

POLYVINYL ALCOHOL-GRAFTED-MULTIWALLED CARBON NANOTUBES  
AS A DELIVERY SYSTEM FOR CURCUMIN IN H<sub>2</sub>O<sub>2</sub>-INDUCED DAMAGED  
NEUROBLASTOMA SH-SY5Y CELLS

NURLIYANA AHMAD ZAWAWI

UNIVERSITI TEKNOLOGI MALAYSIA

POLYVINYL ALCOHOL-GRAFTED-MULTIWALLED CARBON NANOTUBES  
AS A DELIVERY SYSTEM FOR CURCUMIN IN H<sub>2</sub>O<sub>2</sub>-INDUCED DAMAGED  
NEUROBLASTOMA SH-SY5Y CELLS

NURLIYANA AHMAD ZAWAWI

A thesis submitted in fulfilment of the  
requirements for the award of the degree of  
Doctor of Philosophy (Bioscience)

Faculty of Biosciences and Medical Engineering  
Universiti Teknologi Malaysia

AUGUST 2017

Specially dedicated to *Babah* and *Mama*,

my husband and sons,

my sisters and brother,

for their love, support and tolerance

## ACKNOWLEDGEMENTS

### *Bismillahirrahmanirahim*

Alhamdulillah, I am thankful to Allah s.w.t for giving me strength, knowledge, thoughts, ability and opportunity to complete this thesis successfully. Without His blessings, this achievement would not have been possible.

It is a pleasure to acknowledge considerable assistance I had received from the people I worked with during my journey. I wish to express my utmost gratitude to my main supervisor, Prof. Dr. Noor Aini Abdul Rashid who guided me through this work. Thank you for being there when I needed you the most. Thank you for your invaluable advice, understanding, support and trust in me to complete this research.

My heartfelt appreciation to my co-supervisor, the late Prof. Dr. Alias Mohd. Yusof, whose inspiration and motivation had enabled me to develop understanding in the chemistry, especially during the synthesis of PVA-nanotubes. It was such an honour to be working with him. I also would like to express my gratitude to Associate Professor Dr. Zaiton Abdul Majid for her knowledge, time and advice regarding the adsorption studies. Your endless support and guidance are priceless. Also much thanks to Puan Maizatulikhma Md. Zin from Tissue Culture Lab, Institute of Science (IoS), UITM Shah Alam, Selangor. Thank you for allowing to use your laboratory for cytotoxicity, neurotoxicity and neuroprotection experiments. Thank you for introducing me to the excitement of working with live cells!

Special thanks to the laboratory technicians and non-academic staff members at the Faculty of Bioscience and Biomedical Engineering (FBME), UTM especially Madam Siti Fatimah, Miss Nor Shafawani Sarah and Miss Wan Aznida for their help and support. I am also very much indebted to my fellow labmates Dr. Zarita, Azura and Dr. Lau Chew Ping from the Laboratory of Molecular Biology, FBME, and Ain from the Faculty of Science. Special thanks to Nor Syamila and Kamarul Ridzwan who had helped me during the cancer cell experiments in UiTM. Not forgetting, much gratitude to all my C08 and T02 friends who had accompanied me through all ups and downs and never failed to cheer me up and support me. I also would like to thank laboratory staffs from the Faculty of Science, Ibnu Sina Institute and Faculty of Mechanical Engineering in UTM, who had taught me how to use various equipments especially during nanotubes characterization.

Last but not least, I would like to thank my parents Ahmad Zawawi Ibrahim and Puteri Norzian Megat Hamid, this thesis is for the both of you. Thank you for your endless prayers, motivation and support throughout. I hope that this achievement had completed your dreams to ensure the best education for me. Not forgetting my sister Angah for always encouraging me to complete this challenging task too.

Special thanks to my husband Azlan Alias, my greatest support throughout my whole career. Thank you for being so understanding and cheering me since I embarked this journey in 2008, a few days after our wedding. To my PhD babies, Azfar Danish and Ayman Yusuf, you both have keep me motivated and strong. I am dedicating this thesis to the both of you..

## ABSTRACT

Treating neurodegenerative disease using Curcumin, a pigment from turmeric is found difficult due to its low bioavailability. To overcome this problem, polyvinyl alcohol multi-walled carbon nanotubes (PVA-MWCNT) was developed to improve its delivery and uptake by the brain cells. It was first prepared by oxidizing pristine MWCNT (p-MWCNT) in 3:1 sulfuric and nitric acid mixture. Three methods were employed to optimize production of oxidized MWCNT (ox-MWCNT); which is stirring and sonication for 2 and 6 hours. The selected ox-MWCNT with minimal structural damage was then functionalized with PVA via carbodiimide esterification, and confirmed by field-emission scanning electron microscopy (FESEM), Fourier transform infra-red (FTIR) spectroscopy, dispersion test and thermal gravimetric analysis (TGA). Next, Curcumin was loaded onto PVA-MWCNT, p-MWCNT and ox-MWCNT, and evaluated their adsorption capacity and behaviour using adsorption kinetics, isotherm and thermodynamic studies. Percentage of Curcumin desorbed from the MWCNT was analyzed in physiological buffers of pHs 7.4 and 5.5. Lastly, potential of Curcumin loaded on PVA-MWCNT (Cur-PVA-MWCNT) to protect neurons was screened in neuroblastoma SH-SY5Y cells, including other Cur-loaded MWCNT samples. The cells were pre-incubated with hydrogen peroxide ( $H_2O_2$ ) at half the maximal inhibitory concentration ( $IC_{50}$ ) for 1 hour, before concurrent treatment of the samples. Cell survival was compared to controls treated with Curcumin-unloaded MWCNT, i.e. PVA-MWCNT, ox-MWCNT and p-MWCNT. From the results, MWCNT was oxidized with minimal structural damage using stirring method. The evidence of PVA grafting was confirmed through the presence of matrix polymer embedded on ox-MWCNT in FESEM, high stability in water, identification C=O stretching of ester group at  $1736\text{ cm}^{-1}$  in FTIR and its stable structure compared to ox-MWCNT and p-MWCNT in TGA. PVA-MWCNT adsorbed Curcumin at only 5.1 mg/g, which follows the Freundlich isotherm model (physisorption), while the highest amount was loaded on ox-MWCNT at 714 mg/g that follows the Langmuir model (chemisorption). Although Curcumin adsorption on PVA-MWCNT was only at minimal amount, it showed the most efficient desorption occurred at pH 5.5 (25%) rather than pH 7.4 (3%) with sustained release over a 3-day incubation. This suggests Curcumin weak binding through physisorption to the PVA-MWCNT facilitated its release at lower pH. Cur-PVA-MWCNT also protected SH-SY5Y cells from  $H_2O_2$ -induced oxidative stress most significantly at 100 ng/ml, 1  $\mu\text{g/ml}$  and 10  $\mu\text{g/ml}$  compared to PVA-MWCNT. Cur-ox-MWCNT and Cur-p-MWCNT indicated no obvious difference as compared to their controls. The change in the cell environment after damage perhaps encouraged the pH to become acidic which may facilitate Curcumin release from PVA-MWCNT. Overall, PVA-MWCNT was considered promising for loading and the release of Curcumin. The efficacy of the system in *in vitro* cell lines was also enhanced, demonstrating it as a prospective carrier for Curcumin in the treatment of neurodegenerative disease.

## ABSTRAK

Pengobatan penyakit neurodegeneratif menggunakan Curcumin, pigmen dari kunyit didapati sukar kerana bioketerdapatannya yang rendah. Untuk mengatasinya, polivinil alkohol tiub nanokarbon berbilang dinding (PVA-MWCNT) dibangunkan bagi memperbaiki penghantaran dan pengambilannya oleh sel-sel otak. Penyediaannya dimulai dengan oksidasi pristin-MWCNT (p-MWCNT) di dalam 3:1 campuran asid sulfurik dan nitrik. Penghasilan MWCNT teroksida (ox-MWCNT) dioptimum melalui tiga kaedah; iaitu pengacauan, dan sonikasi selama 2 dan 6 jam. Ox-MWCNT dengan sedikit kerosakan struktur kemudiannya difungsikan dengan PVA melalui pengesteran karbodiimida, dan disahkan melalui mikroskop elektron imbasan pancaran medan (FESEM), spektroskopi Fourier transform inframerah (FTIR), ujian penyebaran dan analisis gravimetri terma (TGA). Seterusnya, Curcumin dimuatkan pada PVA-MWCNT, p-MWCNT dan ox-MWCNT, dan dinilai kapasiti dan tingkah laku jerapan melalui kajian kinetik dan isoterma penyerapan, serta termodinamik. Peratus pelepasan Curcumin dari MWCNT pula dikaji menggunakan larutan tampan pH 7.4 dan 5.5. Terakhir, potensi PVA-MWCNT muatan Curcumin (Cur-PVA-MWCNT) melindungi neuron disaring dalam sel neuroblastoma SH-SY5Y, termasuk sampel MWCNT-muatan Cur lain. Sel diaruh hidrogen peroksida ( $H_2O_2$ ) pada kepekatan separuh perencatan maksima ( $IC_{50}$ ) selama 1 jam sebelum diuji serentak dengan sampel. Kebolehhidupan sel dibanding dengan kumpulan kawalan MWCNT-tanpa-muatan-Cur, iaitu PVA-MWCNT, ox-MWCNT dan p-MWCNT. Menurut hasil kajian, teknik pengacauan mengoksidasi MWCNT dengan sedikit kerosakan struktur. Bukti cantuman PVA pada ox-MWCNT ditunjukkan oleh matrik polimer tertanam pada ox-MWCNT dalam FESEM, kestabilan tinggi dalam air, pencaman regangan  $C=O$  dari kumpulan ester pada  $1736\text{ cm}^{-1}$  dalam FTIR serta kestabilan struktur berbanding ox-MWCNT dan p-MWCNT dalam TGA. PVA-MWCNT menyerap Curcumin hanya pada 5.1 mg/g dan mematuhi model isoterma Freundlich (jerapan fizikal), manakala jumlah tertinggi sebanyak 714 mg/g dimuat keatas ox-MWCNT yang mengikuti model isoterma Langmuir (jerapan kimia). Walaupun jerapan Curcumin oleh PVA-MWCNT di kadar yang rendah, penyahjerapannya didapati paling cekap pada pH 5.5 (25%) berbanding pH 7.4 (3%) dengan pelepasan tertahan yang berterusan selama 3 hari. Ia mencadangkan interaksi lemah Curcumin pada PVA-MWCNT melalui jerapan fizikal menggalakkan pelepasannya pada pH yang rendah. Cur-PVA-MWCNT juga melindungi sel-sel SH-SY5Y dari tekanan oksidatif aruhan  $H_2O_2$  dengan ketara pada 100 ng/ml, 1  $\mu\text{g/ml}$  dan 10  $\mu\text{g/ml}$  berbanding PVA-MWCNT. Cur-ox-MWCNT dan Cur-p-MWCNT pula tidak menunjukkan perbezaan berbanding kumpulan kawalannya. Perubahan persekitaran sel SH-SY5Y setelah aruhan berkemungkinan mempengaruhi pH ke arah keasidan, seterusnya menggalakkan penyingkiran Curcumin dari PVA-MWCNT. Keseluruhannya, PVA-MWCNT berpotensi memuat dan menyahjerap Curcumin. Keberkesanan sistem ini di dalam sel *in vitro* juga menunjukkannya sebagai pembawa prospektif Curcumin bagi rawatan penyakit neurodegeneratif.

## TABLE OF CONTENTS

<b>CHAPTER</b>	<b>TITLE</b>	<b>PAGE</b>
	<b>DECLARATION</b>	ii
	<b>DEDICATION</b>	iii
	<b>ACKNOWLEDGEMENT</b>	iv
	<b>ABSTRACT</b>	vi
	<b>ABSTRAK</b>	vii
	<b>TABLE OF CONTENTS</b>	viii
	<b>LIST OF TABLES</b>	xiii
	<b>LIST OF FIGURES</b>	xiv
	<b>LIST OF ABBREVIATIONS</b>	xvii
	<b>LIST OF SYMBOLS</b>	xix
	<b>LIST OF APPENDICES</b>	xx
<b>1</b>	<b>INTRODUCTION</b>	<b>1</b>
	1.1 Background of study	1
	1.2 Problem statement	3
	1.3 Research objectives	4
	1.4 Scope of study	5
	1.5 Significance of study	5
<b>2</b>	<b>LITERATURE REVIEW</b>	<b>7</b>
	2.1 Introduction	7
	2.2 Carbon nanotubes	7
	2.2.1 Synthesis of CNT	8
	2.2.2 Purification of CNT by oxidation	11
	2.2.3 Functionalization of CNT	13

2.2.3.1	Types of functionalization	14
2.2.3.2	Polymeric CNT	15
2.2.3.3	Polymer grafting	17
2.3	CNT-based drug delivery system	18
2.3.1	Drugs attachment on CNT	18
2.3.2	Chronological advances in CNT-drug studies	22
2.4	Neurodegenerative disease	27
2.4.1	Pathophysiology of neurodegenerative disease	28
2.4.2	Treatment strategy	31
2.4.2.1	Mechanism of oxidative damage in aging brain	31
2.4.2.2	Endogenous and nutritional antioxidants	34
2.5	Curcumin	36
2.5.1	Attenuation of oxidative stress by Curcumin	37
2.5.2	Curcumin physicochemical properties	38
2.5.3	Problems with Curcumin	40
2.5.4	Curcumin nanoformulation and delivery to brain	43
2.5.5	CNT as new approach for Curcumin delivery in neurodegenerative disease	46
<b>3</b>	<b>MATERIALS AND METHODS</b>	<b>48</b>
3.1	Research outline	48
3.2	Materials and chemicals	51
3.3	Oxidation of MWCNT	52
3.4	Functionalization of oxidized-MWCNT with PVA	53
3.5	Characterization of pristine- and oxidized-MWCNT	54
3.5.1	Field Emission Scanning Electron Microscopy (FESEM)	54
3.5.2	Energy Dispersive X-Ray (EDX) analysis	55
3.5.3	Fourier transformed infra-red spectroscopy (FTIR)	55
3.5.4	Dispersibility test	56
3.3.2	Thermogravimetric analysis (TGA)	56
3.6	Drug binding and release studies	57
3.6.1	Adsorbents and adsorbate preparation	57

3.6.2	Adsorption kinetics and thermodynamics	58
3.6.3	Adsorption isotherms	59
3.6.4	Curcumin release study	60
3.7	<i>In vitro</i> cell studies	61
3.7.1	Cell line	61
3.7.1.1	SH-SY5Y cell culture and differentiation	61
3.7.2	Sample preparation for neurotoxicity and neuroprotection studies	62
3.7.3	Neurotoxicity test	63
3.7.4	Neuroprotection test	63
3.7.4.1	Determination of hydrogen peroxide (H <sub>2</sub> O <sub>2</sub> ) IC <sub>50</sub>	64
3.7.5	MTS assay	64
3.7.6	Statistical analysis	65
<b>4</b>	<b>FUNCTIONALIZATION OF MULTI- WALLED CARBON NANOTUBES (MWCNT) AND THEIR CHARACTERIZATION</b>	<b>66</b>
4.1	Introduction	66
4.2	Experimental methods	67
4.2.1	MWCNT functionalization	67
4.3	Results and discussion	68
4.3.1	Acid oxidation of MWCNT	68
4.3.1.1	FESEM and EDX analysis	69
4.3.1.2	FTIR spectra	73
4.3.1.3	Validation of functionalization by colloidal dispersion	75
4.3.1.4	Thermogravimetric analysis	77
4.3.2	Surface functionalization of ox-MWCNT with polyvinyl alcohol (PVA)	80
4.3.2.1	FTIR analysis	81
4.3.2.2	Effect of PVA density on dispersion stability	83
4.3.2.3	Thermal characterization and PVA integrity examination	84
4.3.2.4	FESEM analysis	87

4.4	Summary	90
<b>5</b>	<b>ADSORPTION AND DESORPTION BEHAVIOR OF CURCUMIN (CUR) ON PRISTINE AND FUNCTIONALIZED CARBON NANOTUBES</b>	<b>91</b>
5.1	Introduction	91
5.2	Experimental methods	93
5.2.1	Adsorbents and adsorbates	93
5.2.2	Adsorption kinetics	93
5.2.3	Adsorption isotherms	94
5.2.4	Thermodynamic analysis	94
5.2.5	Desorption of Curcumin from MWCNT	94
5.3	Results and discussion	95
5.3.1	Adsorption kinetics	95
5.3.2	Adsorption isotherms	102
5.3.3	Effect of temperature on Curcumin adsorption	110
5.3.4	Desorption studies	113
	5.3.4.1 Curcumin release at pH 5.5 and 7.4	114
5.4	Summary	116
<b>6</b>	<b>EFFECT OF CURCUMIN-FUNCTIONALIZED MULTIWALLED CARBON NANOTUBES (CUR-MWCNT) ON NEUROBLASTOMA CELLS</b>	<b>118</b>
6.1	Introduction	118
6.2	Experimental methods	120
6.2.1	Cell culture	120
6.2.2	Cell treatment and analysis	120
6.3	Results and discussion	121
6.3.1	Differentiation of neuroblastoma cell line SH-SY5Y by retinoic acid (RA)	121
6.3.2	Neurotoxicity effect of Curcumin, Cur-MWCNT and Cur-unloaded-MWCNT	123
6.3.3	Hydrogen peroxide IC <sub>50</sub> determination	127

6.3.4	Neuroprotective effect of Curcumin, Cur-MWCNT and Cur-unloaded-MWCNT	128
6.4	Summary	132
<b>7</b>	<b>CONCLUSIONS AND RECOMMENDATIONS</b>	<b>134</b>
7.1	Conclusion	134
7.2	Recommendations	136
	<b>REFERENCES</b>	<b>138</b>
	Appendices A-I	164-176

## LIST OF TABLES

TABLE NO.	TITLE	PAGE
2.1	<i>In vitro</i> drug delivery studies employing CNT as nanovector	23
3.1	Sample information of MWCNT applied in this thesis	51
2.2	Therapeutic strategies in Alzheimer's disease and correlation to its pathophysiologic mechanism	35
2.3	Other recognized therapeutic strategies for Alzheimer's disease	36
2.4	Five medications approved by US FDA to treat AD symptoms of Alzheimer's disease	37
4.1	EDX analysis data for all MWCNT treated samples	71
4.2	Description of four main stages of MWCNT weight loss according to temperature	77
4.3	Total weight loss of oxygen functionalities in p-MWCNT and ox-MWCNT Treatment A-C	79
5.1	Kinetic parameters for adsorption of Curcumin by different MWCNT	99
5.2	Pseudo-second order constant for adsorption of various drugs on MWCNT	101
5.3	Summary of Langmuir and Freundlich model parameters	119
5.4	Thermodynamic parameters for the adsorption of Curcumin by MWCNT	112

**LIST OF FIGURES**

<b>FIGURE NO.</b>	<b>TITLE</b>	<b>PAGE</b>
2.1	TEM images and schematic drawing of SWCNT, DWCNT and MWCNT (left to right)	9
2.2	Schematic diagram of a simple set-up of CVD	10
2.3	Metallic catalyst particles encapsulated in graphite onions in TEM observation	13
2.4	Functionalization pathway of CNT that involved a defect group functionalization (A), covalent sidewall functionalization (B), non-covalent adsorption with surfactant (C) and wrapping of polymers (D)	15
2.5	Protein corona formation on the CNT surface as a result of exposure to serum proteins (left)	17
2.6	Simple schematic illustration on carbon nanotubes that attach therapeutic payloads for drug delivery	19
2.7	Possible aromatic stacking arrangement	20
2.8	Neuron and synapse anatomy	29
2.9	Neuroanatomical comparison of normal brain and Alzheimer's disease (AD) brain	30
2.10	Imbalance of reactive oxygen species (ROS) and antioxidant level that lead to peroxidation of lipid, protein and DNA	32

2.11	Curcuma rhizome cross section and commercial curcuminoid powder (left) and its structure that has seven carbon linkers and three major functional groups including an alpha, beta-unsaturated beta-diketone moiety and an aromatic o-methoxy phenolic group (right)	36
2.12	Keto-enol tautomerism of Curcumin, three prototropic equilibria and its estimated $pK_a$ and degradation products	39
2.13	Illustration of first-pass metabolism effect of free Curcumin	41
2.14	Various Curcumin nanoformulation were developed to improve Curcumin bioavailability	44
2.15	The blood brain barrier (BBB) is formed by special tight junctions between the epithelial cells that surround the brain tissue.	44
2.16	Solubility (a) and stability (b) of free Curcumin and Curcumin nanoparticulate in phosphate buffer saline at 37 °C	45
3.1	Flow chart of research activities	50
3.2	Steglich esterification reaction	53
4.1	FESEM analysis of p-MWCNT(a), ox-MWCNT Treatment A (b), ox-MWCNT Treatment B (c) and ox-MWCNT Treatment C(d)	70
4.2	FTIR spectra of p MWCNT and ox-MWCNT Treatment A-C.	73
4.3	Colloidal dispersion of p-MWCNT and ox-MWCNT in Treatment A-C after dispersed, at 30 min and at 2-month	76
4.4	Thermogravimetric curves of p-MWCNT and ox-MWCNT Treatment A-C.	78
4.5A	Comparison of FTIR spectra p-MWCNT and ox-MWCNT	81
4.5B	Comparison of PVA and PVA-MWCNT complex	81
4.6	Possible formation of ester (RCOOR') following esterification reaction between PVA with ox-MWCNT	82

4.7	Dispersion stability of PVA-MWCNT in aqueous solution according to concentration ranging at 1 mg/ml (A), 10 mg/ml (B), 40 mg/ml (C), 50 mg/ml (D) and 100 mg/ml (D)	83
4.8	Thermogravimetric curves of p-MWCNT (blue), ox-MWCNT (red), original PVA-MWCNT (green-sonicated 1 hour) and PVA-MWCNT (purple-sonicated 3 hours)	85
4.9	FESEM of p-MWCNT (A), ox-MWCNT (B), pure PVA (C) and PVA-MWCNT (D)	88
5.1	Effect of contact time on the adsorption of Curcumin onto PVA-MWCNT, ox-MWCNT and p-MWCNT	95
5.2	Plot of pseudo first-order kinetic model for Curcumin adsorption on p-MWCNT (A), ox-MWCNT (B) and PVA-MWCNT (C).	97
5.3	Plot of pseudo second-order kinetic model for Curcumin sorption on p-MWCNT (A), ox-MWCNT (B) and PVA-MWCNT (C)	98
5.4	The mechanism of CNT loading with Curcumin	105
5.5	Comparison of Langmuir (a) and Freundlich (b) adsorption isotherm for ox-MWCNT after equilibration of 4 hours in Curcumin solution	106
5.6	Comparison of Langmuir (a) and Freundlich (b) adsorption isotherm for p-MWCNT after equilibration of 1 hour in Curcumin solution	107
5.7	Comparison of Langmuir (a) and Freundlich (b) adsorption isotherm for PVA-MWCNT after equilibration of 1 hour in Curcumin solution	108
5.8	Summary of Curcumin interaction on ox-MWCNT, PVA-MWCNT and p-MWCNT	109
5.9	Effect of temperature on adsorption capacity of Curcumin on p-MWCNT, ox-MWCNT and PVA-MWCNT (Curcumin concentration: 10 ppm, MWCNT dose: 5 mg/60.00 mL, equilibrium time: ox-MWCNT: 4 h, p-MWCNT and PVA-MWCNT: 60 min)	110
5.10	Desorption of Curcumin from MWCNTs at pH 5.5 (A) and pH 7.4.(B). Data are presented as mean $\pm$ SEM, n=3	115

5.11	Summary of Curcumin loading on PVA-MWCNT by physisorption	117
6.1	Phase-contrast micrographs showing the morphological changes of SH-SY5Y cells	122
6.2	Neurotoxicity effect of Curcumin towards neuron cells viability as assessed by MTS assay after 24 hour incubation at 37 °C	124
6.3	Neurotoxic effect of Cur-MWCNT compared to MWCNT according to types (A: Cur-p-MWCNT/p-MWCNT, B: Cur-ox-MWCNT/ox-MWCNT and C: Cur-PVA-MWCNT/PVA-MWCNT)	125
6.4	Dispersion of MWCNT agglomerants in fetal bovine serum (FBS)	126
6.5	IC <sub>50</sub> determination of hydrogen peroxide (H <sub>2</sub> O <sub>2</sub> ) as assessed by MTS assay after 2 hour of incubation at 37 °C	128
6.6	Neuroprotection effect of Curcumin on H <sub>2</sub> O <sub>2</sub> -induced SH-SY5Y cells	129
6.7	Neuroprotection effect of Cur-MWCNT compared to MWCNT according to types (A: Cur-p-MWCNT/p-MWCNT, B: Cur-ox-MWCNT/ox-MWCNT and C: Cur-PVA-MWCNT/PVA-MWCNT)	131

**LIST OF SYMBOLS**

%	- Percentage
°C	- Degree Celcius
K	- Kelvin
$\alpha$	- Alpha
$\beta$	- Beta
$\gamma$	- Gamma
$\mu$	- Micro
n	- Nano
p	- Pico
<i>m</i>	- mass
V	- volume

**LIST OF ABBREVIATIONS**

ACh	- Acetylcholine
AChE	- Acetylcholinesterase
AChEI	- Acetylcholinesterase inhibitors
AD	- Alzheimer's disease
BBB	- Blood brain barrier
CNT	- Carbon Nanotubes
Cur	- Curcumin
Cur-ox-MWCNT	- Curcumin-loaded on oxidized multi-walled carbon nanotubes
Cur-p-MWCNT	- Curcumin-loaded on pristine multi-walled carbon nanotubes
Cur-PVA-MWCNT	- Curcumin-loaded on PVA-grafted multi-walled carbon nanotubes
CNS	- Central nervous system
Cpt	- Camptothecin
CVD	- Chemical vapour deposition
Da	- Dalton
DDS	- Drug Delivery System
DNA	- Deoxyribonucleic acid
Dox	- Doxorubicin
DWCNT	- Double-walled carbon nanotubes
EDX	- Energy dispersive X-ray
Epi	- Epirubicin hydrochloride
FESEM	- Field emission scanning electron microscopy
FTIR	- Fourier transform infrared
H <sub>2</sub> SO <sub>4</sub>	- Sulfuric acid

HNO <sub>3</sub>	- Nitric Acid
IC <sub>50</sub>	- Concentration of an inhibitor that reduces response by half
KBr	- Potassium bromide
m	- mol
M	- Molar
mg g <sup>-1</sup>	- Milligram per gram
MWCNT	- Multi-walled carbon nanotubes
ND	- Neurodegenerative disease
ox-MWCNT	- oxidized multi-walled carbon nanotubes
PD	- Parkinson's disease
PEG	- Polyethylene glycol
PEG-CNT	- Polyethylene glycol grafted on carbon nanotubes
ppm	- Parts per million
PBS	- Phosphate buffer solution
Ptx	- Paclitaxel
PVA	- Polyvinyl alcohol
PVA-MWCNT	- Polyvinyl-alcohol grafted on multi-walled carbon nanotubes
RA	- Retinoic acid
RES	- Reticuloendothelial system
rpm	- Rotation per minute
RNS	- Reactive nitrogen species
ROS	- Reactive oxygen species
SD	- Standard deviation
SDS	- Sodium dodecyl sulphate
SEM	- Standard error mean
SWCNT	- Single-walled carbon nanotubes
t	- time
TGA	- Thermal gravimetric analysis
UV-Vis	- Ultraviolet-visible
V	- Volt
v/v	- Volume per volume
w/w	- Weight per weight

**LIST OF APPENDICES**

<b>APPENDIX</b>	<b>TITLE</b>	<b>PAGE</b>
A	Curcumin standard calibration curve for drug loading and release studies	164
B	Chemical composition for drug release medium	165
C	Preparation of complete DMEM medium	166
D	Detailed preparation of Cur-MWCNT at various concentrations for neurotoxicity and neuroprotection	167
E	Pipetting scheme for neurotoxicity assay	172
F	Pipetting scheme for neuroprotection assay	173
G	Preparation of H <sub>2</sub> O <sub>2</sub> concentration.	174
H	EDX spectrum of p-MWCNT (A), ox-MWCNT Treatment A, stirring 24 hours (B); ox-MWCNT Treatment B, sonication 2 hours (C); and ox-MWCNT Treatment C, sonication 6 hours (D) in FESEM/EDX results	175
I	Plot of thermodynamic parameters for p-MWCNT (A), ox-MWCNT (B) and PVA-MWCNT (C)	176

## CHAPTER 1

### INTRODUCTION

#### 1.1 Background of study

Curcumin (diferuloylmethane) is a bioactive compound found in turmeric rhizomes of *Curcuma longa linn.* This natural compound has been used for centuries as a spice for cooking curry, as food colouring and as ailments, particularly as an anti-inflammatory agent (Aggarwal *et al.* 2003). It has also shown other pharmacological effects including anti-oxidant, anti-proliferative and anti-angiogenic activities to treat various pathological conditions such as cancer, cardiovascular disease, Alzheimer's disease and so on (Anand *et al.* 2007). Despite such phenomenal advances in medicinal applications, the clinical implication of native Curcumin is hindered by its low solubility, physico-chemical instability, poor bioavailability, rapid metabolism, and poor pharmacokinetics. These problems nevertheless, can be circumvented by utilizing an efficient delivery system (Yallapu *et al.* 2015).

With the development of nanotechnology, a number of formulations have been developed and explored upon achieving successful outcomes for pre-clinical and human clinical trials. They involve the use of adjuvants, stabilizers,

nanoparticles, liposomes, and polymer-drug conjugates (Yallapu *et al.* 2015). Carbon nanotubes (CNT) have recently received considerable attention as an efficient drug delivery carrier due to their unique physicochemical properties. They enable easy surface modification for immobilization of therapeutic molecules, such as drugs, proteins, DNA and antibodies (Zhang *et al.* 2011). Compared to other drug delivery carriers, CNT offers several advantages such as exceptionally high drug loading due to its high surface area (Kushwaha *et al.* 2013). Different kinds of therapeutic molecules can also be incorporated into their inner cavity to improve efficacy, for instance providing protective environment for drugs with poor stability. Many studies show that adsorbed molecules could be released from CNT under different conditions (Zhang *et al.* 2014, Wang *et al.* 2012b, Heister *et al.* 2012) and that it can be controlled by varying pH value, temperature and different diameter type (Kumari *et al.* 2014, Liu *et al.* 2007a). The targeting agents attached to the CNT also enable the molecules, for example drugs, to be selectively transported and released to the diseased sites (Zhang *et al.* 2011).

Other important issues such as opsonisation, phagocytosis by macrophages and sequestration by the liver and spleen that lead to its eventual elimination from the body need to be taken into account when developing a nanocarrier (Kotagiri and Kim, 2014). Hence, careful strategies in CNT functionalization are required for it to reach its full clinical potential. The design of CNT that combined coatings made of ligands or polymer in a complete and uniform manner helps to stabilize the carrier and prevents non-specific cell uptake in the bloodstream. A famous example is polyethylene glycol (PEG), a known polymeric steric stabilizer in pharmaceutical and food products, including in the development of CNT nanocarriers (Heister *et al.* 2010, Lay *et al.* 2010). The PEG-CNT did not only show good biocompatibility in biological milieu but also demonstrated prolonged blood circulation. As a result, the drug can be released when reaching the targeted cells. Advances using alternative biocompatible polymers incorporated with CNT have been well-described too, such as poly(lactic-co-glycolic acid) (Gupta *et al.* 2015), phosphatidylcholine (PC) and polyvinylpyrrolidone (PVP) (Zhang *et al.* 2014) and polyvinyl alcohol (PVA) (Sahoo *et al.* 2010). Their efficiency to improve stability, loading and release of Curcumin in a slow manner was, however, scarcely reported.

## 1.2 Problem statement

It was known that many formulations were developed to improve Curcumin delivery, except for CNT where studies are still in its infancy. To date, there is only one report that worked on Curcumin-loaded CNT system, which focused on Curcumin's anti-cancer potential (Zhang *et al.* 2014). The group functionalized single-walled CNT (SWCNT) with PC and PVP polymer for Curcumin loading, and the results showed fast release of the compound to suit its applicability for photothermal therapy.

In this study, the aim is to develop multi-walled CNT (MWCNT) as a carrier for Curcumin towards neurodegenerative treatment. The possible route of administration is through blood circulation; the time taken to reach the blood-brain barrier (BBB) might slow down before the drug can be released. Commonly, CNT was functionalized with PEG, as PEG is the most widely used polymer for increasing various nanocarrier's stability. CNT-PEG was known to provide shielding to the nanotubes to render its resistance to opsonin, macrophage and reticuloendothelial system (RES); showed by its increased blood circulation time in *in vivo* and *in vitro* experiment (Kotagiri and Kim, 2014). The prolonged circulation time of CNT helps the drug to be released effectively at the relevant/ targeted sites, which makes it an ideal drug carrier. In the current situation, there is a need to explore more coating materials that have PEG-like properties due to a number of limitations. First, studies have found anti-PEG antibodies in a population of healthy humans due to an increased exposure of PEG through food product, pharmaceutical formulation and cosmetics (Kinnear *et al.* 2014). These antibodies caused a reduction in circulation time of the PEGylated agent and accelerated clearance from the body due to repeated administration. Secondly, the "stealth" of PEG is potentially undesirable if there is a specific biological target on the carrier, such as the immune system. Also controversial is that PEG requires further synthetic steps to introduce a high number of functional moieties to bind with other therapeutic molecules, such as targeting peptides. The conventional PEG was known to have a low degree of functionality,

where only its end is reactive for attachment. This study has therefore explored new polymer alternatives for functionalization with MWCNT.

### 1.3 Research objectives

The present study was dedicated to develop nanocarriers using MWCNT and biocompatible PVA for Curcumin delivery. This work is regarded as the first study using MWCNT, with the main aim to graft PVA to ox-MWCNT, achieve stability of the PVA-MWCNT and to successfully load and release the compound in a slow manner. Additionally, the study is also aimed at providing recommendations for its potential implementation as a neuroprotective agent.

The specific objectives of the experimental study are as follows:

- i. To develop functionalized MWCNT with PVA for the attachment of Curcumin
- ii. To determine loading and release behavior of Curcumin on PVA-MWCNT in comparison to pristine MWCNT (p-MWCNT) and oxidized MWCNT (ox-MWCNT)
- iii. To determine neurotoxicity and neuroprotective effect of Cur-PVA-MWCNT, Cur-ox-MWCNT and Cur-p-MWCNT, in comparison to PVA-MWCNT, ox-MWCNT and p-MWCNT using neuroblastoma cell line SH-SY5Y

#### **1.4 Scope of study**

This research project investigates the potential of functionalized MWCNT as an effective delivery carrier for Curcumin. In the first step of the study, the p-MWCNT was modified to ox-MWCNT using acid oxidation. The methods include stirring and sonication in the acid mixture and were optimized for its ability to provide substantial functional groups on ox-MWCNT with minimal structural damage. The best method was then selected to reproduce ox-MWCNT for grafting with PVA. Conformation of functional groups generated on ox-MWCNT and PVA-MWCNT were evaluated using field-emission scanning electron microscopy (FESEM), energy dispersive X-ray (EDX), Fourier transform infra-red (FTIR) spectroscopy, dispersion test and thermal gravimetric analysis (TGA). In the second objective, Curcumin was loaded to the PVA-MWCNT, as well as on ox-MWCNT and p-MWCNT for comparison. The Curcumin attached to the MWCNT samples were named Cur-PVA-MWCNT, Cur-ox-MWCNT and Cur-p-MWCNT. Their adsorption behavior was predicted by examining adsorption kinetics, isotherm and thermodynamics using mathematical models. In the drug desorption study, Curcumin's ability to disperse from the MWCNT samples, and its release pattern were determined in physiological buffers. Finally, investigations on neurotoxicity and neuroprotection effect of Cur-PVA-MWCNT, Cur-ox-MWCNT and Cur-p-MWCNT were evaluated using SH-SY5Y cells, which were conducted at Universiti Teknologi MARA, Shah Alam, Selangor. The correlation between Cur-loaded MWCNT and Cur-unloaded MWCNT was statistically validated using paired t-test.

#### **1.5 Significance of study**

In developing a CNT-based drug delivery carrier, careful design of functionalization is crucial. Polymer functionalized CNT has been reported to increase its circulation time in blood due to its "stealth", which helps to regulate drug release more

efficiently to cells and tissues. The present study hence optimized MWCNT functionalization strategies using biocompatible PVA. The discovery made from this study will disseminate knowledge that solved fundamental problems in the use of CNT as a drug carrier, such as their water solubility. The PVA that was employed as an alternative polymer for CNT functionalization will also help overcome PEG limitations that were recently reported. This was investigated through drug adsorption and desorption studies that used Curcumin as a drug model. Although there is still a long way to go for practical use, this study helps increase understanding on polymer-functionalized MWCNT for pharmaceutical industries application. The developed PVA-MWCNT before and after loading with Curcumin was studied for neuroprotective capabilities that will be beneficial in neurodegenerative disease treatment.

## REFERENCES

- Acar, A., Akil, E., Alp, H., Evliyaoglu, O., Kibrisli, E., Inal, A., Unan, F. and Tasdemir, N. (2012). Oxidative Damage is Ameliorated by Curcumin Treatment in Brain and Sciatic Nerve of Diabetic Rats. *International Journal Neuroscience*. 122: 367-372.
- Adeli, M., Zarnegar, Z. and Kabiri, R. (2008). Amphiphilic Star Copolymers Containing Cyclodextrin Core and Their Application as Nanocarrier. *European Polymer Journal*. 44: 1921-1930.
- Aggarwal, B. B., Kumar, A. and Bharti, A. C. (2003). Anticancer Potential of Curcumin: Preclinical and Clinical Studies. *Anticancer Research*. 23: 363-398.
- Ahlemeyer, B. and Krieglstein, J. (2000). Inhibition of Glutathione Depletion by Retinoic Acid and Tocopherol Protects Cultured Neurons from Staurosporine-Induced Oxidative Stress and Apoptosis. *Neurochemistry International*. 36: 1-5.
- Ahlemeyer, B., Bauerbach, E., Plath, M., Steuber, M., Heers, C., Tegtmeier, F. and Krieglstein, J. (2001). Retinoic Acid Reduces Apoptosis and Oxidative Stress by Preservation of SOD Protein Level. *Free Radical Biology and Medicine*. 30: 1067-1077.
- Ahmad Zamri, M. F. M., Zein, S. H. S., Abdullah, A. Z and Basir, N. I. (2011). Improved Electrical Conductivity of Polyvinyl Alcohol/Multiwalled Carbon Nanotube Nanofibre Composite Films with MnO<sub>2</sub> as Filler Synthesized using the Electrospinning Process. *International Journal of Engineering and Technology*. 11(6): 15-21.
- Ahmad, M. Z., Akther, S., Mohsin, N., Abdel-Wahab, B. A., Ahmad, J., Warsi, M. H., Rahman, M., Mallick, N. and Ahmad, F. J. (2014). Transformation of Curcumin from Food Additive to Multifunctional Medicine: Nanotechnology Bridging the Gap. *Current Drug Discovery Technologies*. 11: 197-213.

- Ajayan, P. M., Ebbesen, T. W., Ichihashi, T., Iijima, S., Tanigaki, K. and Hura, H. (1993). Opening Carbon Nanotubes with Oxygen and Implications for Filling. *Nature*. 362: 522-524.
- Ajetunmobi, A., Prina-Mello, A., Volkov, Y., Corvin, A. and Tropea, D. (2014). Nanotechnologies for the Study of the Central Nervous System. *Progress Neurobiology*. 123: 18-36.
- Ajmal, M., Rao, R. A. K., Ahmad, R. and Ahmad, J. (2000). Adsorption Studies on Citrus Reticulate (Fruit Peel of Orange): Removal and Recovery of Ni (II) from Electroplating Wastewater. *Journal of Hazardous Material*. 79: 117-131.
- Ali-Boucetta, H., Al-Jamal, K. T., McCarthy, D., Prato, M., Bianco, A. and Kostarelos, K. (2008). Multiwalled Carbon Nanotube-Doxorubicin Supramolecular Complexes for Cancer Therapeutics. *Chemical Communication*. 4: 459-461.
- Alzheimer's Disease Foundation Malaysia (2012). Retrieve from <http://www.adfm.org.my/Home/about-alzheimer-s>
- Anand, P., Kunnumakkara, A. B., Newman, R. A. and Aggarwal, B. B. (2007). Bioavailability of Curcumin: Problems and Promises. *Molecular Pharmaceutics*. 4(6): 807-818.
- Anand, R., Gill, K. D. and Mahdi, A. A. (2014). Therapeutics of Alzheimer's Disease: Past, Present and Future. *Neuropharmacology*. 76: 27-50.
- Arcaro, C. A., Gutierrez, C. A., Assis, R. P., Moreira, T. F., Costa, P. I., Baviera, A. M. and Brunetti, I. L. (2014). Piperine, a Natural Bioenhancer, Nullifies the Antidiabetic and Antioxidant Activities of Curcumin in Streptozotocin-Diabetic Rats. *PLoS One*. 9(12): e113993.
- Avilés, F., Cauich-Rodríguez, J. V., Moo-Tah, L., May-Pat, A. and Vargas-Coronado, R. (2009). Evaluation of Mild Acid Condition Treatments for MWCNT Functionalization. *Carbon*. 47: 2970-2975.
- Bai, W., Wu, Z., Mitra, S. and Brown. J. M. 2016. Effects of Multiwalled Carbon Nanotubes Surface Modification and Purification on Bovine Serum Albumin Binding and Biological Responses. *Journal of Nanomaterials*. 2159537.
- Balasubramaniam, K. and Burghard. (2005). Chemically Functionalized Carbon Nanotubes. *Small*. 1(2): 180-192.

- Barzegar, A. and Moosavi-Movahedi, A. A. (2011). Intracellular ROS Protection Efficiency and Free-Radical Scavenging Activity of Curcumin. *PLoS One*. 6: e26012.
- Baum, L., Lam, C. W., Cheung, S. K., Kwok, T., Lui, V., Tsoh, J., Lam, L., Leung, V., Hui, E., Ng, C., Woo, J., Chiu, H. F., Goggins, W. B., Zee, B. C., Cheng, K. F., Fong, C. Y., Wong, A., Mok, H., Chow, M. S., Ho, P. C., Ip, S. P., Ho, C. S., Yu, X. W., Lai, C. Y., Chan, M. H., Szeto, S., Chan, I. H. and Mok, V. (2008). Six-Month Randomized, Placebo-Controlled, Double-Blind, Pilot Clinical Trial of Curcumin in Patients with Alzheimer Disease. *Journal of Clinical Psychopharmacology*. 28: 110-113.
- Beg, S., Rizwan, M., Sheikh, A. M., Hasnain, M. S., Anwer, K. and Kohli, K. (2010). Advancement in Carbon Nanotubes: Basics, Biomedical Applications and Toxicity. *Journal of Pharmacy and Pharmacology*. 63(2): 141-163.
- Beyou, E., Akbar, S., Chaumont, P. and Cassagnau, P. (2013). Polymer Nanocomposites Containing Functionalized Multiwalled Carbon Nanotubes: A Particular Attention to Polyolefin Based Materials. In Suzuki, S. (Ed.) *Synthesis of Carbon Nanotubes and Their Composites*. (pp. 77-115). European Union: InTech Publisher.
- Biedler, J. L., Helson, L. and Spengler, B. A. (1973). Morphology and Growth, Tumorigenicity and Cytogenetics of Human Neuroblastoma Cells in Continuous Culture. *Cancer Research*. 33(11): 2643-2652.
- Bigos, K., Hariri, A. R. and Weinberger, D. (2015). *Neuroimaging Genetics: Principles and Practices*. New York: Oxford University Press.
- Bredesen, D.E., Rao, R.V. and Mehlen, P. (2006). Cell Death in the Nervous System. *Nature*. 443: 796-802.
- Briske-Anderson, M. J, Finley, J. W. and Newman, S. M. (1997). The Influence of Culture Time and Passage Number on the Morphological and Physiological Development of Caco-2 cells. *Proceedings of Society for Experimental Biology and Medicine*. 214(3): 248-257.
- Chaudhuri, P., Soni, S., and Sengupta, S. (2010). Single-Walled Carbon Nanotube Conjugated Chemotherapy Exhibits Increased Therapeutic Index in Melanoma. *Nanotechnology*. 21: 025102.
- Chen, J., Rao, A. M., Lyuksyutov, S., Itkis, M. E., Hamon, M. A., Hu, H., Chen, Y., Rao, A. M., Eklund, P. C. and Haddon, R. C. (2001). Dissolution of Full-

- Length Single-Walled Carbon Nanotubes. *The Journal of Physical Chemistry A*. 105: 2525-2528.
- Chen, Z., Pierre, D., He, H., Tan, S., Pham-Huy, C., Hong, H. and Huang, J. (2011). Adsorption Behavior of Epirubicin Hydrochloride on Carboxylated Carbon Nanotubes. *International Journal of Pharmaceutics*. 405(1-2): 153-161.
- Cherukuri, P., Gannon, C. J., Leeuw, T. K., Schmidt, H. K., Smalley, R. E., Curley, S. A. and Weisman, R. B. (2006). Mammalian Pharmacokinetics of Carbon Nanotubes using Intrinsic Near-Infrared Fluorescence. *Proceedings of the National Academy of Sciences of the United States of America*. 103(50): 18882-18886.
- Cheung, Y-T., Lau, W. K-W., Yu, M-S., Lai, C. S-W., Yeung, S-C., So, K-F. and Chang, R. C-C. (2009). Effects of All-Trans-Retinoic Acid on Human SH-SY5Y Neuroblastoma as *In Vitro* Model in Neurotoxicity Research. *Neurotoxicology*. 30(1): 127-135.
- Cirillo, G., Hampel, S., Klingeler, R. , Puoci, F., Iemma, F., Curcio, M., Parisi, O. I., Spizzirri, U. G., Picci, N., Leonhardt, A., Ritschel, M. and Buchner, B. (2011). Antioxidant Multi-Walled Carbon Nanotubes by Free Radical Grafting of Gallic Acid: New Materials for Biomedical Applications. *Journal of Pharmacy and Pharmacology*. 63(2): 179-188.
- Claesson, P. M., Blomberg, E., Froberg, J. C., Nylander, T. and Arnebrant. T. (1995). Protein Interactions at Solid Interface. *Advances in Colloid and Interface Science*. 57: 161-227.
- Constantinescu, R., Constantinescu, A. T., Reichmann, B. and Janetzky, B. (2007). Neuronal Differentiation and Long Term Culture of the Human Neuroblastoma Cell Line SH-SY5Y. *Journal of Neural Transmission Supplementum*. (72): 17-28.
- Cornago, P., Claramunt, R. M., Bouissane, L., Alkorta, I. and Elguero, J. (2008). A Study of the Tautomerism of Beta-Dicarbonyl Compounds with Special Emphasis on Curcuminoids. *Tetrahedron*. 64, 8089-8094.
- Cory, A. H., Owen, T. C., Barltrop, J. A. and Cory, J. G. (1991). Use of an Aqueous Soluble Tetrazolium/Formazan Assay for Cell Growth Assays in Culture. *Cancer Communications*. 3(7): 207-212.
- Craig, D. I. (2003). Brain-Compatible Learning: Principles and Applications in Athletic Training. *Journal of Athletic Training*. 38(4): 342-349.

- Daniel, C., Bell, C., Burton, C., Harguindey, S., Reshkin, S.J. and Rauch, C. (2013). The Role of Proton Dynamics in the Development and Maintenance of Multidrug Resistance in Cancer. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease*. 1832(5): 606-617.
- Datsyuk, V., Kalyva, M., Papagelis, K., Parthenios, J., Tasis, D., Siokou, A., Kallitsis, I. and Galiotis, C. (2008). Chemical Oxidation of Multiwalled Carbon Nanotubes. *Carbon*. 46: 833-840.
- David, J. and Cheek, N. (2012). *Fundamentals and Applications of Ultrasonic Waves: Acoustic Sensors*. (2<sup>nd</sup> ed.) USA: CRC Press.
- Dhar, S., Liu, Z., Thomale, J., Dai, H. and Lippart, S. J. (2008). Targeted Single-Wall Carbon Nanotube Mediated Pt (IV) Prodrug Delivery using Folate as a Homing Device. *Journal of the American Chemical Society*. 130: 11467-11476.
- Di Crescenzo, A., Velluto, D., Hubbell, J. A. and Fontana, A. (2011). Biocompatible Dispersions of Carbon Nanotubes: A Potential Tool for Intracellular Transport of Anticancer Drugs. *Nanoscale*. 3(3): 925-928.
- Díez-Pascual, A. M. and Naffakh, M. (2012). Grafting of An Aminated Poly(phenylene sulphide) Derivative to Functionalized Single-Walled Carbon Nanotubes. *Carbon*. 50: 857-868.
- Ding, F., Jiao, K., Wu, M. and Yakobson, B. I. (2007). Pseudoclimb and Dislocation Dynamics in Superplastic Nanotubes. *Physical Review Letters*. 98(7): 075503.
- Donald, E. O. I. I. I. and Nicholas A. P. (2006). Opsonization, Biodistribution, and Pharmacokinetics of Polymeric Nanoparticles. *International Journal of Pharmaceutics*. 307(1): 93-102.
- Dresselhaus, M. S. (1998). Carbon Nanotubes – Introduction. *Journal of Materials Research*. 13: 2355-2356.
- Ebbesen, T. W. and Ajayan, P. M. (1992). Large-Scale Synthesis of Carbon Nanotubes. *Nature*. 358: 220-222.
- Emerit, J., Edeas, M. and Bricaire, F. (2004). Neurodegenerative Diseases and Oxidative Stress. *Biomedicine and Pharmacotherapy*. 58: 39-46.
- Erental, A., Sharon, I. and Engelberg-Kulka, H. (2012). Two Programmed Cell Death Systems in *Escherichia Coli*: An Apoptotic-Like Death is Inhibited by the mazEF Mediated Death Pathway. *PLoS Biology*. 10: e1001281.

- Esterbauer, H., Schaur, R. J. and Zollner, H. (1991). Chemistry and Biochemistry of 4-Hydroxynenal, Malonaldehyde and Related Aldehydes. *Free Radical Biology and Medicine*. 11: 81-128.
- Fang, Y. Z., Yang, S. and Wu, G. (2002). Free Radicals, Antioxidant and Nutrition. *Nutrition*. 18(10): 872-879.
- Farahani, B. V., Behbahani, G. R. and Javadi, N. (2016). Functionalized Multi-Walled Carbon Nanotubes as a Carrier for Doxorubicin: Drug Adsorption Study and Statistical Optimization of Drug Loading by Factorial Design Methodology. *Journal of the Brazilian Chemical Society*. 27(4): 694-705.
- Farooqui, A. A. (2016). Metabolism, Bioavailability, Biochemical Effects of Curcumin in Visceral Organs. *Therapeutic potentials of Curcumin for Alzheimer's disease*. Switzerland: Springer International Publishing.
- Favaloro, B., Allocati, N., Graziano, V., Dillio, C. and De Laurenzi, V. (2012). Role of Apoptosis in Disease. *Aging (Albany NY)*. 4(5): 330-349.
- Feazell, R. P., Nakayama-Ratchford, N., Dai, H. and Stephen, J. (2007). Soluble Single-Walled Carbon Nanotubes as Longboat Delivery Systems for Platinum (IV) Anticancer Drug Design. *Journal of the American Chemical Society*. 129: 8438-8439.
- Floyd, R. A. and Carney, J. M. (1992). Free Radical Damage to Protein and DNA: Mechanism Involved and Relevant Observations on Brain Undergoing Oxidative Stress. *Annals of Neurology*. 32: 22-27.
- Floyd, R. A. and Hensley, K. (2002). Oxidative Stress in Brain Aging: Implications for Therapeutics of Neurodegenerative Diseases. *Neurobiology of Aging*. 23: 795-807.
- Folch, J., Petrov, D., Etcheto, M., Abad, S., Sánchez-López, E., Garcia, L. G., Ollequequi, J., Beas-Zarate, C., Auladell, C. and Camins, A. (2016). Current Research Therapeutic Strategies for Alzheimer's Disease Treatment. *Neural Plasticity*. 8501693.
- Foldvari, M. (2010). Formulating Nanomedicines: Focus on Carbon Nanotubes as Novel Nanoexcipients. *Key Engineering Materials*. 441: 53-74.
- Foldvari, M. and Bagonluri, M. (2008). Carbon Nanotubes as Functional Excipients for Nanomedicines: II. Drug Biocompatibility Issues. *Nanomedicine: Biology, and Medicine*. 4: 183-200.

- Förch, R. (2009). Tutorial Review: Surface Modification and Adhesion. In: Förch, R., Schönleir, H., Tobias, A. and Jenkins, A. T. A. (Eds.). *Surface Design and Applications in Bioscience and Nanotechnology*. Chichester: Wiley. Pp. 55-80.
- Frankfurt, O. S. and Krishan, A. (2001). Enzyme-Linked Immunosorbent Assay (ELISA) for the Specific Detection of Apoptotic Cells and Its Application to Rapid Drug Screening. *Journal of Immunological Methods*. 253(1-2): 133-144.
- Gaberc-Porekar, V., Zore, I., Podobnik, B. and Menart, V. (2008). Obstacles and Pitfalls in the PEGylation of Therapeutic Proteins. *Current Opinion in Drug Discovery and Development*. 11: 242-250.
- Ganguli, M., Chandra, V., Kamboh, M. I., Johnston, J. M., Dodge, H. H., Thelma, B. K., Juyal, R. C., Pandav, R., Belle, S. H. and De Kosky, S. T. (2000). Apolipoprotein E Polymorphism and Alzheimer Disease: The Indo-US Cross-National Dementia Study. *Archives Neurology*. 57(6): 824-830.
- Gao, Y., Li, Z., Sun, M., Guo, C., Yu, A., Xi, Y., Cui, J., Lou, H. and Zhai, G. (2011). Preparation and Characterization of Intravenously Injectable Curcumin Nanosuspension. *Drug Delivery*. 18(2): 131-142.
- Garcia-Garcia, A., Rodriguez-Rocha, H., Madayiputhiya, N., Pappa, A., Panayiotidis, M. I. and Franco, R. (2012). Biomarkers of Protein Oxidation in Human Disease. *Current Molecular Medicine*. 12: 681-697.
- Geng, H. Z., Zhang, X. B., Mao, S. H., Kleinhammes, A., Shimoda, H., Wu, Y. and Zhou, O. (2004). Opening and Closing of Single-Wall Carbon Nanotubes. *Chemical Physics Letters*. 399: 109-113.
- Georgakilas, V., Tagmatarchis, N., Pantarotto, D., Bianco, A., Briand, J. P. and Prato, M. (2002). Amino Acid Functionalisation of Water Soluble Carbon Nanotubes. *Chemical Communications*. (24): 3050-3051.
- Ghandarlaki, N., Alizadeh, A. M. and Ashkani-Esfahani, S. (2014). Nanotechnology-Applied Curcumin for Different Disease Therapy. *Biomed Research International*. 394264.
- Gimenez, V., Mantecom, A. and Cadiz, V. (1996). Modification of Poly(Vinyl Alcohol) with Acid Chlorides and Crosslinking with Difunctional Hardeners. *Journal of Polymer Science Part A: Polymer Chemistry*. 34: 92534.
- Gota, V. S., Maru, G. B., Soni, T. G., Gandhi, T. R., Kochar, N. and Agarwal, M. G. (2010). Safety and Pharmacokinetics of a Solid Lipid Curcumin Particle

- Formulation in Osteosarcoma Patients and Healthy Volunteers. *Journal of Agricultural and Food Chemistry*. 58: 2095-2099.
- Gotovac, S., Yang, C. M., Hattori, Y. and Kaneko, K. (2007). Adsorption of Polyaromatic Hydrocarbons on Single Wall Carbon Nanotubes of Different Functionalities and Diameters. *Journal of Colloid and Interface Science*. 314, 18-24.
- Gupta, A., Liberati, T. A., Verhulst, S. J., Main, B. J., Roberts, M. H., Potty, A. G. R., Pylawka, T. K. and El-Amin III, S. F. (2015). Biocompatibility of Single-Walled Carbon Nanotube Composites for Bone Regeneration. *Bone and Joint Research*. 4(5): 70-77.
- Hamm, R. J., Temple, M. D., Pike, B. R. and Ellis, E. F. (1996). The Effect of Post Injury Administration of Polyethylene Glycol-Conjugated Superoxide Dismutase (Pegorgotein, Dismutec) or Lidocaine on Behavioral Function Following Fluid Percussion Brain Injury in Rats. *Journal of Neurotrauma*. 13: 325-332
- Hashida, Y., Tanaka, H., Zhou, S., Kawakami, S., Yamashita, F., Murakami, T., Umeyama, T., Imahori, H. and Hashida, M. (2014). Photothermal Ablation of Tumor Cells using a Single-Walled Carbon Nanotube-Peptide Composite. *Journal of Controlled Release*. 173: 59-66.
- Hashimoto, M., Rockenstein, E., Crews, L. and Masliah, E. (2003). Role of Protein Aggregation in Mitochondrial Dysfunction and Neurodegeneration in Alzheimer's And Parkinson's Diseases. *Neuromolecular Medicine*. 4:21-36.
- He, Q. J., Zhang, J. M., Shi, J. L., Zhu, Z. Y., Zhang, L. X., Bu, W. B. Guo, L. and Chen, Y. (2010). The Effect of Pegylation of Mesoporous Silica Nanoparticles on Nonspecific Binding of Serum Proteins and Cellular Responses. *Biomaterials*. 31(6): 1085-1092.
- Heister, E. (2010). *Functionalized Carbon Nanotubes as a Multimodal Drug Delivery System for Targeted Cancer Therapy*. PhD Thesis. University Of Surrey, UK.
- Heister, E., Neves, V., Lamprecht, C., Silva, S. R. P., Coley, H. M. and MacFadden, J. (2012). Drug Loading, Dispersion Stability, and Therapeutic Efficacy in Targeted Drug Delivery with Carbon Nanotubes. *Carbon*. 50: 622-632.
- Higuchi, Y. (2003). Chromosomal DNA Fragmentation in Apoptosis and Necrosis Induced by Oxidative Stress. *Biochemical Pharmacology*. 66: 1527-1535.

- Hirsch, A. (2002). Functionalization of Single-Walled Carbon Nanotubes. *Angewandte Chemie International Edition*. 41(11): 1853-1859.
- Ho, Y. S. and McKay, G. (2000). The Kinetics of Sorption of Divalent Metal Ions onto Sphagnum Moss Peat. *Water Research*. 34(3): 735-742.
- Hou, P., Liu, C., Tong, Y., Xu, S., Liu, M. and Cheng, H. (2001). Purification of Single-Walled Carbon Nanotubes Synthesized by the Hydrogen Arc-Discharge Method. *Journal of Materials Research*. 16: 2526-2529.
- Hou, P. X., Liu, C. and Cheng, H. M. (2008). Purification of Carbon Nanotubes. *Carbon*. 46: 2003-2025.
- Hu, H., Zhao, B., Itkis, M. E. and Haddon R. C. (2003). Nitric Acid Purification of Single-Walled Carbon Nanotubes. *Journal of Physical Chemistry B*. 107: 13838-13842.
- Hwang, S-H., Park, Y-B., Yoon, K. H. and Bang, D. S. (2011). Smart Materials and Structures Based on Carbon Nanotubes Composites. *Carbon Nanotubes-Synthesis, Characterization, Applications*. European Union: Intechopen.
- Hwang, Y., Park, S-H. and Lee, J. W. (2017). Applications of Functionalized Carbon Nanotubes for the Therapy and Diagnosis of Cancer. *Polymers*. 9(13): 2-26.
- Ibrahim, M. L. (2010). *Functionalized Multiwalled Carbon Nanotubes for Salicylic Acid and Pseudoephedrine Drug Carrier System*. Master Thesis. Universiti Teknologi Malaysia, Malaysia.
- Iijima, S. (1991). Helical Microtubules of Graphitic Carbon. *Nature*. 354: 56-58.
- Iscen, C. F., Kiran, I. and Ilhan, S. (2007). Biosorption of Reactive Black 5 Dye by *Penicillium restrictum*: The Kinetic Study. *Journal of Hazardous Materials*. 143: 335-338.
- James, J. A., Shukitt-Hale, B., Denisova, N. A., Bielinski, D., Martin, A., McEwen, J. J. and Bickford, P. C. (1999). Reversals of Age-Related Declines in Neuronal Signal Transduction, Cognitive, and Motor Behavioral Deficits with Blueberry, Spinach, or Strawberry Dietary Supplementation. *Journal of Neuroscience*. 9: 8114-8121.
- Jeon, I-Y, Chang, D. W., Kumar, N. A. and Baek, J. B. (2011). Functionalization of Carbon Nanotubes. In: *Yellampalli, S. Carbon Nanotubes-Polymer Nanocomposites*. Rijieka: InTech. Pp. 91-110.

- Ji, S. (2013). Turmeric Produces “Remarkable” Recovery in Alzheimer’s Patients. Retrieved from <http://www.greenmedinfo.com/blog/turmeric-produces-remarkable-recovery-alzheimers-patients>.
- Jiang, H., Zhu, L., Moon, K. and Wong, C. P. (2007). The Preparation of Stable Metal Nanoparticles on Carbon Nanotubes Whose Surfaces Were Modified During Production. *Carbon*. 45(3): 655-661.
- John, A. A, Subramaniam, A. P., Vellayapan, M. V., Balaji, A., Mohandas, H. and Jaganathan, S. K. (2015). Carbon Nanotubes and Graphene as Emerging Candidates in Neuroregeneration Nan Dneurodrug Delivery. *International Journal of Nanomedicine*. 10: 4267-4277.
- Jovanovic, S. V., Steenken, S., Boone, C. W. and Simic, M. G. (1999). H-Atom Transfer is a Preferred Antioxidant Mechanism of Curcumin. *Journal of the American Chemical Society*. 121: 9677-9681.
- Kam, N. W. S., Jessop, T. C., Wender, P. A. and Dai, H. (2004). Nanotube Molecular Transporters: Internalization of Carbon Nanotube-Protein Conjugates into Mammalian Cells. *Journal of the American Chemical Society*. 126: 6850-6851.
- Kanwar, J. R., Sriramoju, B. and Kanwar, R. K. (2012). Neurological Disorders and Therapeutics Targeted to Surmount the Blood–Brain Barrier. *International Journal of Nanomedicine*. 7: 3259-3278.
- Kathi, J., Rhee, K. Y. and Lee, J. H. (2009). Effect of Chemical Functionalization of Multi-Walled Carbon Nanotubes with 3-Aminopropyltriethoxysilane on Mechanical and Morphological Properties of Epoxy Nanocomposites. *Composites Part A*. 40: 800-809.
- Khan, S., Ahmad, K., Alshammari, E. M., Adnan, M., Baig, M. H., Lohani, M. M., Somvanshi, P. and Haque, S. (2015). Implication of Caspase-3 as a Common Therapeutic Target for Multineurodegenerative Disorders and Its Inhibition Using Nonpeptidyl Natural Compounds. *Biomed Research International*. 379817.
- Kim, S. S., Kim, T., Kim, Y. S., Choi, H. S., Lim, H. J., Yang, S. Y. and Park, C. R. (2012). Surface Modifications for the Effective Dispersion of Carbon Nanotubes in Solvents and Polymers. *Carbon*. 30: 3-33.

- Kim, U. J., Furtado, C. A., Liu, X., Chen, G. and Eklund, P. C. (2005). Raman and IR Spectroscopy of Chemically Processed Single-Walled Carbon Nanotubes. *Journal of the American Chemical Society*. 127(44): 15437-15445.
- Kinningham, K. K., Cardozo, Z. A., Cook, C., Cole, M. P., Stewart, J. C., Tassone, M., Coleman, M. C. and Spitz, D. R. (2008). All-Trans-Retinoic Acid Induces Manganese Superoxide Dismutase in Human Neuroblastoma Through NF-kappaB. *Free Radical Biology and Medicine*. 44: 1610-1616.
- Kinnear, C., Burnand, D., Clift, M. J. D., Kilbinger, A. F. M., Rothen-Rutihäuser, B. and Petri-Fink, A. (2014). Polyvinyl Alcohol as a Biocompatible Alternative for the Passivation of Gold Nanorods. *Angewandte Chemie International Edition*. 53(46): 12613-12617.
- Klein, J. A. and Ackerman, S. L. (2003). Oxidative Stress, Cell Cycle and Neurodegeneration. *Journal of Clinical Investigation*. 111: 785-793.
- Klumpp, C., Kosteralos, K., Prato, M. and Bianco, A. (2006). Functionalized Carbon Nanotubes as Emerging Nanovectors for the Delivery of Therapeutics. *Biochimica et Biophysica Acta*. 1758: 404-412.
- Koh, J. Y. and Choi, D. W. (1987). Quantitative Determination of Glutamate Mediated Cortical Neuronal Injury in Cell Culture by Lactate Dehydrogenase Efflux Assay. *Journal of Neuroscience Methods*. 20(1): 83-90.
- Kohen, R. and Nyska, A. (2002). Oxidation of Biological Systems: Oxidative Stress Phenomena, Antioxidants, Redox Reactions, and Methods for Their Quantification. *Toxicology Pathology*. 30: 620-650.
- Kosteralos, K. (2003). Rational Design and Engineering of Delivery Systems for Therapeutics: Biomedical Exercises in Colloid and Surface Science. *Advances in Colloid Interface Science*. 106: 147-168.
- Kotagiri, N. and Kim, J-W. (2014). Stealth Nanotubes: Strategies of Shielding Carbon Nanotubes to Evade Opsonisation and Improve Biodistribution. *International Journal of Nanomedicine*. 9: 85-105.
- Krashennikov, A. V. and Banhart, F. (2007). Engineering of Nanostructured Carbon Materials with Electron or Ion Beams. *Nature Materials*. 6: 723-733.
- Kumar, M. and Ando, Y. (2010). Chemical Vapor Deposition of Carbon Nanotubes: A Review on Growth Mechanism and Mass Production. *Journal of Nanoscience and Nanotechnology*. 10: 3739-3758.

- Kumari, A., Singla, R., Guliani, A. and Yadav, S.K. (2014). Nanoencapsulation for drug delivery. *EXCLI Journal: Experimental and Clinical Sciences*. 13: 265-286.
- Kurien, B. T. and Scofield, R. H. (2009). Heat Solubilized Curcumin Should Be Considered in Clinical Trials for Increasing Bioavailability. *Clinical Cancer Research*. 15(2): 747.
- Kushwaha, S. K. S., Ghoshal, S., Rai, A. K. and Singh, S. (2013). Carbon Nanotubes as a Novel Drug Delivery System for Anti-Cancer Therapy: A Review. *Brazilian Journal of Pharmaceutical Sciences*. 49: 629-643.
- Lagergren, S. (1898). About the Theory of So-Called Adsorption of Soluble Substance. *Kungliga Svenska Vetenskapsakademiens Handlingar*. 24: 1-39.
- Lay, C. L., Liu, H. Q. and Liu, Y. (2010). Delivery of Paclitaxel by Physically Loading onto Poly(Ethylene Glycol) (PEG)-Graft-Carbon Nanotubes for Potent Cancer Therapeutics. *Nanotechnology*. 21: 065101.
- Lee, G. W., Kim, J., Yoon, J., Bae, J. S., Shin, B. C., Kim, I. S., Oh, W. and Ree, W. (2008). Structural Characterization of Carboxylated Multi-Walled Carbon Nanotubes. *Thin Solid Films*. 516: 5781-5784.
- Lee, H-P., Casadesus, G., Zhu, X., Lee, H-g., Perry, G., Smith, M. A., Gustaw-Rothenberg, K. and Lerner, A. (2009). All-Trans-Retinoic Acid as a Novel Therapeutic Strategy for Alzheimer's Disease. *Expert Review of Neurotherapeutics*. 9(11): 1616-1621.
- Li, H., Zhang, N., Wang, Y., Jia, S., Zhang, H., Zhang, Y. and Zhang, Z. (2014). Formulation of Curcumin Delivery with Functionalized Single-Walled Carbon-Nanotubes: Characteristics and Anticancer Effects *In Vitro*. *Drug Delivery*. 21(5): 379-387.
- Li, L., Braiteh, F. S. and Kurzrock, R. (2005). Liposome-Encapsulated Curcumin: *In Vitro* and *In Vivo* Effects on Proliferation, Apoptosis, Signaling, and Angiogenesis. *Cancer*. 104(6): 1322-1331.
- Li, X., Liu, J., Zhang, Y., Li, Y., Liu, H., Meng, X., Yang, J., Geng, D., Wang, D., Li, R. and Sun, X. (2012). High Concentration Nitrogen Doped Carbon Nanotube Anodes with Superior Li<sup>+</sup> Storage Performance for Lithium Rechargeable Battery Application. *Journal of Power Sources*. 197: 238-245.
- Lim, C. K., Neoh, C. H., Aris, A., Abdul Majid, Z. A. and Ibrahim, Z. (2013). Application of Zeolite-Activated Carbon Macrocomposite for the Adsorption

- of Acid Orange 7: Isotherm, Kinetic and Thermodynamic Studies. *Environmental Science and Pollution Research*. 20(10): 7243-7255.
- Lim, K. J., Bisht, S., Bar, E. E., Maitra, A. and Eberhart, C. G. (2011). A Polymeric Nanoparticle Formulation of Curcumin Inhibits Growth, Clonogenicity and Stem-Like Fraction in Malignant Brain Tumors. *Cancer Biology Therapy*. 11: 464-473.
- Lipton, P. (1999). Ischemic Cell Death in Brain Neurons. *Physiological reviews*. 79(4): 1431-1568.
- Liu, A., Lou, H., Zhao, L. and Fan, P. (2006). Validated LC/MS/MS Assay for Curcumin and Tetrahydrocurcumin in Rat Plasma and Application to Pharmacokinetic Study of Phospholipid Complex of Curcumin. *Journal of Pharmaceutical and Biomedical Analysis*. 40(3): 720-727.
- Liu, J., Rinzler, A. G., Dai, H., Hafner, J. H., Bradley, R. K., Boul, P. J., Lu, A., Iverson, T., Shelimov, K., Huffman, C. B., Rodriguez-Macias, F., Shon, Y. S., Lee, T. R., Colbert, D. T. and Smalley, R. E. (1998). Fullerene Pipes. *Science*. 280: 1253-1256.
- Liu, Z., Sun, X., Nakayama-Ratchford, N. and Dai, H. (2007a). Supramolecular Chemistry on Water-Soluble Carbon Nanotubes for Drug Loading and Delivery. *ACS Nano*. 1(1): 50-56.
- Liu, Z., Cai, W. B., He, L., Nakayama, N., Chen, K., Sun, X., Chen, X. and Dai, H. (2007b). *In Vivo* Biodistribution and Highly Efficient Tumour Targeting of Carbon Nanotubes in Mice. *Nature Nanotechnology*. 2(1): 47-52.
- Liu, Z., Davis, C., Cai, W. B., He, L., Chen, X. and Dai, H. (2008). Circulation and Long-Term Fate of Functionalized, Biocompatible Single-Walled Carbon Nanotubes in Mice Probed by Raman Spectroscopy. *Proceedings of the National Academy of Sciences of the United States of America*. 105: 1410-1415.
- Liu, Y., Pukala, T. L., Musgrave, I. F., Williams, D. M., Dehle, F. C. and Carver, J. A. (2013). Gallic Acid is the Major Component of Grape Seed Extract that Inhibits Amyloid Fibril Formation. *Bioorganic and Medicinal Chemistry Letters*. 23 (23), 6336-6340.
- Liu, Y., Carver, J. A., Calabrese, A. N. and Pukala, T. L. (2014). Gallic Acid Interacts With A-Synuclein to Prevent the Structural Collapse Necessary for Its

- Aggregation. *Biochimica et Biophysica Acta (BBA) - Proteins and Proteomics*. 1844(9): 1481-1485.
- Lockhart, A., Lamb, J. R., Osredkar, T., Sue, L. I., Joyce, J. N., Ye, L., Libri V, Leppert, D. and Beach, T. G. (2007). PIB is a Nonspecific Imaging Marker of Amyloid-Beta (A $\beta$ ) Peptide-Related Cerebral Amyloidosis. *Brain*. 130(10): 2607-2615.
- Longpre, F., Garneau, P., Christen, Y. and Ramassamy, C. (2006). Protection by Egb 761 against Beta-Amyloid-Induced Neurotoxicity: In-Volvement of NF-Kb, SIRT1, and Mapks Pathways and Inhibition of Amyloid Fibril Formation. *Free Radical Biology and Medicine*. 41: 1781-1794.
- Loos, J., Grossiord, N., Koning, C. E. and Regev, O. (2007). On the Fate of Carbon Nanotubes: Morphological Characterizations. *Composites Science and Technology*. 67: 783-788.
- Lotan, R. (1996). Retinoids in Cancer Chemoprevention. *FASEB Journal*. 10(9): 1031-1039.
- Lu, K. L., Lago, R. M., Chen, Y. K., Green, M. L. H., Harris, P. J. F. and Tsang, S. C. (1996). Mechanical Damage of Carbon Nanotubes by Ultrasound. *Carbon*. 34: 814-816.
- Lu, Y. J., Wei, K. C., Ma, C. C. M., Yang, S. Y. and Chen, J. P. (2012). Dual Targeted Delivery of Doxorubicin to Cancer Cells Using Folate-Conjugated Magnetic Multi-Walled Carbon Nanotubes. *Colloids and Surfaces B: Biointerfaces*. 89: 1-9.
- Lugo-Lugo, V., Henandez-Lopez, S., Barrear-Diaz, C., Urena-Nunez, F. and Bilyeu, B. (2009). A Comparative Study of Natural, Formaldehyreated and Co-Polymer Grafted Orange Peel for Pb (II) Adsorption Under Batch and Continuous Mode. *Journal of Hazardous Materials*. 161: 1255-1264.
- Lundgren, J., Zhang, H., Agardh, C-D., Smith, M-L., Evans, P. J., Halliwell, B. and Siesjö, B. K. (1991). Acidosis-Induced Ischemic Brain Damage: Are Free Radicals Involved? *Journal of Cerebral Blood Flow and Metabolism*. 11: 587-596.
- Luo, Y., Sunderland, T., Roth, G. S. and Wolozin, B. (1996). Physiological Levels of Beta-Amyloid Peptide Promote PC12 Cell Proliferation. *Neuroscience Letters*. 217(2-3): 125-128.

- Maiti, K., Mukherjee, K., Gantait, A., Saha, B. P. and Mukherjee, P. K. (2007). Curcumin–Phospholipid Complex: Preparation, Therapeutic Evaluation and Pharmacokinetic Study in Rats. *International Journal of Pharmaceutics*. 330 (1-2): 155-163.
- Majid, Z. A., Sabri, N. A. M, Buang, N. A. and Shahir, S. (2010). Role of Oxidant in Surface Modification of Carbon Nanotubes for Tyrosinase Immobilization. *Journal of Fundamental Science*. 6: 51-55.
- Malik, P. and Mukherjee, T. K. (2014). Structure-Function Elucidation of Antioxidative and Prooxidative Activities of the Polyphenolic Compound Curcumin. *Chinese Journal of Biology*. 39:6708.
- Malikov, E. Y., Muradov, M. B., Akperov, O. H., Eyvazova, G. M., Puskás, R., Madarász, D., Nagy, L., Kukovecz, Á and Kónya, Z. (2014). Synthesis and Characterization of Polyvinyl Alcohol Based Multiwalled Carbon Nanotube Nanocomposites. *Physica E*. 61: 129-134.
- Mariani, E., Polidori, M. C., Cherubini, A. and Mecocci, P. (2005). Oxidative Stress in Brain Aging, Neurodegenerative and Vascular Disease: An Overview. *Journal of Chromatography B*. 827: 65-75.
- Markesbery, W. R. and Carney, J. M. (1999). Oxidative Alterations in Alzheimer's Disease. *Brain Pathology*. 9: 133-146.
- Marsh, M. and McMahon, H. T. (1999). The Structural Era of Endocytosis. *Science*. 285(5425): 215-220.
- Marshall, M. W., Popa-Nita, S. and Shapter, J. G. (2006). Measurement of Functionalized Carbon Nanotube Carboxylic Acid Groups Using a Simple Chemical Process. *Carbon*. 44: 1137-1141.
- Mecocci, P., MacGarvey, U., and Flin. B. M. (1994). Oxidative Damage to Mitochondrial DNA is Increased in Alzheimer's Disease. *Annals of Neurology*. 36(5):747-751.
- Melino, G., Thiele, C. J., Knight, R. A. and Piacentini, M. (1997). Retinoids and the Control of Growth/Death Decisions in Human Neuroblastoma Cell Lines. *Journal of Neuro-Oncology*. 31(1-2): 65-83.
- Mickelson, E. T., Huffman, C. B., Rinzler, A. G., Smalley, R. E., Hauge, R. H. and Magrave, J. L. (1998). Fluorination of Single Wall Carbon Nanotubes. *Chemical Physics Letters*. 296: 188-194.
- Mindell, J. A. (2012). Lysosomal Acidification Mechanisms. *Annual Review of*

*Physiology*. 74: 69-86.

- Morjan, R. E., Nerushev, O. A., Sveningsson, M., Rohmund, F., Falk, L. K. L. and Campbell, E. E. B. (2004). Growth of Carbon Nanotubes from C<sub>60</sub>. *Applied Physics A*. 78: 253-261.
- Mufti, S., Bautista, A. and Pino-Figueroa, A. P. (2015). Evaluation of the Neuroprotective Effects of Curcuminoids on B35 and SH-SY5Y Neuroblastoma Cells. *Medicinal Aromatic Plants*. 4(3): 1000197.
- Muizelaar, J. P. (1994). Clinical Trials with Dismutec (Pegorgotein, Polyethyleneglycol-Conjugated Superoxide Dismutase, PEG-SOD) in the Treatment of Severe Closed Head Injury. *Advances in Experimental Medicine and Biology*. 366: 389-400.
- Nagasawa, S., Yudasaka, M., Hirahara, K., Ichihashi, T. and Iijima, S. (2000). Effect of Oxidation on Single Wall Carbon Nanotubes. *Chemical Physics Letters*. 328: 374-380.
- Naksuriya, O., Okonogi, S. Schiffelers, R. M. and Hennink, W. E. (2014). Curcumin Nanoformulations: A Review of Pharmaceutical Properties and Preclinical Studies and Clinical Data Related to Cancer Treatment. *Biomaterials*. 35(10): 3365–3383.
- Narizzano, R. and Nicolini, C. (2005). Mechanism of Conjugated Polymer Organization on SWNT Surfaces. *Macromolecular Rapid Communications*. 26: 381-385.
- Nerushev, O. A., Dittmar, S., Morjan, R. E., Rohmund, F. and Campbell, E. E. B. (2003). Particle Size Dependence and Model for Iron-Catalyzed Growth of Carbon Nanotubes by Thermal Chemical Vapor Deposition. *Journal of Applied Physics*. 93: 4185-4190.
- Ng, C., Losso, J. N., Marshall, W. E. and Rao, R. M. (2002). Freundlich Adsorption Isotherms of Agricultural By-Product-Based Powdered Activated Carbon S in Geosmin Water System. *Bioresour Technology*. 85: 131-133.
- Ng, T. P., Chiam, P. C., Lee, T., Chua, H. C., Lim, L. and Kua, E. H. (2006). Curry Consumption and Cognitive Function in the Elderly. *American Journal of Epidemiology*. 164(9): 898-906.
- Ni, Y., Hu, H., Malarkey, E. B., Zhao, B., Montana, V., Haddon, C. and Parpura, V. (2005). Chemically Functionalized Water Soluble Single-Walled Carbon

- Nanotubes Modulate Neurite Outgrowth. *Journal of Nanoscience and Nanotechnology*. 5(10): 1707-1712.
- Nie, H., Wang, H., Cao, A., Shi, Z., Yang, S.-T., Yuan, Y. and Liu, Y. (2011). Diameter-Selective Dispersion of Double-Walled Carbon Nanotubes by Lysozyme. *Nanoscale*. 3: 970-973.
- Niu, L., Meng, L. and Lu, Q. (2013). Folate-Conjugated PEG on Single Walled Carbon Nanotubes for Targeting Delivery of Doxorubicin to Cancer Cells. *Macromolecular Bioscience*. 13: 735-744.
- Niu, Y., Ke, D., Yang, Q., Wang, X., Chen, Z., An, X. and Shen, W. (2012). Temperature Dependent Stability and DPPH Scavenging Activity of Liposomal Curcumin at pH 7.0. *Food Chemistry*. 135(3): 1377-1382.
- Nurulhuda, I., Mazatulikhma, M. Z., Poh, H. and Rusop, M. (2013). Carbon Nanotubes in Cancer Treatment: A Preliminary *In Vitro* Study Using Neuroblastoma Cells. *Advanced Materials Research*. 667: 155-159.
- Odom, T. W., Huang, J. L., Kim, P. and Lieber, C. M. (2000). Structure and Electronic Properties of Carbon Nanotubes. *Journal of Physical Chemistry B*. 104: 2794-2809.
- Osorio, A. G., Silveria, I. C. L., Bueno, V. L. and Bergmann, C. P. (2008). H<sub>2</sub>SO<sub>4</sub>/HNO<sub>3</sub>/HCl-Functionalization and Its Effect on Dispersion of Carbon Nanotubes in Aqueous Media. *Applied Surface Science*. 255: 2485-2489.
- Pahlman, S., Odelstad, L., Larsson, E., Grotte, G. and Nilsson, K. (1981). Phenotypic Changes of Human Neuroblastoma Cells in Culture Induced by 12-O-Tetradecanoyl-Phorbol-13-Acetate. *International Journal of Cancer*. 28(5): 583-589.
- Paiva, M. C., Zhou, B., Fernando, K. A. S., Lin, Y., Kennedy, J. M. and Sun, Y-P. (2004). Mechanical and Morphological Characterization of Polymer-Carbon Nanocomposites from Functionalized Carbon Nanotubes. *Carbon*. 42: 2849-2854.
- Pan, B. and Xing, B. (2008) Adsorption Mechanism of Organic Chemicals on Carbon Nanotubes. *Environmental Science and Technology*. 42(24): 9005-9013.
- Pan, M. H., Huang, T. M. and Lin, J. K. (1999). Biotransformation of Curcumin through Reduction and Glucuronidation in Mice. *Drug Metabolism and Disposition*. 27(4): 486-494.

- Pantarotto, D., Briand, J. P., Prato, M. and Bianco, A. (2004). Translocation of Bioactive Peptides across Cell Membranes by Carbon Nanotubes. *Chemical Communications*. 16-17.
- Park, H., Zhao, J. and Lu J. P. (2006). Effects of Sidewall Functionalization on Conducting Properties of SWCNT. *Nano Letters*. 6: 916-919.
- Park, H. R., Lee, H., Park, H., Jeon, J. W., Cho, W-K. and Ma, J. Y. (2015). Neuroprotective Effects of *Liriope Platyphylla* Extract Against Hydrogen Peroxide-Induced Cytotoxicity in Human Neuroblastoma SH-SY5Y Cells. *BMC Complementary and Alternative Medicine*. 15: 171.
- Pastorin, G., Wu, W., Wieckowski, S., Briand, J. P., Kostarelos, K., Prato, M. and Bianco, A. (2006). Double Functionalisation of Carbon Nanotubes for Multimodal Drug Delivery. *Chemical Communications*. (11): 1182-1184.
- Payton, F., Sandusky, P. and Alworth, W. L. (2007). NMR Study of the Solution Structure of Curcumin. *Journal of Natural Products*. 70(2): 143-146.
- Pichardo, S., Gutiérrez-Praena, D., Puerto, M., Sánchez, E., Grilo, A., Cameán, A. M. and Jos, A. (2012). Oxidative Stress Responses to Carboxylic Acid Functionalized Single Wall Carbon Nanotubes on the Human Intestinal Cell Line Caco-2. *Toxicology In Vitro*. 26(5): 672-677.
- Pillai, S. K., Ray, S. S. and Moodley, M. (2007). Purification of Single-Walled Carbon Nanotubes. *Journal of Nanoscience and Nanotechnology*. 7(9): 3011-3047.
- Pirchi, M., Marksteiner, J. and Humpel, C. (2006). Effects of Acidosis on Brain Capillary Endothelial Cells and Cholinergic Neurons: Relevance to Vascular Dementia and Alzheimer's Disease. *Neurological Research*. 28(6): 657-664.
- Poon, H. F., Calabrese, V., Scapagnini, G. and Butterfield, D. A. (2004). Free Radicals and Brain Aging. *Clinics in Geriatric Medicine*. 20(2): 329-359.
- Prencipe, G., Tabakman, S. M., Welsher, K., Liu, Z., Goodwin, A. P., Zhang, L., Henry, J. and Dai, H. (2009). PEG Branched Polymer for Functionalization of Nanomaterials with Ultralong Blood Circulation. *Journal of the American Chemical Society*. 131(13): 4783-4787.
- Priyadarsini, K.I. (2014). The Chemistry of Curcumin: From Extraction to Therapeutic Agent. *Molecules*. 19(12): 20091-20112.
- Qin, S., Qin, D. Q., Ford, W. T., Resasco, D. E. and Herrera, J. E. (2004). Polymer Brushes on Single-Walled Carbon Nanotubes by Atom Transfer Radical

- Polymerization of n-Butyl Methacrylate. *Journal of the American Chemical Society*. 126: 170-176.
- Ramirez-Bermudez, J. (2012). Alzheimer's Disease: Critical Notes on the History of a Medical Concept. *Archives of Medical Research*. 43(8): 595-599.
- Ravindranath, V. and Chandrasekhara. N. (1981). Metabolism of Curcumin-Studies with [3H] Curcumin. *Toxicology*. 22(4): 337-344.
- Ray, B., Bisht, S., Maitra, A., Maitra, A. and Lahiri, D. K. (2011). Neuroprotective and Neurorescue Effects of a Novel Polymeric Nanoparticle Formulation of Curcumin (Nanocurc<sup>TM</sup>) in the Neuronal Cell Culture and Animal Model: Implications for Alzheimer's Disease. *Journal of Alzheimer's Disease*. 23: 61-77.
- Ren, Y. P. and Pastorin, G. (2008). Incorporation of Hexamethylmelamine Inside Capped Carbon Nanotubes. *Advanced Materials*. 20: 2031-2036.
- Ringer, A. L., Sinnokrot, M. O., Lively, R. P. and Sherrill, C. D. (2006). The Effect of Multiple Substituents on Sandwich and T-Shaped pi-pi Interactions. *Chemistry-A European Journal*. 12(14): 3821-3828.
- Rinwa, P. and Kumar, A. (2012). Piperine Potentiates the Protective Effects of Curcumin against Chronic Unpredictable Stress-Induced Cognitive Impairment and Oxidative Damage in Mice. *Brain Research*. 7(1488):38-50.
- Rinzler, A. G., Liu, J., Dai, H., Nikolaev, P., Huffman, C. B., Macias, F. J. R., Boul, P. J., Lu, A. H., Heyman, D., Colbert, D. T., Lee, R. S., Fischer, J. E., Rao, A. M., Eklund, P. C. and Smalley, R. E. (1998). Large-Scale Purification of Single-Wall Carbon Nanotubes: Process, Product, and Characterization. *Applied Physics A*. 67: 29-37.
- Rosa, R., Sanfeliu, C., Suñol, C., Pomés, A., Rodríguez-Farré, E., Schousboe, A. and Frandsen, A. (1997). The Mechanism for Hexachlorocyclohexane-Induced Cytotoxicity and Changes in Intracellular Ca<sup>2+</sup> Homeostasis in Cultured Cerebellar Granule Neurons is Different for the Gamma- and Delta-Isomers. *Toxicology and Applied Pharmacology*. 142(1): 31-39.
- Rosca, I. D., Watari, F., Uo, M. and Akaska, T. (2005). Oxidation of Multiwalled Carbon Nanotubes by Nitric Acid. *Carbon*. 43: 3124-3131.
- Rubinsztein, D. C. (2006). The Roles of Intracellular Protein-Degradation Pathways in Neurodegeneration. *Nature*. 443: 780-786.
- Safari, J. and Zarnegar, Z. (2014). Advanced Drug Delivery Systems:

- Nanotechnology of Health Design: A Review. *Journal of Saudi Chemical Society*. 18: 85-99.
- Sahoo, N. G., Bao, H., Pan, Y., Pal, M., Kakran, M., Cheng, H. K. F., Li, L. and Tan, L. P. (2011). Functionalization Carbon Nanomaterials as Nanocarriers for Loading and Delivery of Poorly Water Soluble Anticancer Drug: A Comparative Study. *Chemical Communications*. 47(18): 5235-5237.
- Sambuy, Y., De Angelis, I., Ranaldi, G., Scarino, M. L., Stammati, A. and Zucco, F. (2005). The Caco-2 Cell Line as a Model of the Intestinal Barrier; Influence of Cell and Culture Related Factors on Caco-2 Cell Functional Characteristics. *Cell Biology and Toxicology*. 21: 1-26.
- Samori, C., Ali-Boucetta, H., Sainz, R., Guo, C., Toma, F. M., Fabbro, C., Ros, d. T., Prato, M., Kostarelos, K. and Bianco, A. (2010). Enhanced Anticancer Activity of Multi-Walled Carbon Nanotube-Methotrexate Conjugates Using Cleavable Linkers. *Chemical Communications*. 46: 1494-1496.
- Scheibe, B., Borowiak-Palen, E., and Kalenczuk, R. J. (2010). Oxidation and Reduction of Multiwalled Carbon Nanotubes-Preparation and Characterization. *Materials Characterization*. 61(2): 185-191.
- Schulz, M. J., Shanov, V. N. and Yun, Y. (2009). *Nanomedicine Design of Particles, Sensors, Motors, Implants, Robots, and Devices*. Norwood, NA: Artech House Publishers.
- Shaffer, M. S. P., Fan, X. and Windle, A. H. (1998). Dispersion and Packing of Carbon Nanotubes. *Carbon*. 36(11): 1603-1612.
- Shanov, V. and Yun, Y. H. (2006). Synthesis and Characterization of Carbon Nanotube Materials. *Journal of the University of Chemical Technology and Metallurgy*. 41: 377-390.
- Shao, L., Tobias, G., Salzmann, C. G., Ballesteros, B., Hong, S. Y., Crossley, A., Davis, B. G. and Green, M. L. H. (2007). Removal of Amorphous Carbon for the Efficient Sidewall Functionalisation of Single-Walled Carbon Nanotubes. *Chemical Communications*. (47): 5090-5092.
- Sharma, R. A., Euden, S. A., Platton, S. L., Cooke, D. N., Shafayat, A., Hewitt, H. R., Marczyklo, T. H., Morgan, B., Hemingway, D., Plummer, S. M., Pirmohamed, M., Gescher, A. J. and Steward, W. P. (2004). Phase 1 Clinical Trial Of Oral Curcumin: Biomarkers of Systemic Activity and Compliance. *Clinical Cancer Research*. 10: 6847-6854.

- Sharma, S., Mehra, N. K. and Kumar, N. (2016). Effect of Functionalization on Drug Delivery Potential of Carbon Nanotubes. *Artificial Cells, Nanomedicine, and Biotechnology*. 44(8): 1851-1860.
- Sheng, G. D., Shao, D. D., Ren, X. M., Wang, X. Q., Li, J. X., Chen, Y. X. and Wang, X. K. (2010). Kinetics and Thermodynamics of Adsorption of Ionizable Aromatic Compounds from Aqueous Solutions by Asprepared and Oxidized Multiwalled Carbon Nanotubes. *Journal of Hazardous Materials*. 178: 505-516.
- Shishodia, S., Singh, T. and Chaturvedi, M. M. (2007). Modulation of Transcription Factors by Curcumin. *Advances in Experimental Medicine and Biology*. 595: 127-148.
- Shoba, G., Joy, D., Joseph, T., Majeed, M., Rajendran, R. and Srivinas, P. S. (1998). Influence of Piperine on the Pharmacokinetics of Curcumin in Animals and Human Volunteers. *Planta Medica*. 64: 353-356.
- Shukitt-Hale, B., Lau, F. C., Carey, A. N., Galli, R. L., Spangler, E. L., Ingram, D. K. and Joseph, J. A. (2008). Blueberry Polyphenols Attenuate Kainic Acid-Induced Decrements in Cognition and Alter Inflammatory Gene Expression in Rat Hippocampus. *Nutrition Neuroscience*. 11:172-182.
- Siesjö, B. K., Katsura, K. and Kristian, T. (1996). Acidosis-Related Damage. *Advances in Neurology*. 71:209-233.
- Singh, M., Arseneault, M., Sanderson, T., Murthy, V. and Ramassamy, C. (2008). Challenges for Research on Polyphenols from Foods in Alzheimer's Disease: Bioavailability, Metabolism, and Cellular and Molecular Mechanism. *Journal of Agricultural and Food Chemistry*. 56: 4855-4873.
- Sinnokrot, M. O. and David, S. C. (2003). Unexpected Substituent Effects in Face-to-Face  $\pi$ -Stacking Interactions. *The Journal of Physical Chemistry A*. 107(41): 8377-8379.
- Skwarczynski, M., Hayashi, Y. and Kiso, Y. (2006). Paclitaxel Prodrugs: Toward Smarter Delivery of Anticancer Agents. *Journal of Medicinal Chemistry*. 49: 7253-7269.
- Smith, M. A., Perry, G., Richey, P. L., Sayre, L. M., Anderson, V. E., Beal, M. F. and Kowall, N. (1996). Oxidative Damage in Alzheimer's. *Nature*. 382: 120-121.

- Soleimani, M., Afshar, M. G. and Sedghi, A. (2013). Amino-Functionalization of Multiwalled Carbon Nanotubes and Its Use for Solid Phase Extraction of Mercury Ions from Fish Sample. *ISRN Nanotechnology*. 674289.
- Soto-Rojas, L. O., Cruz-López, F. d-l., Torres, M. O. A., Viramontes-Pintos, A., Cárdenas-Aguayo, M. d. C., Meraz-Ríos, M. A., Salinas-Lara, C., Florán-Garduño, B. and Luna-Muñoz, J. (2015). Neuroinflammation and Alteration of the Blood-Brain Barrier in Alzheimer's Disease. In: Zerr, I. ed. *Alzheimer's Disease- Challenges for the Future*. European Union: InTech Publisher.
- Stobinski, L., Lesiak, B., Kover, L., Toth, J., Biniak, S., Trykowski, G. and Judek, J. (2010). Multiwall Carbon Nanotubes Purification and Oxidation by Nitric Acid Studied by the FTIR and Electron Spectroscopy Methods. *Journal of Alloys and Compounds*. 501(1): 77-84.
- Sultana, R., Perluigi, M. and Butterfield, D. A. (2006). Protein Oxidation and Lipid Peroxidation in Brain of Subjects with Alzheimer's Disease: Insights into Mechanism of Neurodegeneration from Redox Proteomics. *Antioxidants and Redox Signaling*. 8: 2021-2037.
- Su-Mian, T., Wan Ngah, W.Z., Mat Top, G. and Mazlan, M. (2010). Comparison of the Effects of  $\alpha$ -Tocopherol and  $\gamma$ -Tocotrienol against Oxidative Stress in Two Different Neuronal Cultures. *Sains Malaysiana*. 39(1): 145-156.
- Sun, A. Y., Wang, Q., Simonyi, A. and Sun, G. Y. (2008). Botanical Phenolics and Brain Health. *NeuroMolecular Medicine*. 4: 259-274.
- Sun-Wada, G. H., Wada, Y. and Futai, M. (2003). Lysosome and Lysosome-Related Organelles Responsible for Specialized Functions in Higher Organisms, with Special Emphasis on Vacuolar-Type Proton ATPase. *Cell Structure and Function*. 28: 455-463.
- Tannock, I. F. and Rotin, D. (1989). Acid pH in Tumors and Its Potential for Therapeutic Exploitation. *Cancer Research*. 49: 4373-4384.
- Thakur, V. K. and Thakur M. K. (2015). *Chemical Functionalization of Carbon Nanomaterials: Chemistry and Applications*. Boca Raton: CRC Press.
- Tian, Y., Gao, B., Chen, H., Wang, Y., and Li, H. (2013). Interactions between Carbon Nanotubes and Sulfonamide Antibiotics in Aqueous Solutions under Various Physicochemical Conditions. *Journal of Environmental Science and Health, Part A*. 48: 1136-1144.

- Tîlmaciu, C-M. and Morris, M. C. (2015). Carbon Nanotubes Biosensor. *Frontier in Chemistry*. 3(59): 1-21.
- Tønnesen, H. H. and Karlsen, J. (1985). Studies on Curcumin and Curcuminoids: VI. Kinetics of Curcumin Degradation in Aqueous Solution. *Zeitschrift für Lebensmittel-Untersuchung und Forschung*. 180(5): 402-404.
- Toshiya, M., Kayo, H., Ayumi, S., Tomomi, M., Yoshio, T. and Hidemasa, Y. (1999). Chemical Studies on Antioxidant Mechanism of Curcuminoid: Analysis of Radical Reaction Products from Curcumin. *Journal of Agricultural and Food Chemistry*. 47: 71-77.
- Uzun, I. (2006). Kinetics of the Adsorption of Reactive Dyes by Chitosan. *Dyes Pigments*. 70(2): 76-83.
- Vashist, S. K., Zheng, D., Pastorin, G., Al-Rubeaan, K., Luong, J. H. T. and Sheu, F. S. (2011). Delivery of Drugs and Biomolecules Using Carbon Nanotubes. *Carbon*. 49: 4077-4097.
- Vauzour, D. (2012). Dietary Polyphenols as Modulators of Brain Functions: Biological Actions and Molecular Mechanisms Underpinning their Beneficial Effects. *Oxidative Medicine and Cellular Longevity*. 914273.
- Vivekchand, S. R. C., Jayakanth, R., Govindaraj, A. and Rao, C. N. R. (2005). The Problem of Purifying Single-Walled Carbon Nanotubes. *Small*. 1: 920-923.
- Wahlstorm, B. and Blennow, G. (1978). A Study on the Fate of Curcumin in the Rat. *Acta Pharmacologica et Toxicologica (Copenhagen)*. 43: 86-92.
- Wang, J., Zhang, Y. J. and Du, S. (2012c). The Protective Effect of Curcumin on A $\beta$  Induced Aberrant Cell Cycle Reentry on Primary Cultured Rat Cortical Neurons. *European Review for Medical and Pharmacological Sciences*. 16: 445-454.
- Wang, J. H., Han, X. J., Ma, H. R., Ji, Y. F. and Bi, L. J. (2011). Adsorption Removal of Humic Acid from Aqueous Solution on Polyaniline/Attapulgate Composite. *Chemical Engineering Journal*. 173: 171-177.
- Wang, N., Wang, G., Hao, J., Ma, J., Wang, Y., Jiang, X. and Jiang, H. (2012a). Curcumin Ameliorates Hydrogen Peroxide-Induced Epithelial Barrier Disruption by Upregulating Heme Oxygenase-1 Expression in Human Intestinal Epithelial Cells. *Digestive Disease and Science*. 57(7): 1792-1801.
- Wang, Y. J., Thomas, P., Zhong, J. H., Bi, F. F., Kosaraju, S., Pollard, A., Fenech, M. and Zhou, X. F. (2009). Consumption of Grape Seed Extract Prevents

- Amyloid-Beta Deposition and Attenuates Inflammation in Brain of an Alzheimer's Disease Mouse. *Neurotoxicity Research*. 15(1): 3-14.
- Wang, Y., Yang, S. T., Wang, Y., Liu, Y. and Wang, H. (2012b). Adsorption and Desorption of Doxorubicin on Oxidized Carbon Nanotubes. *Colloids and Surfaces B: Biointerfaces*. 97: 62-69.
- Wang, Y. J., Pan, M. H., Cheng, A. L., Lin, L. I., Ho, Y. S., Hsieh, C. Y. and Lin, J. K. (1997). Stability of Curcumin in Buffer Solutions and Characterization of Its Degradation Products. *Journal of Pharmaceutical and Biomedical Analysis*. 15(12): 1867-1876.
- Wang, Z. and Sadee, W. (2000). Tolerance to Morphine at the Mu-Opioid Receptor Differentially Induced by Camp-Dependent Protein Kinase Activation and Morphine. *European Journal of Pharmacology*. 245: 350-355.
- Weiss, N., Miller, F., Cazaubon, S. and Couraud, P-O. (2009). The Blood-Brain Barrier in Brain Homeostasis and Neurological Diseases. *Biochimica et Biophysica Acta*. 1788: 842-857.
- Wepasnick, K. A., Smith, B. A., Schrote, K. E., Wilson, H. K., Diegelmann, S. R and Fairbrother, D. H. (2011). Surface and Structural Characterization of Multi-Walled Carbon Nanotubes Following Different Oxidative Treatments. *Carbon*. 49: 24-36.
- Williams, T. I., Lynn, B. C., Markesbery, W. R. and Lovell, M. A. (2006). Increased Level of 4-Hydroxynenal and Acrolein, Neurotoxic Markers of Lipid Peroxidation in the Brain in Mild Cognitive Impairment and Early Alzheimer's Disease. *Neurobiology of Aging*. 27: 1094-1099.
- Wong, B. S., Yoong, S. L., Jagusiak, A., Panczyk, T., Ho, H. K., Ang, W. H. and Pastorin, G. (2013). Carbon Nanotubes for Delivery of Small Molecule Drugs. *Advanced Drug Delivery Reviews*. 65: 1964-2015.
- Wu, W., Wieckowski, S., Pastorin, G., Benincasa, M., Klumpp, C., Briand, J-P, Gennaro, R., Prato, M. and Bianco, A. (2005). Targeted Delivery of Amphotericin B to Cells Using Functionalized Carbon Nanotubes. *Angewandte Chemie International Edition*. 44: 6358-6362.
- Xue, Y. J., Hou, H. B. and Zhu, S. J. (2009). Adsorption Removal of Reactive Dyes from Aqueous Solution by Modified Basic Oxygen Furnace Slag: Isotherm and Kinetic Study. *Chemical Engineering Journal*. 147: 272-279.

- Yallapu, M. M., Jaggi, M. and Chauhan, S. C. (2012). Curcumin Nanoformulations: A Future Nanomedicine for Cancer. *Drug Discovery Today*. 17: 71-80.
- Yallapu, M. M., Nagesh, P. K. B., Jaggi, M. and Chauhan, S. C. (2015). Therapeutic Applications of Curcumin Nanoformulations. *American Association of Pharmaceutical Scientists*. 17(6): 1341-1356.
- Yan, A., Bussche, A. V. D., Kane, A. B. and Hurt, R. H. (2007). Tocopheryl Polyethylene Glycol Succinate as a Safe, Antioxidant Surfactant for Processing Carbon Nanotubes and Fullerenes. *Carbon*. 45: 2463-2470.
- Yang, K. Y., Lin, L. C., Tseng, T. Y., Wang, S. C. and Tsai, T. H. (2007). Oral Bioavailability of Curcumin in Rat and the Herbal Analysis from *Curcuma Longa* by LC-MS/MS. *Journal of Chromatography B: Analytical Technologies in Biomedical and Life Sciences*. 853 (1-2): 183-189.
- Yang, Z., Zhang, Y. G., Yang, Y. L. A., Sun, L., Han, D., Li, H. and Wang, C. (2010). Pharmacological and Toxicological Target Organelles and Safe Use of Single-Walled Carbon Nanotubes as Drug Carriers in Treating Alzheimer Disease. *Nanomedicine*. 6: 427-441.
- Yu, B. P. (1994). Cellular Defense against Damage from Reactive Oxygen Species. *Physiological Research*. 74: 139-162.
- Yu, Y., Kong, L. J., Li, L., Li, N. E. and Yan, P. (2015). Antitumor Activity of Doxorubicin-Loaded Carbon Nanotubes Incorporated Poly(Lactic-co-glycolic acid) Electrospun Composite Nanofibers. *Nanoscale Research Letters*. 10: 1-9.
- Yuan, R., Zheng, F., Zhong, S., Tao, X., Zhang, Y., Gao, F., Yao, F., Chen, J., Chen, Y. and Shi, G. (2014). Self-Assembled Nanoparticles of Glycyrrhetic Acid-Modified Pullulan as a Novel Carrier of Curcumin. *Molecules*. 19(9): 13305-13318.
- Zeineldin, R., Al-Haik, M. and Hudson, L. (2009). Role of Polyethylene Glycol Integrity in Specific Receptor Targeting of Carbon Nanotubes to Cancer Cells. *Nano Letters*. 9: 751-757
- Zhang, F., Chang, J. and Eberhard, B. (2010). Dissolution of Poly(Vinyl Alcohol)-Modified Carbon Nanotubes in a Buffer Solution. *New Carbon Materials*. 25(4): 241-247.

- Zhang, F., Liu, M-R. and Wan, H-T. (2014). Discussion about Several Potential Drawbacks of PEGylated Therapeutic Proteins. *Biological and Pharmaceutical Bulletin*. 37(3): 335-339.
- Zhang, J., Zou, H. L., Qing, Q., Yang, Y., Li, Q., Liu, Z., Guo, X. and Du, Z. (2003). Effect of Chemical Oxidation on the Structure of Single-Walled Carbon Nanotubes. *Journal of Physical Chemistry B*. 107: 3712-3718.
- Zhang, W., Zhang, Z. and Zhang, Y. (2011). The Application of Carbon Nanotubes in Target Drug Delivery Systems for Cancer Therapy. *Nanoscale Research Letters*. 6(555): 1-22.
- Zhang, X. K., Meng, L. J., Lu, Q. G., Fei, Z. F. and Dyson, P. J. (2009). Targeted Delivery and Controlled Release of Doxorubicin to Cancer Cells Using Modified Single Wall Carbon Nanotubes. *Biomaterials*. 30: 6041-6047.
- Ziegler, K. J., Gu, Z., Peng, H., Flor, E. L, Hauge, R. H. and Smalley, R. E. (2005). Controlled Oxidative Cutting Of Single-Walled Carbon Nanotubes. *Journal of American Chemical Society*. 127(5): 1541-1547.