UNIVERSITI PUTRA MALAYSIA

INVOLVEMENT OF ENDOPLASMIC RETICULUM STRESS-INDUCED APOPTOTIC PATHWAY IN CERVICAL CANCER CELLS TREATED WITH CYTOTOXIC AGENTS

WAN NOR HAFIZA BINTI WAN ABD GHANI

FPSK(M) 2014 57

INVOLVEMENT OF ENDOPLASMIC RETICULUM STRESS-INDUCED APOPTOTIC PATHWAY IN CERVICAL CANCER CELLS TREATED WITH CYTOTOXIC AGENTS

WAN NOR HAFIZA BINTI WAN ABD GHANI

MASTER OF SCIENCE
UNIVERSITI PUTRA MALAYSIA

2014

INVOLVEMENT OF ENDOPLASMIC RETICULUM STRESS-INDUCED APOPTOTIC PATHWAY IN CERVICAL CANCER CELLS TREATED WITH CYTOTOXIC AGENTS

By

WAN NOR HAFIZA BINTI WAN ABD GHANI

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Master of Science

December 2014

In the Name of Allah, the Most Gracious, the Most Merciful

I would like to dedicate this thesis to my husband and parents who spare no effort and face all hardships in supporting me throughout my life.

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirements for the degree of Master of Science

INVOLVEMENT OF ENDOPLASMIC RETICULUM STRESS-INDUCED APOPTOTIC PATHWAY IN CERVICAL CANCER CELLS TREATED WITH CYTOTOXIC AGENTS

By

WAN NOR HAFIZA BINTI WAN ABD GHANI

December 2014

Chairman : Latifah Binti Saiful Yazan, PhD

Faculty : Medicine and Health Sciences

Cervical cancer is one of the most common cancer in women. Cisplatin is used to treat cervical cancer but it has adverse effects. Therefore, prediction of chemosensitivity or response towards any drug based on certain biomarkers is vital. Glucose regulated protein (GRP58) is predicted to become the potential biomarker or prognostic marker. This study investigated the response of human cervical cancer cells to cisplatin, thymoquinone (TQ), ethyl acetate and dichloromethane extracts of *Dillenia suffruticosa* root (EADS and DCMDS) based on the expression of GRP58 at gene and protein level which was measured by RT-qPCR and Western blot, respectively. The effects of EADS and DCMDS on the growth of HeLa and SiHa cervical cancer cell lines and expression of apoptotic-related genes and proteins were also investigated. Cytotoxicity was determined by MTT assay. The effects on cell cycle progression and mode of cell death of EADS were analyzed by flow cytometry technique. The effects on expression on apoptotic-related genes and proteins were evaluated by RT-qPCR, Western blot and ELISA, respectively. Cisplatin was more cytotoxic towards the cells than TQ in a dose-and time-dependent manner (P<0.05). However, cisplatin was more toxic to the normal cell lines 3T3 and Vero than TQ. Significant correlation was only found between cytotoxicity of cisplatin towards the cervical cancer cells and the expression of GRP58 (P<0.05). Therefore, the response of cervical cancer cells to cisplatin can be predicted on the basis of GRP58. Meanwhile, EADS and DCMDS were found to significantly (P<0.05) inhibit cell growth and proliferation of HeLa and SiHa. DCMDS was more cytotoxic towards the cells than EADS in a dose-and time-dependent manner. DCMDS caused downregulation of the expression of cyclin B_1 that led to G_2/M arrest in the cells. DCMDS induced apoptosis as evidenced by Annexin-V/FITC assay. DCMDS induced apoptosis in the cervical cancer cells via dysregulation of mitochondrial-mediated and ER stress-induced apoptotic pathways. DCMDS triggered the extrinsic apoptotic pathway via activation of caspase-8. Meanwhile, the intrinsic apoptotic

pathway was triggered upon activation of PARP-1, NF-κB, p53 and JNK. Increased expression of Bax, but decreased expression of Bcl-2 further enhanced the release of cytochrome C and increased in caspase-3 and -9 activities which ultimately led to apoptosis. DCMDS also upregulated ER stress genes chaperones *GRP78* and *CRT*; and ER transcription factors *CHOP/GADD153*, *XBP-1* and *ATF4.* Nevertheless, the level of GRP58 reduced in a dose-dependent manner. The number of apoptotic cells increased as the concentration of DCMDS increases. Thus, GRP58 might play a role in DCMDS-induced ER stress-induced apoptosis since other ER stress proteins were upregulated but only GRP58 level was downregulated. The data suggest the potential application of DCMDS in the treatment of cervical cancer.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

PENGLIBATAN LALUAN APOPTOSIS TERARUH OLEH TEKANAN ENDOPLASMIK RETIKULUM DALAM SEL KANSER SERVIKS DIRAWAT DENGAN AGEN SITOTOKSIK

Oleh

WAN NOR HAFIZA BINTI WAN ABD GHANI

Disember 2014

Pengerusi : Latifah Binti Saiful Yazan, PhD

Fakulti : Perubatan dan Sains Kesihatan

Kanser serviks merupakan salah satu jenis kanser yang paling biasa berlaku di kalangan wanita. Cisplatin digunakan untuk merawat kanser serviks tetapi mempunyai kesan sampingan yang buruk. Oleh itu, ramalan tindakbalas ubat-ubatan berdasarkan penanda bio tertentu adalah amat penting. *Glucose regulated protein* (GRP58) dijangka boleh menjadi potensi penanda bio atas penanda prognostik. Kajian ini menyiasat tindak balas jujukan sel kanser serviks manusia terhadap cisplatin dan timokuinon (TQ) daripada *Nigella sativa* dan ekstrak *ethyl acetate* dan *dichloromethane* daripada akar *Dillenia suffruticosa* (EADS dan DCMDS) berdasarkan ekspresi GRP58 pada peringkat gen dan protein yang diukur menggunakan RT-qPCR dan *Western blot*. Kesan rawatan EADS dan DCMDS ke atas pertumbuhan jujukan sel kanser serviks HeLa dan SiHa dan ekspresi gen dan protein yang berkaitan apoptosis turut disiasat. Sitotoksisiti telah ditentukan oleh asai MTT. Kesan ke atas kitaran sel dan kematian sel dianalisis dengan menggunakan teknik aliran sitometri manakala kesan rawatan ekstrak DCMDS terhadap gen dan protein yang berkaitan dengan apoptotis masing-masing telah diukur dengan menggunakan teknik RT-qPCR, Western blot dan ELISA. Cisplatin adalah lebih sitotoksik terhadap sel berbanding TQ dan ianya bergantung kepada dos dan masa (P<0.05). Cisplatin lebih toksik terhadap sel-sel normal 3T3 dan Vero berbanding TQ. Korelasi yang signifikan hanya didapati antara sitotoksisiti cisplatin terhadap jujukan sel kanser serviks dan aras GRP58 (P<0.05). Oleh itu, tindakbalas jujukan sel kanser serviks terhadap cisplatin boleh diramal berdasarkan GRP58. Sementara itu, EADS dan DCMDS menghalang pertumbuhan dan proliferasi HeLa dan Siha (P<0.05). DCMDS adalah lebih sitotoksik terhadap sel daripada EADS dan ianya bergantung kepada dos dan masa. DCMDS mengurangkan ekspresi *cyclin* B_1 yang membawa kepada penahanan G_2/M dalam sel. DCMDS mengaruh apoptosis seperti yang dibuktikan oleh asai *Annexin-V/FITC*. DCMDS mengaruh apoptosis dalam sel kanser serviks adalah melalui ketidakaturan mitokondria dan laluan apoptosis aruhan tekanan ER. DCMDS mengaktifkan laluan apoptosis ekstrinsik melalui caspase-8.

Sementara itu, laluan apoptosis intrinsik diaktifkan oleh molekul PARP-1, NF-κB, p53 and JNK. Peningkatan ekspresi Bax dan penurunan ekspresi Bcl-2 seterusnya meningkatkan pembebasan sitokrom C dan aktiviti *caspase-3* dan *caspase-9* yang membawa kepada apoptosis. DCMDS juga meningkatkan gen tekanan ER iaitu *chaperonesGRP78* dan *CRT*, dan faktor transkripsi ER *CHOP/GADD153*, *XBP-1* and *ATF4.* Walau bagaimanapun, aras GRP58 menurun apabila dos meningkat. Jumlah sel apoptotik meningkat dengan peningkatan kepekatan DCMDS. Oleh itu,GRP58 berkemungkinan memainkan peranan dalam laluan apoptosis teraruh tekanan ER oleh DCMDS memandangkan aras protein tekanan ER yang lain meningkat tetapi hanya aras GRP58 sahaja yang menurun. Data mencadangkan potensi aplikasi DCMDS dalam rawatan kanser serviks.

ACKNOWLEDGEMENTS

First of all, I would like to express my deepest gratitude to Allah s.w.t for providing me the blessings to complete this research. I would also like to wish my sincere appreciation to my supervisor, Assoc. Prof. Dr. Latifah Saiful Yazan, for her guidance, continuous support, and for the generous gift of her time throughout this project. I am truly and deeply indebted to her ceaseless efforts to educate me as a postgraduate candidate and for her expert advice. I am very grateful to my co-supervisor Dr. Huzwah Khaza'ai for her willingness to lend her intellectual advice, knowledge and encouragementwhen necessary. The contribution of Datin Dr. Fauziah Kassim who was co-advising me in the cervical cancer part is duly acknowledged. Great thanks for her scientific advice and comments. This work would not have been possible without their assistance.

My countless appreciation go to all staff of the Laboratory of Vaccines and Immunotherapeutics, the Laboratory of Molecular Biomedicine and the Laboratory of Cancer Research UPM-MAKNA, Institute of Bioscience, Universiti Putra Malaysia for their technical expertise, guidance and assistance throughout my research project and kindly allowing me to access to the facilities. I am also very grateful to all my colleagues at IBS, past and present (especially Tor Yin Sim, Foo Jhi Biau, Ng Wei Keat and Armania Nurdin), too many to list, for their technical assistance and made my work in the lab more enjoyable.

The most precious help during my study came from my beloved husband, Dr. Muhamad Hafizi Sulaiman. He had been very supportive and patient especially during my difficult times completing this study. I would not have gotten this far without his help. Last but by no means least; special thanks go to my family, especially my parents, Mr. Wan Abd Ghani Wan Ismail and Mrs. Nik Mah Nik Yusoff for their love, care and continuous encouragement throughout my life.

I certify that a Thesis Examination Committee has met on 23rd December 2014 of to conduct the final examination of Wan Nor Hafiza Binti Wan Abd Ghani on her thesis entitled 'Involvement of Endoplasmic Reticulum Stress-Induced Apoptotic Pathway in Cervical Cancer Cells Treated With Cytotoxic Agents'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 Master of Science.

Members of the Thesis Examination Committee were as follows:

Mohd Nasir bin Mohd Desa, PhD
Associate Professor,
Faculty of Medicine and Health Sciences,
Universiti Putra Malaysia
(Chairman)

Sabrina bt Sukardi, PhD
Associate Professor,
Faculty of Medicine and Health Sciences,
Universiti Putra Malaysia
(Internal Examiner)

Norhafizah binti Mohtarrudin, PhD
Lecturer,
Faculty of Medicine and Health Sciences,
Universiti Putra Malaysia
(Internal Examiner)

Shar Mariam Mohamed, PhD
Associate Professor,
Human Biology Department,
International Medical University,
Malaysia
(External Examiner)

ZULKARNAIN ZAINAL, PhD
Professor and Deputy Dean
School of Graduate Studies
Universiti Putra Malaysia

Date:

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

Latifah Binti Saiful Yazan, PhD
Associate Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Chairman)

Huzwah Binti Khaza'ai, PhD
Lecturer
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

Datin Fauziah Binti Kassim, MBBS
Consultant Pathologist
Department of Pathology
Hospital Kuala Lumpur
(Member)

BUJANG KIM HUAT, PhD
Professor and Dean
School of Graduate Studies
Universiti Putra Malaysia

Date:

Declaration by Graduate Student

I hereby confirm that:

- This thesis is my original work
- Quotations, illustrations and citations have been duly referenced;
- This thesis has not been submitted previously or concurrently for any other degree at any other institutions;
- Intellectual property fron the thesis and copyright of thesis are fully-owned by Universiti Putra Malaysia, as according to the Universiti Putra Malaysia (Research) Rules 2012;
- Written permission must be obtained from supervisor and the office of Deputy Vice-Chancellor (Research and Innovation) before thesis is published (in the written, printed or in electronic form) including books, journals, modules, proceedings, popular writings, seminar papers, manuscripts, posters, reports, lecture notes, learning modules or any other materials as stated in the Universiti Putra Malaysia (Research) Rules 2012;
- The is no plagiarism or data falsification/ fabrication in the thesis, and scholarly integrity is upheld as according to the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) and the Universiti Putra Malaysia (Research) Rules 2012. The thesis has undergone plagiarism detection software.

Signature: _____ Date:_____

Name and Matric No: Wan Nor Hafiza Binti Wan Abd Ghani (GS31982)

Declaration by Members of Supervisory Committee

This is to confirm that:

- The research conducted and the writing of this thesis was under our supervision;
- Supervision responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) are adhered to.

Signature: _____
Name of Chairman of Supervisory Committee: Latifah Saiful Yazan

Signature: _____
Name of Member of Supervisory Committee: Huzwah Binti Khaza'ai

Signature: _____
Name of Member of Supervisory Committee: Fauziah binti Kassim

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

5-FU	5-fluorouracil
AGC	Atypical glandular cells
AIF	Apoptosis-inducing factor
AIS	Adenocarcinoma *in situ*
ASC-H	Atypical squamous cell of undetermined significance-cannot exclude HSIL
ASC-US	Atypical squamous cell of undetermined significance
ASK1	Apoptosis signal regulating kinase 1
ATF6	Activating transcription factor-6
ATM	Ataxia-telangiectasia mutated
ATR	Ataxia telangiectasia mutated and Rad3 related
Bad	Bcl-2 antagonist of cell death
Bak	Bcl-2 homologous killer
Bax	Bcl-2 associated X
Bcl-2	B-cell lymphoma 2
BIM	Bcl-2 interacting protein
Bim	BH3-only protein
CA125	Carbohydrate antigen 125
CAD	Caspase-activated deoxyribonuclease
Caspase	Cysteinyl aspartic acid-protease
cdk	Cyclin dependent kinase
CEA	Carcinoembryonic antigen
CHOP	CCAAT-enhancer binding protein (C/EBP) homologous protein transcription factor
CKI	Cyclin-dependent kinase inhibitor
CNX	Calnexin
CRT	Calreticulin
CTLS	Cytotoxic T lymphocytes
DISC	Death-inducing signaling complex
DRG	Drug response gene
Elf2	Initiation factor 2 alpha
ER	Endoplasmic reticulum
FADD	Fas-associated death domain protein
FasL	Fatty acid synthetase receptor
GADD153	Growth-arrest and DNA-damage-inducible gene 153
GRP58	Glucose-regulated protein 58-kDa
GRP78	Glucose-regulated protein 78-kDa
HPV	Human papilloma virus
HSIL	High grade squamous intraepithelial lesion
HSV-2	Herpes simplex virus-2
IRE1	Inositol-requiring protein-1
JAK	Janus-activated kinase
JIK	c-Jun NH2-terminal inhibitory kinase
JNK	c-Jun N-terminal protein kinase
LBC	Liquid-based cytology
LEEP	Loop electrosurgical excision procedure
LLETZ	Large loop excision of the transformation zone
LSIL	Low grade squamous intraepithelial lesion

MAPK	Mitogen-activated protein kinase
MHC1	Major histocompatibility complex 1
MOMP	Mitochondrial outer membrane permeabilization
mTOR1	Mammalian target of rapamycin 1
NF-kB	Necrocis factor-kB
Oligo-dT	Oligodeoxythymidylic acid
P13K/Akt	Phosphatidylinositol-3-kinase/Akt (protein kinase B)
PAR	Poly(ADP-ribose)
PARP-1	Poly(ADP-ribose) polymerase 1
PCNA	Proliferating cell nuclear antigen
PDIA3	Protein disulfide isomerase associated 3
PERK	Protein kinase RNA (PKR)-like ER kinase
PKC	Protein kinase C
PKR	Protein kinase R
PLK-1	Polo-like kinase 1
PMSF	Phenylmethanesulfonylfluoride
PUMA	p53 up-regulated modulator of apoptosis
RIP	Receptor-interacting protein
ROS	Reactive oxygen species
SCC	Squamous cell carcinoma
SCC-Ag	Squamous cell carcinoma antigen
sIL-2R	Interleukin-2 receptor
STAT3	Signal transducer and activator of transcription 3
TATI	Tumor-associated trypsin inhibitor
TF	Transcription factor
TNF	Tumor necrosis factor receptor
TRADD	NF receptor-associated death domain protein
TRAF	TNF receptor-associated factor 2
Tu M2-PK	Pyruvate kinase isoenzyme tumor
VEGF	Vascular endothelial growth factor
VIA	Visual inspection with acetic acid
VLPS	Virus-liked particles
XBP-1	X-box-binding protein 1

CHAPTER 1

INTRODUCTION

Carcinoma of the cervix is the second most common gynecological cancer after breast cancer (Ferlay *et al*., 2013). In Malaysia, cervical cancer was the third most common cancer among women after breast and colorectal cancer. Current clinical scenario in the management of cervical cancer would significantly improve by discovering appropriate biomarkers that can predict the cancer formation and progression. It is also vital for the evaluation of prognosis in cervical cancer patients especially on the choice of treatment or drugs. At present, *cis*-diamminedichloroplatinum II (cisplatin) is the single active chemotherapeutic agent used to treat patients that have been diagnosed with cervical cancer (Rose *et al.*, 2012). Despite the effectiveness, there are serious side effects associated with cisplatin, notably nausea and vomiting, emesis, renal toxicity, bone marrow suppression, neurotoxicity and hearing loss (Kong *et al*., 2012; Rose *et al.*, 2012; Long *et al*., 2005). Prediction of chemosensitivity before decision on the treatment should be given to certain individual, who is most likely to benefit from this drug is particularly challenging and vital to avoid or minimize any harmful effects.

One of the protein molecules that may be used as a potential marker in predicting the response of cervical cancer cells towards cisplatin is thiol-disulfide oxidoreductase, glucose-regulated protein 58 kDa (GRP58/ Erp57/ ER60/ PDIA3/ ERp60/ ERp61/ P58/ Q2/ HIP-70). Studies reported that GRP58 modulated invasiveness of cervical cancer (Liao *et al*., 2011). Downregulation of GRP58 was associated with poor prognosis in early stage of cervical cancer (Chung *et al*., 2013). Knock-down of GRP58 in HeLa cells led to decreased tumour invasiveness and inhibition of lung metastasis in a xenograft mouse model (Liao *et al*., 2011). In addition, knock-down of GRP58 was also associated with inhibition of proliferation of breast cancer cells (Lwin *et al*., 2012) and melanoma cells (Corazzari *et al*., 2007). There was evidence showing that cisplatin exerted antitumor activity in cancer cells via nucleus-independent activation of caspase-12 and upregulation of the hallmark of ER stress molecule, GRP78 (Mandic *et al*., 2003). Therefore, it is speculated that cytotoxicity of cisplatin is influenced by the level of GRP58 expression.

Although there is a potential for further reducing the occurrence of cervical cancer with approved vaccination programs by Gardasil and Cervarix against the human papillomavirus (HPV), the vaccines do not confer full protection against all HPV infections and HPV-related cancers; specifically that cause cervical cancer (Nayereh and Khadem, 2012; Tovar *et al*., 2008). Even though cervical cancer screening by Pap smear tests either conventional or liquid-based cytology (LBC) method have been shown to successfully reduce the incidence in Western countries (Denny *et al*., 2006; Gustafsson *et al*., 1997), the incidence and mortality rate of cervical cancer in the second and third world countries are still high due to inefficient screening program (Ferlay *et al*., 2013). This warrants the need to search for a better anticancer agent to treat cervical cancer.

Currently, the use of natural products to treat cervical cancer has been in demand. Many research focusing on herbal extracts that are believed to have less side effects. In fact, approximately 60% of anticancer drugs originated either from natural

products or natural products derived (Cragg and Newman, 2005). A few drugs that have been approved as the anticancer agents are doxorubicin from bacteria *Streptomyces peucetius* var. Caesius (Lomovskaya *et al*., 1999), paclitaxel from plant *Taxus brevifolia* (Witherup *et al*., 1990) and topotecan from plant *Camptotheca acuminata* **(**Newman and Cragg, 2012; Kusari*et al*., 2009**).**

Previous reports have shown that the active constituent of *Nigella sativa* i.e thymoquinone (TQ), has anticancer properties. TQ inhibited the proliferation of lung cancer, breast cancer, colon cancer, melanoma (Attoub *et al*., 2013; Woo *et al*., 2011), liver cancer (Raghunandhakumar *et al*., 2013), neuroblastoma (Paramasivam *et al*., 2012), oral cancer (Abdelfadil *et al*., 2013) and cervical cancer cells with minimal toxicity towards the normal cells (Latifah *et al*., 2009; Ng *et al*., 2011). Based on that, TQ was selected in this study.

Dillenia suffruticosa (Griffith ex Hook. F. & Thomson) Martelli (*Wormia suffruticosa*/ *Borneensis ridl*/ *Wormia burbidgei*/ *Wormia subsessilis*) was another potential candidate used in this study. This plant has been traditionally used totreat the growth of cancer (Armania *et al*., 2013a; Armania *et al*., 2013b; Ahmad and Holdsworth, 1995). Dichloromethane (DCMDS) and ethyl acetate (EADS) extract of the root of *D. suffruticosa* were found to be cytotoxic towards HeLa, MCF-7, MDA-MB- 231, A549 and HT29 human cancer cell lines. The toxicity may be due to the presence of saponins, triterpenes, sterols and polyphenolic compounds in the extract. DCMDS induced cell cycle arrest and apoptosis in cervical cancer and breast cancer cells (Tor *et al.,* 2014; Armania *et al*., 2013a; Armania *et al*., 2013b).

Apoptosis or programmed cell death is distinguished from necrosis by definite morphological and biochemical features (Kuznetsov *et al*., 2004; Hickman, 1992). There are two main apoptotic pathways: the extrinsic or death receptor pathway and the intrinsic pathway as well as an additional pathway that involves T-cell mediated cytotoxicity and perforin-granzyme-dependent killing of the cell (Elmore, 2007). The intrinsic signaling pathway is a mitochondrial or/and endoplasmic reticulum (ER)-triggered event. These three pathways converge on an execution pathway. This pathway affects biochemical changes including cleavage of protein and DNA degradation that result in cytomorphological changes such as cell shrinkage, karyopiknosis, cytoplasmic blebbing and formation of apoptotic bodies. Finally, the apoptotic bodies are phagocytosed by phagocytic cells (Savill and Fadok, 2000). Targeting apoptosis is important because cancer is a disease where too little apoptosis occurs, resulting in malignant cells keeping on growing and proliferating (Wong, 2011). Thus, anticancer agents with the ability to induce **apoptosis** are of preference as they can **stop** the continual **growth** of **cancerous cells.**

1.1 Problem Statement

Besides various adverse and side effects, treatment of cervical cancer with cisplatin also leads to a response that is highly heterogeneous (Xiong *et al*., 2011). Some patients may respond well whereas others with histologically identical disease are resistant to the same treatment. The treatment was often unsuccessful due to development of chemoresistance.Therefore, the analysis of expression of a potential tumour marker (GRP58 in this study) in response to the treatment with any anticancer agents needs to be established. It is hoped that the response towards cisplatin in patients of different stages of cervical cancer can be predicted. On that

note, for those patients who are resistant towards cisplatin, other drugs can be considered to help to minimise the adverse effects of cisplatin.

Thymoquinone and extracts of *D. suffruticosa* could be the potential candidates for management of cervical cancer. In this study, the mechanisms underlying their cytotoxicity towards cervical cancer cells was the major focus.

1.2 Objectives

In general, this study was divided into Part I and Part II.

a) Part I

General objective:

To determine the response of human cervical cancer cells to cisplatin and thymoquinone based on the expression level of GRP58

Specific objective:

1. To determine the expression level of GRP58 in HeLa and SiHa cells upon cisplatin and thymoquinone treatment
2. To analyse the association between the expression level of GRP58 in HeLa and SiHa cells and their respective IC50

b) Part II

General objective:

To determine the cytotoxic effects of ethyl acetate (EADS) and dichloromethane (DCMDS) extract of root of D. suffruticosa towards human cervical cancer cell lines, HeLa and SiHa

Specific objectives:

1. To determine and compare the cytotoxicity of EADS and DCMDS towards the human cervical cancer cell lines
2. To determine the mode of cell death induced by EADS and DCMDS in the human cervical cancer cell lines
3. To determine the effects of DCMDS on cell cycle progression in the human cervical cancer cell lines
4. To evaluate the expression of apoptotic-related proteins (GRP58 and other endoplasmic reticulum stress proteins) in the human cervical cancer cell lines following treatment with DCMDS

1.3 Hypotheses

a) Part I

1. The expression level of GRP58 in HeLa and SiHa cells will decrease upon cisplatin and thymoquinone treatment
2. There will be an association between the expression level of GRP58 in HeLa and SiHa cells and their respective IC_{50} following cisplatin and thymoquinone treatment

b) Part II

1. There will be differences between the cytotoxicity of EADS and DCMDS towards the human cervical cancer cell lines

2. EADS/DCMDS will induce apoptosis in the human cervical cancer cell lines
3. EADS/DCMDS will cause cell cycle arrest in the human cervical cancer cell lines
4. EADS/DCMDS will downregulate/upregulate the expression of apoptotic-related proteins (GRP58 and other endoplasmic reticulum stress proteins) in the human cervical cancer cell lines after the treatment

REFERENCES

Abdelfadil, E., Cheng, Y. H., Bau, D. T., Ting, W. J., Chen, L. M., Hsu, H. H., *et al*. (2013). Thymoquinone induces apoptosis in oral cancer cells through p38beta inhibition. *American Journal of Chinese Medicine.* 41(3): 683-696.

Abdille, M. H., Singh, R. P., Jayaprakasha, G. K., & Jena, B. S. (2005). Antioxidant activity of the extracts from *Dillenia indica* fruits. *Food Chemistry.* 90(4): 891-896.

About cervical cancer: the cervix, Cancer Research UK, London,http://www.cancerresearchuk.org. Retrieved 29th July 2013.

Abraham, A. G., D'Souza, G., Jing, Y., Gange, S. J., Sterling, T. R., Silverberg, M. J., *et al.* (2013). Invasive cervical cancer risk among HIV-infected women: a North American multicohort collaboration prospective study. *Journal of Acquired Immune Deficiency Syndromes.* 62(4): 405-413.

Achavanuntakul, K., & Charoenkwan, K. (2012). Factors affecting operative blood loss from open radical hysterectomy and pelvic lymphadenectomy for early-stage cervical cancer. *Archives of Gynecology and Obstetrics.* 286(4): 1001-1005.

Agarwal, S., Mathur, M., Shukla, N. K., & Ralhan, R. (1998). Expression of cyclin dependent kinase inhibitor p21waf1/cip1 in premalignant and malignant oral lesions: relationship with p53 status. *Oral Oncology.* 34(5): 353-360.

Ahmad, F. B., & Holdsworth, D. K. (1995). Traditional medicinal plants of Sabah, Malaysia. Part III. The Rungus people of Kudat. *International Journal of Pharmacognosy.* 33(3): 262-264.

Ahmad, M., Srinivasula, S. M., Hegde, R., Mukattash, R., Fernandes-Alnemri, T., & Alnemri, E. S. (1998). Identification and characterization of murine caspase-14, a new member of the caspase family. *Cancer Research.* 58(22): 5201-5205.

Alanen, H. I., Salo, K. E., Pekkala, M., Siekkinen, H. M., Pirneskoski, A., & Ruddock, L. W. (2003). Defining the domain boundaries of the human protein disulfide isomerases. *Antioxidant Redox Signaling.* 5(4): 367-374.

Alberts, B., Johnson, A., & Lewis, J. (2002). *Molecular Biology of the Cell* (4th edition). New York: Garland Science.

Alberts, D. S., Garcia, D., & Mason-Liddil, N. (1991). Cisplatin in advanced cancer of the cervix: an update. *Seminars in Oncology.* 18(1 Suppl 3): 11-24.

Alsbeih, G., Al-Harbi, N., El-Sebaie, M., & Al-Badawi, I. (2013). HPV prevalence and genetic predisposition to cervical cancer in Saudi Arabia. *Infectious Agents and Cancer.* 8(1): 15.

Al-Shabanah, O. A., Badary, O. A., Nagi, M. N., al-Gharably, N. M., al-Rikabi, A. C., & al-Bekairi, A. M. (1998). Thymoquinone protects against doxorubicin-induced cardiotoxicity without compromising its antitumor activity. *Journal of Experimental & Clinical Cancer Research.* 17(2): 193-198.

Andikyan, V., Khoury-Collado, F., Denesopolis, J., Park, K. J., Hussein, Y. R., Brown, C. L., *et al.* (2014). Cervical conization and sentinel lymph node mapping in the treatment of stage I cervical cancer: is less enough? *International Journal of Gynecological Cancer.* 24(1): 113-117.

Arbyn, M., Anttila, A., Jordan, J., Ronco, G., Schenck, U., Segnan, N., et al. (2010). European guidelines for quality assurance in cervical cancer screening. Second edition--summary document. *Annal Oncology.* 21(3): 448-458.

Arima, Y., Hirota, T., Bronner, C., Mousli, M., Fujiwara, T., Niwa, S., *et al.* (2004). Down-regulation of nuclear protein ICBP90 by p53/p21Cip1/WAF1-dependent DNA-damage checkpoint signals contributes to cell cycle arrest at G_1/S transition. *Genes to Cells.* 9(2): 131-142.

Armania, N., Latifah, S. Y., Ismail, I. S., Foo, J. B., Tor, Y. S., Ishak, N., *et al.* (2013a). *Dillenia suffruticosa* extract inhibits proliferation of human breast cancer cell lines (MCF-7 and MDA-MB-231) via induction of G2/M arrest and apoptosis. *Molecules.* 18(11): 13320-13339.

Armania, N., Latifah, S. Y., Musa, S. N., Ismail, I. S., Foo, J. B., Wei, C. K., *et al.* (2013b). *Dillenia suffruticosa* exhibited antioxidant and cytotoxic activity through induction of apoptosis and G(2)/M cell cycle arrest. *Journal of Ethnopharmacology.* 14 (2): 525-535.

Arya, M., Shergill, I.S., Williamson, M., Gommersall, L., Arya, N., &Patel, H.R. (2005). Basic principles of real-time quantitative PCR. *Expert Review in Molecular Diagnostic*. 5(2):209-19.

Ashkenazi, A., & Dixit, V. M. (1998). Death receptors: signaling and modulation. *Science.* 281(5381): 1305-1308.

Attoub, S., Sperandio, O., Raza, H., Arafat, K., Al-Salam, S., Al Sultan, M. A., *et al.* (2013). Thymoquinone as an anticancer agent: evidence from inhibition of cancer cells viability and invasion *in vitro* and tumor growth *in vivo*. *Fundamental & Clinical Pharmacology.* 27(5): 557-569.

Autier, P., Coibion, M., Huet, F., & Grivegnee, A. R. (1996). Transformation zone location and intraepithelial neoplasia of the cervix uteri. *British Journal of Cancer.* 74(3): 488-490.

Ayshamgul, H., Ma, H., Ilyar, S., Zhang, L. W., & Abulizi, A. (2011). Association of the chaperone glucose-regulated protein 58 (GRP58/ER-60/ERp57) with Stat3 in cytosol and plasma membrane complexes. *Journal of Interferon & Cytokine Research*. 22: 555-563.

Bacso, Z., Everson, R.B. & Eliason, J.F. (2000). The DNA of Annexin V-binding apoptotic cells is highly fragmented. *Cancer Research*. 60:4623–4628.

Bae, J. H., Lee, S. J., Lee, A., Park, Y. G., Bae, S. N., Park, J. S., & Namkoong, S. E. (2008). Neoadjuvant cisplatin and etoposide followed by radical hysterectomy for stage 1B-2B cervical cancer. *Gynecology Oncology,* 111(3): 444-448.

Bae, J. H., Lee, S. J., Lee, A., Park, Y. G., Bae, S. N., Park, J. S., *et al.* (2013). Effectiveness of thymoquinone in the treatment of experimental asthma. *Clinica Terapeutica*. 164 (3): 155-158.

Bai, H., Sung, C. J., & Steinhoff, M. M. (2000). ThinPrep Pap Test promotes detection of glandular lesions of the endocervix. *Diagnostic Cytopathology.* 23(1): 19-22.

Bajt, M. L., Cover, C., Lemasters, J. J., & Jaeschke, H. (2006). Nuclear translocation of endonuclease G and apoptosis-inducing factor during acetaminophen-induced liver cell injury. *Journal of Toxicological Sciences.* 94(1): 217-225.

Balunas, M. J., & Kinghorn, A. D. (2005). Drug discovery from medicinal plants. *Life Sciences.* 78(5): 431-441.

Banerjee, S., Wang, Z., Kong, D., & Sarkar, F. H. (2009). 3,3'-Diindolylmethane enhances chemosensitivity of multiple chemotherapeutic agents in pancreatic cancer. *Cancer Research,* 69(13): 5592-5600.

Barry, M., & Bleackley, R. C. (2002). Cytotoxic T lymphocytes: all roads lead to death. *Nature Review of Immunology.* 2(6): 401-409.

Basic, E., Kozaric, H., Kozaric, M., & Suko, A. (2010). Conization as treatment of choice for precancerous changes and university cervical cancer at the Department of Obstetrics and Gynecology of Clinical Center of Sarajevo University in 2009. *Medical Arhives.* 64(3): 171-174.

Beale, P. J., Rogers, P., Boxall, F., Sharp, S. Y., & Kelland, L. R. (2000). BCL-2 family protein expression and platinum drug resistance in ovarian carcinoma. *British Journal of Cancer.* 82(2): 436-440.

Bedard, K., Szabo, E., Michalak, M., & Opas, M. (2005). Cellular functions of endoplasmic reticulum chaperones calreticulin, calnexin, and ERp57. *International Review of Cytology.* 245: 91-121.

Beresford, P. J., Zhang, D., Oh, D. Y., Fan, Z., Greer, E. L., Russo, M. L., *et al.* (2001). Granzyme A activates an endoplasmic reticulum-associated caspase-independent nuclease to induce single-stranded DNA nicks. *Journal of Biological Chemistry.* 276(46): 43285-43293.

Bernardini, M., Lee, C. H., Beheshti, B., Prasad, M., Albert, M., Marrano, P., *et al.* (2005). High-resolution mapping of genomic imbalance and identification of gene expression profiles associated with differential chemotherapy response in serous epithelial ovarian cancer. *Neoplasia,* 7(6): 603-613.

Bhakuni, D. S., Dhar, M. L., Dhar, M. M., Dhawan, B. N., & Mehrotra, B. N. (1969). Screening of Indian plants for biological activity. II. *Indian Journal of Experimental Biology.* 7(4): 250-262.

Boonlikit, S., & Thitisagulwong, S. (2012). C-LETZ versus large loop excision of the transformation zone for the treatment of cervical intraepithelial neoplasia: a randomized controlled trial. *Archives of Gynecology & Obstetric.* 286(5): 1173-1179.

Bosch, F. X., Lorincz, A., Munoz, N., Meijer, C. J., & Shah, K. V. (2002). The causal relation between human papillomavirus and cervical cancer. *Journal of Clinical Pathology.* 55(4): 244-265.

Bradford, M. M. (1976). A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. *Analytical Biochemistry.* 72: 248-254.

Bragado, P., Armesilla, A., Silva, A., & Porras, A. (2007). Apoptosis by cisplatin requires p53 mediated p38alpha MAPK activation through ROS generation. *Apoptosis.* 12(9): 1733-1742.

Bratton, D. L., Fadok, V. A., Richter, D. A., Kailey, J. M., Guthrie, L. A., & Henson, P. M. (1997). Appearance of phosphatidylserine on apoptotic cells requires calcium-mediated nonspecific flip-flop and is enhanced by loss of the aminophospholipid translocase. *Journal of Biological Chemistry.* 272(42): 26159-26165.

Brimer, N., & Vande Pol, S. B. (2014). Papillomavirus E6 PDZ interactions can be replaced by repression of p53 to promote episomal human papillomavirus genome maintenance. *Journal of Virology.* 88(5): 3027-3030.

Broderick, R., Rainey, M. D., Santocanale, C., & Nasheuer, H. P. (2013). Cell cycle-dependent formation of Cdc45-Claspin complexes in human cells is compromized by UV-mediated DNA damage. *Federation of European Biochemical Societies Journal.* 280(19): 4888-4902.

Brunner, T., & Mueller, C. (2003). Apoptosis in disease: about shortage and excess. *Essays Biochemistry,* 39: 119-130.

Brymora, A., Duggin, I. G., Berven, L. A., van Dam, E. M., Roufogalis, B. D., & Robinson, P. J. (2012). Identification and characterisation of the RalA-ERp57 interaction: evidence for GDI activity of ERp57. *PLoS One.* 7(11): e50879.

Buchsbaum, H. J. (1979). Extrapelvic lymph node metastases in cervical carcinoma. *American Journal of Obstetrics & Gynecology.* 133(7): 814-824.

Budanov, A.V., Sablina, A.A., Feinstein, E. Koonin, E.V., & Chumakov, P.M. (2004). Regeneration of peroxiredoxins by p53-regulated sestrins, homologs of bacterial AhpD. *Science*.304: 596–600.

Buxton, E. J., Meanwell, C. A., Hilton, C., Mould, J. J., Spooner, D., Chetiyawardana, A., *et al.* (1989). Combination bleomycin, ifosfamide, and cisplatin chemotherapy in cervical cancer. *Journal of the National Cancer Institute.* 81(5): 359-361.

Byock, I. (2000). Completing the continuum of cancer care: integrating life-prolongation and palliation. *Cancer Journal for Clinicians.* 50(2): 123-132.

Cai, Z., Brunmark, A. B., Luxembourg, A. T., Garcia, K. C., Degano, M., Teyton, L., *et al.* (1998). Probing the activation requirements for naive CD8+ T cells with Drosophila cell transfectants as antigen presenting cells. *Immunology Review,* 165: 249-265.

Cao, G., Pei, W., Lan, J., Stetler, R. A., Luo, Y., Nagayama, T., *et al.* (2001). Caspase-activated DNase/DNA fragmentation factor 40 mediates apoptotic DNA fragmentation in transient cerebral ischemia and in neuronal cultures. *Journal of Neuroscience.* 21(13): 4678-4690.

Casimiro, M. C., Crosariol, M., Loro, E., Li, Z., & Pestell, R. G. (2012). Cyclins and cell cycle control in cancer and disease. *Genes Cancer.* 3(11-12): 649-657.

Castellsague, X., & Munoz, N. (2003). Chapter 3: Cofactors in human papillomavirus carcinogenesis--role of parity, oral contraceptives, and tobacco smoking. *Journal of National Cancer Institute Monographs,* 31: 20-28.

Castle, P. E., Stoler, M. H., Solomon, D., & Schiffman, M. (2007). The relationship of community biopsy-diagnosed cervical intraepithelial neoplasia grade 2 to the quality control pathology-reviewed diagnoses: an ALTS report. *American Journal of Clinical Pathology.* 127(5): 805-815.

Catlett-Falcone, R., Landowski, T. H., Oshiro, M. M., Turkson, J., Levitzki, A., Savino, R., *et al.* (1999). Constitutive activation of Stat3 signaling confers resistance to apoptosis in human U266 myeloma cells. *Immunity.* 10(1): 105-115.

Cazanave, S. C., Elmi, N. A., Akazawa, Y., Bronk, S. F., Mott, J. L., & Gores, G. J. (2010). CHOP and AP-1 cooperatively mediate PUMA expression during lipoapoptosis. *American Journal of Physiology-Gastrointestinal and Liver Physiology.* 299(1): 236-243.

Celli, C. M., & Jaiswal, A. K. (2003). Role of GRP58 in mitomycin C-induced DNA cross-linking. *Cancer Research.* 63(18): 6016-6025.

Chan, D. W., & Schwartz, M. (2002). Tumor markers: Introduction and general principles. *Tumor Markers: Physiology, Pathobiology, Technology, and Clinical Applications*. 9-18. Washington, D. C.: AACC Press.

Chan, P. G., Sung, H. Y., & Sawaya, G. F. (2003). Changes in cervical cancer incidence after three decades of screening US women less than 30 years old. *Obstetrics & Gynaecology.* 102(4): 765-773.

Chang, A. Y., Lopes, G., Hsin, K. W., Lim, R., Fong, F. K., & Wong, J. (2007). Phase II trial of 5-fluorouracil/leucovorin/gemcitabine/cisplatin as second-line treatment in patients with metastatic or recurrent colorectal carcinoma: a cancer therapeutics research group study. *Clinical Colorectal Cancer.* 6(9): 646-651.

Chao, D. T., & Korsmeyer, S. J. (1998). Bcl-2 family: regulators of cell death. *Annual Review of Immunology.* 16(1): 395-419.

Chase, D. M., Kalouyan, M., & DiSaia, P. J. (2009). Colposcopy to evaluate abnormal cervical cytology in 2008. *American Journal of Obstetric and Gynecology.* 200(5): 472-480.

Chay, D., Cho, H., Lim, B. J., Kang, E. S., Oh, Y. J., Choi, S. M., *et al.* (2010). ER-60 (PDIA3) is highly expressed in a newly established serous ovarian cancer cell line, YDOV-139. *International Journal of Oncology,* 37(2): 399-412.

Chay, D., Cho, H., Lim, B. J., Kang, E. S., Oh, Y. J., Choi, S. M., *et al.* (2009). Anti-inflammatory effects of the *Nigella sativa* seed extract, thymoquinone, in pancreatic cancer cells. ***Oxford*** *Hepato-Pancreato-Biliary (**HPB**).* 11(5): 373-381.

Chemical structure of thymoquinone. Sigma-Aldrich Co. LLC, http://www.sigmaaldrich.com/catalog/product/aldrich/274666. Retrieved 12th May, 2013.

Chen, C. Y., Hsu, H. C., Lee, A. S., Tang, D., Chow, L. P., Yang, C. Y., *et al.* (2012). The most negatively charged low-density lipoprotein L5 induces stress pathways in vascular endothelial cells. *Journal of Vascular Research.* 49(4): 329-341.

Chen, J., Lobachev, K. S., Grindel, B. J., Farach-Carson, M. C., Hyzy, S. L., El-Baradie, K. B., *et al*. (2013). Chaperone properties of pdia3 participate in rapid membrane actions of 1alpha,25-dihydroxyvitamin d3. *Molecular Endocrinology.* 27(7): 1065-1077.

Chen, J., Macdonald, O. K., & Gaffney, D. K. (2008). Incidence, mortality, and prognostic factors of small cell carcinoma of the cervix. *Obstetrics & Gynecology.* 111(6): 1394-1402.

Chen, J., Olivares-Navarrete, R., Wang, Y., Herman, T. R., Boyan, B. D., & Schwartz, Z. (2010). Protein-disulfide isomerase-associated 3 (Pdia3) mediates the membrane response to 1,25-dihydroxyvitamin D3 in osteoblasts. *Journal of Biological Chemistry.* 285(47): 37041-37050.

Chen, X. J., Song, Y. Y., Cai, L. Z., Du, K. H., Lin, C. Q., Su, Y. Z., *et al.* (2010). [Influence of urodynamic factors on urinary retention in patients with cervical carcinoma after radical hysterectomy]. *Zhonghua Fu Chan Ke Za Zhi.* 45(9): 677-681.

Chen, X., Bargonetti, J., & Prives, C. (1995). p53, through p21 (WAF1/CIP1), induces cyclin D1 synthesis. *Cancer Research.* 55(19): 4257-4263.

Chen, Y. M.; Tsai, R. J.; Tsai, F. J.; C. H., & Huang, C. Y. (2013). Thymoquinone induces apoptosis in oral cancer cells through p38beta inhibition. *American Journal of Chinese Medicine.* 41: 683-696.

Cherasse, Y., Maurin, A. C., Chaveroux, C., Jousse, C., Carraro, V., Parry, L., *et al.* (2007). The p300/CBP-associated factor (PCAF) is a cofactor of ATF4 for amino acid-regulated transcription of CHOP. *Nucleic Acids Research.* 35(17): 5954-5965.

Chichiarelli, S., Ferraro, A., Altieri, F., Eufemi, M., Coppari, S., Grillo, C., *et al.* (2007). The stress protein ERp57/GRP58 binds specific DNA sequences in HeLa cells. *Journal of Cellular Physiology.* 210(2): 343-351.

Chichiarelli, S., Gaucci, E., Ferraro, A., Grillo, C., Altieri, F., Cocchiola, R., *et al.* (2010). Role of ERp57 in the signaling and transcriptional activity of STAT3 in a melanoma cell line. *Archives of Biochemistry & Biophysics.* 494(2): 178-183.

Chinnaiyan, A. M. (1999). The apoptosome: heart and soul of the cell death machine. *Neoplasia.* 1(1): 5-15.

Chipuk, J. E., Bouchier-Hayes, L., & Green, D. R. (2006). Mitochondrial outer membrane permeabilization during apoptosis: the innocent bystander scenario. *Cell Death & Differentiation.* 13(8): 1396-1402.

Chopin, V., Toillon, R. A., Jouy, N., & Le Bourhis, X. (2004). P21(WAF1/CIP1) is dispensable for G1 arrest, but indispensable for apoptosis induced by sodium butyrate in MCF-7 breast cancer cells. *Oncogene.* 23(1): 21-29.

Chu, Q., Vincent, M., Logan, D., Mackay, J. A., & Evans, W. K. (2005). Taxanes as first-line therapy for advanced non-small cell lung cancer: a systematic review and practice guideline. *Lung Cancer.* 50(3): 355-374.

Chung, H., Cho, H., Perry, C., Song, J., Ylaya, K., Lee, H., *et al*. (2013). Downregulation of ERp57 expression is associated with poor prognosis in early-stage cervical cancer. *Biomarkers.* 18(7): 573-579.

Chvalova, K., Brabec, V., & Kasparkova, J. (2007). Mechanism of the formation of DNA-protein cross-links by antitumor cisplatin. *Nucleic Acids Research.* 35(6): 1812-1821.

Clarke, B., & Chetty, R. (2002). Postmodern cancer: the role of human immunodeficiency virus in uterine cervical cancer. *Molecular Pathology.* 55(1): 19-24.

Clarke, E. A., & Anderson, T. W. (1979). Does screening by "Pap" smears help prevent cervical cancer? A case-control study. *Lancet.* 2(8132): 1-4.

Clifford, G. M., Rana, R. K., Franceschi, S., Smith, J. S., Gough, G., & Pimenta, J. M. (2005). Human papillomavirus genotype distribution in low-grade cervical lesions: comparison by geographic region and with cervical cancer. *Cancer Epidemiology & Biomarkers Prevention.* 14(5): 1157-1164.

Clifford, G. M., Smith, J. S., Aguado, T., & Franceschi, S. (2003). Comparison of HPV type distribution in high-grade cervical lesions and cervical cancer: a meta-analysis. *British Journal of Cancer.* 89(1): 101-105.

Coe, H., Jung, J., Groenendyk, J., Prins, D., & Michalak, M. (2010). ERp57 modulates STAT3 signaling from the lumen of the endoplasmic reticulum. *Journal of Biological Chemistry.* 285(9): 6725-6738.

Cohen, S. M., & Lippard, S. J. (2001). Cisplatin: from DNA damage to cancer chemotherapy. *Progress in* ***Nucleic Acid Research&Molecular Biology.*** 67: 93-130.

Coker, A. L., Bond, S. M., Williams, A., Gerasimova, T., & Pirisi, L. (2002). Active and passive smoking, high-risk human papillomaviruses and cervical neoplasia. *Cancer Detection & Prevention.* 26(2): 121-128.

Coling, D. E., Ding, D., Young, R., Lis, M., Stofko, E., Blumenthal, K. M., *et al.* (2007). Proteomic analysis of cisplatin-induced cochlear damage: methods and early changes in protein expression. *Heart Research.* 226(1-2): 140-156.

Colombo, N., Carinelli, S., Colombo, A., Marini, C., Rollo, D., & Sessa, C.; ESMO Guidelines Working Group. (2012).Cervical cancer**:** ESMO Clinical Practice Guidelines for diagnosis**,** treatment and follow**-**up**.***Annals of Oncology.* Suppl 7:vii27-32.

Cooper, S. (2000). The continuum model and G1-control of the mammalian cell cycle. *Progress in Cell Cycle Research.* 4: 27-39.

Coppari, S., Altieri, F., Ferraro, A., Chichiarelli, S., Eufemi, M., & Turano, C. (2002). Nuclear localization and DNA interaction of protein disulfide isomerase ERp57 in mammalian cells. *Journal of Cellular Biochemistry.* 85(2): 325-333.

Corazzari, M., Lovat, P. E., Armstrong, J. L., Fimia, G. M., Hill, D. S., Birch-Machin, M., *et al.* (2007). Targeting homeostatic mechanisms of endoplasmic reticulum stress to increase susceptibility of cancer cells to fenretinide-induced apoptosis: the role of stress proteins ERdj5 and ERp57. *British Journal of Cancer.* 96(7): 1062-1071.

Cory, S., & Adams, J. M. (2002). The Bcl2 family: regulators of the cellular life-or-death switch. *Nature Review of Cancer.* 2(9): 647-656.

Coverley, D., Laman, H., & Laskey, R. A. (2002). Distinct roles for cyclins E and A during DNA replication complex assembly and activation. *Nature Cell Biology.* 4(7): 523-528.

Cox, J. T. (2004). Liquid-based cytology: evaluation of effectiveness, cost-effectiveness, and application to present practice. *Journal of the National Comprehensive Cancer Network.* 2(6): 597-611.

Cragg, G. M., & Newman, D. J. (2005). Plants as a source of anti-cancer agents. *Journal of Ethnopharmacology.* 100(1-2): 72-79.

Cregan, S. P., Fortin, A., MacLaurin, J. G., Callaghan, S. M., Cecconi, F., Yu, S. W., *et al*. (2002). Apoptosis-inducing factor is involved in the regulation of caspase-independent neuronal cell death. *Journal of Cell Biology.* 158(3): 507-517.

Crum, C. P., Ikenberg, H., Richart, R. M., & Gissman, L. (1984). Human papillomavirus type 16 and early cervical neoplasia. *New England Journal of Medicine.* 310(14): 880-883.

Cullen, S. P., & Martin, S. J. (2008). Mechanisms of granule-dependent killing. *Cell Death & Differentiation.* 15(2): 251-262.

Dames, D. N., Blackman, E., Butler, R., Taioli, E., Eckstein, S., Devarajan, K., *et al*. (2014). High-risk cervical human papillomavirus infections among human immunodeficiency virus-positive women in the Bahamas. *PLoS One.* 9(1): e85429.

Darzynkiewicz, Z., Bruno, S., Del Bino, G., Gorczyca, W., Hotz, M.A., Lassota, P. & Traganos, F. (1992). Features of apoptotic cells measured by flow cytometry. *Cytometry*. 13:795–808.

Daugaard, G., Skoneczna, I., Aass, N., De Wit, R., De Santis, M., Dumez, H., *et al*. (2011). A randomized phase III study comparing standard dose BEP with sequential high-dose cisplatin, etoposide, and ifosfamide (VIP) plus stem-cell support in males with poor-prognosis germ-cell cancer. An intergroup study of EORTC, GTCSG, and Grupo Germinal (EORTC 30974). *Annals of Oncology.* 22(5): 1054-1061.

de Bekker-Grob, E. W., de Kok, I. M., Bulten, J., van Rosmalen, J., Vedder, J. E., Arbyn, M., *et al*. (2012). Liquid-based cervical cytology using ThinPrep technology: weighing the pros and cons in a cost-effectiveness analysis. *Cancer Causes & Control.* 23(8): 1323-1331.

de Boer, M. A., Vet, J. N., Aziz, M. F., Cornain, S., Purwoto, G., van den Akker, B. E., *et al*. (2006). Human papillomavirus type 18 and other risk factors for cervical cancer in Jakarta, Indonesia. *International Journal of Gynecologic Cancer*. 16: 1809-1814.

de Lima, C. A., Barcelos, A. C., Paschoini Mde, C., Silva, J. H., de Lima, M. A., Murta, E. F., *et al*. (2013). Conservative treatment of uterine cervical adenocarcinoma in pregnancy. *Case Reports in Obstetrics and Gynecology.* 2013:4.

de Sanjose, S., Quint, W., Alemany, L., Geraets, D., Klaustermeier, J., Lloveras, B., *et al*. (2010). Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. *Lancet Oncology.* 11: 1048-1056.

De Vita, F., Orditura, M., Martinelli, E., Vecchione, L., Innocenti, R., Sileni, V. C., *et al*. (2011). A multicenter phase II study of induction chemotherapy with FOLFOX-4 and cetuximab followed by radiation and cetuximab in locally advanced oesophageal cancer. *British Journal of Cancer.* 104(3): 427-432.

Devita, V. T., Jr., Serpick, A. A., & Carbone, P. P. (1970). Combination chemotherapy in the treatment of advanced Hodgkin's disease. *Annal International Medicine.* 73(6): 881-895.

Dejeans, N., Tajeddine, N., Beck, R., Verrax, J., Taper, H., Gailly, P., *et al*. (2010). Endoplasmic reticulum calcium release potentiates the ER stress and cell death caused by an oxidative stress in MCF-7 cells. *Biochemical Pharmacology.* 79(9): 1221-1230.

Denny, L., Quinn, M., & Sankaranarayanan, R. (2006). Chapter 8: Screening for cervical cancer in developing countries. *Vaccine.* 31(24): 71-77.

Dickison, W. C. (1979). A note on the wood anatomy of *Dillenia* (Dilleniaceae), *IAWA bulletin,* 2-3.

Dimitroulis, J., Rapti, A., Stathopoulos, G. P., Rigatos, S., Stathopoulos, J., Koutantos, J., *et al*. (2008). Comparison of cisplatin-paclitaxel combination versus cisplatin-etoposide in patients with small-cell lung cancer: a Phase III study. *Oncology Reports.* 20(4): 879-884.

Domingo, E. J., Noviani, R., Noor, M. R. M., Ngelangel, C. A., Limpaphayom, K. K., Van Thuan, T., *et al.* (2008). Epidemiology and prevention of cervical cancer in Indonesia, Malaysia, the Philippines, Thailand and Vietnam. *Vaccine. 26* (SUPPL. 12): 71-79.

Du, C., Fang, M., Li, Y., Li, L., & Wang, X. (2000). Smac, a mitochondrial protein that promotes cytochrome c-dependent caspase activation by eliminating IAP inhibition. *Cell.* 102(1): 33-42.

Du, L., Sanchez, C., Chen, M., Edwards, D. J., & Shen, B. (2000). The biosynthetic gene cluster for the antitumor drug bleomycin from *Streptomyces verticillus* ATCC15003 supporting functional interactions between nonribosomal peptide synthetases and a polyketide synthase. *Chemistry & Biology.* 7(8): 623-642.

Dueñas-González, A., Orlando, M., Zhou, Y., Quinlivan, M., & Barraclough, H. (2012). Efficacy in high burden locally advanced cervical cancer with concurrent gemcitabine and cisplatin chemoradiotherapy plus adjuvant gemcitabine and cisplatin: Prognostic and predictive factors and the impact of disease stage on outcomes from a prospective randomized phase III trial. *Gynecologic Oncology.* 126: 334-340.

Durst, M., Gissmann, L., Ikenberg, H., & zur Hausen, H. (1983). A papillomavirus DNA from a cervical carcinoma and its prevalence in cancer biopsy samples from different geographic regions. *Proceedings National Academic of Science U.S.A.* 80(12): 3812-3815.

El Gazzar, M., El Mezayen, R., Marecki, J. C., Nicolls, M. R., Canastar, A., & Dreskin, S. C. (2006). Anti-inflammatory effect of thymoquinone in a mouse model of allergic lung inflammation. *International Immunopharmacology.* 6(7): 1135-1142.

El Mezayen, R., El Gazzar, M., Nicolls, M. R., Marecki, J. C., Dreskin, S. C., & Nomiyama, H. (2006). Effect of thymoquinone on cyclooxygenase expression and prostaglandin production in a mouse model of allergic airway inflammation. *Immunology Letter.* 106(1): 72-81.

El-Deiry, W. S., Tokino, T., Velculescu, V. E., Levy, D. B., Parsons, R., Trent, J. M., *et al.* (1993). WAF1, a potential mediator of p53 tumor suppression. *Cell.* 75(4): 817-825.

El-Mahdy, M. A., Zhu, Q., Wang, Q. E., Wani, G., & Wani, A. A. (2005). Thymoquinone induces apoptosis through activation of caspase-8 and mitochondrial events in p53-null myeloblastic leukemia HL-60 cells. *International Journal of Cancer.* 117(3): 409-417.

Elledge, S. J. (1996). Cell cycle checkpoints: preventing an identity crisis. *Science.* 274(5293): 1664-1672.

Elmore, S. (2007). Apoptosis: a review of programmed cell death. *Toxicology Pathology.* 35(4): 495-516.

Elson, D. A., Riley, R. R., Lacey, A., Thordarson, G., Talamantes, F. J., & Arbeit, J. M. (2000). Sensitivity of the cervical transformation zone to estrogen-induced squamous carcinogenesis. *Cancer Research.* 60(5): 1267-1275.

Enari, M., Sakahira, H., Yokoyama, H., Okawa, K., Iwamatsu, A., & Nagata, S. (1998). A caspase-activated DNase that degrades DNA during apoptosis, and its inhibitor ICAD. *Nature.* 391(6662): 43-50.

Esajas, M. D., Duk, J. M., de Bruijn, H. W., Aalders, J. G., Willemse, P. H., Sluiter, W.*, et al.* (2001). Clinical value of routine serum squamous cell carcinoma antigen in follow-up of patients with early-stage cervical cancer. *Journal of Clinical Oncology.* 19(19): 3960-3966.

Eschenlauer, S. C., & Page, A. P. (2003). The *Caenorhabditis elegans* ERp60 homolog protein disulfide isomerase-3 has disulfide isomerase and transglutaminase-like cross-linking activity and is involved in the maintenance of body morphology. *Journal of Biological Chemistry.* 278(6): 4227-4237.

Eufemi, M., Coppari, S., Altieri, F., Grillo, C., Ferraro, A., & Turano, C. (2004). ERp57 is present in STAT3-DNA complexes. *Biochemical and Biophysical Research Communications.* 323(4): 1306-1312.

Fadok, V. A., & Henson, P. M. (2003). Apoptosis: giving phosphatidylserine recognition an assist with a twist. *Current Biology.* 13(16): R655-R657.

Fedele, P., Avery, S., Patil, S., Spencer, A., Haas, M., & Wei, A. (2014). Health economic impact of high-dose versus standard-dose cytarabine induction chemotherapy for acute myeloid leukaemia. *International Medical Journal.* 27(10): 12478.

Feliers, D., Frank, M. A., & Riley, D. J. (2002). Activation of cyclin D1-Cdk4 and Cdk4-directed phosphorylation of RB protein in diabetic mesangial hypertrophy. *Diabetes.* 51(11): 3290-3299.

Feng, R., Zhai, W. L., Yang, H. Y., Jin, H., & Zhang, Q. X. (2011). Induction of ER stress protects gastric cancer cells against apoptosis induced by cisplatin and doxorubicin through activation of p38 MAPK. *Biochemistry & Biophysics Research Communications.* 406(2): 299-304.

Ferenschild, F. T., Vermaas, M., Verhoef, C., Ansink, A. C., Kirkels, W. J., Eggermont, A. M., *et al.* (2009). Total pelvic exenteration for primary and recurrent malignancies. *World Journal of Surgery.* 33(7): 1502-1508.

Ferrari, D. M., & Soling, H. D. (1999). The protein disulphide-isomerase family: unravelling a string of folds. *Biochemistry Journal.* 339(1): 1-10.

Ferguson, R. L., & Maller, J. L. (2010). Centrosomal localization of cyclin E-Cdk2 is required for initiation of DNA synthesis. *Current Biology.* 20(9): 856-860.

Ferlay, J., Steliarova-Foucher, E., Lortet-Tieulent, J., Rosso, S., Coebergh, J. W., Comber, H., *et al*. (2013). Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *European Journal of Cancer.* 49(6): 1374-1403.

Fidler, I. J. (2011). The biology of cancer metastasis. *Seminar in Cancer Biology.* 21(2): 71.

Fiers, W., Beyaert, R., Declercq, W., & Vandenabeele, P. (1999). More than one way to die: apoptosis, necrosis and reactive oxygen damage. *Oncogene.* 18(54): 7719-7730.

Flores-Diaz, M., Higuita, J. C., Florin, I., Okada, T., Pollesello, P., Bergman, T., *et al*. (2004). A cellular UDP-glucose deficiency causes overexpression of glucose/oxygen-regulated proteins independent of the endoplasmic reticulum stress elements. *Journal of Biological Chemistry.* 279(21): 21724-21731.

Franceschi, S., Clifford, G., & Plummer, M. (2003). Prospects for primary prevention of cervical cancer in developing countries. *Salud Publica Mexico.* 45(3): S430-436.

Frasconi, M., Chichiarelli, S., Gaucci, E., Mazzei, F., Grillo, C., Chinazzi, A., *et al*. (2012). Interaction of ERp57 with calreticulin: Analysis of complex formation and effects of vancomycin. *Biophysical Chemistry.* 160(1): 46-53.

Fremont-Smith, M., Marino, J., Griffin, B., Spencer, L., & Bolick, D. (2004). Comparison of the SurePath liquid-based Papanicolaou smear with the conventional Papanicolaou smear in a multisite direct-to-vial study. *Cancer.* 102(5): 269-279.

Fruscio, R., Villa, A., Chiari, S., Vergani, P., Ceppi, L., Dell'Orto, F., *et al*. (2012). Delivery delay with neoadjuvant chemotherapy for cervical cancer patients during pregnancy: a series of nine cases and literature review. *Gynecologic Oncology.* 126(2): 192-197.

Fujimoto, J., Aoki, I., Toyoki, H., Khatun, S., & Tamaya, T. (2002). Clinical implications of expression of ETS-1 related to angiogenesis in uterine cervical cancers. *Annals of Oncology.* 13(10): 1598-1604.

Fujimoto, J., Sakaguchi, H., Aoki, I., & Tamaya, T. (2000). Clinical implications of expression of interleukin 8 related to angiogenesis in uterine cervical cancers. *Cancer Research.* 60(10): 2632-2635.

Fulda, S., & Debatin, K. M. (2006). Extrinsic versus intrinsic apoptosis pathways in anticancer chemotherapy. *Oncogene.* 25(34): 4798-4811.

Fury, M. G., Lee, N. Y., Sherman, E., Ho, A. L., Rao, S., Heguy, A., *et al*. (2013). A phase 1 study of everolimus + weekly cisplatin + intensity modulated radiation therapy in head-and-neck cancer. *Iternational Journal of Radiation Oncology.* 87(3): 479-486.

Gaarenstroom, K. N., Kenter, G. G., Bonfrer, J. M., Korse, C. M., Van de Vijver, M. J., Fleuren, G. J., *et al*. (2000). Can initial serum cyfra 21-1, SCC antigen, and TPA levels in squamous cell cervical cancer predict lymph node metastases or prognosis? *Gynecology Oncology.* 77(1): 164-170.

Gadducci, A., Tana, R., Cosio, S., & Genazzani, A. R. (2008). The serum assay of tumour markers in the prognostic evaluation, treatment monitoring and follow-up of patients with cervical cancer: a review of the literature. *Critical Review in Oncology Hematology.* 66(1): 10-20.

Gali-Muhtasib, H. U., Abou Kheir, W. G., Kheir, L. A., Darwiche, N., & Crooks, P. A. (2004). Molecular pathway for thymoquinone-induced cell-cycle arrest and apoptosis in neoplastic keratinocytes. *Anticancer Drugs.* 15(4): 389-399.

Gali-Muhtasib, H. U., Abou Kheir, W. G., Kheir, L. A., Darwiche, N., & Crooks, P. A. (2004). Molecular pathway for thymoquinone-induced cell-cycle arrest and apoptosis in neoplastic keratinocytes. *Anticancer Drugs.* 15(4): 389-399.

Gali-Muhtasib, H., Ocker, M., Kuester, D., Krueger, S., El-Hajj, Z., Diestel, A., *et al*. (2008). Thymoquinone reduces mouse colon tumor cell invasion and inhibits tumor growth in murine colon cancer models. *Journal of Cellular & Molecular Medicine.* 12(1), 330-342.

Gandhi, A. K., Sharma, D. N., Rath, G. K., Julka, P. K., Subramani, V., Sharma, S., *et al*. (2013). Early clinical outcomes and toxicity of intensity modulated versus conventional pelvic radiation therapy for locally advanced cervix carcinoma: a prospective randomized study. *International Journal of Radiation Oncology Biology Physics.* 87(3): 542-548.

Garrido, C., Galluzzi, L., Brunet, M., Puig, P. E., Didelot, C., & Kroemer, G. (2006). Mechanisms of cytochrome c release from mitochondria. *Cell Death & Differentiation.* 13(9): 1423-1433.

Gasch A. P., Spellman P. T., Kao C. M., Carmel-Harel O., Eisen M. B., Storz G., *et al*. (2000). Genomic expression programs in the response of yeast cells to environmental changes. *Molecular Biology of the Cell.* 11(12): 4241-4257.

Geus-Oei, L. F., Verhagen, A. F., Lok, J., van der Heijden, H. F., Rademakers, S. E., Span, P. N., *et al.* (2012). Differences in metabolism between adeno- and squamous cell non-small cell lung carcinomas: spatial distribution and prognostic value of GLUT1 and MCT4. *Lung Cancer*. 76: 316-323.

Ghobrial, I. M., Witzig, T. E. & Adjei, A. A. (2005). Targeting apoptosis pathways in cancer therapy. *Cancer Journal for Clinicians.* 55: 178-194.

Giacinti, C., & Giordano, A. (2006). RB and cell cycle progression. *Oncogene.* 25(38): 5220-5227.

Gibb, A., Greystoke, A., Ranson, M., Linton, K., Neeson, S., Hampson, G. *et al*. (2013). A study to investigate dose escalation of doxorubicin in ABVD chemotherapy for Hodgkin lymphoma incorporating biomarkers of response and toxicity. *British Journal of Cancer.* 109(10): 2560-2565.

Gierisch, J. M., Coeytaux, R. R., Urrutia, R. P., Havrilesky, L. J., Moorman, P. G., Lowery, W. J., *et al*. (2013). Oral contraceptive use and risk of breast, cervical, colorectal, and endometrial cancers: a systematic review. *Cancer Epidemiology Biomarkers Prevention.* 22(11): 1931-1943.

Gilani, A. H., Aziz, N., Khurram, I. M., Chaudhary, K. S., & Iqbal, A. (2001). Bronchodilator, spasmolytic and calcium antagonist activities of *Nigella sativa* seeds (Kalonji): a traditional herbal product with multiple medicinal uses. *Journal of Pakistan Medical Association.* 51(3): 115-120.

Gilmore, W. J., & Kirby, G. M. (2004). Endoplasmic reticulum stress due to altered cellular redox status positively regulates murine hepatic CYP2A5 expression. *Journal of Pharmacology and Experimental Therapeutics.* 308(2): 600-608.

Godwin, M., Crellin, J., Mathews, M., Chowdhury, N. L., Newhook, L. A., Pike, A., *et al*. (2013). Use of natural health products in children: survey of parents in waiting rooms. *Canadian Family Physician.* 59(8): 364-371.

Gottlieb, T. M., & Oren, M. (1998). p53 and apoptosis. *Seminar in Cancer Biology.* 8(5): 359-368.

Graeber, T. G., Osmanian, C., Jacks, T., Housman, D. E., Koch, C. J., Lowe, S. W., *et al*. (1996). Hypoxia-mediated selection of cells with diminished apoptotic potential in solid tumours. *Nature.* 379(6560): 88-91.

Gray, R. H., Serwadda, D., Kong, X., Makumbi, F., Kigozi, G., Gravitt, P. E., *et al*. (2010). Male circumcision decreases acquisition and increases clearance of high-risk human papillomavirus in HIV-negative men: a randomized trial in Rakai, Uganda. *Journal of Infectious Diseases.* 201(10): 1455-1462.

Grimm, C., Polterauer, S., Natter, C., Rahhal, J., Hefler, L., Tempfer, C. B*., et al*. (2012). Treatment of cervical intraepithelial neoplasia with topical imiquimod: a randomized controlled trial. *Obstetric & Gynecology.* 120(1): 152-159.

Grimm, S., Stanger, B. Z., & Leder, P. (1996). RIP and FADD: two "death domain"-containing proteins can induce apoptosis by convergent, but dissociable, pathways. *Proceedings of the National Academic of Science of the U.S.A*. 93(20): 10923-10927.

Guo, G. G., Patel, K., Kumar, V., Shah, M., Fried, V. A., Etlinger, J. D., *et al*. (2002). Association of the chaperone glucose-regulated protein 58 (GRP58/ER-60/ERp57) with Stat3 in cytosol and plasma membrane complexes. *Journal of Interferon & Cytokine Research.* 22(5): 555-563.

Gustafsson, L., Ponten, J., Zack, M., & Adami, H. O. (1997). International incidence rates of invasive cervical cancer after introduction of cytological screening. *Cancer Causes & Control.* 8(5): 755-763.

Gynecologic Lymph Nodes,, http://www.aboutcancer.com/cervix_nodes_spread.gif. Retrieved 4th September 2014

Hannaford, P. C., Selvaraj, S., Elliott, A. M., Angus, V., Iversen, L., & Lee, A. J. (2007). Cancer risk among users of oral contraceptives: cohort data from the Royal College of General Practitioner's oral contraception study. *British Medical Journal.* 335(7621): 651.

Harper, D. M., Franco, E. L., Wheeler, C. M., Moscicki, A. B., Romanowski, B., Roteli-Martins, C. M., *et al*. (2006). Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial. *Lancet.* 367(9518): 1247-1255.

Hartwell, L. H., & Kastan, M. B. (1994). Cell cycle control and cancer. *Science.* 266(5192): 1821-1828.

Hassanim, N. I. & Hassan F. M. (1996). A preliminary study on the effect of *Nigella sativa* seeds on hypoglycemia. *Veterinary Medical Journal (Giza)*. 44: 699–708.

Hatae, M. & Ohashi, Y. (2000). Phase II study of irinotecan and cisplatin as first-line chemotherapy in advanced or recurrent cervical cancer. *Oncology*. 58: 31-37.

Haverkos, H. W., Soon, G., Steckley, S. L., & Pickworth, W. (2003). Cigarette smoking and cervical cancer: Part I: a meta-analysis. *Biomedicine & Pharmacotherapy.* 57(2): 67-77.

Hayes, D. F., Bast, R. C., Desch, C. E., Fritsche, H., Jr., Kemeny, N. E., Jessup, J. M., *et al*. (1996). Tumor marker utility grading system: a framework to evaluate clinical utility of tumor markers. *Journal of the National Cancer Institute.* 88(20): 1456-1466.

Heinrich, S., Kraft, D., Staib-Sebler, E., Schwarz, W., Gog, C., Vogl, T., *et al*. (2013). Phase II study on combined intravenous and intra-arterial chemotherapy with gemcitabine and mitomycin C in patients with advanced pancreatic cancer. *Hepatogastroenterology.* 60(126): 1492-1496.

Hermeking, H., Lengauer, C., Polyak, K., He, T. C., Zhang, L., Thiagalingam, S., *et al*. (1997). 14-3-3 sigma is a p53-regulated inhibitor of G2/M progression. *Molecular Cell.* 1(1): 3-11.

Hernandez, B. Y., Shvetsov, Y. B., Goodman, M. T., Wilkens, L. R., Thompson, P., Zhu, X., *et al*. (2010). Reduced clearance of penile human papillomavirus infection in uncircumcised men. *Journal of Infectious Diseases.* 201(9): 1340-1343.

Herr, I., & Debatin, K. M. (2001). Cellular stress response and apoptosis in cancer therapy. *Blood.* 98(9): 2603-2614.

Hetz, C., Russelakis-Carneiro, M., Walchli, S., Carboni, S., Vial-Knecht, E., Maundrell, K., *et al*. (2005). The disulfide isomerase Grp58 is a protective factor against prion neurotoxicity. *Journal of Neuroscience.* 25: 2793-2802.

Hickman, J. A. (1992). Apoptosis induced by anticancer drugs. *Cancer Metastasis Review.* 11(2): 121-139.

Hikisz, P., & Kilianska, Z. M. (2012). PUMA, a critical mediator of cell death-one decade on from its discovery. *Cellular & Molecular Biology Letters.* 17(4): 646-669.

Hildesheim, A., Herrero, R., Castle, P. E., Wacholder, S., Bratti, M. C., Sherman, M. E., *et al.* (2001). HPV co-factors related to the development of cervical cancer: results from a population-based study in Costa Rica. *British Journal of Cancer.* 84(9): 1219-1226.

Hildesheim, A., Schiffman, M. H., Tsukui, T., Swanson, C. A., Lucci, J., 3rd, Scott, D. R., *et al.* (1997). Immune activation in cervical neoplasia: cross-sectional association between plasma soluble interleukin 2 receptor levels and disease. *Cancer Epidemiology & Biomarkers Prevention.*6(10): 807-813.

Hill, M. M., Adrain, C., Duriez, P. J., Creagh, E. M., & Martin, S. J. (2004). Analysis of the composition, assembly kinetics and activity of native Apaf-1 apoptosomes. *EMBO Journal.* 23(10): 2134-2145.

Hockenbery, D., Nunez, G., Milliman, C., Schreiber, R. D., & Korsmeyer, S. J. (1990). Bcl-2 is an inner mitochondrial membrane protein that blocks programmed cell death. *Nature.* 348(6299): 334-336.

Hoebers, F. J., Pluim, D., Hart, A. A., Verheij, M., Balm, A. J., Fons, G., *et al.* (2008). Cisplatin-DNA adduct formation in patients treated with cisplatin-based chemoradiation: lack of correlation between normal tissues and primary tumor. *Cancer Chemotherapy and Pharmacology.* 61(6): 1075-1081.

Hogewoning, C. J., Bleeker, M. C., van den Brule, A. J., Voorhorst, F. J., Snijders, P. J., Berkhof, J., *et al*. (2003). Condom use promotes regression of cervical intraepithelial neoplasia and clearance of human papillomavirus: a randomized clinical trial. *International Journal of Cancer.* 107(5): 811-816.

Hoogland, R.D. (1972) Dilleniaceae. In: Smitinand T, Larsen K, eds. *Flora of Thailand*, Vol. 2 Part 2. Bangkok: The ASRCT Press. pp 95-108.

Hopfl, R., Heim, K., Christensen, N., Zumbach, K., Wieland, U., Volgger, B., et al. (2000). Spontaneous regression of CIN and delayed-type hypersensitivity to HPV-16 oncoprotein E7. *Lancet.* 356(9246): 1985-1986.

Hu, S., Snipas, S. J., Vincenz, C., Salvesen, G., & Dixit, V. M. (1998). Caspase-14 is a novel developmentally regulated protease. *Journal of Biological Chemistry.* 273(45): 29648-29653.

Hu, W. H., Johnson, H., & Shu, H.-B. (2000). Activation of NF-κB by FADD, Casper, and Caspase-8. *Journal of Biological Chemistry.* 275(15): 10838-10844.

Huang, J., Han, H. Y., Li, G. Y., Wang, H. Y., Zhang, C., Zhang, K., *et al*. (2013). Two new terpenoid benzoates with antitumor activity from the roots of *Ferula dissecta*. *Journal of Asian Natural Products Research.* 15(10): 1100-1106.

Huang, S., Liu, L. N., Hosoi, H., Dilling, M. B., Shikata, T., & Houghton, P. J. (2001). p53/p21(CIP1) cooperate in enforcing rapamycin-induced G1 arrest and determine the cellular response to rapamycin. *Cancer Research.* 61(8): 3373-3381.

Hung, J. H., Su, I. J., Lei, H. Y., Wang, H. C., Lin, W. C., Chang, W. T., *et al*. (2004). Endoplasmic reticulum stress stimulates the expression of cyclooxygenase-2 through activation of NF-kappaB and pp38 mitogen-activated protein kinase. *Journal of Biological Chemistry.* 279(45): 46384-46392.

Hutchinson, M. L., Isenstein, L. M., Goodman, A., Hurley, A. A., Douglass, K. L., Mui, K. K., *et al.* (1994). Homogeneous sampling accounts for the increased diagnostic accuracy using the ThinPrep Processor. *American Journal of Clinical Pathology.* 101(2): 215-219.

Hwang, J. H., Yoo, H. J., Lim, M. C., Seo, S. S., Kang, S., Kim, J. Y., *et al*. (2013). Brain metastasis in patients with uterine cervical cancer. *Journal of Obstetric & Gynaecology Research.* 39(1): 287-291.

Ibrahim, F. H., & Hamzah, N. (1999). The use of medicinal plant species by the Temuan tribe of Ayer Hitam Forest, Selangor, Peninsular Malaysia. *Pertanika Journal of Tropical Agricultural Science.* 22(2): 85-94.

Igney, F. H., & Krammer, P. H. (2002). Death and anti-death: tumour resistance to apoptosis. *National Review of Cancer.* 2(4): 277-288.

Imadome, K., Iwakawa, M., Nakawatari, M., Fujita, H., Kato, S., Ohno, T., *et al*. (2010). Subtypes of cervical adenosquamous carcinomas classified by EpCAM expression related to radiosensitivity. *Cancer Biology & Therapy.* 10(10): 1019-1026.

Insinga, R. P., Dasbach, E. J., Elbasha, E. H., Liaw, K. L., Barr, E. (2007) Progression and regression of incident cervical HPV 6, 11, 16 and 18 infections in young women.*Infectious Agent and Cancer*. 2:15.

Ivankovic, S., Stojkovic, R., Jukic, M., Milos, M., & Jurin, M. (2006). The antitumor activity of thymoquinone and thymohydroquinone *in vitro* and *in vivo*. *Experimental Oncology.* 28(3): 220-224.

Izadi-Mood, N., Sarmadi, S., Eftekhar, Z., Jahanteegh, H. A., & Sanii, S. (2013). Immunohistochemical expression of p16 and HPV L1 capsid proteins as predictive markers in cervical lesions. *Archives of Gynecology and Obstetrics.* 18:18.

Jacob, M., Broekhuizen, F. F., Castro, W., & Sellors, J. (2005). Experience using cryotherapy for treatment of cervical precancerous lesions in low-resource settings. *International Journal of Gynaecology & Obstetrics.* 89(2): 13-20.

Jensen, K. E., Schmiedel, S., Norrild, B., Frederiksen, K., Iftner, T., & Kjaer, S. K. (2013). Parity as a cofactor for high-grade cervical disease among women with persistent human papillomavirus infection: a 13-year follow-up. *British Journal of Cancer.* 108(1): 234-239.

Jessop, C. E., Tavender, T. J., Watkins, R. H., Chambers, J. E., & Bulleid, N. J. (2009). Substrate specificity of the oxidoreductase ERp57 is determined primarily by its interaction with calnexin and calreticulin. *Journal of Biological Chemistry.* 284(4): 2194-2202.

Jimbo, A., Fujita, E., Kouroku, Y., Ohnishi, J., Inohara, N., Kuida, K., *et al*. (2003). ER stress induces caspase-8 activation, stimulating cytochrome c release and caspase-9 activation. *Experimental Cell Research.* 283(2): 156-166.

Jo, Y., & Debose-Boyd, R. A. (2010). Control of cholesterol synthesis through regulated ER-associated degradation of HMG CoA reductase. *Critical Reviews in Biochemistry and Molecular Biology.* 45(3): 185-198.

Johnny, L., Yusuf, U. K., & Nulit, R. (2010). The effect of herbal plant extracts on the growth and sporulation of *Colletotrichum gloeosporioides*. *Journal of Applied Biosciences.* 34: 2218-2224.

Jurado, M., Martinez-Monge, R., Garcia-Foncillas, J., Azinovic, I., Aristu, J., Lopez-Garcia, G., *et al*. (1999). Pilot study of concurrent cisplatin, 5-fluorouracil, and external beam radiotherapy prior to radical surgery +/- intraoperative electron beam radiotherapy in locally advanced cervical cancer. *Gynecologic Oncology.* 74(1): 30-37.

Kalemci, S., Cilaker Micili, S., Acar, T., Senol, T., Dirican, N., Omeroglu, G., *et al*. (2013). Effectiveness of thymoquinone in the treatment of experimental asthma. *Clinica Terapeutica.* 164(3): 155-158.

Kalof, A. N., & Cooper, K. (2006). p16INK4a immunoexpression: surrogate marker of high-risk HPV and high-grade cervical intraepithelial neoplasia. *Advanced Anatomy Pathology.* 13(4): 190-194.

Kalus, U., Pruss, A., Bystron, J., Jurecka, M., Smekalova, A., Lichius, J. J., & Kiesewetter, H. (2003). Effect of Nigella sativa (black seed) on subjective feeling in patients with allergic diseases. *Phytotherapy Reseasrch.* 17(10): 1209-1214.

Kanazawa, T., Taneike, I., Akaishi, R., Yoshizawa, F., Furuya, N., Fujimura, S., *et al*. (2004). Amino acids and insulin control autophagic proteolysis through different signaling pathways in relation to mTOR in isolated rat hepatocytes. *Journal of Biological Chemistry.* 279(9): 8452-8459.

Kaneko, M., Niinuma, Y., & Nomura, Y. (2003). Activation signal of nuclear factor-kappa B in response to endoplasmic reticulum stress is transduced via IRE1 and tumor necrosis factor receptor-associated factor 2. *Biological & Pharmaceutical Bulletin.* 26(7): 931-935.

Kang, S. J., Wang, S., Hara, H., Peterson, E. P., Namura, S., Amin-Hanjani, S., *et al*. (2000). Dual role of caspase-11 in mediating activation of caspase-1 and caspase-3 under pathological conditions. *Journal of Cell Biology.* 149(3): 613-622.

Karam, A., Feldman, N., & Holschneider, C. H. (2007). Neoadjuvant cisplatin and radical cesarean hysterectomy for cervical cancer in pregnancy. *Nature Clinical Practice Oncology.* 4(6): 375-380.

Kaseb, A. O., Chinnakannu, K., Chen, D., Sivanandam, A., Tejwani, S., Menon, M., *et al*. (2007). Androgen receptor and E2F-1 targeted thymoquinone therapy for hormone-refractory prostate cancer. *Cancer Research.* 67(16): 7782-7788.

Kaser, A., Lee, A. H., Franke, A., Glickman, J. N., Zeissig, S., Tilg, H., *et al*. (2008). XBP1 links ER stress to intestinal inflammation and confers genetic risk for human inflammatory bowel disease. *Cell.* 134(5): 743-756.

Kaufman, R. J. (2002). Orchestrating the unfolded protein response in health and disease. *Journal of Clinical Investigation.* 110(10): 1389-1398.

Kaura, B., Bagga, R., & Patel, F. D. (2004). Evaluation of the pyruvate kinase isoenzyme tumor (Tu M2-PK) as a tumor marker for cervical carcinoma. *Journal of Obstetrics & Gynaecology Research.* 30(3): 193-196.

Kendrick, N. (2012). A gene's mRNA level measured by microarrays or RT-PCR does not necessarily predict its protein level: R2 (or Rs) for plots of mRNA versus protein is <0.4. Kendrick Labs Inc, Madison, WI.http://www.kendricklabs.com/WP1_mRNAvsProtein_KendrickLabs.pdf.

Kerr, J. F., Wyllie, A. H., & Currie, A. R. (1972). Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. *British Journal of Cancer.* 26(4): 239-257.

Kester, L. M., Shedd-Steele, R. B., Dotson-Roberts, C. A., Smith, J., & Zimet, G. D. (2013). The effects of a brief educational intervention on human papillomavirus knowledge and intention to initiate HPV vaccination in 18-26 year old young adults. *Gynecology & Oncology.* 31(13): 01397-01398.

Keys, H. M., Bundy, B. N., Stehman, F. B., Muderspach, L. I., Chafe, W. E., Suggs, C. L*., et al.* (1999). Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. *New England Journal of Medicine.* 340(15): 1154-1161.

Khattab, M. M., & Nagi, M. N. (2007). Thymoquinone supplementation attenuates hypertension and renal damage in nitric oxide deficient hypertensive rats. *Phytotherapy Research.* 21(5): 410-414.

Kim, G. J., Chandrasekaran, K., & Morgan, W. F. (2006). Mitochondrial dysfunction, persistently elevated levels of reactive oxygen species and radiation-induced genomic instability: a review. *Mutagenesis.* 21(6): 361-367.

Kim, I., Xu, W. & Reed, J. C. (2008). Cell death and endoplasmic reticulum stress: disease relevance and therapeutic opportunities. *Nature Reviews Drug Discovery.* 7(12): 1013-1030.

Kim, K., Yu, M., Han, S., Oh, I., Choi, Y. J., Kim, S., *et al.* (2009). Expression of human peroxiredoxin isoforms in response to cervical carcinogenesis. *Oncology Reports.* 21(6): 1391-1396.

Kim, M. H., Song, Y. M., Kim, B. K., Park, S. M., & Ko, G. P. (2013). Trends in cervical cancer mortality by socioeconomic status in Korean women between 1998 and 2009. *Korean Journal of Family Medicine.* 34(4): 258-264.

Kino, T., Gragerov, A., Valentin, A., Tsopanomihalou, M., Ilyina-Gragerova, G., Erwin-Cohen, R., *et al.* (2005). Vpr protein of human immunodeficiency virus type 1 binds to 14-3-3 proteins and facilitates complex formation with Cdc25C: implications for cell cycle arrest. *Journal of Virology.* 79(5): 2780-2787.

Kischkel, F. C., Hellbardt, S., Behrmann, I., Germer, M., Pawlita, M., Krammer, P. H., et al. (1995). Cytotoxicity-dependent APO-1 (Fas/CD95)-associated proteins form a death-inducing signaling complex (DISC) with the receptor. *EMBO Journal.* 14(22): 5579-5588.

Kochummen, K. M. (1960). *Manual of Malayan Timber Trees: Dilleniaceae*. Forest Research Institute, Forest Department, Federation of Malaya.

Koenig, U., Eckhart, L., & Tschachler, E. (2001). Evidence that *caspase-13* is not a human but a bovine gene. *Biochemical & Biophysical Research Communications.* 285(5): 1150-1154.

Koivunen, P., Horelli-Kuitunen, N., Helaakoski, T., Karvonen, P., Jaakkola, M., Palotie, A., *et al*. (1997). Structures of the human gene for the protein disulfide isomerase-related polypeptide ERp60 and a processed gene and assignment of these genes to 15q15 and 1q21. *Genomics.* 42(3): 397-404.

Kong, T. W., Chang, S. J., Paek, J., Yoo, S. C., Yoon, J. H., Chang, K. H., *et al*. (2012). Comparison of concurrent chemoradiation therapy with weekly cisplatin versus monthly fluorouracil plus cisplatin in FIGO stage IIB-IVA cervical cancer. *Journal of Gynecologic Oncology.* 23(4): 235-241.

Kouidhi, B., Zmantar, T., Jrah, H., Souiden, Y., Chaieb, K., Mahdouani, K., *et al*. (2011). Antibacterial and resistance-modifying activities of thymoquinone against oral pathogens. *Annals of Clinical Microbiology and Antimicrobials.* 10(29): 1476-0711.

Koutsky, L. A., Ault, K. A., Wheeler, C. M., Brown, D. R., Barr, E., Alvarez, F. B., *et al*. (2002). A controlled trial of a human papillomavirus type 16 vaccine. *New England Journal of Medicine.* 347(21): 1645-1651.

Kozaki, K., Miyaishi, O., Asai, N., Iida, K., Sakata, K., Hayashi, M., *et al.* (1994). Tissue distribution of ERp61 and association of its increased expression with IgG production in hybridoma cells. *Experimental Cell Research.* 213(2): 348-358.

Kuhnel, F., Zender, L., Paul, Y., Tietze, M. K., Trautwein, C., Manns, M., *et al*. (2000). NFkappaB mediates apoptosis through transcriptional activation of Fas (CD95) in adenoviral hepatitis. *Journal of Biological Chemistry.* 275(9): 6421-6427.

Kumar, B. N., Sarkar, S., Das, S., Azab, B., Santhekadur, P. K., *et al*. (2013). Targeted apoptotic effects of thymoquinone and tamoxifen on XIAP mediated Akt regulation in breast cancer. *PLoS One.* 8(4): e61342.

Kumar, D., Mallick, S., Vedasiromoni, J. R., & Pal, B. C. (2010). Anti-leukemic activity of *Dillenia indica* L. fruit extract and quantification of betulinic acid by HPLC. *Phytomedicine.* 17(6): 431-435.

Kumar, S., Kumar, V., & Prakash, O. (2011). Antidiabetic and hypolipidemic activities of *Dillenia indica* extract in diabetic rats. *Zhong Xi Yi Jie He Xue Bao.* 9(5): 570-574.

Kurien, B.T. & Scofield, R.H. (2006). Western blotting. *Methods*. 38:283–293.

Kusari, S., Zühlke, S., & Spiteller, M. (2009). An endophytic fungus from *Camptotheca acuminata* that produces camptothecin and analogues. *Journal of Natural Products.* 72(1): 2-7.

Kuznetsov, G., Towle, M. J., Cheng, H., Kawamura, T., TenDyke, K., Liu, D., *et al*. (2004). Induction of morphological and biochemical apoptosis following prolonged mitotic blockage by halichondrin B macrocyclic ketone analog E7389. *Cancer Research.* 64(16): 5760-5766.

Kyndi, M., Frederiksen, K., & Kruger Kjaer, S. (2006). Cervical cancer incidence in Denmark over six decades (1943-2002). *Acta Obstetrica et Gynecologica Scandinavica.* 85(1): 106-111.

La Torre, G., de Waure, C., Chiaradia, G., Mannocci, A., & Ricciardi, W. (2007). HPV vaccine efficacy in preventing persistent cervical HPV infection: A systematic review and meta-analysis. *Vaccine.* 25(50): 8352-8358.

Langley, R. R., & Fidler, I. J. (2011). The seed and soil hypothesis revisited-the role of tumor-stroma interactions in metastasis to different organs. *International Journal of Cancer.* 128(11): 2527-2535.

Lanks, K. W., Gao, J. P., & Kasambalides, E. J. (1988). Nucleoside restoration of heat resistance and suppression of glucose-regulated protein synthesis by glucose-deprived L929 cells. *Cancer Research.* 48(6): 1442-1445.

Latifah, S. Y., Ng, W. K., Al-Naqeeb, G., and Ismail, M. (2009). Cytotoxicity of thymoquinone (TQ) from *Nigella sativa* towards human cervical carcinoma cells (HeLa).*Journal of Pharmacy Research*. 2(4): 585-589.

Le Pennec, S., Mirebeau-Prunier, D., Boutet-Bouzamondo, N., Jacques, C., Guillotin, D., Lauret, E., *et al.* (2011). Nitric oxide and calcium participate in the fine regulation of mitochondrial biogenesis in follicular thyroid carcinoma cells. *Journal of Biological Chemistry.* 286(20): 18229-18239.

Lee, A. H., Iwakoshi, N. N., & Glimcher, L. H. (2003). XBP-1 regulates a subset of endoplasmic reticulum resident chaperone genes in the unfolded protein response. *Molecular and Cellular Biology.* 23(21): 7448-7459.

Lehtinen, M., Koskela, P., Jellum, E., Bloigu, A., Anttila, T., Hallmans, G., *et al*. (2002). Herpes simplex virus and risk of cervical cancer: a longitudinal, nested case-control study in the nordic countries. *American Journal of Epidemiology.* 156(8): 687-692.

Lei, X., Lv, X., Liu, M., Yang, Z., Ji, M., Guo, X., *et al*. (2012). Thymoquinone inhibits growth and augments 5-fluorouracil-induced apoptosis in gastric cancer cells both *in vitro* and *in vivo*. *Biochemistry & Biophysics Research Communication.* 417(2): 864-868.

Leminen, A. (1990). Tumor markers CA-125, carcinoembryonic antigen and tumor-associated trypsin inhibitor in patients with cervical adenocarcinoma. *Gynecologic Oncology.* 39(3): 358-363.

Lesnikova, I., Lidang, M., Hamilton-Dutoit, S., & Koch, J. (2009). p16 as a diagnostic marker of cervical neoplasia: a tissue microarray study of 796 archival specimens. *Diagnostic Pathology.* 4(22): 1746-1596.

Levine, A. J. (1997). p53, the cellular gatekeeper for growth and division. *Cell.* 88: 323-331.

Leys, C. M., Nomura, S., LaFleur, B. J., Ferrone, S., Kaminishi, M., Montgomery, E., *et al*. (2007). Expression and prognostic significance of prothymosin-alpha and ERp57 in human gastric cancer. *Surgery.* 141(1): 41-50.

Li, A. P., Bode, C., & Sakai, Y. (2004). A novel *in vitro* system, the integrated discrete multiple organ cell culture (IdMOC) system, for the evaluation of human drug toxicity: comparative cytotoxicity of tamoxifen towards normal human cells from five major organs and MCF-7 adenocarcinoma breast cancer cells. *Chemico-Biological Interactions.* 150(1): 129-136.

Li, F., Rajendran, P., & Sethi, G. (2010). Thymoquinone inhibits proliferation, induces apoptosis and chemosensitizes human multiple myeloma cells through suppression of signal transducer and activator of transcription 3 activation pathway. *British Journal of Pharmacology.* 161(3): 541-554.

Li, L. Y., Luo, X., & Wang, X. (2001). Endonuclease G is an apoptotic DNase when released from mitochondria. *Nature.* 412(6842): 95-99.

Li, W., & Melton, D. W. (2012). Cisplatin regulates the MAPK kinase pathway to induce increased expression of DNA repair gene *ERCC1* and increase melanoma chemoresistance. *Oncogene.* 31(19): 2412-2422.

Li, Y., & Camacho, P. (2004). Ca^{2+}-dependent redox modulation of SERCA 2b by ERp57. *Journal of Cell Biology.* 164(1): 35-46.

Liao, C. J., Wu, T. I., Huang, Y. H., Chang, T. C., Wang, C. S., Tsai, M. M., *et al*. (2011). Glucose-regulated protein 58 modulates cell invasiveness and serves as a prognostic marker for cervical cancer. *Cancer Science.* 102(12): 2255-2263.

Lim, D. S., Kim, S. T., Xu, B., Maser, R. S., Lin, J., Petrini, J. H., *et al*. (2000). ATM phosphorylates p95/nbs1 in an S-phase checkpoint pathway. *Nature.* 404(6778): 613-617.

Lim, K. H., Baines, A. T., Fiordalisi, J. J., Shipitsin, M., Feig, L. A., Cox, A. D., *et al*. (2005). Activation of RalA is critical for Ras-induced tumorigenesis of human cells. *Cancer Cell.* 7(6): 533-545.

Lin, B., Williams-Skipp, C., Tao, Y., Schleicher, M. S., Cano, L. L., Duke, R. C., *et al*. (1999). NF-kappaB functions as both a proapoptotic and antiapoptotic regulatory factor within a single cell type. *Cell Death & Differentiation.* 6(6): 570-582.

Lin, W. C., Chuang, Y. C., Chang, Y. S., Lai, M. D., Teng, Y. N., Su, I. J., *et al.* (2012). Endoplasmic reticulum stress stimulates p53 expression through NF-kappaB activation. *PLoS One.* 7(7): 39120.

Lindquist, J. A., Jensen, O. N., Mann, M., & Hammerling, G. J. (1998). ER-60, a chaperone with thiol-dependent reductase activity involved in MHC class I assembly. *EMBO Journal.* 17(8), 2186-2195.

Liu, F. T., Newland, A. C., & Jia, L. (2003). Bax conformational change is a crucial step for PUMA-mediated apoptosis in human leukemia. *Biochemistry & Biophysics Research Communication.* 310(3): 956-962.

Liu, H. R., Peng, X. D., He, H. B., Wang, Y. H., Li, Y., He, G. X., *et al*. (2008). Antiproliferative activity of the total saponin of *Solanum lyratum* Thunb in Hela cells by inducing apoptosis. *Pharmazie.* 63(11): 836-842.

Locksley, R. M., Killeen, N., & Lenardo, M. J. (2001). The TNF and TNF receptor superfamilies: integrating mammalian biology. *Cell.* 104(4): 487-501.

Lomovskaya, N., Otten, S. L., Doi-Katayama, Y., Fonstein, L., Liu, X. C., Takatsu, T., *et al*. (1999). Doxorubicin overproduction in *Streptomyces peucetius*: cloning and characterization of the *dnrU ketoreductase* and *dnrV* genes and the *doxA cytochrome P-450 hydroxylase* gene. *Journal of Bacteriology.* 181(1): 305-318.

Loncaster, J. A., Cooper, R. A., Logue, J. P., Davidson, S. E., Hunter, R. D., & West, C. M. (2000). Vascular endothelial growth factor (VEGF) expression is a prognostic factor for radiotherapy outcome in advanced carcinoma of the cervix. *British Journal of Cancer.* 83(5): 620-625.

Long, H. J., Bundy, B. N., Grendys, E. C., Benda, J. A., McMeekin, D. S., Sorosky, J.*, et al*. (2005). Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: A gynecologic oncology group study. *Journal of Clinical Oncology.* 23(21): 4626-4633.

Longworth, M. S., & Laimins, L. A. (2004). Pathogenesis of human papillomaviruses in differentiating epithelia. *Microbiology & Molecular Biology Review.* 68(2): 362-372.

Lopez-Girona, A., Furnari, B., Mondesert, O., & Russell, P. (1999). Nuclear localization of Cdc25 is regulated by DNA damage and a 14-3-3 protein. *Nature.* 397(6715): 172-175.

Lowenberg, B., Pabst, T., Vellenga, E., van Putten, W., Schouten, H. C., Graux, C., *et al*. (2011). Cytarabine dose for acute myeloid leukemia. *New England Journal of Medicine.* 364(11): 1027-1036.

Lu, B., Wu, Y., Nielson, C. M., Flores, R., Abrahamsen, M., Papenfuss, M., *et al*. (2009). Factors associated with acquisition and clearance of human papillomavirus infection in a cohort of US men: a prospective study. *Journal of Infectious Diseases.* 199(3): 362-371.

Lundberg, A. S., & Weinberg, R. A. (1998). Functional inactivation of the retinoblastoma protein requires sequential modification by at least two distinct cyclin-cdk complexes. *Molecular and Cellular Biology.* 18(2): 753-761.

Lwin, Z. M., Yip, G. W., Chew, F. T., & Bay, B. H. (2012). Downregulation of ER60 protease inhibits cellular proliferation by inducing G1/S arrest in breast cancer cells *in vitro*. *Anatomical Record (Hoboken).* 295(3): 410-416.

Ly, J. D., Grubb, D. R., & Lawen, A. (2003). The mitochondrial membrane potential (delta psi(m)) in apoptosis: an update. *Apoptosis.* 8(2): 115-128.

Lynch, H. T., Casey, M. J., Shaw, T. G., & Lynch, J. F. (1998). Hereditary factors in gynecologic cancer. *Oncologist.* 3(5): 319-338.

Ma, X., & Wang, Z. (2009). Anticancer drug discovery in the future: an evolutionary perspective. *Drug Discovery Today.* 14(23-24): 1136-1142.

Mahmood, T. & Yang, P.C. (2012). Western Blot: Technique, theory, and trouble shooting. *National American Journal of Medical Sciences*. 4:429–34

Majno, G., & Joris, I. (1995). Apoptosis, oncosis, and necrosis. An overview of cell death. *American Journal of Pathology.*146(1): 3-15.

Manci, N., Marchetti, C., Di Tucci, C., Giorgini, M., Esposito, F., Palaia, I., *et al*. (2011). A prospective Phase II study of topotecan (Hycamtin(R)) and cisplatin as neoadjuvant chemotherapy in locally advanced cervical cancer. *Gynecologic Oncology.* 122(2): 285-290.

Mandic, A., Hansson, J., Linder, S., & Shoshan, M. C. (2003). Cisplatin induces endoplasmic reticulum stress and nucleus-independent apoptotic signaling. *Journal of Biological Chemistry.* 278(11): 9100-9106.

Manfredi, J. J. (2010). The Mdm2-p53 relationship evolves: Mdm2 swings both ways as an oncogene and a tumor suppressor. *Genes & Development.* 24(15): 1580-1589.

Marchiole, P., Benchaib, M., Buenerd, A., Lazlo, E., Dargent, D., & Mathevet, P. (2007). Oncological safety of laparoscopic-assisted vaginal radical trachelectomy (LARVT or Dargent's operation): a comparative study with laparoscopic-assisted vaginal radical hysterectomy (LARVH). *Gynecologic Oncology.* 106(1): 132-141.

Martinez, J. A., Zhang, Z., Svetlov, S. I., Hayes, R. L., Wang, K. K., & Larner, S. F. (2010). Calpain and caspase processing of caspase-12 contribute to the ER stress-induced cell death pathway in differentiated PC12 cells. *Apoptosis.* 15(12): 1480-1493.

Mat Salleh, K., & Latiff, A. (2002). *Medicinal Plants of Malaysia (Tumbuhan Ubatan Malaysia)*. Pusat Pengurusan Penyelidikan, Bangi: Universiti Kebangsaan Malaysia.

Mayer, M., Frey, S., Koivunen, P., Myllyharju, J., & Buchner, J. (2004). Influence of the oxidoreductase ER57 on the folding of an antibody FAB fragment. *Journal of Molecular Biology.* 341(4): 1077-1084.

McCluggage, W.G. (2013). New developments in endocervical glandular lesions. *Histopathology.* 62(1):138–160

McIndoe, W. A., McLean, M. R., Jones, R. W., & Mullins, P. R. (1984). The invasive potential of carcinoma *in situ* of the cervix. *Obstetrics & Gynecology.* 64(4): 451-458.

McNutt, N., Saenz-Santamaria, C., Volkenandt, M., Shea, C. R., & Albino, A. P. (1994). Abnormalities of p53 protein expression in cutaneous disorders. *Archives of Dermatology.* 130(2): 225-232.

Medina-Holguin, A. L., Holguin, F. O., Micheletto, S., Goehle, S., Simon, J. A., & O'Connell, M. A. (2008). Chemotypic variation of essential oils in the medicinal plant, *Anemopsis californica*. *Phytochemistry.* 69(4): 919-927.

Mehta, A. M., Jordanova, E. S., Kenter, G. G., Ferrone, S., & Fleuren, G. J. (2008). Association of antigen processing machinery and HLA class I defects with clinicopathological outcome in cervical carcinoma. *Cancer Immunology & Immunotherapy.* 57(2): 197-206.

Meijer, T. W., Schuurbiers, O. C., Kaanders, J. H., Looijen-Salamon, M. G., de Geus-Oei, L. F., Verhagen, A. F., *et al*. (2012). Differences in metabolism between adeno- and squamous cell non-small cell lung carcinomas: spatial distribution and prognostic value of GLUT1 and MCT4. *Lung Cancer,* 76(3): 316-323.

Michaud, W. A., Nichols, A. C., Mroz, E. A., Faquin, W. C., Clark, J. R., Begum, S., *et al*. (2009). Bcl-2 blocks cisplatin-induced apoptosis and predicts poor outcome following chemoradiation treatment in advanced oropharyngeal squamous cell carcinoma. *Clinical Cancer Research.* 15(5): 1645-1654.

Milgrom, S. A., Kollmeier, M. A., Abu-Rustum, N. R., Tew, W. P., Sonoda, Y., Barakat, R. R., *et al*. (2013). Postoperative external beam radiation therapy and concurrent cisplatin followed by carboplatin/paclitaxel for stage III (FIGO 2009) endometrial cancer. *Gynecologic Oncology.* 130(3): 436-440.

Mishra, K. P., Shweta, Diwaker, D., & Ganju, L. (2012). Dengue virus infection induces upregulation of hn RNP-H and PDIA3 for its multiplication in the host cell. *Virus Research.* 163(2): 573-579.

Mitsuhashi, A., Matsui, H., Usui, H., Nagai, Y., Tate, S., Unno, Y., *et al*. (2009). Serum YKL-40 as a marker for cervical adenocarcinoma. *Annals of Oncology.* 20(1): 71-77.

Miyashita, T., Krajewski, S., Krajewska, M., Wang, H. G., Lin, H. K., Liebermann, D. A., *et al*. (1994). Tumor suppressor *p53* is a regulator of *Bcl-2* and *Bax* gene expression *in vitro* and *in vivo*. *Oncogene.* 9(6): 1799-1805.

Mizoroki, T., Meshitsuka, S., Maeda, S., Murayama, M., Sahara, N., & Takashima, A. (2007). Aluminum induces TAU aggregation *in vitro* but not *in vivo*. *Journal of Alzheimer's Disease.* 11(4): 419-427.

Mobbs, C. V., Fink, G., & Pfaff, D. W. (1990). HIP-70: a protein induced by estrogen in the brain and LH-RH in the pituitary. *Science.* 247(4949 Pt 1): 1477-1479.

Mocarski, E. S., Upton, J. W., & Kaiser, W. J. (2011). Viral infection and the evolution of caspase 8-regulated apoptotic and necrotic death pathways. *Nature Reviews of Immunology.* 12(2): 79-88.

Mock, J., McPhee, S. J., Nguyen, T., Wong, C., Doan, H., Lai, K. Q., *et al.* (2007). Effective lay health worker outreach and media-based education for promoting cervical cancer screening among Vietnamese American women. *American Journal of Public Health.* 97(9): 1693-1700.

Molina, R., Filella, X., Auge, J. M., Bosch, E., Torne, A., Pahisa, J., *et al.* (2005). CYFRA 21.1 in patients with cervical cancer: comparison with SCC and CEA. *Anticancer Research.* 25(3A): 1765-1771.

Monie, A., Hung, C. F., Roden, R., & Wu, T. C. (2008). Cervarix: a vaccine for the prevention of HPV 16, 18-associated cervical cancer. *Biologics.* 2(1): 97-105.

Monk, B. J., Tian, C., Rose, P. G., & Lanciano, R. (2007). Which clinical/pathologic factors matter in the era of chemoradiation as treatment for locally advanced cervical carcinoma? Analysis of two Gynecologic Oncology Group (GOG) trials. *Gynecology & Oncology.* 105(2): 427-433.

Monsonego, J., Autillo-Touati, A., Bergeron, C., Dachez, R., Liaras, J., Saurel, J., *et al*. (2001). Liquid-based cytology for primary cervical cancer screening: a multi-centre study. *British Journal of Cancer.* 84(3): 360-366.

Moore, D. H. (2008). Chemotherapy for advanced, recurrent, and metastatic cervical cancer. *Journal of the National Comprehensive Cancer Network.* 6(1): 53-57.

Moore, D. H., Blessing, J. A., McQuellon, R. P., Thaler, H. T., Cella, D., Benda, J., *et al*. (2004). Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: a gynecologic oncology group study. *Journal of Clinical Oncology.* 22(15): 3113-3119.

Morgan, D. O. (1997). Cyclin-dependent kinases: engines, clocks, and microprocessors. *Annual Review of Cell and Developmental Biology.* 13: 261-291.

Morishima, N., Nakanishi, K., Takenouchi, H., Shibata, T., & Yasuhiko, Y. (2002). An endoplasmic reticulum stress-specific caspase cascade in apoptosis. Cytochrome c-independent activation of caspase-9 by caspase-12. *Journal of Biological Chemistry.* 277(37): 34287-34294.

Morrice, N. A., & Powis, S. J. (1998). A role for the thiol-dependent reductase ERp57 in the assembly of MHC class I molecules. *Current Biology.* 8(12): 713-716.

Morrison, T. B., Weis, J. J., & Wittwer, C. T. (1998). Quantification of low-copy transcripts by continuous SYBR Green I monitoring during amplification. *Biotechniques.*24:954–8.

Moscicki, A. B., & Cox, J. T. (2010). Practice improvement in cervical screening and management (PICSM): symposium on management of cervical abnormalities in adolescents and young women. *Journal of Low Genital Tract Diseases.* 14(1): 73-80.

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

Muliawan, S. Y. (2008). Effect of *Dillenia suffruticosa* extract on dengue virus type 2 replication. *Universa Medicina.* 27(1): 1-5.

Munoz, N., Franceschi, S., Bosetti, C., Moreno, V., Herrero, R., Smith, J. S., *et al*. (2002). Role of parity and human papillomavirus in cervical cancer: the IARC multicentric case-control study. *Lancet.* 359(9312): 1093-1101.

Murray, N., & Turrisi, A. T. (2006). A review of first-line treatment for small-cell lung cancer. *Journal of Thoracic Oncology.* 1(3): 270-278.

Murthy, N. S., & Mathew, A. (2000). Risk factors for precancerous lesions of the cervix. *European Journal of Cancer Prevention.* 9(1): 5-14.

Murthy, M. S., & Pande, S. V. (1994). A stress-regulated protein, GRP58, a member of thioredoxin superfamily, is a carnitine palmitoyltransferase isoenzyme. *Biochemistry Journal.* 304(1): 31-34.

Nakagawa, T., & Yuan, J. (2000). Cross-talk between two cysteine protease families. Activation of caspase-12 by calpain in apoptosis. *Journal of Cell Biology.* 150(4): 887-894.

Nakagawa, T., Zhu, H., Morishima, N., Li, E., Xu, J., Yankner, B. A*., et al*. (2000). Caspase-12 mediates endoplasmic-reticulum-specific apoptosis and cytotoxicity by amyloid-beta. *Nature.* 403(6765): 98-103.

Nakano, K., & Vousden, K. H. (2001). *PUMA*, a novel proapoptotic gene, is induced by p53. *Molecular Cell.* 7(3): 683-694.

Nakatani, K., Nakamura, M., Uzawa, K., Wada, T., Seki, N., Tanzawa, H., *et al*. (2005). Establishment and gene analysis of a cisplatin-resistant cell line, Sa-3R, derived from oral squamous cell carcinoma. *Oncology Reports.* 13(4): 709-714.

Nayereh, K. G., & Khadem, G. (2012). Preventive and therapeutic vaccines against human papillomaviruses associated cervical cancers. *Iran Journal of Basic Medical Sciences.* 15(1): 585-601.

NCI (National Cancer Institue) (2010). Cervical Cancer Treatment (PDQ®), Patient Version. http://www.cancer.gov/cancertopics/pdq/treatment/cervical/PatientU.S. Department of Health and Human Services, National Institutes of Health, U.S.A. Retrieved 2nd March 2014.

NCI (National Cancer Institute) (2013). Drugs Approved for Cervical Cancer. http://www.cancer.gov/cancertopics/druginfo/cervicalcancerU.S. Department of Health and Human Services, National Institutes of Health, U.S.A. Retrieved 2 March 2014.

Nemere, I. (2005). The 1,25D3-MARRS protein: contribution to steroid stimulated calcium uptake in chicks and rats. *Steroids.* 70(5-7): 455-457.

Nemere, I., Garbi, N., Hammerling, G. J., & Khanal, R. C. (2010). Intestinal cell calcium uptake and the targeted knockout of the 1,25D3-MARRS (membrane-associated, rapid response steroid-binding) receptor/PDIA3/Erp57. *Journal of Biological Chemistry.* 285(41): 31859-31866.

Newell, D. R., Searle, K. M., Westwood, N. B., & Burtles, S. S. (2003). Professor Tom Connors and the development of novel cancer therapies by the Phase I/II Clinical Trials Committee of Cancer Research UK. *British Journal of Cancer.* 89(3): 437-454.

Newman, D. J., & Cragg, G. M. (2007). Natural products as sources of new drugs over the last 25 years. *Journal of Natural Products.* 70(3): 461-477.

Newman, D. J., & Cragg, G. M. (2012). Natural products as sources of new drugs over the 30 years from 1981 to 2010. *Journal of Natural Products.* 75(3): 311-335.

Newmeyer, D. D., Bossy-Wetzel, E., Kluck, R. M., Wolf, B. B., Beere, H. M., & Green, D.R. (2000). Bcl-xL does not inhibit the function of Apaf-1. *Cell Death & Differentiation.* 7(4): 402-407.

Ng, W. K., Latifah S. Y. & Ismail, M. (2011). Thymoquinone from *Nigella sativa* was more potent than cisplatin in eliminating of SiHa cells via apoptosis with down-regulation of Bcl-2 protein. *Toxicology In Vitro.* 25(7): 1392-1398.

Ni, M., & Lee, A. S. (2007). ER chaperones in mammalian development and human diseases. *FEBS Letters.* 581(19): 3641-3651.

NIEHS (National Institute of Environmental Health Sciences) (2001). Validation study of in vitro cytotoxicity test methods. National Institutes of Health. U.S.A. http://ntp.niehs.nih.gov/go/40361. Retrieved 3 February 2014.

Nishikawa, S., Brodsky, J. L., & Nakatsukasa, K. (2005). Roles of molecular chaperones in endoplasmic reticulum (ER) quality control and ER-associated degradation (ERAD). *Journal of Biochemistry.* 137(5): 551-555.

Nordlinger, B., Rougier, P., Arnaud, J. P., Debois, M., Wils, J., Ollier, J. C., *et al*. (2005). Adjuvant regional chemotherapy and systemic chemotherapy versus systemic chemotherapy alone in patients with stage II-III colorectal cancer: a multicentre randomised controlled phase III trial. *Lancet Oncology.* 6(7): 459-468.

Nowak, G., Price, P. M., & Schnellmann, R. G. (2003). Lack of a functional p21WAF1/CIP1 gene accelerates caspase-independent apoptosis induced by cisplatin in renal cells. *American Journal of Physiology: Renal Physiology.* 285(3): 440-450.

Oda, E., Ohki, R., Murasawa, H., Nemoto, J., Shibue, T., Yamashita, T., *et al*. (2013). A phase III concurrent chemoradiotherapy trial with cisplatin and paclitaxel or docetaxel or gemcitabine in unresectable non-small cell lung cancer: KASLC 0401. *Cancer Chemotherapy and Pharmacology.* 72(6): 1247-1254.

Oda, E., Ohki, R., Murasawa, H., Nemoto, J., Shibue, T., Yamashita, T., *et al*. (2000). Noxa, a BH3-Only Member of the Bcl-2 Family and Candidate Mediator of p53-Induced Apoptosis. *Science,* 288(5468): 1053-1058.

Ogura, M., Itoh, K., Ishizawa, K., Kobayashi, Y., Tobinai, K., Kinoshita, T., *et al*. (2013). Phase II study of ABV (doxorubicin with increased dose, bleomycin and vinblastine) therapy in newly diagnosed advanced-stage Hodgkin lymphoma: Japan Clinical Oncology Group study (JCOG9705). *Leukemia & Lymphoma.* 54(1): 46-52.

Oh, I. J., Kim, K. S., Kim, Y. C., Ban, H. J., Kwon, Y. S., Kim, Y. I., *et al.* (2013). A phase III concurrent chemoradiotherapy trial with cisplatin and paclitaxel or docetaxel or gemcitabine in unresectable non-small cell lung cancer: KASLC 0401. *Cancer Chemotherapy & Pharmacology. 72*(6): 1247-1254.

Oike, T., Ohno, T., Noda, S. E., Sato, H., Tamaki, T., Kiyohara, H., *et al*. (2012). Comparison of hematological toxicities between innovator and generic cisplatin formulations in cervical cancer patients treated with concurrent chemoradiotherapy. *Journal of Radiation Research.* 14: 14.

Okudo, H., Kato, H., Arakaki, Y., & Urade, R. (2005). Cooperation of ER-60 and BiP in the oxidative refolding of denatured proteins *in vitro*. *Journal of Biochemistry.* 138(6): 773-780.

Orlando, G., Fasolo, M., Mazza, F., Ricci, E., Esposito, S., Frati, E., *et al*. (2014). Risk of cervical HPV infection and prevalence of vaccine-type and other high-risk HPV types among sexually active teens and young women (13-26 years) enrolled in the VALHIDATE study. *Human Vaccine & Immunotherapy.*10: 4.

Oubrahim, H., Stadtman, E. R., & Chock, P. B. (2001). Mitochondria play no roles in Mn(II)-induced apoptosis in HeLa cells. *Proceedings National Academic of Science U.S.A.* 98(17): 9505-9510.

Owen-Schaub, L. B., Zhang, W., Cusack, J. C., Angelo, L. S., Santee, S. M., Fujiwara, T., *et al.* (1995). Wild-type human p53 and a temperature-sensitive mutant induce Fas/APO-1 expression. *Molecular Cell Biology.* 15(6): 3032-3040.

Oyadomari, S., & Mori, M. (2004). Roles of CHOP/GADD153 in endoplasmic reticulum stress. *Cell Death & Differentiation.* 11(4): 381-389.

Ozaki, T., Yamashita, T., & Ishiguro, S. (2008). ERp57-associated mitochondrial micro-calpain truncates apoptosis-inducing factor. *Biochimica & Biophysica Acta.* 1783(10): 1955-1963.

Ozaki, T., Yamashita, T., & Ishiguro, S. (2011). Ca^{2+}-induced release of mitochondrial m-calpain from outer membrane with binding of calpain small subunit and Grp75. *Archives of Biochemistry & Biophysics.* 507(2): 254-261.

Paavonen, J., Naud, P., Salmeron, J., Wheeler, C. M., Chow, S. N., Apter, D., *et al*. (2009). Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. *Lancet.* 374(9686): 301-314.

Paba, P., Bonifacio, D., Di Bonito, L., Ombres, D., Favalli, C., Syrjanen, K.*, et al*. (2008). Co-expression of HSV2 and *Chlamydia trachomatis* in HPV-positive cervical cancer and cervical intraepithelial neoplasia lesions is associated with aberrations in key intracellular pathways. *Intervirology.* 51(4): 230-234.

Paramasivam, A., Sambantham, S., Shabnam, J., Raghunandhakumar, S., Anandan, B., Rajiv, R., *et al.* (2012). Anti-cancer effects of thymoquinone in mouse neuroblastoma (Neuro-2a) cells through caspase-3 activation with down-regulation of XIAP. *Toxicology Letters.* 213(2): 151-159.

Paraskevaidis, E., Koliopoulos, G., Lolis, E., Papanikou, E., Malamou-Mitsi, V., & Agnantis, N. J. (2002). Delivery outcomes following loop electrosurgical excision procedure for microinvasive (FIGO stage IA1) cervical cancer. *Gynecologic Oncology.* 86(1): 10-13.

Park, S., J., Rhyu, J. W., Kim, C. J., Kim, H. S., Lee, S. Y., *et al*. (2003). Neoplastic change of squamo-columnar junction in uterine cervix and vaginal epithelium by exogenous estrogen in hpv-18 URR E6/E7 transgenic mice. *Gynecology & Oncology.* 89(3): 360-368.

Park, S. Y., Bae, D. S., Nam, J. H., Park, C. T., Cho, C. H., Lee, J. M., *et al.* (2007). Quality of life and sexual problems in disease-free survivors of cervical cancer compared with the general population. *Cancer.* 110(12): 2716-2725.

Parkin, D. M., Bray, F., Ferlay, J., & Pisani, P. (2005). Global Cancer Statistics, 2002. *CA: A Cancer Journal for Clinicians.* 55(2): 74-108.

Pascal, L. E., True, L. D., Campbell, D. S., Deutsch, E. W., Risk, M., Coleman, I. M., *et al.* (2008). Correlation of mRNA and protein levels: cell type-specific gene expression of cluster designation antigens in the prostate. *BMC Genomics, 9*(246), 1471-2164.

Paulovich, A. G., & Hartwell, L. H. (1995). A checkpoint regulates the rate of progression through S phase in *S. cerevisiae* in response to DNA damage. *Cell.* 82(5): 841-847.

Peng, L., Liu, A., Shen, Y., Xu, H. Z., Yang, S. Z., Ying, X. Z., *et al*. (2013). Antitumor and anti-angiogenesis effects of thymoquinone on osteosarcoma through the NF-kappaB pathway. *Oncology Reports.* 29(2): 571-578.

Pereira, L., Igea, A., Canovas, B., Dolado, I., & Nebreda, A. R. (2013). Inhibition of p38 MAPK sensitizes tumour cells to cisplatin-induced apoptosis mediated by reactive oxygen species and JNK. *EMBO Molecular Medicine.* 5(11): 1759-1774.

Perez, E. A., Suman, V. J., Davidson, N. E., Gralow, J. R., Kaufman, P. A., Visscher, D. W., *et al*. (2011). Sequential versus concurrent trastuzumab in adjuvant chemotherapy for breast cancer. *Journal of Clinical Oncology.* 29(34): 4491-4497.

Peter, M. E., & Krammer, P. H. (1998). Mechanisms of CD95 (APO-1/Fas)-mediated apoptosis. *Current Opinion in Immunology.* 10(5): 545-551.

Pettit, G. R., Singh, S. B., Niven, M. L., Hamel, E., & Schmidt, J. M. (1987). Isolation, structure, and synthesis of combretastatins A-1 and B-1, potent new inhibitors of microtubule assembly, derived from *Combretum caffrum*. *Journal of Natural Products.* 50(1): 119-131.

Pfeifer, G. P., Denissenko, M. F., Olivier, M., Tretyakova, N., Hecht, S. S., & Hainaut, P. (2002). Tobacco smoke carcinogens, DNA damage and *p53* mutations in smoking-associated cancers. *Oncogene.* 21(48): 7435-7451.

Piccart-Gebhart, M. J., Procter, M., Leyland-Jones, B., Goldhirsch, A., Untch, M., Smith, I., *et al*. (2005). Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *New England Journal of Medicine.* 353(16): 1659-1672.

Pietila, M., Lahteenmaki, K., Lehtonen, S., Leskela, H. V., Narhi, M., Lonnroth, M., *et al*. (2012). Monitoring mitochondrial inner membrane potential for detecting early changes in viability of bacterium-infected human bone marrow-derived mesenchymal stem cells. *Stem Cell Research & Therapy.* 3(6): 53.

Pignata, S., Silvestro, G., Ferrari, E., Selvaggi, L., Perrone, F., Maffeo, A., *et al*. (1999). Phase II study of cisplatin and vinorelbine as first-line chemotherapy in patients with carcinoma of the uterine cervix. *Journal of Clinical Oncology.* 17(3): 756-760.

Pirog, E.C., Kleter, B., Olgac, S., Bobkiewicz, P., Lindeman, J., Quint, W.G., *et al*. (2000). Prevalence of human papillomavirus DNA in different histological subtypes of cervical adenocarcinoma. *American Journal of Pathology.* 157(4):1055–1062.

Plummer, M., Herrero, R., Franceschi, S., Meijer, C. J., Snijders, P., Bosch, F. X., *et al.* (2003). Smoking and cervical cancer: pooled analysis of the IARC multi-centric case-control study. *Cancer Causes & Control.* 14(9): 805-814.

Polyak, K., Waldman, T., He, T. C., Kinzler, K. W., & Vogelstein, B. (1996). Genetic determinants of p53-induced apoptosis and growth arrest. *Genes & Development.* 10(15): 1945-1952.

Prendiville, W., Cullimore, J., & Norman, S. (1989). Large loop excision of the transformation zone (LLETZ). A new method of management for women with cervical intraepithelial neoplasia. *British Journal of Obstetrics & Gynaecology.* 96(9): 1054-1060.

Pressinotti, N. C., Klocker, H., Schafer, G., Luu, V. D., Ruschhaupt, M., Kuner, R., *et al*. (2009). Differential expression of apoptotic genes *PDIA3* and *MAP3K5* distinguishes between low- and high-risk prostate cancer. *Molecular Cancer.* 8(130): 1476-4598.

Preuss, S. B., & Britt, A. B. (2003). A DNA-damage-induced cell cycle checkpoint in *Arabidopsis*. *Genetics.* 164(1): 323-334.

Price, P. M.; Yu, F.; Kaldis, P.; Aleem, E.; Nowak, G.; Safirstein, R. L.; Megyesi, J.(2006) Dependence of cisplatin-induced cell death in vitro and in vivo on cyclin-dependent kinase 2. *Journal of American Society of Nephrology,* 17(9): 2434-2442.

Prins, D., Groenendyk, J., Touret, N., & Michalak, M. (2011). Modulation of STIM1 and capacitative Ca^{2+} entry by the endoplasmic reticulum luminal oxidoreductase ERp57. *EMBO Reports.* 12(11): 1182-1188.

Protein Disulfide Isomerase Family A, Weizmann Institute of Science Crown Human Genome Center USA http://www.genecards.org/cgi-bin/carddisp.pl?gene=PDIA3. Retrieved 4th September 2014.

Raghunandhakumar, S., Paramasivam, A., Senthilraja, S., Naveenkumar, C., Asokkumar, S., Binuclara, J., *et al*. (2013a). Thymoquinone inhibits cell proliferation through regulation of G1/S phase cell cycle transition in N-nitrosodiethylamine-induced experimental rat hepatocellular carcinoma. *Toxicology Letters.* 3(13): 1290-1293.

Raghunandhakumar, S., Paramasivam, A., Senthilraja, S., Naveenkumar, C., Rajput, S., Kumar, B. N., *et al*. (2013b). Targeted apoptotic effects of thymoquinone and tamoxifen on XIAP mediated Akt regulation in breast cancer. *PLoS One.* 8(4): e61342.

Rai, N. K., Tripathi, K., Sharma, D., & Shukla, V. K. (2005). Apoptosis: a basic physiologic process in wound healing. *International Journal of LowerExtremityWounds,* 4(3): 138-144.

Rajput, S., Kumar, B. N., Sarkar, S., Das, S., Azab, B., Santhekadur, P. K., *et al.* (2013). Targeted apoptotic effects of thymoquinone and tamoxifen on XIAP mediated Akt regulation in breast cancer. *PLoS One.* 8(4): e61342.

Ramana, K. V., Tammali, R., & Srivastava, S. K. (2010). Inhibition of aldose reductase prevents growth factor-induced G1-S phase transition through the AKT/phosphoinositide 3-kinase/E2F-1 pathway in human colon cancer cells. *Molecular Cancer Therapeutics.* 9(4): 813-824.

Ramirez-Rangel, I., Bracho-Valdes, I., Vazquez-Macias, A., Carretero-Ortega, J., Reyes-Cruz, G., & Vazquez-Prado, J. (2011). Regulation of mTORC1 complex assembly and signaling by GRp58/ERp57. *Molecular Cell Biology.* 31(8): 1657-1671.

Rao, R. V., Ellerby, H. M., & Bredesen, D. E. (2004). Coupling endoplasmic reticulum stress to the cell death program. *Cell Death & Differentiation.* 11(4): 372-380.

Rasheva, V. I., & Domingos, P. M. (2009). Cellular responses to endoplasmic reticulum stress and apoptosis. *Apoptosis.* 14(8): 996-1007.

Ridley, H. N. (1922). *The flora of the Malay Peninsula.* (Volume 5). L. Reeve & Co., Ltd, Covent Garden, U.K.

Ries L. A. G., Melbert D., Krapcho M., Stinchcomb D. G., Howlader N., Horner M. J., et al. (2007). SEER Cancer Statistics Review, 1975-2005, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2005/

Rifaioglu, M. M., Nacar, A., Yuksel, R., Yonden, Z., Karcioglu, M., Zorba, O. U., *et al.* (2013). Antioxidative and anti-inflammatory effect of thymoquinone in an acute *Pseudomonas prostatitis* rat model. *Urology International.* 91(4): 474-481.

Righetti, S. C., Perego, P., Carenini, N., & Zunino, F. (2008). Cooperation between p53 and p73 in cisplatin-induced apoptosis in ovarian carcinoma cells. *Cancer Letters.* 263(1): 140-144.

Roberts, J. D., Van Houten, B., Qu, Y., & Farrell, N. P. (1989). Interaction of novel bis(platinum) complexes with DNA. *Nucleic Acids Research.* 17(23): 9719-9733.

Roden, R., & Wu, T. C. (2006). How will HPV vaccines affect cervical cancer? *Nature Review Cancer.* 6(10): 753-763.

Roepke, M., Diestel, A., Bajbouj, K., Walluscheck, D., Schonfeld, P., Roessner, A., *et al*. (2007). Lack of p53 augments thymoquinone-induced apoptosis and caspase activation in human osteosarcoma cells. *Cancer Biology & Therapy.* 6(2): 160-169.

Ron, D., & Walter, P. (2007). Signal integration in the endoplasmic reticulum unfolded protein response. *Nature Review Molecular & Cellular Biology.* 8(7): 519-529.

Rose, P. G., Sill, M. W., McMeekin, D. S., Ahmed, A., Salani, R., Yamada, S. D., *et al.* (2012). A phase I study of concurrent weekly topotecan and cisplatin chemotherapy with whole pelvic radiation therapy in locally advanced cervical cancer: a gynecologic oncology group study. *Gynecologic Oncology.* 125(1): 158-162.

Rouette, A., Parent, S., Girouard, J., Leblanc, V., & Asselin, E. (2012). Cisplatin increases B-cell-lymphoma-2 expression via activation of protein kinase C and Akt2 in endometrial cancer cells. *International Journal of Cancer.* 130(8): 1755-1767.

Rubio-Moscardo, F., Blesa, D., Mestre, C., Siebert, R., Balasas, T., Benito, A., *et al*. (2005). Characterization of 8p21.3 chromosomal deletions in B-cell lymphoma: TRAIL-R1 and TRAIL-R2 as candidate dosage-dependent tumor suppressor genes. *Blood.* 106(9). 3214-3222.

Rughooputh, S., Manraj, S., Eddoo, R., & Greenwell, P. (2009). Expression of the *c-myc* oncogene and the presence of HPV 18: possible surrogate markers for cervical cancer? *British Journal of Biomedical Science.* 66(2): 74-78.

Sabbatini, P., Lin, J., Levine, A. J., & White, E. (1995). Essential role for p53-mediated transcription in E1A-induced apoptosis. *Genes & Development.* 9(17): 2184-2192.

Sakahira, H., Enari, M., & Nagata, S. (1998). Cleavage of CAD inhibitor in CAD activation and DNA degradation during apoptosis. *Nature.* 391(6662): 96-99.

Said, T. K., & Medina, D. (1998). Interaction of retinoblastoma protein and D cyclins during cell-growth inhibition by hexamethylenebisacetamide in TM2H mouse epithelial cells. *Molecular Carcinogenesis.* 22(2): 128-143.

Sakalar, C., Yuruk, M., Kaya, T., Aytekin, M., Kuk, S., &Canatan, H. (2013). Pronounced transcriptional regulation of apoptotic and *TNF-NF-kappa-B* signaling genes during the course of thymoquinone mediated apoptosis in HeLa cells. *Molecular Cell Biochemistry*. 383(1-2): 243-51.

Salmon, S. E. & Sartorelli, A. C. (1998). *Cancer Chemotherapy, in Basic and Clinical Pharmacology* (Katzung, B. G., Ed) Appleton-Lange, 1998: pp. 881-911.

Salem, M. L. (2005). Immunomodulatory and therapeutic properties of the *Nigella sativa* L. seed. *International Immunopharmacology.* 5(13-14): 1749-1770.

Sancho-Martinez, S. M., Piedrafita, F. J., Cannata-Andia, J. B., Lopez-Novoa, J. M., & Lopez-Hernandez, F. J. (2011). Necrotic concentrations of cisplatin activate the apoptotic machinery but inhibit effector caspases and interfere with the execution of apoptosis. *Journal of Toxicological Sciences.* 122(1): 73-85.

Sankaranarayanan, R., Wesley, R., Thara, S., Dhakad, N., Chandralekha, B., Sebastian, P.*, et al.* (2003). Test characteristics of visual inspection with 4% acetic acid (VIA) and Lugol's iodine (VILI) in cervical cancer screening in Kerala, India. *International Journal of Cancer.* 106(3): 404-408.

Saraste, A., & Pulkki, K. (2000). Morphologic and biochemical hallmarks of apoptosis. *Cardiovascular Research.* 45(3): 528-537.

Sasieni, P., Castanon, A., & Cuzick, J. (2009). Effectiveness of cervical screening with age: population based case-control study of prospectively recorded data. *British Medical Journal.* 28(339): 2968.

Saslow, D., Solomon, D., Lawson, H. W., Killackey, M., Kulasingam, S. L., Cain, J., *et al*. (2012). American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. *CA: A Cancer Journal for Clinicians.* 62(3): 147-172.

Satyavati G. V. & Gupta A. K. (1987). Medicinal plants of India, 2. New Delhi: *Indian Ccouncil of Medical Research.* Page 257–261.

Savill, J. & Fadok, V. (2000). Corpse clearance defines the meaning of cell death. *Nature.* 407(6805): 784-788.

Scheffner, M., Werness, B. A., Huibregtse, J. M., Levine, A. J., & Howley, P. M. (1990). The E6 oncoprotein encoded by human papillomavirus types 16 and 18 promotes the degradation of p53. *Cell.* 63(6): 1129-1136.

Schiffman, M., Castle, P. E., Jeronimo, J., Rodriguez, A. C., & Wacholder, S. (2007). Human papillomavirus and cervical cancer. *Lancet.* 370(9590): 890-907.

Schiffman, M. H., & Castle, P. (2003). Epidemiologic studies of a necessary causal risk factor: Human papillomavirus infection and cervical neoplasia. *Journal of the National Cancer Institute.* 95(6): 2.

Schlecht, N. F., Platt, R. W., Duarte-Franco, E., Costa, M. C., Sobrinho, J. P., Prado, J. C., *et al.* (2003). Human papillomavirus infection and time to progression and regression of cervical intraepithelial neoplasia. *Journal of the National Cancer Institute.* 95(17): 1336-1343.

Schimmer, A. D., Welsh, K., Pinilla, C., Wang, Z., Krajewska, M., Bonneau, M. J., et al. (2004). Small-molecule antagonists of apoptosis suppressor XIAP exhibit broad antitumor activity. *Cancer Cell.* 5(1): 25-35.

Schmitt, A., Harry, J. B., Rapp, B., Wettstein, F. O., & Iftner, T. (1994). Comparison of the properties of the *E6* and *E7* genes of low- and high-risk cutaneous papillomaviruses reveals strongly transforming and high Rb-binding activity for the E7 protein of the low-risk human papillomavirus type 1. *Journal of Virology.* 68(11): 7051-7059.

Schrohl, A. S., Holten-Andersen, M., Sweep, F., Schmitt, M., Harbeck, N., Foekens, J., *et al*. (2003). Tumor markers: from laboratory to clinical utility. *Molecular Cell Proteomics.* 2(6): 378-387.

Schuler, M., Bossy-Wetzel, E., Goldstein, J. C., Fitzgerald, P., & Green, D. R. (2000). p53 induces apoptosis by caspase activation through mitochondrial cytochrome c release. *Journal of Biological Chemistry.* 275(10): 7337-7342.

Schwartsmann, G., Brondani da Rocha, A., Berlinck, R. G., & Jimeno, J. (2001). Marine organisms as a source of new anticancer agents. *Lancet Oncology.* 2(4): 221-225.

Seoud, M. (2012). Burden of human papillomavirus-related cervical disease in the extended middle East and north Africa-a comprehensive literature review. *Journal of LowerGenital Tract Disease,* 16: 106 - 120.

Serra, V., Markman, B., Scaltriti, M., Eichhorn, P. J., Valero, V., Guzman, M., *et al.* (2008). NVP-BEZ235, a dual PI3K/mTOR inhibitor, prevents PI3K signaling and inhibits the growth of cancer cells with activating PI3K mutations. *Cancer Research.* 68(19): 8022-8030.

Sethi, G., Ahn, K. S., & Aggarwal, B. B. (2008). Targeting nuclear factor-κB activation pathway by thymoquinone: Role in suppression of antiapoptotic gene products and enhancement of apoptosis. *Molecular Cancer Research.* 6(6): 1059-1070.

Sharma, D. N., Rath, G. K., Julka, P. K., Gandhi, A. K., Jagadesan, P., & Kumar, S. (2013). Role of gefitinib in patients with recurrent or metastatic cervical carcinoma ineligible or refractory to systemic chemotherapy: first study from Asia. *International Journal of Gynecological Cancer.* 23(4): 705-709.

Sharma, H. K., Chhangte, L., & Dolui, A. K. (2001). Traditional medicinal plants in Mizoram, India. *Fitoterapia.* 72(2): 146-161.

Shepherd, J., Peersman, G., Weston, R., & Napuli, I. (2000). Cervical cancer and sexual lifestyle: a systematic review of health education interventions targeted at women. *Health & Education Research.* 15(6): 681-694.

Shieh, S. Y., Ahn, J., Tamai, K., Taya, Y., & Prives, C. (2000). The human homologs of checkpoint kinases Chk1 and Cds1 (Chk2) phosphorylate p53 at multiple DNA damage-inducible sites. *Genes & Development.* 14(3): 289-300.

Shimada, M., Kigawa, J., Nishimura, R., Yamaguchi, S., Kuzuya, K., Nakanishi, T., *et al*. (2006). Ovarian metastasis in carcinoma of the uterine cervix. *Gynecology & Oncology.* 101(2): 234-237.

Shimizu, S., Eguchi, Y., Kamiike, W., Itoh, Y., Hasegawa, J., Yamabe, K., *et al* (1996). Induction of apoptosis as well as necrosis by hypoxia and predominant prevention of apoptosis by Bcl-2 and Bcl-XL. *Cancer Research.* 56(9): 2161-2166.

Shiraishi, H., Okamoto, H., Yoshimura, A., & Yoshida, H. (2006). ER stress-induced apoptosis and caspase-12 activation occurs downstream of mitochondrial apoptosis involving Apaf-1. *Journal of Cell Science.* 119(19): 3958-3966.

Shoieb, A. M., Elgayyar, M., Dudrick, P. S., Bell, J. L., & Tithof, P. K. (2003). *In vitro* inhibition of growth and induction of apoptosis in cancer cell lines by thymoquinone. *International Journal of Oncology.* 22(1): 107-113.

Shome, U., Khanna, R. K. & Sharma, H. P. (1980). Pharmacognostic studies on *Dillenia indica* Linn: II-Fruit and Seed. *Proceedings of the Indian Academy of Sciences Plant*, 89: 91-104.

Siddik, Z. H. (2003). Cisplatin: mode of cytotoxic action and molecular basis of resistance. *Oncogene.* 22(47): 7265-7279.

Siegel, R., Ma, J., Zou, Z., & Jemal, A. (2014). Cancer statistics, 2014. *CA: A Cancer Journal for Clinicians.* 64(1): 9-29.

Siegel, R., Naishadham, D., & Jemal, A. (2013). Cancer statistics, 2013. *CA: A Cancer Journal for Clinicians.* 63(1): 11-30.

Sinkule, J. A. (1984). Etoposide: a semisynthetic epipodophyllotoxin. Chemistry, pharmacology, pharmacokinetics, adverse effects and use as an antineoplastic agent. *Pharmacotherapy.* 4(2): 61-73.

Slattery, M. L., Robison, L. M., Schuman, K. L., French, T. K., Abbott, T. M., Overall, J. C., *et al.* (1989). Cigarette smoking and exposure to passive smoke are risk factors for cervical cancer. *Journal of the American Medical Association,* 261(11): 1593-1598.

Smith, J., Tho, L. M., Xu, N., & Gillespie, D. A. (2010). The ATM-Chk2 and ATR-Chk1 pathways in DNA damage signaling and cancer. *Advances in Cancer Research.* 108: 73-112.

Smith, J. S., Herrero, R., Bosetti, C., Munoz, N., Bosch, F. X., Eluf-Neto, J., *et al*. (2002). Herpes simplex virus-2 as a human papillomavirus cofactor in the etiology of invasive cervical cancer. *Journal of the National Cancer Institute.* 94(21): 1604-1613.

Solda, T., Garbi, N., Hammerling, G. J., & Molinari, M. (2006). Consequences of ERp57 deletion on oxidative folding of obligate and facultative clients of the calnexin cycle. *Journal of Biological Chemistry.* 281(10): 6219-6226.

Solomon, D., Davey, D., Kurman, R., Moriarty, A., O'Connor, D., Prey, M., *et al.* (2002). The 2001 Bethesda System: terminology for reporting results of cervical cytology. *Jama.* 287(16): 2114-2119.

Somigliana, E., Vigano, P., Tirelli, A. S., Felicetta, I., Torresani, E., Vignali, M., *et al*. (2004). Use of the concomitant serum dosage of CA 125, CA 19-9 and interleukin-6 to detect the presence of endometriosis. Results from a series of reproductive age women undergoing laparoscopic surgery for benign gynaecological conditions. *Human Reproduction.* 19(8): 1871-1876.

Song, T., Kim, M. K., Lee, Y. Y., Choi, C. H., Kim, T. J., Lee, J. W., *et al*. (2013). Phase II study of ifosfamide and cisplatin for the treatment of recurrent ovarian cancer. *Cancer Chemotherapy and Pharmacology.* 72(3): 653-660.

Spannuth, W. A., Leath, C. A., 3rd, Huh, W. K., Barnes, M. N., 3rd, Davidson, S. A., Kilgore, L. C., et al. (2007). A phase II trial of weekly topotecan for patients with secondary platinum-resistant recurrent epithelial ovarian carcinoma following the failure of second-line therapy. *Gynecology & Oncology.* 104(3): 591-595.

Spencer, S. L., Cappell, S. D., Tsai, F. C., Overton, K. W., Wang, C. L., & Meyer, T. (2013). The proliferation-quiescence decision is controlled by a bifurcation in CDK2 activity at mitotic exit. *Cell.* 155(2): 369-383.

Stanley, M. (2010). Pathology and epidemiology of HPV infection in females. *Gynecologic Oncology.* 117(2 Suppl): S5-10.

Stehman, F. B., Bundy, B. N., DiSaia, P. J., Keys, H. M., Larson, J. E., & Fowler, W. C. (1991). Carcinoma of the cervix treated with radiation therapy. I. A multi-variate analysis of prognostic variables in the Gynecologic Oncology Group. *Cancer.* 67(11): 2776-2785.

Sternberg, C. N., Skoneczna, I. A., Castellano, D., Theodore, C., Blais, N., Voog, E., *et al.* (2013). Larotaxel with Cisplatin in the first-line treatment of locally advanced/metastatic urothelial tract or bladder cancer: a randomized, active-controlled, phase III trial (CILAB). *Oncology.* 85(4): 208-215.

Strasser, A., Harris, A. W., Jacks, T., & Cory, S. (1994). DNA damage can induce apoptosis in proliferating lymphoid cells via p53-independent mechanisms inhibitable by Bcl-2. *Cell.* 79(2): 329-339.

Sudarshan, S. R., Schlegel, R., & Liu, X. (2010). The HPV-16 E5 protein represses expression of stress pathway genes *XBP-1* and *COX-2* in genital keratinocytes. *Biochemical & Biophysical Research Communications.* 399(4): 617-622.

Sugimoto, N., Fujitani, K., Imamura, H., Uedo, N., Iijima, S., Imano, M., *et al*. (2014). Randomized phase II trial of S-1 plus irinotecan versus S-1 plus paclitaxel as first-line treatment for advanced gastric cancer (OGSG0402). *Anticancer Research.* 34(2): 851-857.

Sugiyama, T., Yakushiji, M., Noda, K., Ikeda, M., Kudoh, R., Yajima, A., *et al*. (2000). Phase II study of irinotecan and cisplatin as first-line chemotherapy in advanced or recurrent cervical cancer. *Oncology.* 58(1): 31-37.

Suliman, A., Lam, A., Datta, R., & Srivastava, R. K. (2001). Intracellular mechanisms of TRAIL: apoptosis through mitochondrial-dependent and -independent pathways. *Oncogene.* 20(17): 2122-2133.

Szegezdi, E., Logue, S. E., Gorman, A. M., & Samali, A. (2006). Mediators of endoplasmic reticulum stress-induced apoptosis. *EMBO Reports.* 7(9): 880-885.

Tabata, T., Takeshima, N., Tanaka, N., Hirai, Y., & Hasumi, K. (2000). Clinical value of tumor markers for early detection of recurrence in patients with cervical adenocarcinoma and adenosquamous carcinoma. *Tumour Biology.* 21(6): 375-380.

Tan, M., Li, S., Swaroop, M., Guan, K., Oberley, L.W., & Sun, Y. (1999). Transcriptional activation of the human glutathione peroxidise promoter by p53.*Journal of Biological Chemistry*. 274(17):12061-12066.

Tan, Y., Dourdin, N., Wu, C., De Veyra, T., Elce, J. S., & Greer, P. A. (2006). Ubiquitous calpains promote caspase-12 and JNK activation during endoplasmic reticulum stress-induced apoptosis. *Journal of Biological Chemistry.* 281(23): 16016-16024.

Tanaka, T., Kuramitsu, Y., Fujimoto, M., Naito, S., Oka, M., & Nakamura, K. (2008). Downregulation of two isoforms of ubiquitin carboxyl-terminal hydrolase isozyme L1 correlates with high metastatic potentials of human SN12C renal cell carcinoma cell clones. *Electrophoresis.* 29(12): 2651-2659.

Tang, H. Y., Zhao, K., Pizzolato, J. F., Fonarev, M., Langer, J. C., & Manfredi, J. J. (1998). Constitutive expression of the cyclin-dependent kinase inhibitor p21 is transcriptionally regulated by the tumor suppressor protein p53. *Journal of Biological Chemistry.* 273(44): 29156-29163.

Taylor, W. R., & Stark, G. R. (2001). Regulation of the G2/M transition by p53. *Oncogene.* 20(15): 1803-1815.

Teh, J., Yap, S. P., Tham, I., Sethi, V. K., Chua, E. J., Yeo, R., *et al*. (2010). Concurrent chemoradiotherapy incorporating high-dose rate brachytherapy for locally advanced cervical carcinoma: survival outcomes, patterns of failure, and prognostic factors. *International Journal of Gynecological Cancer.* 20(3): 428-433.

Terry, G., Ho, L., Londesborough, P., Cuzick, J., Mielzynska-Lohnas, I., & Lorincz, A. (2001). Detection of high-risk HPV types by the hybrid capture 2 test. *Journal of Medical Virology.* 65(1): 155-162.

Tharavichitkul, E., Chakrabandhu, S., Wanwilairat, S., Tippanya, D., Nobnop, W., Pukanhaphan, N., *et al.* (2013). Intermediate-term results of image-guided brachytherapy and high-technology external beam radiotherapy in cervical cancer: Chiang Mai University experience. *Gynecologic Oncology.* 130(1): 81-85.

The solution structure of the second thioredoxin domain of human Protein disulfide-isomerase A3,The Protein Data Bank http://www. http://www.rcsb.org/pdb/explore/images.do?structureId=2DMM. Retrieved 23rd August 2013.

Tian, X. J., Liu, F., Zhang, X. P., Li, J., & Wang, W. (2012). A two-step mechanism for cell fate decision by coordination of nuclear and mitochondrial p53 activities. *PLoS One.* 7(6): e38164.

Toama, M. A., El-Alfy, T. S., & El-Fatatry, H. M. (1974). Antimicrobial activity of the volatile oil of *Nigella sativa* Linneaus seeds. *Antimicrobial Agents and Chemotherapy.* 6(2): 225-226.

Tobian, A. A., Serwadda, D., Quinn, T. C., Kigozi, G., Gravitt, P. E., Laeyendecker, O., *et al*. (2009). Male circumcision for the prevention of HSV-2 and HPV infections and syphilis. *New England Journal of Medicine.* 360(13): 1298-1309.

Tokunaga, H., Nagase, S., Yoshinaga, K., Tanaka, S., Nagai, T., Kurosawa, H., *et al*. (2013). Small cell carcinoma of the uterine cervix: clinical outcome of concurrent chemoradiotherapy with a multidrug regimen. *Tohoku Journal of Experimental Medicine.* 229(1): 75-81.

Tong, S. Y., Lee, J. M., Song, E. S., Lee, K. B., Kim, M. K., Lee, J. K., *et al*. (2009). Functional polymorphism in manganese superoxide dismutase and antioxidant status: their interactions on the risk of cervical intraepithelial neoplasia and cervical cancer. *Gynecology & Oncology.* 115(2): 272-276.

Torck, M., & Pinkas, M. (1996). Camptothecin and derivatives: a new class of antitumor agents. *Journal de Pharmacie de Belgique.* 51(4): 200-207.

Torres, M. P., Ponnusamy, M. P., Chakraborty, S., Smith, L. M., Das, S., Arafat, H. A., *et al*. (2010). Effects of thymoquinone in the expression of mucin 4 in pancreatic cancer cells: implications for the development of novel cancer therapies. *Molecular Cancer Therapeutics.* 9(5): 1419-1431.

Toshiyuki, M., & Reed, J. C. (1995). Tumor suppressor p53 is a direct transcriptional activator of the human *Bax* gene. *Cell.* 80(2): 293-299.

Tovar, J. M., Bazaldua, O. V., Vargas, L., & Reile, E. (2008). Human papillomavirus, cervical cancer, and the vaccines. *Postgraduate Medicine.* 120(2): 79-84.

Traen, K., Svane, D., Kryger-Baggesen, N., Bertelsen, K., & Mogensen, O. (2006). Stage Ib cervical cancer during pregnancy: planned delay in treatment-case report. *European Journal of Gynaecological Oncology.* 27(6): 615-617.

Trapani, J. A., & Smyth, M. J. (2002). Functional significance of the perforin/granzyme cell death pathway. *Nature Reviews Immunology.* 2(10): 735-747.

Turchi, J. J., Patrick, S. M., & Henkels, K. M. (1997). Mechanism of DNA-dependent protein kinase inhibition by cis-diamminedichloroplatinum(II)-damaged DNA. *Biochemistry.* 36(24): 7586-7593.

Umar, S., Zargan, J., Umar, K., Ahmad, S., Katiyar, C. K., & Khan, H. A. (2012). Modulation of the oxidative stress and inflammatory cytokine response by thymoquinone in the collagen induced arthritis in Wistar rats. *Chemico-Biological Interactions.* 197(1): 40-46.

Umezawa, H., Maeda, K., Takeuchi, T., & Okami, Y. (1966). New antibiotics, bleomycin A and B. *Journal of Antibiotic (Tokyo).* 19(5): 200-209.

Undurraga, M., Loubeyre, P., Dubuisson, J. B., Schneider, D., & Petignat, P. (2010). Early-stage cervical cancer: is surgery better than radiotherapy? *Expert Review of Anticancer Therapy.* 10(3): 451-460.

Ungureanu, C., Socolov, D., Anton, G., Mihailovici, M. S., & Teleman, S. (2010). Immunocytochemical expression of p16INK4a and HPV L1 capsid proteins as predictive markers of the cervical lesions progression risk. *Rome Journal of Morphology Embryology.* 51(3): 497-503.

Urade, R., & Kito, M. (1992). Inhibition by acidic phospholipids of protein degradation by ER-60 protease, a novel cysteine protease, of endoplasmic reticulum. *FEBS Letter.* 312(1): 83-86.

Urano, F., Wang, X., Bertolotti, A., Zhang, Y., Chung, P., Harding, H. P., *et al*. (2000). Coupling of stress in the ER to activation of JNK protein kinases by transmembrane protein kinase IRE1. *Science.* 287(5453): 664-666.

van de Bunt, L., van der Heide, U. A., Ketelaars, M., de Kort, G. A., & Jurgenliemk-Schulz, I. M. (2006). Conventional, conformal, and intensity-modulated radiation therapy treatment planning of external beam radiotherapy for cervical cancer: The impact of tumor regression. *International Journal of Radiation Oncology Biology Physics.* 64(1): 189-196.

Van de Craen, M., Van Loo, G., Pype, S., Van Criekinge, W., Van den brande, I., Molemans, F., *et al*. (1998). Identification of a new caspase homologue: caspase-14. *Cell Death & Differentiation.* 5(10): 838-846.

van Engeland, M., Nieland, L. J. W., Ramaekers, F. C. S., Schutte, B., & Reutelingsperger, C. P. M. (1998). Annexin V-affinity assay: A review on an apoptosis detection system based on phosphatidylserine exposure. *Cytometry.* 31(1): 1-9.

van Lonkhuijzen, L., & Thomas, G. (2011). Palliative radiotherapy for cervical carcinoma, a systematic review. *Radiotherapy & Oncology.* 98(3): 287-291.

van Loo, G., Saelens, X., Matthijssens, F., Schotte, P., Beyaert, R., Declercq, W., et al. (2002). Caspases are not localized in mitochondria during life or death. *Cell Death & Differentiation.* 9(11): 1207-1211.

Vandesompele, J., De Preter, K., Pattyn, F., Poppe, B., Van Roy, N., De Paepe, A., & Speleman, F. (2002). Accurate normalization of real-time quantitative RT-PCR data by geometric averaging of multiple internal control genes. *Genome Biology*.3 RESEARCH0034.

Vermes, I., Haanen, C. & Reutelingsperger, C. (2000). Flow cytometry of apoptotic cell death. *Journal of Immunology Methods.* 243:167–190.

Vermes, I., Haanen, C., Steffens-Nakken, H., Reutelingsperger, C. (1995). A novel assay for apoptosis. Flow cytometric detection of phosphatidylserine expression on early apoptotic cells using fluorescein labeled Annexin V. *Journal of Immunology Methods.* 184:39–51.

Vermeulen, K., Van Bockstaele, D. R., & Berneman, Z. N. (2003). The cell cycle: a review of regulation, deregulation and therapeutic targets in cancer. *Cell Proliferation.* 36(3): 131-149.

Vidyasagar, M. S., Ramanujam, A. S., Fernandes, D. J., Koteshwar Rao, K., Jadhav, G. K., Hospet, C. S., *et al*. (1999). Vincristine (vinca-alkaloid) as a sclerosing agent for malignant pleural effusions. *Acta Oncologica.* 38(8): 1017-1020.

Wada, T., & Penninger, J. M. (2004). Mitogen-activated protein kinases in apoptosis regulation. *Oncogene.* 23(16): 2838-2849.

Wajant, H. (2002). The Fas signaling pathway: more than a paradigm. *Science.* 296(5573): 1635-1636.

Wakaki, S., Marumo, H., Tomioka, K., Shimizu, M., Kato, E., Kamada, H., *et al.* (1958). Purification and isolation study on gancidins. *Journal of Antibiotic (Tokyo).* 11(4): 150-155.

Walboomers, J., Jacobs, M., Manos, M., Bosch, F., Kummer, J., Shah, K., *et al.* (1999). Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *Journal of Pathology.* 189(1): 12-21.

Wang, J. Y. (1999). The tyrosine kinase c-Abl regulates p73 in apoptotic response to cisplatin-induced DNA damage. *Nature*. 399: 806-809.

Wang, Y., Chen, J., Lee, C. S., Nizkorodov, A., Riemenschneider, K., Martin, D., *et al*. (2010). Disruption of *Pdia3* gene results in bone abnormality and affects 1alpha,25-dihydroxy-vitamin D3-induced rapid activation of PKC. *Journal of Steroid Biochemistry & Molecular Biology.* 121(1-2): 257-260.

Watari, H., Kanuma, T., Ohta, Y., Hassan, M. K., Mitamura, T., Hosaka, M., *et al*. (2010). Clusterin expression inversely correlates with chemosensitivity and predicts poor survival in patients with locally advanced cervical cancer treated with cisplatin-based neoadjuvant chemotherapy and radical hysterectomy. *Pathology & Oncology Research.* 16(3): 345-352.

Waterfield, C. J., Delaney, J., Kerai, M. D. J., & Timbrell, J. A. (1997). Correlations between *in vivo* and *in vitro* effects of toxic compounds: Studies with hydrazine. *Toxicology in Vitro.* 11(3): 217-227.

Westendorp, B., Mokry, M., Groot Koerkamp, M. J., Holstege, F. C., Cuppen, E., & de Bruin, A. (2012). E2F7 represses a network of oscillating cell cycle genes to control S-phase progression. *Nucleic Acids Research.* 40(8): 3511-3523.

Wheeler, C. M., Castellsague, X., Garland, S. M., Szarewski, A., Paavonen, J., Naud, P., *et al.* (2012). Cross-protective efficacy of HPV-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by non-vaccine oncogenic HPV types: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. *Lancet Oncology.* 13(1): 100-110.

Whitney, C. W., Sause, W., Bundy, B. N., Malfetano, J. H., Hannigan, E. V., Fowler, W. C., Jr., *et al.* (1999). Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study. *Journal of Clinical Oncology.* 17(5): 1339-1348.

WHO (World Health Organisation) (2014). Human Vaccines http://www.who.int/rabies/vaccines/human_vaccines/en/. Retrieved 2nd January 2014.

Wiart, C., Mogan, S., Khalifah, M., Mahan, S., Ismail, M., Buckle, *et al*. (2004). Antimicrobial screening of plants used for traditional medicine in the state of Perak, Peninsular Malaysia. *Fitoterapia.* 75(1): 68-73.

Willis, D., Li, K. W., Zheng, J. Q., Chang, J. H., Smit, A. B., Kelly, T., *et al.* (2005). Differential transport and local translation of cytoskeletal, injury-response and neurodegeneration protein mRNAs in axons. *Journal of Neuroscience.* 25(4): 778-791.

Wilson, C. M., & High, S. (2010). Studying endoplasmic reticulum function *in vitro* using siRNA. *Methods in Molecular Biology.* 619: 389-402.

Winer, R. L., Hughes, J. P., Feng, Q., O'Reilly, S., Kiviat, N. B., Holmes, K. K., *et al.* (2006). Condom use and the risk of genital human papillomavirus infection in young women. *New England Journal of Medicine.* 354(25): 2645-2654.

Witherup, K. M., Look, S. A., Stasko, M. W., Ghiorzi, T. J., Muschik, G. M., & Cragg, G. M. (1990). *Taxus spp*. needles contain amounts of taxol comparable to the bark of *Taxus brevifolia*: analysis and isolation. *Journal of Natural Products.* 53(5): 1249-1255.

Wong, R. S. (2011). Apoptosis in cancer: from pathogenesis to treatment. *Journal of Experimental and Clinical Cancer Research.* 30(1): 87-87

Wong, Y. H., Abdul Kadir, H., & Ling, S. K. (2012). Bioassay-guided isolation of cytotoxic cycloartane triterpenoid glycosides from the traditionally used medicinal plant *Leea indica*. *Evidence Based Complementary & Alternative Medicine.* 164689(10): 29.

Woo, C. C., Loo, S. Y., Gee, V., Yap, C. W., Sethi, G., Kumar, A. P., *et al*. (2011). Anticancer activity of thymoquinone in breast cancer cells: possible involvement of PPAR-gamma pathway. *Biochemical Pharmacology.* 82(5): 464-475.

Woo, C. W., Cui, D., Arellano, J., Dorweiler, B., Harding, H., Fitzgerald, K. A., *et al*. (2009). Adaptive suppression of the ATF4-CHOP branch of the unfolded protein response by toll-like receptor signalling. *Nature Cell Biology.* 11(12): 1473-1480.

Worthen, D. R., Ghosheh, O. A., & Crooks, P. A. (1998). The *in vitro* anti-tumor activity of some crude and purified components of blackseed, *Nigella sativa* L. *Anticancer Research.* 18(3A): 1527-1532.

Woyengo, T. A., Ramprasath, V. R., & Jones, P. J. H. (2009). Anticancer effects of phytosterols. *European Journal of Clinical Nutrition.* 63(7): 813-820.

Wozniak, K., & Blasiak, J. (2002). Recognition and repair of DNA-cisplatin adducts. *Acta Biochimica Polonica.*. 49(3): 583-596.

Wright, A. A., Howitt, B. E., Myers, A. P., Dahlberg, S. E., Palescandolo, E., Van Hummelen, P., *et al*. (2013). Oncogenic mutations in cervical cancer: genomic differences between adenocarcinomas and squamous cell carcinomas of the cervix. *Cancer.* 119(21): 3776-3783.

Wright, J. D., NathavithArana, R., Lewin, S. N., Sun, X., Deutsch, I., Burke, W. M., *et al*. (2010). Fertility-conserving surgery for young women with stage IA1 cervical cancer: safety and access. *Obstetrics & Gynecology.* 115(3): 585-590.

Wright, T. C. J., Massad, L. S., Dunton, C. J., Spitzer, M., Wilkinson, E. J., & Solomon, D. (2007). 2006 consensus guidelines for the management of women with cervical intraepithelial neoplasia or adenocarcinoma *in situ*. *American Journal of Obstetrics & Gynecology.* 197(4): 340-345.

Wu, H. S., Yen, M. S., Lai, C. R., & Ng, H. T. (1997). Ovarian metastasis from cervical carcinoma. *International Journal of Gynecology and Obstetrics,* 57(2): 173-178.

Wu, J., Rutkowski, D. T., Dubois, M., Swathirajan, J., Saunders, T., Wang, J., *et al*. (2007). ATF6alpha optimizes long-term endoplasmic reticulum function to protect cells.from chronic stress. *Developmental Cell.* 13(3): 351-364.

Wullschleger, S., Loewith, R., & Hall, M. N. (2006). TOR signaling in growth and metabolism. *Cell.* 124(3): 471-484.

Xia, S., Yu, S., Fu, Q., Liu, F., Zheng, W., Fu, X., *et al*. (2010). Inhibiting PI3K/Akt pathway increases DNA damage of cervical carcinoma HeLa cells by drug radiosensitization. *JournalofHuazhong UniversityofScienceandTechnology.*30(3): 360-364.

Xiong, Y., Liang, L. Z., Cao, L. P., Min, Z., & Liu, J. H. (2011). Clinical effects of irinotecan hydrochloride in combination with cisplatin as neoadjuvant chemotherapy in locally advanced cervical cancer. *Gynecology Oncology.* 123(1): 99-104.

Xu, D., Perez, R. E., Rezaiekhaligh, M. H., Bourdi, M., & Truog, W. E. (2009). Knockdown of ERp57 increases BiP/GRP78 induction and protects against hyperoxia and tunicamycin-induced apoptosis. *American Journal of Physiology-Lung Cellular and Molecular Physiology.* 297(1): 44-51.

Yam, C. H., Fung, T. K., & Poon, R. Y. (2002). Cyclin A in cell cycle control and cancer. *Cellular & Molecular Life Sciences.* 59(8): 1317-1326.

Yang, H. Y., Wen, Y. Y., Chen, C. H., Lozano, G., & Lee, M. H. (2003). 14-3-3 sigma positively regulates p53 and suppresses tumor growth. *Molecular and Cellular Biology.* 23(20): 7096-7107.

Yang, S.H., Kong, S.K., Lee, S.H., Lim, S.Y., & Park, C.Y. (2014). Human papillomavirus 18 as a poor prognosticfactor in stage I-IIA cervical cancer following primary surgical treatment.*Obstetric & Gynecological Sciences*. 57(6):492-500

Yang, X., Fraser, M., Moll, U. M., Basak, A., & Tsang, B. K. (2006). Akt-mediated cisplatin resistance in ovarian cancer: modulation of p53 action on caspase-dependent mitochondrial death pathway. *Cancer Research.* 66(6): 3126-3136.

Yap, P. S. X., Chong, Y. E. T., Wong, Y. Y., Lim, X. Y., Ang, J. H., Goh, H. S. L., *et al*. (2013). Antibacterial and antifungal testing of the different extracts of *Dillenia obovata* (Blume) Hoogl. *World Journal of Pharmacy and Pharmaceutical Sciences*, 2(5): 3946-3962.

Yeshwante,S. B., Juvekar**,** A. R., Nagmoti,D. M., Wankhede, S. S., Shah, A. S., Pimprikar, R. B., ***et*** *al.* (2009). Anti-inflammatory activity of methanolic extracts of *Dillenia indica* L. leaves. *Journal of Young Pharmacist*. 1: 63-66.

Yeom, S. Y., Jang, H. L., Lee, S. J., Kim, E., Son, H. J., Kim, B. G*., et al*. (2010). Interaction of testisin with maspin and its impact on invasion and cell death resistance of cervical cancer cells. *FEBS Letter.* 584(8): 1469-1475.

Yinjun, L., Jie, J., Weilai, X., & Xiangming, T. (2004). Homoharringtonine mediates myeloid cell apoptosis via upregulation of pro-apoptotic Bax and inducing caspase-3-mediated cleavage of poly(ADP-ribose) polymerase (PARP). *American Journal of Hematology.* 76(3): 199-204.

Yokota, J. (2000). Tumor progression and metastasis. *Carcinogenesis.* 21(3): 497-503.

Yoon, K.A., Nakamura, Y., Arakawa, H. (2004). Identification of ALDH4 as a p53-inducible gene and its protective role in cellular stresses. *Journal of Human Genetics*. 49(3): 134-40.

Yoon, S. M., Shin, K. H., Kim, J. Y., Seo, S. S., Park, S. Y., Kang, S., *et al*. (2007). The clinical values of squamous cell carcinoma antigen and carcinoembryonic antigen in patients with cervical cancer treated with concurrent chemoradiotherapy. *International Journal of Gynecological Cancer.* 17(4): 872-878.

Yoon, S. M., Shin, K. H., Kim, J. Y., Seo, S. S., Park, S. Y., Moon, S. H., *et al*. (2010). Use of serum squamous cell carcinoma antigen for follow-up monitoring of cervical cancer patients who were treated by concurrent chemoradiotherapy. *Radiation Oncology.* 5(78): 5-78.

Yoshimura, F. K., & Luo, X. (2007). Induction of endoplasmic reticulum stress in thymic lymphocytes by the envelope precursor polyprotein of a murine leukemia virus during the preleukemic period. *Journal of Virology.* 81(8): 4374-4377.

Yoshizawa, F., Mochizuki, S., Doi, M., Yamaoka, I., & Sugahara, K. (2009). Ethionine-induced ATP depletion represses mTOR signaling in the absence of increases in AMP-activated protein kinase activity in the rat liver. *Biosciences & Biotechnology Biochemistry.* 73(9): 1984-1988.

Yu, F., Megyesi, J., Safirstein, R. L., & Price, P. M. (2007). Involvement of the CDK2-E2F1 pathway in cisplatin cytotoxicity *in vitro* and *in vivo*. *American Journal of Physiology: Renal Physiology.* 293(1): 52-59.

Zainal Ariffin, O., & Nor Saleha, I. T. (2011). *National Cancer Registry Report 2007*. Malaysia: Ministry of Health.

Zaoui, A., Cherrah, Y., Lacaille-Dubois, M. A., Settaf, A., Amarouch, H., & Hassar, M. (2000). Diuretic and hypotensive effects of *Nigella sativa* in the spontaneously hypertensive rat. *Therapie.* 55(3): 379-382.

Zapun, A., Darby, N. J., Tessier, D. C., Michalak, M., Bergeron, J. J., & Thomas, D. Y. (1998). Enhanced catalysis of ribonuclease B folding by the interaction of calnexin or calreticulin with ERp57. *Journal of Biological Chemistry.* 273(11): 6009-6012.

Zeiss, C. J. (2003). The apoptosis-necrosis continuum: Insights from genetically altered mice. *Veterinary Pathology Online.* 40(5): 481-495.

Zender, L., Hutker, S., Mundt, B., Waltemathe, M., Klein, C., Trautwein, C., *et al*. (2005). NFkappaB-mediated upregulation of Bcl-xL restrains TRAIL-mediated apoptosis in murine viral hepatitis. *Hepatology.* 41(2): 280-288.

Zha, J., Harada, H., Osipov, K., Jockel, J., Waksman, G., & Korsmeyer, S. J. (1997). BH3 domain of Bad is required for heterodimerization with Bcl-xL and pro-apoptotic activity. *Journal of Biological Chemistry.* 272(39): 24101-24104.

Zha, J., Harada, H., Yang, E., Jockel, J., & Korsmeyer, S. J. (1996). Serine phosphorylation of death agonist BAD in response to survival factor results in binding to 14-3-3 not BCL-X(L). *Cell,* 87(4): 619-628.

Zhang, L., & Wang, A. (2012). Virus-induced ER stress and the unfolded protein response. *Frontiers in Plant Science.* 3(293): 1-16.

Zhang, Y., Liu, Y., Yang, Y. X., Xia, J. H., Zhang, H. X., Li, H. B., *et al*. (2009). The expression of PLK-1 in cervical carcinoma: a possible target for enhancing chemosensitivity. *Journal of Experimental and Clinical Cancer Research.* 28(1): 130.

Zhu, W., Chen, J., Cong, X., Hu, S., & Chen, X. (2006). Hypoxia and serum deprivation-induced apoptosis in mesenchymal stem cells. *Stem Cells.* 24(2): 416-425.

Ziegler, U., & Groscurth, P. (2004). Morphological features of cell death. *News Physiology Sciences.* 19: 124-128.

Zong, W. X., Li, C., Hatzivassiliou, G., Lindsten, T., Yu, Q. C., Yuan, J., *et al*. (2003). Bax and Bak can localize to the endoplasmic reticulum to initiate apoptosis. *Journal of Cell Biology.* 162(1): 59-69.

Zou, C. G., Cao, X. Z., Zhao, Y. S., Gao, S. Y., Li, S. D., Liu, X. Y., *et al* (2009). The molecular mechanism of endoplasmic reticulum stress-induced apoptosis in PC-12 neuronal cells: the protective effect of insulin-like growth factor I. *Endocrinology,* 150(1): 277-285.

Zou, D. M., Brewer, M., Garcia, F., Feugang, J. M., Wang, J., Zang, R., *et al*. (2005). Cactus pear: a natural product in cancer chemoprevention. *Nutrition Journal.* 4: 25-36.

zur Hausen, H. (2009). Papillomaviruses in the causation of human cancers - a brief historical account. *Virology,* 384(2): 260-265.

zur Hausen, H. (1991). Human papillomaviruses in the pathogenesis of anogenital cancer. *Virology.* 184(1): 9-13.