chemistry* C, 114(44): 18940-18945.

Wang, T., Petrenko, V. A., & Torchilin, V. P. (2010b). Paclitaxel-loaded polymeric micelles modified with MCF-7 cell-specific phage protein: enhanced binding to target cancer cells and increased cytotoxicity. *Molecular Pharmaceutics*, 7(4): 1007-1014.

Wang, W. (2015). *Changes of breast cancer growth and metastasis in murine models modulated by an aromatase inhibitor, a low calcium diet or a high fat diet*. (pp105). University of Illinois at Urbana-Champaign.

Waynforth, H. B. and Flecknell, P. A. (1992). *In Experimental and Surgical Technique in the Rat* (eds H. B. Waynforth and P. A. Flecknell), (pp1–67). Academic Press, London.

Weigelt, B., Peterse, J. L., & Van't Veer, L. J. (2005). Breast cancer metastasis: markers and models. *Nature reviews cancer*, 5(8): 591-602.

Wendy R, Sanhai, Sakamoto, Jason H, Canady, Richard, Ferrari, Mauro (2008). Seven challenges for nanomedicine. *Nature nanotechnology*, 3(5): 242-244.

Wiseman BS, Werb Z: Stromal effects on mammary gland development and breast cancer. (2002), *Science*, 296:1046-1049.

Woodard, G. (1965). *In Methods of Animal Experimentation* 343–359. Academic Press, New York.

Wyld, L., Gutteridge, E., Pinder, S.E., James, J.J., Chan, S.Y., Cheung, K.L., Robertson, J.F.R. and Evans, A.J., (2003). Prognostic factors for patients with hepatic metastases from breast cancer. *British journal of cancer,* 89(2):284.

Xu, P., Meng, Q., Sun, H., Yin, Q., Yu, H., Zhang, Z., & Li, Y. (2015). Shrapnel nanoparticles loading docetaxel inhibit metastasis and growth of breast cancer. *Biomaterials*, 64:10-20.

Xu, Z. P., Zeng, Q. H., Lu, G. Q., & Yu, A. B. (2006). Inorganic nanoparticles as carriers for efficient cellular delivery. *Chemical Engineering Scienc*e, 61(3): 1027-1040.

Yang W, Yao C, Cui Z, *et al*. (2016). (Poly (acrylic acid)-regulated synthesis of rod-like calcium carbonate nanoparticles for inducing the osteogenic differentiation of MC3T3-E1 cells. *Int J Mol Sci.*; 17 (11):639.

Yip, C. H., Taib, N., & Mohamed, I. (2006). Epidemiology of breast cancer in Malaysia. *Asian Pacific Journal of Cancer Prevention*, 7(3): 369.

Youm, I., Bazzil, J. D., Otto, J. W., Caruso, A. N., Murowchick, J. B., & Youan, B.-B. C. (2014). Influence of surface chemistry on cytotoxicity and cellular uptake of nanocapsules in breast cancer and phagocytic cells. *The AAPS journal,* 16(3): 550-567.

Yuan, Q., Han, J., Cong, W., Ge, Y., Ma, D., Dai, Z., Li, Y., & Bi, X. (2014). Docetaxel-loaded solid lipid nanoparticles suppress breast cancer cells growth with reduced myelosuppression toxicity.*International journal of nanomedicine,* 9: 4829.

Zahedi, P., De Souza, R., Piquette-Miller, M., & Allen, C. (2011). Docetaxel distribution following intraperitoneal administration in mice. *Journal of Pharmacy & Pharmaceutical Sciences,* 14(1): 90-99.

Zhang, L., & Zhang, N. (2013). How nanotechnology can enhance docetaxel therapy. *International journal of nanomedicine*, 8: 2927.

Zhang, Y., Ma, P., Wang, Y., Du, J., Zhou, Q., Zhu, Z., Yang, X., & Yuan, J... (2012). Biocompatibility of porous spherical calcium carbonate microparticles on hela cells. *World Journal of Nano Science and Engineering*, 2(01):25-31.

Zhao W, Brook M, Li Y. Design of gold nanoparticle based colorimetric biosensing assays. (2008), *ChemBioChem*, 9(15):2363–2371.

Zhao, M., Su, M., Lin, X., Luo, Y., He, H., CAI, C., & Tang, X. (2010). Evaluation of docetaxel-loaded intravenous lipid emulsion: pharmacokinetics, tissue distribution, antitumor activity, safety and toxicity. *Pharmaceutical Research,* 27(8): 1687-1702.

Zielinski, L Kettle. (2013). Physical Characterization: Surface Area and Porosity

Zijl, F., V., Krupitza, G., & Mikulits, W. (2011). Initial steps of metastasis: cell invasion and endothelial transmigration. *Mutation Research/Reviews in Mutation Research*, 728(1):23-34.

Zubair A.J, Zuki Abu Bakar Zakaria & Rozi Mahmud & Mohamad Yusof Loqman & Mohamad Noor Mohamad Hezmee *et al*., (2017). Safety assessments of subcutaneous doses of aragonite calcium carbonate nanocrystals in rats *J Nanopart Res* 19:175.