POLYSACCHARIDE-BASED MAGNETIC NANOCOMPOSITES AS DRUG CARRIERS FOR POTENTIAL COLORECTAL CANCER TREATMENT

MOSTAFA YUSEFI

UNIVERSITI TEKNOLOGI MALAYSIA

POLYSACCHARIDE-BASED MAGNETIC NANOCOMPOSITES AS DRUG CARRIERS FOR POTENTIAL COLORECTAL CANCER TREATMENT

MOSTAFA YUSEFI

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

Malaysia-Japan International Institute of Technology
Universiti Teknologi Malaysia

JUNE 2022

DEDICATION

This thesis is dedicated to my parents for their unlimited love, great encouragement, and wonderful support to achieve my goal.

ACKNOWLEDGEMENT

The author would like to express gratitude and appreciation to his supervisor Assoc. Prof. Kamyar Shameli for his supervision, guidance, patience and support throughout the project. His great knowledge, professional experience and enthusiasm have helped me to develop ideas to successfully complete this project. The author would like to express gratitude and appreciation to his co-supervisors Assoc. Prof. Roshafima Rasit Ali, Dr. Sin-Yeang Teow, and Prof. Ezzat Chan Abdullah for their supervision and support throughout the project.

The author would also like to sincerely thank Prof. Mohamed Mahmoud Nasef, Prof. Mikio Miyake and all members of Chemical Energy Conversion and Applications (CheCA) *iKohza* for their guidance, discussions, advice and motivation during this research study. Without their continuous support and interest, this research and thesis would not be carried out smoothly. Special thanks to School of Medical and Life Sciences, Sunway University Malaysia for the cell culture and laboratory facilities.

Finally, the author is very grateful to his family members and friends for their wonderful emotional and moral support throughout the research period and also for their love, patience, and encouragement.

ABSTRACT

Colorectal cancer is one of the most diagnosed malignant diseases in the world. The green-based, multifunctional, and highly biocompatible polysaccharide-based magnetic nanocomposites (PMNCs) as smart drug carriers can satisfy targeted cancer treatments to circumvent off-target cytotoxicity from conventional chemotherapy. This comprehensive research has sought to introduce five different green-based 5-Fluorouracil (5-FU) drug carriers, including Fe_3O_4 nanoparticles stabilized with *Punica granatum* fruit peel extract (Fe_3O_4/*P. granatum*/5-FU), rice straw cellulose fiber (CF/5-FU), magnetic cellulose fiber (MC/5-FU), cellulose nanocrystals (CNC/5-FU), and chitosan-coated magnetic CNC (CH/MCNC/5-FU) bionanocomposites. For this aim, spherical Fe_3O_4 nanoparticles was produced by a facile co-precipitation technique and using four different weight percentages of *Punica granatum* fruit peel extract as a green stabilizer. Then, the rod-shaped CF was isolated from rice straw waste by employing bleaching and alkali treatments. Fe_3O_4 nanoparticles were supported onto the CF matrix to fabricate MC nanoocmposites. The needle-like CNC was isolated from rice straw cellulose by the acid hydrolysis process. In addition, the ionic gelation method and the sodium tripolyphosphate cross-linker were used to fabricate layer-by-layer bionanocomposites of CH/MCNC/5-FU. The successful fabrication of the samples with desired physiochemical properties was indicated by X-ray powder diffraction (XRD), Fourier-transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM), transmission electron microscopy (TEM), energy dispersion X-ray spectroscopy (EDX), dynamic light scattering (DLS), thermogravimetric analysis (TGA), vibrating-sample magnetometry (VSM) of the swelling analysis, and ultraviolet-visible (UV) spectroscopy. The use of 2 weight % extract as stabilizer and capping agent appropriately decreased the size of spherical Fe_3O_4 NPs with enhanced stability and anticancer effects. Compared to CF/5-FU formulation, CNC/5-FU showed higher crystallinity, smaller size, and prolonged drug release at targeted pH media. The PMNCs samples of MC/5-FU and CH/MCNC/5-FU showed multifunctional physiochemical properties and also magnetic and heat-responsive manner. The use of chitosan coating in CH/MCNC/5-FU improved drug encapsulation efficiency and controlled drug release at various pH and heat induction conditions. From images of TEM and SEM, the size of all the synthesized samples was estimated to be below 80 nm, showing their potential usage in nanodrug delivery systems. In in vitro anticancer assay, the fabricated Fe_3O_4/*P. granatum*/5-FU, CF/5-FU, and CNC/5-FU desirably exhibited negligible damage against CCD112 normal cells and appropriate anticancer actions against HCT116 colorectal cancer cells. MC/5-FU with magnetic targeting and heat induction improved the anticancer effects, guide ability, and tolerable toxicity in targeted drug delivery systems. Further, CH/MCNC/5-FU showed not only high biocompatibility but also caused enhanced selectivity and elimination of the cancer cells. In conclusion, the fabricated the fabricated Fe_3O_4 nanoparticles, polysaccharides, PMNCs as innovative, low-cost, and topical nanodrug formulations could offer promising potential to tackle most, if not all, of the conventional drug delivery issues in colorectal cancer therapy.

ABSTRAK

Kanser kolorektal adalah salah satu penyakit malignan yang paling banyak didiagnosis di dunia. Ini merupakan fakta yang telah dibuktikan dengan baik bahawa ketoksikan ubat kemoterapi luar sasaran seperti 5-Fluorouracil (5-FU) mempengaruhi tubuh dengan kesan goyah. Nanokomposit magnetik berasaskan polisakarida (PMDC) berasaskan hijau, pelbagai fungsi, dan sangat biokompatibel sebagai pembawa ubat pintar dapat memenuhi rawatan barah yang disasarkan untuk mengelakkan *sitotoksik* yang tidak disasarkan daripada kemoterapi konvensional. Penyelidikan komprehensif ini telah berusaha untuk memperkenalkan lima pembawa ubat 5-FU berasaskan hijau yang berbeza, termasuk nanopartikel Fe3O4 yang distabilkan dengan ekstrak kulit buah *granatum Punica* (Fe_3O_4/*P. granatum*/5-FU), serat selulosa jerami padi (CF/5-FU), serat selulosa magnetik (MC/5-FU), nanokristal selulosa (CNC/5-FU), dan bionanokomposit magnetik bersalut chitosan (CH/MCNC/5-FU). Untuk tujuan ini, nanopartikel Fe_3O_4 sfera dihasilkan dengan teknik pemendakan bersama dan menggunakan empat peratusan berat yang berbeza dari ekstrak kulit buah granatum Punica sebagai penstabil hijau. Kemudian, CF berbentuk batang telah diasingkan daripada sisa jerami padi dengan menggunakan pelunturan dan rawatan alkali. Kemudian, CF berbentuk batang diasingkan daripada sisa jerami beras dengan menggunakan pelunturan dan rawatan alkali. Nanopartikel Fe_3O_4 telah disokong ke matriks CF untuk menghasilkan bionanokomposit MC. CNC seperti jarum telah diasingkan daripada selulosa jerami padi melalui proses hidrolisis asid. Di samping itu, kaedah gelasi ionik dan natrium tripolyfosfat *cross-linker* digunakan untuk menghasilkan lapisan demi lapisan bionanokomposit CH/MCNC/5-FU. Kejayaan fabrikasi sampel dengan sifat fisiokimia yang dikehendaki ditunjukkan oleh difraksi serbuk X-ray (XRD), spektroskopi Inframerah Transformasi Fourier (FTIR), pengimbasan mikroskopi elektron (SEM), mikroskop elektron penghantaran (TEM) sinar-X penyebaran tenaga spektroskopi (EDX), penyebaran cahaya dinamik (DLS), analisis termogravimetrik (TGA), magnetometri bergetar-sampel (VSM) analisis bengkak, dan spektroskopi ultraviolet-visible (UV). Penggunaan ekstrak 2 % berat sebagai penstabil dan ejen penutup dengan sewajarnya menurunkan saiz sfera Fe_3O_4 NPs dengan peningkatan kestabilan dan kesan antikanser untuk sistem penyampaian ubat 5-FU. Berbanding dengan formulasi CF/5-FU, CNC/5-FU menunjukkan kristal yang lebih tinggi, saiz yang lebih kecil, dan pelepasan ubat yang berpanjangan pada media pH yang disasarkan. Sampel PMNCs MC/5-FU dan CH/MCNC/5-FU menunjukkan sifat fisiokimia pelbagai fungsi dan juga cara magnet dan responsif haba. Penggunaan salutan chitosan dalam CH/MCNC/5-FU meningkatkan kecekapan encapsulasi ubat dan pelepasan ubat terkawal pada pelbagai pH dan keadaan induksi haba. Daripada imej TEM dan SEM, saiz semua sampel yang disintesis dianggarkan di bawah 80 nm, menunjukkan potensi penggunaannya dalam sistem penghantaran nanodrug. Dalam ujian antikanser in vitro, Fe3O4/*P. granatum*/5-FU, CF/5-FU, dan CNC/5-FU yang dihasilkan dengan pasti menunjukkan kerosakan yang boleh diabaikan terhadap sel biasa CCD112 dan tindakan antikanser yang sesuai terhadap sel barah kolorektal HCT116. MC/5-FU dengan penyasaran magnetik dan induksi haba meningkatkan kesan antikanser, keupayaan panduan, dan ketoksikan yang boleh diterima dalam sistem penghantaran ubat yang disasarkan. Selanjutnya, CH/MCNC/5-FU menunjukkan bukan sahaja biokompatibiliti yang tinggi tetapi juga menyebabkan peningkatan dan penghapusan sel-sel barah. Kesimpulannya, nanopartikel Fe_3O_4, polisakarida, dan PMDC yang dibuat sebagai formulasi *nanodrug* yang inovatif, kos rendah, dan topikal boleh menawarkan potensi yang menjanjikan untuk menangani kebanyakan, jika tidak semua, masalah penghantaran ubat konvensional dalam terapi barah kolorektal.

TABLE OF CONTENTS

TITLE		PAGE
DECLARATION		**iii**
DEDICATION		**iv**
ACKNOWLEDGEMENT		**v**
ABSTRACT		**vi**
ABSTRAK		**vii**
TABLE OF CONTENTS		**viii**
LIST OF TABLES		**xiv**
LIST OF FIGURES		**xv**
LIST OF ABBREVIATIONS		**xxx**
LIST OF SYMBOLS		**xxiii**
LIST OF APPENDICES		**xxiv**
CHAPTER 1	**INTRODUCTION**	**1**
1.1	Research Background	1
1.2	Problem Statement	5
1.3	Objectives	6
1.4	Scope of Study	7
1.5	Significance of Research	9
1.6	Outline of Thesis	9
CHAPTER 2	**LITERATURE REVIEW**	**11**
2.1	Introduction	11
2.2	Synthesis of Magnetic Nanoparticles	12
	2.5.1 Chemical Methods	13
	2.5.2 Green Synthesis Methods	14
	2.5.1 Physical Methods	15
2.3	Polysaccharides	17

2.4 Nanocellulose as a Vehicle for Anticancer Drug Delivery Systems 21

2.4.1 Fabrications of Nanocellulose 21

2.4.2 Nanocellulose in Drug Delivery Systems and Cancer Treatments 24

2.5 Polysaccharide-Based Magnetic Nanocomposites 26

2.6 In Vitro Studies on Polysaccharide-Based Magnetic Nanocomposites as Drug Carriers for Targeted Cancer Therapy 29

2.7 In Vivo Studies on Polysaccharide-Based Magnetic Nanocomposites as Drug Carriers for Hyperthermia and Targeted Cancer Therapy 41

2.8 Gap Analysis and Concluding Remarks 45

CHAPTER 3 RESEARCH METHODOLOGY 47

3.1 Introduction 47

3.2 Materials and Chemicals 49

3.3 Preparation of Drug Nanocarrier Systems 50

3.3.1 Green Synthesis of Fe_3O_4 Nanoparticles Stabilized With *P. granatum* Fruit Peel Extract as 5-Fluorouracil Carrier (Fe_3O_4/*P. granatum*/5-FU) 51

3.3.2 Preparation of Cellulose fiber as 5-Fluorouracil Carrier (CF/5-FU) 52

3.3.3 Preparation of Magnetic Cellulose Fiber Bionanocomposites as a 5-Fluorouracil Carrier (MC/5-FU) 53

3.3.4 Preparation of Cellulose Nanocrystals as a 5-Fluorouracil Carrier (CNC/5-FU) 53

3.3.5 Fabrication of Chitosan-Coated Magnetic Cellulose Nanocrystals Bionanocomposites as a 5-Fluorouracil Carrier (CH/MCNC/5-FU) 53

3.4 Instrument for Physicochemical Characterizations 54

3.4.1 X-Ray Powder Diffraction (XRD) 54

3.4.1 Fourier-Transform Infrared (FTIR) 55

3.4.3 Transmission Electron Microscopy (TEM) 55

3.4.4 Scanning Electron Microscopy (SEM) 55
3.4.5 Energy-Dispersive X-Ray Spectroscopy (EDX) 56
3.4.6 Dynamic Light Scattering (DLS) 56
3.4.7 Vibrating Sample Magnetometer (VSM) 56
3.4.8 Thermogravimetric Analysis (TGA) 56
3.4.9 Swelling Analysis 56
3.4.10 Drug Loading Study 57
3.4.11 In Vitro Drug Release 57
3.5 Cytotoxicity and Anticancer Assays 58
3.5.1 Cell Lines and Reagents 58
3.5.2 In Vitro Cytotoxicity Assays 58
3.5.3 Tumor-On-Chip Experiment 60
3.5.4 Tumour-On-Chip Experiment and Magnetic Targeting Assay 60
3.5.5 Short-Term Heat Induction Assay 60
3.6 Statistical Analysis 61

CHAPTER 4 RESULTS AND DISCUSSIONS 63

4.1 Introduction 63
4.2 Green Synthesis of Fe_3O_4 Nanoparticles as 5-Fluorouracil Carrier (Fe_3O_4/*P. granatum*/5-FU) for Potential Colorectal Cancer Treatment 64
4.2.1 X-Ray Powder Diffraction (XRD) 66
4.2.2 Fourier-Transform Infrared Spectroscopy (FTIR) 68
4.2.3 Scanning Electron Microscopy (SEM) 69
4.2.4 X-Ray Spectroscopy (EDX) 71
4.2.5 Transmission Electron Microscopy (TEM) 72
4.2.6 Vibrating Sample Magnetometer (VSM) 73
4.2.7 Dynamic Light Scattering (DLS) 74
4.2.8 Physiochemical Analysis of Fe_3O_4 Nanoparticles Synthesised without Stabilizer (S0) 75

4.2.9 Drug Loading Study and Encapsulation Efficiency (EE) 76

4.2.10 In Vitro Drug Release Study 77

4.2.11 In Vitro Cytotoxicity Assay 78

4.3 Cellulose fiber Isolated from Rice Straw Waste for 5-Fluorouracil Carrier (CF/5-FU) and Potential Colorectal Cancer Treatment 82

4.3.1 X-Ray Powder Diffraction (XRD) 82

4.3.2 Fourier-Transform Infrared Spectroscopy (FTIR) 83

4.3.3 Scanning Electron Microscope (SEM) and Energy Dispersive X-Ray (EDX) 85

4.3.4 Dynamic Light Scattering (DLS) 86

4.3.5 Thermogravimetric Analysis (TGA) 87

4.3.6 Drug Loading Study and Encapsulation Efficiency (EE) 88

4.3.7 In Vitro Drug Release Study 89

4.3.8 In Vitro Cytotoxicity Assay 90

4.4 Magnetic Cellulose Fiber Bionanocomposites for 5-Fluorouracil Carrier (MC/5-FU) and Potential Colorectal Cancer Treatment 92

4.4.1 X-Ray Powder Diffraction (XRD) 93

4.4.2 Fourier Transform Infrared (FTIR) Spectroscopy 95

4.4.3 Scanning Electron Microscopy (SEM) 96

4.4.4 Transmission Electron Microscopy (TEM) and Energy-Dispersive X-Ray (EDX) 97

4.4.5 Dynamic Light Scattering (DLS) 99

4.4.6 Thermogravimetric Analysis (TGA) 100

4.4.7 Vibrating Sample Magnetometer (VSM) 100

4.4.8 Swelling Analysis 101

4.4.9 Drug Loading Capacity and Encapsulation Efficiency 102

4.4.10 In Vitro Drug Release 103

4.4.11 In Vitro Cytotoxicity Assays in 2D and 3D Culture 103

4.4.12 Tumour-On-Chip Coculture Assay 106

4.4.13 Effect of Magnetic Targeting and Temperature on HCT116 Tumour Spheroid Killing 107

4.5 Synthesis of Cellulose Nanocrystals as 5-Fluorouracil Carrier (CNC/5-FU) for Potential Colorectal Cancer Treatment 108

4.5.1 X-Ray Powder Diffraction (XRD) 109

4.5.2 Fourier-Transform Infrared (FTIR) Spectroscopy 110

4.5.3 Transmission Electron Microscopy (TEM) and Energy Dispersive X-Ray (EDX) 111

4.5.4 Thermogravimetric Analysis (TGA) 113

4.5.5 Dynamic Light Scattering (DLS) 113

4.5.6 Swelling Analysis 114

4.5.7 Drug Loading Study and Encapsulation Efficiency (EE) 115

4.5.8 In Vitro Drug Release 115

4.5.9 In Vitro Cytotoxicity Assays in 2D and 3D Culture 116

4.6 Synthesis of Chitosan-Coated Magnetic Cellulose Nanocrystals as 5-Fluorouracil Carrier (CH/CNC/5-FU) for Potential Colorectal Cancer Treatment 121

4.6.1 Physiochemical properties of chitosan nanoparticles (CH NPs) 122

4.6.2 X-Ray Powder Diffraction (XRD) 125

4.6.3 Fourier Transform Infrared (FTIR) Spectroscopy 126

4.6.4 Transmission Electron Microscopy (TEM) and Energy Dispersive X-Ray (EDX)) 127

4.6.5 Dynamic Light Scattering (DLS) 129

4.6.6 Vibrating Sample Magnetometer (VSM) 130

4.6.7 Thermogravimetric Analysis (TGA) 131

4.6.8 Drug Loading and Encapsulation Efficiency 132

4.6.9 Swelling Analysis 133

4.6.10 In Vitro Drug Release 133

4.6.11 In Vitro Cytotoxicity Assay 134

CHAPTER 5 CONCLUSION AND RECOMMENDATIONS 137

5.1 Introduction 137

5.2 Conclusions 139

5.1.1 Synthesis of Fe_3O_4 NPs Stabilized with *Punica granatum* as 5- Fluorouracil Carrier for Potential Colorectal cancer Treatment 140

5.2.2 Synthesis of Rice Straw Cellulose Fiber as 5-Fluorouracil Carrier (CF/5-FU) for Potential Colorectal Cancer Treatment 140

5.2.3 Synthesis of Magnetic Cellulose as 5-Fluorouracil Carrier (MC/5-FU) for Potential Colorectal Cancer Treatment 141

5.2.4 Fabrication of Cellulose Nanocrystals as 5-Fluorouracil Carrier for Potential Colorectal Cancer Treatment 141

5.2.5 Fabrication of Chitosan/Magnetic Cellulose Nanocrystal Bionanocomposites as 5-Fluorouracil Carrier (CH/MCNC/5-FU) for Potential Colorectal Cancer Treatment 142

5.3 Recommendation for Future Works 143

REFERENCES 145

LIST OF PUBLICATIONS 177

LIST OF TABLES

TABLE NO.	TITLE	PAGE
Table 2.1	Various methods for synthesis of MNPs	16
Table 2.2	Various polysaccharides utilized in fabrication of nanocomposites	19
Table 2.3	Estimation for the reported annual global fabrication of polysaccharides from wood-based materials	21
Table 2.4	Typical geometrical features for the isolation of nanocellulose from different sources and procedures	23
Table 2.5	Nanocellulose-based drug delivery systems for cancer treatment and biomedical applications	25
Table 2.6	Overview of recent in vitro studies on MNCs and PMNCs for targeted cancer therapy	32
Table 2.7	Overview of recent in vivo studies on MNCs and PMNCs for targeted cancer therapy	42
Table 3.1	Materials and manifactures	49
Table ٣.2	Synthesized drug nanocarrier systems in this research	50
Table ٤.1	Hydrodynamic analysis of S1-S5	74
Table 4.2	IC_{50} of 5-FU, CF, and CF/5-FU on the tested cell lines	92
Table 4.3	IC_{50} and SI values of MC, MC/5-FU, and 5-FU in various cell lines	104
Table 4.4	The calculated IC_{50} values for CNC, CNC/5-FU, and 5-FU on CCD-112, HCT116, and HT-29 cell lines	118
Table 4.5	Zeta potential of the synthesized samples	130
Table 4.6	The calculated IC_{50} values for the synthesized samples on CCD-112 and HCT116 cell lines	136
Table 5.1	Summary of the obtained results in this project	138

LIST OF FIGURES

FIGURE NO.	TITLE	PAGE
Figure 2.1	Schematic of popular methods for synthesis of MNPs	13
Figure 2.2	Some polysaccharide sources: (a) hard wood (beech tree), (b) bamboo, (c) cotton, (d) sisal, (e) tunicine, and (f) Gluconacetobacter xylinum. (g) Molecular structures of common polysaccharide	20
Figure 2.3	Inorganic and organic materials and their properties regarding their use as functionalizing and coatings agents for synthesis of MNCs and PMNCs	28
Figure 2.4	Different coating structures for synthesis of PMNCs and common shapes of magnetic core	29
Figure 2.5	TEM morphologies and size distribution of (A) Fe_3O_4 NPs and (B) PMNCs of Fe_3O_4@C. (C) Raman spectrum, (D) XRD, (E) FTIR spectra (F), TGA curves, and (G) Ms of Fe_3O_4 and Fe_3O_4@C [155].	31
Figure 2.6	TEM images of (a) SPIONs, (b) SPION@CA, (c) SPION@CA-Dox, and (d) SPION@CA-epirubicin [184]. (e) TEM image and the particle size distribution analysis of DOX-Fe_3O_4@agar, (f) magnetic strength of Fe_3O_4 and DOX-Fe_3O_4@agar, (g) drug release profiles of DOX-Fe_3O_4@agar at pH 7, (h) the SAR values and temperature achieved by Fe_3O_4, DOX-Fe_3O_4@agar, and DOX-Fe_3O_4@agar in HT-29 cells under applied heat induction by AMF (applied field = 400 A, frequency = 250 kHz), (i) schematic of effects of DOX-Fe_3O_4@agar for eliminating HT-29 cancer cells under hyperthermia, (j) fluorescence38 microscopy images of HT-29 cells after 1 h of incubation with DOX-Fe_3O_4@agar, and (k) cell survival of HT-29 cells treated by DOX-Fe_3O_4@agar with and without MHT [150]	37
Figure 2.7	(a) Interaction of BMNPs with 4T1 cells in the presence/absence of a continuous gradient magnetic field analyzed at TEM, micrographs of the cells incubated with the 100 µg/mL of BMNPs for different periods of time. The micrographs are representative of alternate serial cuts of the cell pellets of each sample. Scale bar, 5 µm. (b) In vivo antitumor activity of BMNPs under the influence of AMF, Images were captured using a thermic camera of a representative mouse without (left) and with (right) injected	

	BMNPs during AMF treatment. Note the different colors within the circle on the backside of the mouse [198]	39
Figure 2.8	MFMNPs behavior inside the cells in a constant magnetic field exposure. (a) Light microscopy micrograph of cells incubated with MFMNPs for 24 h, then placed in a magnetic field for 16-hr and embedded in epoxy resin. (b-g) Correlative light-electron microscopy of the cell, marked with red oval on the panel a, with Alexa Fluor 647 labeled MFMNPs inside: (b) phase-contrast microscopy, (c) confocal microscopy, (d-g) TEM images. Ultrastructure of the cell after 40-hr incubation with MFMNPs (last 16-hr in the magnetic field). (h) Small magnification TEM image. (i) High magnification of the region with MFMNPs [199]	41
Figure۲,۹	Schematic of pH, magneto, and thermo responsive drug delivery systems using drug loaded PMNCs	46
Figure 3.1	Overall methodology of this research	48
Figure 4.1	Schematic of the green-synthesized Fe_3O_4 NPs as a 5-FU carrier for potentialcolorectal cancer treatment	65
Figure 4.2	Schematic of synthesized Fe_3O_4 interactions with activated functional groups of *P. granatum* fruit peel extract	66
Figure 4.3	XRD results of (a) S1, (b) S2, (c) S3, (d) S4, and (e) *P. granatum* fruit peel extract	67
Figure 4.4	FTIR spectroscopy of (a) S1, (b) S2, (c) S3, (d) S4, and (e) *P. granatum* fruit peel extract	69
Figure 4.5	SEM image of (a) S1, (b) S2, (c) S3, (d) S4, and (e) *P. granatum* fruit peel extract	70
Figure 4.6	EDX result of (a) S1, (b) S2, (c) S3, (d) S4, and (e) *P. granatum* fruit peel extract	71
Figure 4.7	(a) TEM image, (b) particle size distribution histogram, (c) SAED pattern, (d) the electron diffraction pattern of S1	72
Figure 4.8	(a) Ms and (b) coercivity of S1, S2, and S3	73
Figure 4.9	Zeta potential of S1, S2, S3, and S4	75
Figure 4.10	(a) FTIR, (b) XRD, (c) VSM, (d) SEM, (e) EDX, and (f) SAED pattern of Fe_3O_4 NPs (S0) synthesized by co-precipitation method without the extract stabilizer	76
Figure 4.11	Drug release performance from Fe_3O_4/*P. granatum*/5-FU in a pH 7.4 medium	77

Figure 4.12 Anticancer activity of of S0 (Fe_3O_4 NPs without stabilizer) against (a) CCD112 colorectal normal and (b) HCT116 cancer cell line 78

Figure 4.13 Anticancer activity of S1, S2, S3, S4, and S5 against CCD112 colorectal normal cell 79

Figure 4.14 Anticancer activity of S1, S2, S3, S4, and S5 against HCT116 colorectal cancer cell 79

Figure 4.15 Cytotoxic effects of the anticancer drug 5-FU and S2/5-FU against (a) CCD112 colon normal cell lines and (b) HCT116 colorectal cancer cell lines. (c) The comparison of cell killing of S2/5-FU in both HCT116 and CCD112 cells 80

Figure 4.16 Microscopic images of Fe_3O_4/*P. granatum*/5-FU treated (a) HCT116 and (b) CC112 cells at different concentration 81

Figure 4.17 Schematic process for CF isolation from rice straw waste as a 5-FU carrier for colorectal cancer treatments 82

Figure 4.18 XRD results of (a) rice straw waste, (b) bleached rice straw, and (c) CF 83

Figure 4.19 FTIR results of (a) rice straw waste, (b) bleached rice straw (c), CF, (d) CF/5-FU, and (e) 5-FU 84

Figure 4.20 SEM images of (a and b) bleached rice straw, (c and d) CF, and (e) CF/5-FU. (f) EDX result of CF and CF/5-FU 86

Figure 4.21 Zeta potential values of CF and CF/5-FU 87

Figure 4.22 TGA results of (a) CF, (b) CF/5-FU, and (c) 5-FU 88

Figure 4.23 Drug release performance from CF/5-FU in a pH 1.2 and 7.4 medium 90

Figure 4.24 Anticancer activity of 5-FU, CF, and CF/5-FU against (a) CCD112 normal and (b) HCT116 colorectal cancer cell line. (c) Anticancer activity of CF/5-FU against CCD112 and HCT116 91

Figure 4.25 The schematic processes of MC/5-FU preparation for elimination of colorectal cancer cells 93

Figure 4.26 XRD results of (a) rice straw waste, (b) cellulose, (c) MC, (d) MC/5-FU, and (e) 5-FU 94

Figure 4.27 FTIR results of (a) rice straw waste, (b) cellulose, (c) MC, (d) MC/5-FU, and (e) 5-FU 96

Figure 4.28 SEM image of (a) dewaxed rice straw waste and (b) CF. (c) Histogram of diameter distribution for CF. SEM images of (d) MC and (e,f) MC/5-FU. (g-i) TEM images, (j) histogram of Fe_3O_4 NPs size distribution, (k) the electron diffraction

pattern, and (l) SAED pattern of MC/5-FU. (m) EDX results of MC and (n) MC/5-FU 98

Figure 4.29 (a) Hydrodynamic size and (b) zeta potential value of cellulose, MC, and MC/5-FU 90

Figure 4.30 (a) TGA of cellulose, MC, MC/5-FU, and 5-FU. (b) VSM of MC 101

Figure 4.31 (a) Swelling kinetics of MC/5-FU and (b) 5-FU release from MC/5-FU in different media at pH 1.2 and 7.4 under temperature induction from 34.2 to 44.2 °C 103

Figure 4.32 Anticancer activity of MC and MC/5-FU against (a) CCD112, (b) HCT116, and (c) HT29 2D monolayer models. Anticancer activity of MC and MC/5-FU against (d) HCT116 and (e) HT29 3D tumour spheroid models 105

Figure 4.33 Tumour spheroid-on-chip testing with MC/5-FU. (a) Schematic diagram showing the design of tumour spheroid-on-chip co-culture model with MC/5-FU treatment. (b) Microscopic examination (left) and spheroid growth analysis (right) of HCT116 spheroids treated with 100 µg/mL MC/5-FU in comparison with untreated control. Scale bars represent 100 µm. (c) Magnetic property of MC/5-FU separated by external magnet (left) and schematic diagram showing the magnetic targeting towards tumour spheroid (right) 106

Figure 4.34 Effect of short-term temperature induction on tumour spheroid killing. Tumour spheroids were exposed to 1 h temperature induction from 34.2 to 44.2 °C and the anticancer action of MC/5-FU was determined after 1 h and 24 h incubation 107

Figure 4.35 (a) Schematic procedures for CNC/5-FU fabrication for in vitro anticancer analysis towards colorectal cancer cells. (b) The possible intermolecular chemical interactions between active functional groups in CNC/5-FU 109

Figure 4.36 XRD results of (a) cellulose, (b) CNC, (c) CNC/5-FU, and (d) 5-FU 110

Figure 4.37 FTIR results of (a) cellulose, (b) CNC, (c) CNC/5-FU, and (d) 5-FU 111

Figure 4.38 (a and b) TEM images of CNC/5-FU, the average (c) width and (d) length of CNC/5-FU. EDX result of (e) CNC and (f) CNC/5-FU 112

Figure 4.39 TGA and DTGA traces of (a) CNC, (b) CNC/5-FU, and (c) 5-FU 113

Figure 4.40 (a) Hydrodynamic size distributions and (b) zeta potential values of CNC and CNC/5-FU 113

Figure 4.41 Swelling kinetics of (a) CNC and (b) CNC/5-FU initiated from the wet state in a pH 1.2, 4.2, and 7.4 medium. (c) Drug release performance from CNC/5-FU in a pH 1.2, 4.2, and 7.4 medium 116

Figure 4.42 Anticancer activity of (a) CNC, (b) CNC/5-FU, and (c) 5-FU against colorectal cell lines in 2D monolayer cultures. * p< 0.05 117

Figure 4.43 Anticancer activity of (a) CNC, (b) CNC/5-FU, and (c) 5-FU against 3D tumor spheroids generated from HCT116 and HT-29 colorectal cancer cells. * p< 0.05 119

Figure 4.44 Tumor spheroid-on-chip testing using CNC/5-FU. (a) Schematic diagram showing the design of the spheroid-on-chip co-culture model and CNC/5-FU treatment. (b) Microscopic examination and (c) spheroid size analysis of HCT116 spheroids treated with 100 µg/mL CNC and CNC/5-FU. Scale bar represents 100 µm. * p< 0.05 120

Figure 4.45 Schematic process for synthesis of CH/MCNC/5-FU for in vitro cytotoxicity assay towards colorectal cancer lines 122

Figure 4.46 (a) The potential interactions between active functional groups of LMWC and TPP in the fabrication of CH NPs. (b) XRD spectra and (c) FTIR results of LMWC, TPP, and CH NPs. (d) Hydrodynamic size, (e-f) SEM images, (h) average estimated diameter, and EDX result of CH NP 124

Figure 4.47 XRD results of (a) rice straw waste, (b) CNC, (c) MCNC, (d), CH/MCNC, (e) CH/MCNC/5-FU, and (f) 5-FU 125

Figure 4.48 FTIR results of (a) rice straw waste, (b) CNC, (c) MCNC, (d) CH/MCNC, (e) CH/MCNC/5-FU, and (f) 5-FU 127

Figure 4.49 Figure 4.49 TEM image of (a) CNC and (b) MCNC (c) the electron diffraction pattern of MCNC, (d) TEM image of CH/MCNC, (e) the electron diffraction pattern of CH/MCNC, (f and g) TEM image, (h) the electron diffraction pattern, (i) and SAED pattern of CH/MCNC/5-FU, and (k) EDX and (j) histogram of size distribution of the fabricated samples 128

Figure 4.50 Hydrodynamic size distributions of (a) CNC, (b) MCNC, (c) CS/MCNC, and (d) CS/MCNC/5-FU 130

Figure 4.51 VSM of MC, CH/MC, and CH/MC/5-FU 131

Figure 4.52 TGA and DTGA results of (a) CNC, (b) MCNC, (c) CH/MCNC, (d) CH/MCNC/5-FU and (e) 5-FU 132

Figure 4.53 Swelling kinetic of CH/MCNC/5-FU initiated from the wet state in two different media at pH 1.2 and 7.4 (a) without and (b) with heat induction at 44 °C. Drug release of CH/MCNC/5-

FU in two different media at pH 1.2 and 7.4 (c) without and (d) with heat induction at 44 °C 134

Figure 4.54 Anticancer activity of (a) MCNC, (b) CH NPs, (c) CH/MCNC, and (d) CH/MCNC/5-FU against HCT116 and HT-29 colorectal cancer cells 135

LIST OF ABBREVIATIONS

5-FU	-	5-Fluorouracil
AFM	-	Atomic force microscopy (AFM)
AMF	-	Applied magnetic field
BET	-	Brunauer–Emmett–Teller
BJH	-	Barrett–Joyner–Halenda
CF/5-FU	-	Cellulose fiber as 5-Fluorouracil carrier
CF	-	Cellulose fiber
CH NPs	-	Chitosan nanoparticles
CH/MCNC	-	Chitosan-coated magnetic cellulose nanocrystals
CH/MCNC/5-FU	-	Chitosan-coated magnetic cellulose nanocrystals as 5-Fluorouracil carrier
CNC	-	Cellulose nanocrystals
CNC/5-FU	-	Cellulose nanocrystals as 5-Fluorouracil carrier
CNF	-	Cellulose nanofibers
CNW	-	Cellulose nanowhiskers
d	-	Day
DLS	-	Dynamic light scattering
DMEM	-	Dulbecco's Modified Eagle's medium
DOX	-	Doxorubicin
DRS	-	Delignificated rice straw
EDX	-	Energy dispersive spectroscopy
EE	-	Encapsulation efficiency
EMF	-	External magnetic field
FBS	-	Fetal bovine serum
Fe_3O_4/*P. granatum*	-	Fe_3O_4 stabilized with *Punica granatum* fruit peel extract
FTIR	-	Fourier transform infrared
FWHM	-	Full width at half maximum
HCl	-	Hydrochloric acid

IC_{50}	-	50 % growth inhibition
IONPs	-	Iron oxide nanoparticles
LC	-	Loading capacity
LMWC	-	Low molecular weight chitosan
MARDI	-	Malaysian Agricultural Research and Development Institute
MC	-	Magnetic cellulose fiber
MC/5-FU	-	Magnetic cellulose fiber/5-Fluorouracil
MCNC	-	Magnetic cellulose nanocrystals
MHT	-	Magnetic hyperthermia therapy
MNCs	-	Magnetic nanocomposites
MNPs	-	Magnetic nanoparticles
MRI	-	Magnetic resonance imaging
Ms	-	Saturation magnetization
NCC	-	Nanocrystalline cellulose
NFC	-	Nanofibrous cellulose
NPs	-	Nanoparticles
P. granatum	-	*Punica granatum*
PAA	-	Polyacrylic acid
PBS	-	Phosphate-buffered saline
PCR	-	Polymerase chain reaction
PEG	-	Polyethylene glycol
PEI	-	Polyethylenimine
PLA	-	Polylactic acid
PLGA	-	Poly(lactic-co-glycolic acid)
PMMA	-	Polymethyl methacrylate
PMNCs	-	Polysaccharide-based magnetic nanocomposites
PVP	-	Polyvinyl pyrrolidone
RLU	-	Relative luminescence unit
S0	-	Fe_3O_4 nanoparticles synthesized without the extract stabilizer
S1	-	Fe_3O_4 nanoparticles stabilized with 1 wt % *Punica granatum* fruit peel extract
S2	-	Fe_3O_4 nanoparticles stabilized with 2 wt % *Punica granatum* fruit peel extract

S3	-	Fe_3O_4 nanoparticles stabilized with 4 wt % *Punica granatum* fruit peel extract
S4	-	Fe_3O_4 nanoparticles stabilized with 8 wt % *Punica granatum* fruit peel extract
S5	-	*Punica granatum* fruit peel extract
SAED	-	Selected-area electron diffraction
SAR	-	Specific absorption rate
SPIONs	-	Superparamagnetic iron oxide nanoparticles
SEM	-	Scanning electron microscopy
TEM	-	Transmission electron microscopy
TGA	-	Thermogravimetric analysis
TPP	-	Tripolyphosphate
UV	-	Ultraviolet
UV-vis	-	Ultraviolet-visible
VSM	-	Vibrating sample magnetometer
XPS	-	X-ray photoelectron spectroscopy
XRD	-	X-ray diffraction

LIST OF SYMBOLS

A	-	Constant
C	-	Concentration
D	-	Crystallite size
eV	-	Electron volt
Eg	-	Band gap energy
R^2	-	Correlation coefficient
t	-	Time
wt	-	Weight
β	-	Full width at half the maximum
θ	-	Diffraction angle
λ	-	X-ray wavelength of radiation

LIST OF APPENDICES

APPENDIX	TITLE	PAGE
Appendix A	Band gap of Fe_3O_4 NPs stabilized with (a) 1 wt %, (b) 2 wt %, (c) 4 wt %, and (d) 8 wt % *P. granatum* extract	166
Appendix B	Cytotoxic effects of plant mediated Fe_3O_4 NPs (S1-S4) and *P. granatum* extract (S5) on HONE1 and HEK293 cancer cell lines	167
Appendix C	(a) Nitrogen adsorption–desorption isotherms at 77 K for the selfassembled products from CF and delignificated rice straw (DRS). The inset table lists the Brunauer–Emmett–Teller (BET) surface area and Barrett–Joyner–Halenda (BJH) cumulative pore volume calculated from the adsorption branch of each isotherm and (b) average pore diameter of DRS and CF	168
Appendix D	Cytotoxic effects of 5-FU, CF, and CF/5-FU against (a) NP 460 nasopharyngeal normal cell lines and (b) HONE-1 cancer cell lines	169
Appendix E	Atomic Force Microscopy (AFM) analysis of CNC/5-FU	170
Appendix F	The 5-FU absorbance and (ii) calibration curve at λmax = 266 nm from known concentrations of 5-FU (5–25 ppm); (iii) UV-vis spectra of the unentrapped 5-FU; (b) UV-vis spectra and (c) a schematic of possible drug release	171
Appendix G	XPS analysis of MC/5-FU, (a) wide scan, (b) Fe 2P, (c) O 1s, and (d) C 1s	172
Appendix H	Caspase detection of untreated control and MC/5-FU-treated HCT116 and HT29 cells in (a) fluorescence ratio and by (b) fluorescence microscopic analysis. Mitochondrial membrane potential analysis of untreated control and MC/5-FU-treated HCT116 and HT29 cells in (c) fluorescence ratio and by (d) fluorescence microscopy. Hemolysis assay (e) of MC and MC/5-FU	173
Appendix K	Magnetic property of MC/5-FU separated by external magnet (left) and schematic diagram showing the magnetic targeting towards tumour spheroid (right). (d) Calcein AM (live cells) and propidium iodide (dead cells) staining of untreated, MC/5-FU-treated spheroids with and without magnetic targeting. Scale bar represents 50 µm	174

Appendix L Clonogenic assay by CNC/5-FU on colorectal cell lines. (a) Images from colony-formation assays of the colorectal cell lines following a 0, 31.3, 62.5, 125, 250, and 500 μg/mL treatment of CNC/5-FU; (b) The survival curve of HCT116 and HT-29 colorectal cancer cells treated with various concentrations of CNC/5-FU. * $p < 0.05$ 175

Appendix M XPS analysis of CH/MCNC/5-FU, (a) wide scan, (b) Fe 2P, (c) O 1s, and (d) C 1s 176

CHAPTER 1

INTRODUCTION

1.1 Research Background

Colorectal cancer causes the death of more than 600,000 patients every year [1]. It is attributed to colon, rectal, and bowel cancer and is developed inside polyps (adenoma) and formed within the bowel wall. Chemotherapy is the most prominent route in colorectal cancer therapy to prolong the life span of cancer patients. Anticancer drug 5-Fluorouracil (5-FU) is widely used to treat colorectal cancer. However, it may cause harmful side effects and unwanted damages against normal cells. Since two decades ago, nanotechnology has advantageously gained its reputation in nanomedicine and various biomedical applications. Magnetic nanoparticles (MNPs) as smart nanoagent possesses numerous advantages such as low cost of preparation, magnetic and heat-responsive properties, guide ability, and low toxicity [2]. It can be used in different biomedical applications, including targeted drug delivery [3], magnetic hyperthermia and thermoablation [4], bioseparation [5], biosensing [6], cancer therapy [7], cell labeling [8], magnetic resonance imaging (MRI) [9], and targeting and immunoassays [10]. For therapeutic and biomedical applications, Fe_3O_4 and γ-Fe_2O_3 are popular since these MNPs have small size and narrow size distribution as well as high magnetization [11]. An investigation analyzed the in vitro toxicity of copper, titanium dioxide, $CuZnFe_2O_4$, and Fe_3O_4 NPs at concentrations ranging between 20 to 100 μg/mL, which found no toxicity from the tested Fe_3O_4 NPs [12]. Despite this, the bare MNPs may exert weak colloidal stability, poor drug conjugation, low drug encapsulation efficiency, quick drug release, and undesired toxicity against normal cells [13].

The colloidal stability and biocompatibility of the MNPs can be improved by using green-based materials such as plant extract [13, 14], natural cellulose [15], and chitosan [16] as stabilizer, capping agent, or solid supports and coating agent. In addition green-synthesized nanocarrier system can trigger increased drug loading and sustained drug release for advanced cancer treatments, Therefore, MNPs have been

synthesized by using different plant extracts including *calliandra haematocephal* leaf [17] *juglans regia* fruit peel [18], *couroupita guianensis Aubl* fruit [19], *mimosa pudica* root [20], coffee waste [21], seaweed marine plant [22], *syzygium cumini* seed [23], and Arabic gum [24]. MNPs prepared by a combination of facile co-precipitation and green synthesis using stabilizer/capping agents of the plant extract can lead to obtaining green-based MNPs with enhanced anticancer effects [13, 25]. Interestingly, the peel of some fruits has higher antioxidant and anticancer activities than the pulp [26]. The extract of fruit peels such as *Garcinia mangostana* and *Punica granatum* (*P. granatum*) are rich sources of antioxidants and anticancer [13, 14], due to their metabolite content of polyphenol or flavonoid subclass [27]. Although *P. granatum* fruit peel contains 30-40 % of the fruit protein, it is considered a waste material [28]. Polyphenols, including anthocyanins, may show structural modification at in vitro or in vivo evaluation, along with enhanced bioavailability and biological properties [29]. *P. granatum* caused remarkable effects against various cancer cell lines, including bladder T24 [30], cervical HeLa [31], prostate [32-34], breast cancer [35-38], and thyroid [39].

Fascinating and enlightening studies on novel natural-based carriers are prone to assert solutions for many issues in global health and drug delivery systems. In this manner, insights into polysaccharide nanocomposites have eminently illuminated several authentic features for medical applications in the past few years that are linked to evidence of bias for developing sophisticated technologies to promote a healthy society [40]. As the most obtained polysaccharides, natural cellulose with a desirable structure, improved crystallinity or ordered regions, and also nano-dimensional scale can be isolated from various wood-based materials, including rice straw waste, which is the highest agro-waste material in South East Asia [41-43]. The polysaccharide-based products advantageously can bind with various drugs and show desired swelling behavior, pH gradient behavior, and high biodegradability for innovative antitumor drug delivery systems [44]. Each property has its particular pros and cons for developing a topical nanodrug formulation with improved stability and therapeutic effects [45]. The vitality of drug-loaded polysaccharides is a consequence of its potential to deliver a sufficient amount of drugs to cancer cells without significant effects against normal cells to decrease medical malpractice derived from the drug alone [45, 46]. The disadvantages of side-effects of chemotherapy have been alleviated

by loading a sufficient dosage of chemo-drugs onto various polymer and polysaccharide-based carrier systems, for instance, poly(2-vinyl pyridine)-b-poly(ethylene oxide) nanomicelles [47], chitosan microspheres [48, 49], carboxymethyl cellulose [50], and crystalline nanocellulose to name a few [51]. Further, curcumin was loaded onto crystalline nanocellulose and caused almost three times higher colorectal cancer cell death than that of curcumin alone [52]. Gao et al. in a different report used rice husk to extract acid hydrolyzed nanocellulose and then analyzed its phytochemical bioactivities [41]. Thus, with the immense demand for using biocompatible nanocarriers in anticancer drug delivery systems, natural polysaccharides should be explored as a treatment for killing colorectal cancer cells.

The use of polymer blends leads to fabricating innovative composites with enhanced drug encapsulation efficiency and prolonged drug release. In drug delivery applications, chitosan is the second most popular biopolymer after cellulose, with a production of over 100 million tons per year [16, 49]. It may be derived from chitin and is a cationic linear and natural amino-polysaccharide containing-(1-4)-linked d-glucosamine and *N*-acetyld-glucosamine in deacetylated and acetylated form, respectively. Among diverse methods to synthesize layer-by-layer chitosan-based composites, the ionic gelation approach is an organic solvent-free solution, straightforward, and a facile method with minimal toxicity [53]. In this method, the phosphate groups of sodium tripolyphosphate (TPP) may act as a physical crosslinking agent, which has advantages over emulsifying and chemical crosslinking agents, such as less toxicity to the organs and no destruction to the structure of the loaded-drugs in chitosan nanocomposites. In addition, the crosslinking procedure might considerably improve physiochemical properties of the polymer composites. In medically-related applications, the most popular antimicrobial coating agent on cellulose is currently chitosan to synthesize composites with suitable biocompatibility and water-rich structures to encapsulate both hydrophilic and hydrophobic drugs. Furthermore, the bionanocomposites of chitosan and cellulose possess intermolecular interactions, owing to H-bonds and Van der Waals forces [54]. Most importantly, chitosan/cellulose bionanocomposites may possess a tremendous swelling capacity, water absorption ability, and pH-sensitivity to release the drug at the targeted cells [55]. Therefore, the biocompatibility and physiochemical properties of both cellulose and chitosan can be

modified by using cellulose as a reinforcement or solid support and chitosan as a coating agent to synthesize double polysaccharide composites.

Polysaccharides-based nanocomposites with desired pH-responsive structures could be a promising nanodrug system for future cancer treatment. However, changing pH in the human body is required a long time with incapability to be adjusted externally. This issue can be tackled via using polysaccharides as solid supports or coating agents for MNPs as fillers to fabricate multifunctional, biocompatible, and biodegradable polysaccharide-based magnetic nanocomposites (PMNCs) to obtain remotely controlled drug delivery systems, combination therapy of heat induction and magnetic targeting, switchable synthetic cell surfaces, and magnetothermal therapy [56, 57]. Numberless studies indicated the fabrication of different magnetic nanocomposites (MNCs) and PMNCs (with various size ranges) by using, for example, chitosan coated $MnFe_2O_4$ (18 nm) [58], dextran coated Fe_3O_4 (21 nm) [59], cellulose matrix (87.12 nm)/Fe_3O_4 fillers (11.01 nm) [15], PEG coated $NiFe_2O_4$ (16 nm) [60], phosphate coated Fe_3O_4 (14 nm) [61], tetraethyl orthosilicate coated $MnFe_2O_4$ (14 nm) [62], $Zn_{0.9}Fe_{0.1}Fe_2O_4$ (11 nm) [63], stevioside coated Fe_3O_4 (3 nm) [64], citric acid coated $Mn_xFe_{3-x}O_4$ (34 nm) [65], aminosilane coated Fe_3O_4 (100 nm) [66], and oleic acid coated Fe_3O_4 (45 nm) [67].

The use of various natural counterparts and coating agents such as polysaccharides for MNPs can lead to synthesize PMNCs with increased multifunctional properties, biocompatibility, and free magnetic ions onto the target organ causing oxidative stress and toxicity against target cancer cells. In this manner, the therapeutic nature of PMNCs with arsenal of magnetothermal drug delivery systems have manifested several advantages over the conventional cancer therapy methods due to their low damage to normal cells and ability to deliver sufficient drug dosage to the tumor. Thus, anticancer drug-loaded PMNCs under heat induction and external magnetic field (EMF) can perform a desired multifunctional cancer therapy. In addition to the high drug loading capacity, pH sensitivity structure of PMNCs, intervention of both EMF and heat inductions are capable of remotely switchable on-demand drug release and precisely steering the magnetothermal effects for local ablation of cancer cells in future colorectal cancer therapy. Most importantly, the

green-based nano-magnetic carrier systems using for example plant-extract, cellulose and chitosan can show sophisticated, biocompatibility, biodegradability, colloidal stability and different physiochemical to obtain increased drug loading and desired cancer treatments.

1.2 Problem Statement

Cancer statistics from over 185 countries have demonstrated 18.1 million new cancer cases from 36 different types of cancers in just 2018 alone. Colorectal cancer is the second and third most diagnosed cancer for males and females, respectively, globally. Anticancer drug 5-FU has been the top-choice chemotherapy drug in both adjuvant and advanced colorectal cancer treatment for over six decades. Despite this, chemo-drugs possess issues of morbidity and harmful side-effects due to their lack of bioavailability and consequent high doses. In addition, 5-FU is poorly water-soluble that can cause a weak and heterogeneous distribution of drugs in tumors and thereby therapeutic failure.

The peel of *P. granatum* has higher antioxidant activities than the pulp, but it is considered a waste material. MNPs fabricated without stabilizer or capping agent undesirably show low colloidal stability and poor biodegradability. Further, the bare MNPs in drug delivery systems are no longer welcome because of their low drug loading capacity and undesired biocompatibility. It is worth to mention that coating MNPs with non-biodegradable and synthetic materials could be costly and toxic to the environment.

Over the years, rice straw has been the second and first highest agro-waste in the world, causing toxicity and the reduction in landfill space. Rice straw waste contains a high ratio of natural cellulose to be used in advanced biomedical applications. Yet, rice straw cellulose has not been used in drug delivery applications and colorectal cancer treatments. Untreated natural cellulose possesses some drawbacks, including low thermal stability, undesired crystallinity, poor crease-resistance, and low solubility in solvent fluids. Although it has obtained success in

some cases, cellulose-based single-modality with pH-sensitive carrier structure may not be externally guided for the multi-stage drug release procedures.

Chitosan alone as a drug carrier shows only single-functionality. It can be considered that chitosan-based composites without a crosslinking agent indicate inappropriate physiochemical properties and weak intermolecular interactions. Uncoated magnetic natural nanocellulose composites can display pH, magnetic, and heat responsive properties, but with lower drug encapsulation efficiency and faster drug release compared to that containing a coating agent. However the synthesis of polymer-based drug delivery systems using chemical and physical methods so far has been great, the synthesis of low-cost polysaccharide-based magnetic Fe_3O_4 bionanocomposites as smart drug carriers for targeted cancer therapy is still beginning and limited. Many questions remain unanswered about production methods, the ratio among MNPs, type of polysaccharide as solid support and coating agent, and the loaded-drug, along with the mechanisms of the components in the synthesis of PMNCs as 5-FU carriers for effective colorectal cancer treatments. Above all, the green-based carrier formulations can be fabricated via novel and low cost materials such as example plant-extract, cellulose and chitosan due to their biocompatibility, biodegradability, stability, and great conjugation with various anticancer drug to produce natural-based nanodrug formulation for targeted colorectal cancer therapy.

1.3 Objectives

The main objective of this study is to introduce plant-mediated MNPs, polysaccharides, and PMNCs as novel, low-cost, facile, and advanced drug delivery systems for potential colorectal cancer treatments. Based on the background and problem statement, the following objectives are derived:

(a) To synthesize and evaluate physiochemical properties of various anticancer drug delivery systems including magnetic Fe_3O_4/*P. granatum*/5-FU, rice straw cellulose fiber (CF/5-FU), magnetic cellulose fiber (MC/5-FU), cellulose nanocrystals (CNC/5-FU), and chitosan-coated magnetic cellulose nanocrystals (CH/MCNC/5-FU) bionanocomposites.

(b) To determine the drug loading and release of Fe_3O_4/*P. granatum*/5-FU, CF/5-FU, MC/5-FU, CNC/5-FU, and CH/MCNC/5-FU bionanocomposites.

(c) To assess colorectal cancer effects of Fe_3O_4/*P. granatum*/5-FU, CF/5-FU, MC/5-FU, CNC/5-FU, and CH/MCNC/5-FU bionanocomposites.

1.4 Scope of Study

To complete all the objectives in this project, the research scopes for this study are:

The co-precipitation method and green stabilizer are used to synthesize magnetic Fe_3O_4 NPs, in which *P. granatum* peel extract (1, 2, 4, and 8 wt %) and the sodium hydroxide are served as a stabilizer and a reducing agent, respectively. The reason to use *P. granatum* peel as agro-waste materials is due to the presence of the phenolic compounds in the extract. The plant extract improves the colloidal stability, biocompatibility, and anticancer effects of the green-synthesized Fe_3O_4 NPs. The Fe_3O_4 NPs mediated with 2 wt % extract is ideally selected for drug loading procedure.

CF as natural polysaccharide is extracted from rice straw waste using a series of procedures, including bleaching, delignification, and alkali treatments. CF shows the rod-shaped structure, desired purity, and physiochemical properties. The obtained rice straw cellulose is loaded with the 5-FU drug to obtain a pH-sensitive and green-based drug delivery system.

CF as solid support collects the cluster of magnetic Fe_3O_4 NPs as fillers to fabricate MC bionanocomposites, indicating both pH-sensitive and magnetothermal responses for a 5-FU carrier system. In addition, the CF matrix increases the biocompatibility and multifunctionality of the magnetic bionanocomposites. Since CF is also served as a stabilizer, the use of another stabilizer such as extract is unnecessary.

For isolation of CNC, acid hydrolysis treatment on CF removes the amorphous regions and liberates the crystalline regions. Compared to CF, the hydrolysed CNC with a needle-like structure indicates smaller nanodimension. CNC is also effectively loaded with 5-FU for a pH-sensitive drug delivery system.

CNC matrix and Fe_3O_4 nanofillers are used for the synthesis of magnetic CNC bionanocomposites. To improve drug encapsulation efficiency and prolonged drug release, double polysaccharide-based magnetic bionanocomposites of CH/MCNC/5-FU is fabricated using cross-linked chitosan coater, CNC reinforcement or solid support, and Fe_3O_4 nanofillers to not only obtain enhanced pH-sensitive, but also magnetothermal responses for novel and advanced 5-FU carrier system. Thus, the fruit peel, the rice straw and chitosan are natural materials with their specific properties to fabricate green-based and low-cost nanocarrier systems.

Physicochemical properties of all the synthesized samples are evaluated by various characterization methods, such as, X-ray powder diffraction (XRD), Fourier transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM), transmission electron microscopy (TEM), energy dispersive spectroscopy (EDX), dynamic light scattering (DLS), thermogravimetric analysis (TGA), vibrating sample magnetometer (VSM), and swelling analysis. Ultraviolet (UV)-visible spectroscopy estimates the drug encapsulation and release of all the synthesized samples. The potential targeted drug delivery systems and in vitro cancer treatments of all the fabricated samples are carried out against colorectal cancer and normal cell lines.

1.5 Significance of Research

Colorectal cancer is one of the significant reasons of death, globally. The significance of this study is to use agro-waste materials in developing five new anticancer drug delivery systems for colorectal cancer treatments. Fe_3O_4 NPs stabilized with *P. granatum* peel extract or rice straw cellulose trigger enhanced physiochemical properties, biocompatibility, biodegradability, and tolerable toxicity. The use of plant-mediated MNPs, chitosan, and CF and CNC extracted from rice straw (as the highest agro waste in South East Asia) to fabricate various nanodrug delivery

systems are prone to assert solutions for colorectal cancer that are linked to evidence of bias for developing sophisticated nanomaterials to promote a healthy society. Magnetic chitosan and cellulose-based drug delivery systems with great swelling property, well biocompatibility, and targeted actions can decrease the issues of 5-FU chemotherapy such as diarrhea, stomatitis, and gastrointestinal mucosal injury. In addition, the use of nanopolysaccharide-based magnetic composites for combination therapy of heat treatment, tumor pH targeting, and magnetic targeting offer promising potential to tackle issues of single-modality drug delivery systems.

Thus, polysaccharide-based magnetic bionanocomposites are exceptional in smart and remotely guided drug delivery systems due to not only their magneto effects and guide-ability, but also their heat capacity develops thermal-stimuli and on-demand drug release performance and subsequent thermo-chemosensitisation. This research would show fabrication and characterizations of various MNPs, polysaccharides, and magnetic polysaccharide bionanocomposites to achieve affordable scale-up of natural-based drug delivery systems and advanced colorectal cancer treatments to assist attainment of cancer survivors' aims.

1.6 Outline of Thesis

This thesis consists of five chapters.

Chapter 1 is the introduction of the thesis to explain background, problem statement, objectives, scope, and significance of this research. This chapter indicates the knowledge required to tackle the issue, hypothesis, scope and limitation, conceptual framework, aims, and significance of this research.

Chapter 2 is the literature review to indicate findings of the previous studies. This chapter identifies gaps on why mpolysaccharide-based magnetic nanocomposites for targeted drug delivery systems have yet to fulfil reliable magnetothermal chemotherapy for colorectal cancer. Given the presumed important role magnetic nanocomposites (MNCs) and polysaccharide-based magnetic nanocomposites (PMNCs) as well as their synthesis methods, surface modifications, and coating, it

presents recent studies on targeted drug delivery systems for development of inexpensive, minimal invasiveness, and advanced cancer therapy.

Chapter 3 contains the research materials, fabrication methods of Fe_3O_4/*P. granatum*/5-FU, CF/5-FU, MC/5-FU, CNC/5-FU, and CH/MCNC/5-FU bionanocomposites as green-based drug delivery systems for colorectal cancer treatments. The physiochemical analysis of the samples is explained using various techniques, including XRD, FTIR, SEM, TEM, EDX, DLS, TGA, VSM, and swelling analysis. The drug loading and release study for all synthesized drug carrier systems are indicated using UV-visible spectroscopy. Cytotoxicity and anticancer effects of the synthesized samples are explained using colorectal normal and cancer cell lines.

Chapter 4 discusses the obtained results of various physiochemical properties for Fe_3O_4/*P. granatum*/5-FU, CF/5-FU, MC/5-FU, CNC/5-FU, and CH/MCNC/5-FU bionanocomposites. This chapter indicates the drug loading and release performance of the synthesized samples. In addition, results of cytotoxicity assays and anticancer effects of the samples are explained to indicate the potential use of the fabricated drug nanocarrier systems for colorectal cancer treatments.

Chapter 5 presents summary of the obtained results in this project. This chapter shows the research conclusion for synthesis of Fe_3O_4/*P. granatum*/5-FU, CF/5-FU, MC/5-FU, CNC/5-FU, and CH/MCNC/5-FU for colorectal cancer therapy, followed by the recommendation for future works in smart drug delivery systems.

REFERENCES

[1] K. Van der Jeught, H.-C. Xu, Y.-J. Li, X.-B. Lu, G. Ji, Drug resistance and new therapies in colorectal cancer, World journal of gastroenterology 24(34) (2018) 3834.

[2] A.H. Lu, E.e.L. Salabas, F. Schüth, Magnetic nanoparticles: synthesis, protection, functionalization, and application, Angewandte Chemie International Edition 46(8) (2007) 1222-1244.

[3] S. Senapati, A.K. Mahanta, S. Kumar, P. Maiti, Controlled drug delivery vehicles for cancer treatment and their performance, Signal transduction and targeted therapy 3(1) (2018) 7.

[4] C. Huang, S.J. Soenen, J. Rejman, J. Trekker, L. Chengxun, L. Lagae, W. Ceelen, C. Wilhelm, J. Demeester, S.C. De Smedt, Magnetic electrospun fibers for cancer therapy, Advanced Functional Materials 22(12) (2012) 2479-2486.

[5] Q. Zhao, Q. Wu, P. Ma, L. Xu, F. Zhang, D. Li, X. Liu, S. Xu, Y. Sun, D. Song, Selective and sensitive fluorescence detection method for pig IgG based on competitive immunosensing strategy and magnetic bioseparation, Talanta 195 (2019) 103-108.

[6] M. Nikitin, A. Orlov, S. Znoyko, V. Bragina, B. Gorshkov, T. Ksenevich, V. Cherkasov, P. Nikitin, Multiplex biosensing with highly sensitive magnetic nanoparticle quantification method, Journal of Magnetism and Magnetic Materials 459 (2018) 260-264.

[7] M. Mühlberger, C. Janko, H. Unterweger, E. Schreiber, J. Band, C. Lehmann, D. Dudziak, G. Lee, C. Alexiou, R. Tietze, Functionalization of T lymphocytes for magnetically controlled immune therapy: selection of suitable superparamagnetic iron oxide nanoparticles, Journal of Magnetism and Magnetic Materials 473 (2019) 61-67.

[8] D. Ye, Y. Li, N. Gu, Magnetic labeling of natural lipid encapsulations withiron-based nanoparticles, Nano Research (2018) 1-22.

[9] S. Arsalani, E.J. Guidelli, M.A. Silveira, C.E. Salmon, J.F. Araujo, A.C. Bruno, O. Baffa, Magnetic Fe3O4 nanoparticles coated by natural rubber latex as MRI contrast agent, Journal of Magnetism and Magnetic Materials 475 (2019) 458-464.

[10] W. Li, G.-C. Fan, F. Gao, Y. Cui, W. Wang, X. Luo, High-activity Fe3O4 nanozyme as signal amplifier: A simple, low-cost but efficient strategy for ultrasensitive photoelectrochemical immunoassay, Biosensors and Bioelectronics 127 (2019) 64-71.

[11] W. Wu, Z. Wu, T. Yu, C. Jiang, W.-S. Kim, Recent progress on magnetic iron oxide nanoparticles: synthesis, surface functional strategies and biomedical applications, Science and technology of advanced materials 16(2) (2015) 023501.

[12] A. García, R. Espinosa, L. Delgado, E. Casals, E. González, V. Puntes, C. Barata, X. Font, A. Sánchez, Acute toxicity of cerium oxide, titanium oxide and iron oxide nanoparticles using standardized tests, Desalination 269(1-3) (2011) 136-141.

[13] M. Yusefi, K. Shameli, O.S. Yee, S.-Y. Teow, Z. Hedayatnasab, H. Jahangirian, T.J. Webster, K. Kuča, Green synthesis of Fe3O4 nanoparticles stabilized by a

Garcinia mangostana fruit peel extract for hyperthermia and anticancer activities, International Journal of Nanomedicine 16 (2021) 2515.
[14] M. Yusefi, K. Shameli, R.R. Ali, S.-W. Pang, S.-Y. Teow, Evaluating anticancer activity of plant-mediated synthesized iron oxide nanoparticles using Punica granatum fruit peel extract, J. Mol. Struct. 1204 (2020) 127539.
[15] M. Yusefi, M.S. Lee-Kiun, K. Shameli, S.-Y. Teow, R.R. Ali, K.-K. Siew, H.-Y. Chan, M.M.-T. Wong, W.-L. Lim, K. Kuča, 5-fluorouracil loaded magnetic cellulose bionanocomposites for potential colorectal cancer treatment, Carbohydrate Polymers (2021) 118523.
[16] M. Yusefi, H.-Y. Chan, S.-Y. Teow, P. Kia, M. Lee-Kiun Soon, N.A.B.C. Sidik, K. Shameli, 5-Fluorouracil Encapsulated Chitosan-Cellulose Fiber Bionanocomposites: Synthesis, Characterization and In Vitro Analysis towards Colorectal Cancer Cells, Nanomaterials 11(7) (2021) 1691.
[17] K.D. Sirdeshpande, A. Sridhar, K.M. Cholkar, R. Selvaraj, Structural characterization of mesoporous magnetite nanoparticles synthesized using the leaf extract of Calliandra haematocephala and their photocatalytic degradation of malachite green dye, Applied Nanoscience (2018) 1-9.
[18] Z. Izadiyan, K. Shameli, M. Miyake, H. Hara, S.E.B. Mohamad, K. Kalantari, S.H.M. Taib, E. Rasouli, Cytotoxicity assay of plant-mediated synthesized iron oxide nanoparticles using Juglans regia green husk extract, Arabian Journal of Chemistry (2018).
[19] G. Sathishkumar, V. Logeshwaran, S. Sarathbabu, P.K. Jha, M. Jeyaraj, C. Rajkuberan, N. Senthilkumar, S. Sivaramakrishnan, Green synthesis of magnetic Fe3O4 nanoparticles using Couroupita guianensis Aubl. fruit extract for their antibacterial and cytotoxicity activities, Artificial cells, nanomedicine, and biotechnology 46(3) (2018) 589-598.
[20] V. Niraimathee, V. Subha, R.E. Ravindran, S. Renganathan, Green synthesis of iron oxide nanoparticles from Mimosa pudica root extract, International Journal of Environment and Sustainable Development 15(3) (2016) 227-240.
[21] A. Khataee, B. Kayan, D. Kalderis, A. Karimi, S. Akay, M. Konsolakis, Ultrasound-assisted removal of Acid Red 17 using nanosized Fe3O4-loaded coffee waste hydrochar, Ultrasonics sonochemistry 35 (2017) 72-80.
[22] Y.P. Yew, K. Shameli, M. Miyake, N. Kuwano, N.B.B.A. Khairudin, S.E.B. Mohamad, K.X. Lee, Green synthesis of magnetite (Fe 3 O 4) nanoparticles using seaweed (Kappaphycus alvarezii) extract, Nanoscale research letters 11(1) (2016) 276.
[23] S. Venkateswarlu, B.N. Kumar, C. Prasad, P. Venkateswarlu, N. Jyothi, Bio-inspired green synthesis of Fe3O4 spherical magnetic nanoparticles using Syzygium cumini seed extract, Physica B: Condensed Matter 449 (2014) 67-71.
[24] M.F. Horst, D.F. Coral, M.B.F. van Raap, M. Alvarez, V. Lassalle, Hybrid nanomaterials based on gum Arabic and magnetite for hyperthermia treatments, Materials Science and Engineering: C 74 (2017) 443-450.
[25] M. Yusefi, K. Shameli, Z. Hedayatnasab, S.-Y. Teow, U.N. Ismail, C.A. Azlan, R.R. Ali, Green synthesis of Fe 3 O 4 nanoparticles for hyperthermia, magnetic resonance imaging and 5-fluorouracil carrier in potential colorectal cancer treatment, Research on Chemical Intermediates 47(5) (2021) 1789-1808.
[26] W. Suttirak, S. Manurakchinakorn, In vitro antioxidant properties of mangosteen peel extract, J. Food Sci. Technol. 51(12) (2014) 3546-3558.

[27] D. Tungmunnithum, A. Thongboonyou, A. Pholboon, A. Yangsabai, Flavonoids and other phenolic compounds from medicinal plants for pharmaceutical and medical aspects: An overview, Medicines 5(3) (2018) 93.
[28] M. Çam, N.C. İçyer, F. Erdoğan, Pomegranate peel phenolics: microencapsulation, storage stability and potential ingredient for functional food development, LWT-Food Science and Technology 55(1) (2014) 117-123.
[29] P. Pan-In, S. Wanichwecharungruang, J. Hanes, A.J. Kim, Cellular trafficking and anticancer activity of Garcinia mangostana extract-encapsulated polymeric nanoparticles, International journal of nanomedicine 9 (2014) 3677.
[30] A. Masci, A. Coccia, E. Lendaro, L. Mosca, P. Paolicelli, S. Cesa, Evaluation of different extraction methods from pomegranate whole fruit or peels and the antioxidant and antiproliferative activity of the polyphenolic fraction, Food chemistry 202 (2016) 59-69.
[31] H. Guo, D. Zhang, Q. Fu, Inhibition of cervical cancer by promoting IGFBP7 expression using ellagic acid from pomegranate peel, Medical science monitor: international medical journal of experimental and clinical research 22 (2016) 4881.
[32] Y. Deng, Y. Li, F. Yang, A. Zeng, S. Yang, Y. Luo, Y. Zhang, Y. Xie, T. Ye, Y. Xia, The extract from Punica granatum (pomegranate) peel induces apoptosis and impairs metastasis in prostate cancer cells, Biomedicine & Pharmacotherapy 93 (2017) 976-984.
[33] G.-Z. Ma, C.-M. Wang, L. Li, N. Ding, X.-L. Gao, Effect of pomegranate peel polyphenols on human prostate cancer PC-3 cells in vivo, Food Science and Biotechnology 24(5) (2015) 1887-1892.
[34] O. Orgil, E. Schwartz, L. Baruch, I. Matityahu, J. Mahajna, R. Amir, The antioxidative and anti-proliferative potential of non-edible organs of the pomegranate fruit and tree, LWT-Food Science and Technology 58(2) (2014) 571-577.
[35] N.D. Kim, R. Mehta, W. Yu, I. Neeman, T. Livney, A. Amichay, D. Poirier, P. Nicholls, A. Kirby, W. Jiang, Chemopreventive and adjuvant therapeutic potential of pomegranate (Punica granatum) for human breast cancer, Breast cancer research and treatment 71(3) (2002) 203-217.
[36] M. Dikmen, N. Ozturk, Y. Ozturk, The antioxidant potency of Punica granatum L. Fruit peel reduces cell proliferation and induces apoptosis on breast cancer, Journal of Medicinal Food 14(12) (2011) 1638-1646.
[37] H. Moreira, A. Slezak, A. Szyjka, J. Oszmianski, K. Gasiorowski, ANTIOXIDANT AND CANCER CHEMOPREVENTIVE ACTIVITIES OF CISTUS AND POMEGRANATE POLYPHENOLS, Acta poloniae pharmaceutica 74(2) (2017) 688-698.
[38] A.B. Shirode, P. Kovvuru, S.V. Chittur, S.M. Henning, D. Heber, R. Reliene, Antiproliferative effects of pomegranate extract in MCF-7 breast cancer cells are associated with reduced DNA repair gene expression and induction of double strand breaks, Molecular carcinogenesis 53(6) (2014) 458-470.
[39] Y. Li, T. Ye, F. Yang, M. Hu, L. Liang, H. He, Z. Li, A. Zeng, Y. Li, Y. Yao, Punica granatum (pomegranate) peel extract exerts potent antitumor and anti-metastasis activity in thyroid cancer, RSC Advances 6(87) (2016) 84523-84535.

[40] A. Ali, P. Garg, R. Goyal, G. Kaur, X. Li, P. Negi, M. Valis, K. Kuca, S. Kulshrestha, A Novel Herbal Hydrogel Formulation of Moringa oleifera for Wound Healing, Plants 10(1) (2021) 25.
[41] Y. Gao, X. Guo, Y. Liu, Z. Fang, M. Zhang, R. Zhang, L. You, T. Li, R.H. Liu, A full utilization of rice husk to evaluate phytochemical bioactivities and prepare cellulose nanocrystals, Scientific reports 8(1) (2018) 1-8.
[42] E. Derman, R. Abdulla, H. Marbawi, M.K. Sabullah, Oil palm empty fruit bunches as a promising feedstock for bioethanol production in Malaysia, Renewable energy 129 (2018) 285-298.
[43] N. Hastuti, K. Kanomata, T. Kitaoka, Hydrochloric acid hydrolysis of pulps from oil palm empty fruit bunches to produce cellulose nanocrystals, Journal of Polymers and the Environment 26(9) (2018) 3698-3709.
[44] C.J. Wijaya, S. Ismadji, S. Gunawan, A Review of Lignocellulosic-Derived Nanoparticles for Drug Delivery Applications: Lignin Nanoparticles, Xylan Nanoparticles, and Cellulose Nanocrystals, Molecules 26(3) (2021) 676.
[45] W. Long, H. Ouyang, C. Zhou, W. Wan, S. Yu, K. Qian, M. Liu, X. Zhang, Y. Feng, Y. Wei, Simultaneous surface functionalization and drug loading: A novel method for fabrication of cellulose nanocrystals-based pH responsive drug delivery system, International Journal of Biological Macromolecules (2021).
[46] L.E. Low, L.T.-H. Tan, B.-H. Goh, B.T. Tey, B.H. Ong, S.Y. Tang, Magnetic cellulose nanocrystal stabilized Pickering emulsions for enhanced bioactive release and human colon cancer therapy, International journal of biological macromolecules 127 (2019) 76-84.
[47] C.-E. Iurciuc-Tincu, M.S. Cretan, V. Purcar, M. Popa, O.M. Daraba, L.I. Atanase, L. Ochiuz, Drug delivery system based on pH-sensitive biocompatible poly (2-vinyl pyridine)-b-poly (ethylene oxide) nanomicelles loaded with curcumin and 5-fluorouracil, Polymers 12(7) (2020) 1450.
[48] T. He, W. Wang, B. Chen, J. Wang, Q. Liang, B. Chen, 5-Fluorouracil monodispersed chitosan microspheres: Microfluidic chip fabrication with crosslinking, characterization, drug release and anticancer activity, Carbohydrate polymers 236 (2020) 116094.
[49] R. Parhi, Drug delivery applications of chitin and chitosan: a review, Environmental Chemistry Letters 18(3) (2020) 577-594.
[50] F. Wang, Q. Zhang, K. Huang, J. Li, K. Wang, K. Zhang, X. Tang, Preparation and characterization of carboxymethyl cellulose containing quaternized chitosan for potential drug carrier, International journal of biological macromolecules 154 (2020) 1392-1399.
[51] D. Mohan, N.F. Khairullah, Y.P. How, M.S. Sajab, H. Kaco, 3D Printed Laminated CaCO3-Nanocellulose Films as Controlled-Release 5-Fluorouracil, Polymers 12(4) (2020) 986.
[52] G.M.N. Ntoutoume, R. Granet, J.P. Mbakidi, F. Brégier, D.Y. Léger, C. Fidanzi-Dugas, V. Lequart, N. Joly, B. Liagre, V. Chaleix, Development of curcumin–cyclodextrin/cellulose nanocrystals complexes: new anticancer drug delivery systems, Bioorganic & Medicinal Chemistry Letters 26(3) (2016) 941-945.
[53] U. Ruman, K. Buskaran, G. Pastorin, M.J. Masarudin, S. Fakurazi, M.Z. Hussein, Synthesis and characterization of chitosan-based nanodelivery systems to enhance the anticancer effect of sorafenib drug in hepatocellular carcinoma and colorectal adenocarcinoma cells, Nanomaterials 11(2) (2021) 497.

[54] T.S. Anirudhan, J. Christa, Multi-polysaccharide based stimuli responsive polymeric network for the in vitro release of 5-fluorouracil and levamisole hydrochloride, New Journal of Chemistry 41(20) (2017) 11979-11990.
[55] M.A. Mohammed, J. Syeda, K.M. Wasan, E.K. Wasan, An overview of chitosan nanoparticles and its application in non-parenteral drug delivery, Pharmaceutics 9(4) (2017) 53.
[56] R. Hoogenboom, Temperature-responsive polymers: properties, synthesis, and applications, Smart Polymers and their Applications, Elsevier2019, pp. 13-44.
[57] Y.P. Yew, K. Shameli, S.E.B. Mohamad, Y. Nagao, S.-Y. Teow, K.X. Lee, E.D.M. Isa, Potential anticancer activity of protocatechuic acid loaded in montmorillonite/Fe3O4 nanocomposites stabilized by seaweed Kappaphycus alvarezii, Int. J. Pharm. 572 (2019) 118743.
[58] Y. Oh, N. Lee, H.W. Kang, J. Oh, In vitro study on apoptotic cell death by effective magnetic hyperthermia with chitosan-coated MnFe2O4, Nanotechnology 27(11) (2016) 115101.
[59] M. Soleymani, S. Khalighfard, S. Khodayari, H. Khodayari, M.R. Kalhori, M.R. Hadjighassem, Z. Shaterabadi, A.M. Alizadeh, Effects of multiple injections on the efficacy and cytotoxicity of folate-targeted magnetite nanoparticles as theranostic agents for MRI detection and magnetic hyperthermia therapy of tumor cells, Scientific reports 10(1) (2020) 1-14.
[60] Y. Iqbal, H. Bae, I. Rhee, S. Hong, Control of the saturation temperature in magnetic heating by using polyethylene-glycol-coated rod-shaped nickel-ferrite (NiFe 2 O 4) nanoparticles, Journal of the Korean Physical Society 68(4) (2016) 587-592.
[61] B. Lahiri, T. Muthukumaran, J. Philip, Magnetic hyperthermia in phosphate coated iron oxide nanofluids, Journal of Magnetism and Magnetic Materials 407 (2016) 101-113.
[62] Y. Iqbal, H. Bae, I. Rhee, S. Hong, Magnetic heating of silica-coated manganese ferrite nanoparticles, Journal of Magnetism and Magnetic Materials 409 (2016) 80-86.
[63] A. Hanini, L. Lartigue, J. Gavard, K. Kacem, C. Wilhelm, F. Gazeau, F. Chau, S. Ammar, Zinc substituted ferrite nanoparticles with Zn0. 9Fe2. 1O4 formula used as heating agents for in vitro hyperthermia assay on glioma cells, Journal of Magnetism and Magnetic Materials 416 (2016) 315-320.
[64] R. Gupta, D. Sharma, Biofunctionalization of magnetite nanoparticles with stevioside: effect on the size and thermal behaviour for use in hyperthermia applications, International Journal of Hyperthermia (2019).
[65] R. Gupta, D. Sharma, Manganese-doped magnetic nanoclusters for hyperthermia and photothermal glioblastoma therapy, ACS Applied Nano Materials 3(2) (2020) 2026-2037.
[66] G.N. Rego, M.P. Nucci, J.B. Mamani, F.A. Oliveira, L.C. Marti, I.S. Filgueiras, J.M. Ferreira, C.C. Real, D.d.P. Faria, P.L. Espinha, Therapeutic efficiency of multiple applications of magnetic hyperthermia technique in glioblastoma using aminosilane coated iron oxide nanoparticles: in vitro and in vivo study, International journal of molecular sciences 21(3) (2020) 958.
[67] R. Patil, N. Thorat, P. Shete, S. Otari, B. Tiwale, S. Pawar, In vitro hyperthermia with improved colloidal stability and enhanced SAR of magnetic core/shell nanostructures, Materials Science and Engineering: C 59 (2016) 702-709.

[68] P. Boyle, B. Levin, World cancer report 2008, IARC Press, International Agency for Research on Cancer2008.
[69] H. Jahangirian, K. Kalantari, Z. Izadiyan, R. Rafiee-Moghaddam, K. Shameli, T.J. Webster, A review of small molecules and drug delivery applications using gold and iron nanoparticles, International journal of nanomedicine 14 (2019) 1633.
[70] K.N.M. Nawawi, N.M. Mokhtar, Z. Wong, Z.A.M. Azman, D.C.H. Chew, R. Rehir, J. Leong, F. Ismail, I.M. Rose, Y. Yaacob, Incidence and clinicopathological features of colorectal cancer among multi-ethnic patients in Kuala Lumpur, Malaysia: a hospital-based retrospective analysis over two decades, PeerJ 9 (2021) e12425.
[71] S.-W. Wong, D.-Y. Ling, R.-Q. Yeow, R.-W. Chong, M.R.A. Aziz, N.A. Aziz, K.-S. Poh, A.C. Roslani, Clinicopathological patterns and survival outcomes of colorectal cancer among young adults in Malaysia: an institutional cohort study, Singapore Med J 1 (2021) 18.
[72] T.S. Anirudhan, Binusreejayan, S.R. Rejeena, Synthesis and characterization of chitosan based multilayer and pH sensitive co-polymeric system for the targeted delivery of 5-fluorouracil, an in vitro study, International Journal of Polymeric Materials and Polymeric Biomaterials 63(11) (2014) 539-548.
[73] Z. Hedayatnasab, A. Dabbagh, F. Abnisa, W.M.A.W. Daud, Polycaprolactone-coated superparamagnetic iron oxide nanoparticles for in vitro magnetic hyperthermia therapy of cancer, European Polymer Journal 133 (2020) 109789.
[74] M. Yusefi, K. Shameli, Z. Hedayatnasab, S.-Y. Teow, U.N. Ismail, C.A. Azlan, R. Rasit Ali, Green synthesis of Fe3O4 nanoparticles for hyperthermia, magnetic resonance imaging and 5-fluorouracil carrier in potential colorectal cancer treatment, Research on Chemical Intermediates 47(5) (2021) 1789-1808.
[75] R. Kavkhani, A. Hajalilou, E. Abouzari-Lotf, L.P. Ferreira, M.M. Cruz, M. Yusefi, E. Parvini, A.B. Ogholbeyg, U.N. Ismail, CTAB assisted synthesis of MnFe2O4@ SiO2 nanoparticles for magnetic hyperthermia and MRI application, Materials Today Communications 31 (2022) 103412.
[76] A.S. Lübbe, C. Bergemann, H. Riess, F. Schriever, P. Reichardt, K. Possinger, M. Matthias, B. Dörken, F. Herrmann, R. Gürtler, Clinical experiences with magnetic drug targeting: a phase I study with 4′-epidoxorubicin in 14 patients with advanced solid tumors, Cancer Res. 56(20) (1996) 4686-4693.
[77] M. Yusefi, K. Shameli, S.N.A.M. Sukri, Magnetic Nanoparticles In Hyperthermia Therapy: A Mini-Review, Journal of Research in Nanoscience and Nanotechnology 2(1) (2021) 51-60.
[78] Z. Izadiyan, K. Shameli, S.-Y. Teow, M. Yusefi, P. Kia, E. Rasouli, M.A. Tareq, Anticancer Activity of 5-Fluorouracil-Loaded Nanoemulsions Containing Fe3O4/Au Core-Shell Nanoparticles, J. Mol. Struct. (2021) 131075.
[79] M.J. Stolt, Z.-A. Li, B. Phillips, D. Song, N. Mathur, R.E. Dunin-Borkowski, S. Jin, Selective chemical vapor deposition growth of cubic FeGe nanowires that support stabilized magnetic skyrmions, Nano letters 17(1) (2017) 508-514.
[80] N. Mathur, M.J. Stolt, K. Niitsu, X. Yu, D. Shindo, Y. Tokura, S. Jin, Electron Holography and Magnetotransport Measurements Reveal Stabilized Magnetic Skyrmions in Fe1–x Co x Si Nanowires, ACS nano 13(7) (2019) 7833-7841.
[81] D. Farhanian, G. De Crescenzo, J.R. Tavares, Large-scale encapsulation of magnetic iron oxide nanoparticles via syngas photo-initiated chemical vapor deposition, Scientific reports 8(1) (2018) 1-11.

[82] S.L. Arias, A. Shetty, J. Devorkin, J.-P. Allain, Magnetic targeting of smooth muscle cells in vitro using a magnetic bacterial cellulose to improve cell retention in tissue-engineering vascular grafts, Acta biomaterialia 77 (2018) 172-181.
[83] M. Siddiqui, S. Nizamuddin, H.A. Baloch, N. Mubarak, D.K. Dumbre, A.M. Asiri, A. Bhutto, M. Srinivasan, G. Griffin, Synthesis of magnetic carbon nanocomposites by hydrothermal carbonization and pyrolysis, Environmental Chemistry Letters 16(3) (2018) 821-844.
[84] T. Kumeria, S. Maher, Y. Wang, G. Kaur, L. Wang, M. Erkelens, P. Forward, M.F. Lambert, A. Evdokiou, D. Losic, Naturally derived Iron oxide nanowires from Bacteria for magnetically triggered drug release and Cancer hyperthermia in 2D and 3D culture environments: Bacteria biofilm to potent Cancer therapeutic, Biomacromolecules 17(8) (2016) 2726-2736.
[85] T. Shanmugasundaram, M. Radhakrishnan, A. Poongodi, K. Kadirvelu, R. Balagurunathan, Bio-inspired synthesis of superparamagnetic iron oxide nanoparticles for enhanced in vitro anticancer therapy, MRS Communications 8(2) (2018) 604-609.
[86] Y.P. Yew, K. Shameli, M. Miyake, N.B.B.A. Khairudin, S.E.B. Mohamad, T. Naiki, K.X. Lee, Green biosynthesis of superparamagnetic magnetite Fe3O4 nanoparticles and biomedical applications in targeted anticancer drug delivery system: A review, Arabian Journal of Chemistry 13(1) (2020) 2287-2308.
[87] M. Yusefi, O.S. Yee, K. Shameli, Bio-mediated production and characterisation of magnetic nanoparticles using fruit peel extract, Journal of Research in Nanoscience and Nanotechnology 1(1) (2021) 53-61.
[88] X. Gao, N. Yokota, H. Oda, S. Tanaka, K. Hokamoto, P. Chen, One step preparation of Fe–FeO–graphene nanocomposite through pulsed wire discharge, Crystals 8(2) (2018) 104.
[89] T.K.O. Vuong, T.T. Le, H.D. Do, X.T. Nguyen, X.C. Nguyen, T.T. Vu, T.L. Le, PMAO-assisted thermal decomposition synthesis of high-stability ferrofluid based on magnetite nanoparticles for hyperthermia and MRI applications, Materials Chemistry and Physics 245 (2020) 122762.
[90] J.s.A. Fuentes-García, A. Carvalho Alavarse, A.C. Moreno Maldonado, A. Toro-Córdova, M.R. Ibarra, G.F.n. Goya, Simple Sonochemical Method to Optimize the Heating Efficiency of Magnetic Nanoparticles for Magnetic Fluid Hyperthermia, ACS omega 5(41) (2020) 26357-26364.
[91] S.J. Arteaga-Díaz, S.I. Meramo-Hurtado, J. León-Pulido, A. Zuorro, A.D. González-Delgado, Environmental assessment of large scale production of magnetite (Fe3O4) nanoparticles via coprecipitation, Applied Sciences 9(8) (2019) 1682.
[92] A. Esmaeilkhanian, F. Sharifianjazi, N. Parvin, M.A. Koti, Cytotoxicity of Thermoresponsive Core/Shell NixCo1-xFe2O4/PEG Nanoparticles Synthesized by Sol-gel Method, Journal of Physics D: Applied Physics (2021).
[93] D. Karoblis, A. Zarkov, K. Mazeika, D. Baltrunas, G. Niaura, A. Beganskiene, A. Kareiva, Sol-gel synthesis, structural, morphological and magnetic properties of BaTiO3–BiMnO3 solid solutions, Ceramics International 46(10) (2020) 16459-16464.
[94] A. Chauhan, S. Midha, R. Kumar, R. Meena, P. Singh, S.K. Jha, B.K. Kuanr, Rapid tumor inhibition via magnetic hyperthermia regulated by caspase 3 with

time-dependent clearance of iron oxide nanoparticles, Biomaterials science 9(8) (2021) 2972-2990.
[95] R. Kumar, A. Chauhan, S.K. Jha, B.K. Kuanr, Localized cancer treatment by radio-frequency hyperthermia using magnetic nanoparticles immobilized on graphene oxide: from novel synthesis to in vitro studies, Journal of Materials Chemistry B 6(33) (2018) 5385-5399.
[96] M. Asgari, M. Soleymani, T. Miri, A. Barati, Design of thermosensitive polymer-coated magnetic mesoporous silica nanocomposites with a core-shell-shell structure as a magnetic/temperature dual-responsive drug delivery vehicle, Polymers for Advanced Technologies (2021).
[97] A. Manohar, C. Krishnamoorthi, C. Pavithra, N. Thota, Magnetic Hyperthermia and Photocatalytic Properties of MnFe 2 O 4 Nanoparticles Synthesized by Solvothermal Reflux Method, Journal of Superconductivity and Novel Magnetism 34(1) (2021) 251-259.
[98] S.M. Fotukian, A. Barati, M. Soleymani, A.M. Alizadeh, Solvothermal synthesis of CuFe2O4 and Fe3O4 nanoparticles with high heating efficiency for magnetic hyperthermia application, Journal of Alloys and Compounds 816 (2020) 152548.
[99] G. Fracasso, P. Ghigna, L. Nodari, S. Agnoli, D. Badocco, P. Pastore, E. Nicolato, P. Marzola, D. Mihajlović, M. Markovic, Nanoaggregates of iron poly-oxo-clusters obtained by laser ablation in aqueous solution of phosphonates, Journal of colloid and interface science 522 (2018) 208-216.
[100] E. Fazio, M. Santoro, G. Lentini, D. Franco, S.P.P. Guglielmino, F. Neri, Iron oxide nanoparticles prepared by laser ablation: Synthesis, structural properties and antimicrobial activity, Colloids and Surfaces A: Physicochemical and Engineering Aspects 490 (2016) 98-103.
[101] S. Shaw, J. Kailashiya, A. Gangwar, S. Alla, S.K. Gupta, C. Prajapat, S.S. Meena, D. Dash, P. Maiti, N. Prasad, γ-Fe2O3 Nanoflowers as efficient Magnetic Hyperthermia and Photothermal agent, Applied Surface Science (2021) 150025.
[102] K. Kombaiah, J.J. Vijaya, L.J. Kennedy, M. Bououdina, B. Al-Najar, Conventional and microwave combustion synthesis of optomagnetic CuFe2O4 nanoparticles for hyperthermia studies, Journal of Physics and Chemistry of Solids 115 (2018) 162-171.
[103] M. Salvador, G. Gutiérrez, S. Noriega, A. Moyano, M.C. Blanco-López, M. Matos, Microemulsion Synthesis of Superparamagnetic Nanoparticles for Bioapplications, International Journal of Molecular Sciences 22(1) (2021) 427.
[104] J. Nayeem, M.A.A. Al-Bari, M. Mahiuddin, M.A. Rahman, O.T. Mefford, H. Ahmad, M.M. Rahman, Silica coating of iron oxide magnetic nanoparticles by reverse microemulsion method and their functionalization with cationic polymer P (NIPAm-co-AMPTMA) for antibacterial vancomycin immobilization, Colloids and Surfaces A: Physicochemical and Engineering Aspects 611 (2021) 125857.
[105] M.A. Dheyab, A.A. Aziz, M.S. Jameel, O.A. Noqta, P.M. Khaniabadi, B. Mehrdel, Excellent relaxivity and X-ray attenuation combo properties of Fe3O4@ Au CSNPs produced via Rapid sonochemical synthesis for MRI and CT imaging, Materials Today Communications 25 (2020) 101368.
[106] M. Solzi, F. Cugini, N.S. Amade, C. Frigeri, G. Attolini, N.N. Musayeva, A.B. Huseynov, S.H. Abdullayeva, C.A. Sultanov, High-temperature magnetic coercivity of CNTs filled with multi-phase Fe-based nanoparticles, Journal of Magnetism and Magnetic Materials 496 (2020) 165917.

[107] L. Mohammed, H.G. Gomaa, D. Ragab, J. Zhu, Magnetic nanoparticles for environmental and biomedical applications: A review, Particuology 30 (2017) 1-14.
[108] F. Afinjuomo, S. Abdella, S.H. Youssef, Y. Song, S. Garg, Inulin and its application in drug delivery, Pharmaceuticals 14(9) (2021) 855.
[109] N. Kaur, A.K. Gupta, Applications of inulin and oligofructose in health and nutrition, J. Biosci. (Bangalore) 27(7) (2002) 703-714.
[110] L.O. Souza, O.A. Lessa, M.C. Dias, G.H.D. Tonoli, D.V.B. Rezende, M.A. Martins, I.C.O. Neves, J.V. de Resende, E.E.N. Carvalho, E.V.d.B.V. Boas, Study of morphological properties and rheological parameters of cellulose nanofibrils of cocoa shell (Theobroma cacao L.), Carbohydrate polymers 214 (2019) 152-158.
[111] A. Blanco, M.C. Monte, C. Campano, A. Balea, N. Merayo, C. Negro, Nanocellulose for industrial use: Cellulose nanofibers (CNF), cellulose nanocrystals (CNC), and bacterial cellulose (BC), Handbook of nanomaterials for industrial applications, Elsevier2018, pp. 74-126.
[112] N. Lin, A. Dufresne, Nanocellulose in biomedicine: Current status and future prospect, European Polymer Journal 59 (2014) 302-325.
[113] M. Yusefi, R. Bte Rasit Ali, E.C. Abdullah, K. Shameli, Analysis on Physiochemical Properties of Cellulose Fiber from Rice Straw Waste, MS&E 808(1) (2020) 012038.
[114] M. Kaushik, A. Moores, nanocelluloses as versatile supports for metal nanoparticles and their applications in catalysis, Green Chem. 18(3) (2016) 622-637.
[115] P.K. Gupta, S.S. Raghunath, D.V. Prasanna, P. Venkat, V. Shree, C. Chithananthan, S. Choudhary, K. Surender, K. Geetha, An update on overview of cellulose, its structure and applications, Cellulose, IntechOpen2019.
[116] Y. Li, H. Sun, Y. Zhang, M. Xu, S.Q. Shi, The three-dimensional heterostructure synthesis of ZnO/cellulosic fibers and its application for rubber composites, Composites Science and Technology 177 (2019) 10-17.
[117] K.Y. Lee, G. Buldum, A. Mantalaris, A. Bismarck, More than meets the eye in bacterial cellulose: biosynthesis, bioprocessing, and applications in advanced fiber composites, Macromol. Biosci. 14(1) (2014) 10-32.
[118] A.B. Seabra, J.S. Bernardes, W.J. Fávaro, A.J. Paula, N. Durán, Cellulose nanocrystals as carriers in medicine and their toxicities: A review, Carbohydrate polymers 181 (2018) 514-527.
[119] M. Österberg, E.D. Cranston, Special issue on nanocellulose, Nordic Pulp & Paper Research Journal 29(1) (2014).
[120] L.A. Nor, A. Ishak, Extraction and Characterization of Nano cellulose from Coconut Fiber, Malaysian Journal of Analytical Sciences 17(1) (2013) 109-118.
[121] B.M. Cherian, A.L. Leão, S.F. De Souza, S. Thomas, L.A. Pothan, M. Kottaisamy, Isolation of nanocellulose from pineapple leaf fibres by steam explosion, Carbohydrate polymers 81(3) (2010) 720-725.
[122] P. Satyamurthy, N. Vigneshwaran, A novel process for synthesis of spherical nanocellulose by controlled hydrolysis of microcrystalline cellulose using anaerobic microbial consortium, Enzyme and microbial technology 52(1) (2013) 20-25.

[123] J.P.S. Morais, M. de Freitas Rosa, L.D. Nascimento, D.M. do Nascimento, A.R. Cassales, Extraction and characterization of nanocellulose structures from raw cotton linter, Carbohydrate polymers 91(1) (2013) 229-235.
[124] N. Johari, I. Ahmad, N. Halib, Comparison Study ofHydrogels Properties Synthesized with Micro-andNano-Size Bacterial Cellulose Particles Extracted from Nata de coco, Chemical and biochemical engineering quarterly 26(4) (2012) 399-404.
[125] J.P. Reddy, J.-W. Rhim, Characterization of bionanocomposite films prepared with agar and paper-mulberry pulp nanocellulose, Carbohydrate Polymers 110 (2014) 480-488.
[126] A. Mandal, D. Chakrabarty, Isolation of nanocellulose from waste sugarcane bagasse (SCB) and its characterization, Carbohydrate Polymers 86(3) (2011) 1291-1299.
[127] N. Lani, N. Ngadi, A. Johari, M. Jusoh, Isolation, characterization, and application of nanocellulose from oil palm empty fruit bunch fiber as nanocomposites, Journal of Nanomaterials 2014 (2014).
[128] S. Jung, B.Y. Swamy, J.B. Moon, D.H. Kim, I. Chung, Anti-AIDS active polyrotaxane-AZT conjugates with bioactive bulky stoppers and their nanoparticles, Journal of Polymer Science Part A: Polymer Chemistry 50(23) (2012) 4895-4901.
[129] M. Yusefi, K. Shameli, A.F. Jumaat, Preparation and properties of magnetic iron oxide nanoparticles for biomedical applications: A brief review, Journal of Advanced Research in Materials Science 75(1) (2020) 10-18.
[130] H. Hamrayev, K. Shameli, M. Yusefi, Preparation of zinc oxide nanoparticles and its cancer treatment effects: A review paper, Journal of Advanced Research in Micro and Nano Engineering 2(1) (2020) 1-11.
[131] S. Srivastava, S. Mohammad, S. Gupta, A.A. Mahdi, R.K. Dixit, V. Singh, F.M. Samadi, Chemoprotective effect of nanocurcumin on 5-fluorouracil-induced-toxicity toward oral cancer treatment, National journal of maxillofacial surgery 9(2) (2018) 160.
[132] A.P. Rokhade, N.B. Shelke, S.A. Patil, T.M. Aminabhavi, Novel hydrogel microspheres of chitosan and pluronic F-127 for controlled release of 5-fluorouracil, J. Microencapsul. 24(3) (2007) 274-288.
[133] Z. Song, E. Chen, J. Qian, J. Xu, G. Cao, W. Zhou, F. Wang, M. Chen, D. Xu, X. Wang, Serum chitinase activity prognosticates metastasis of colorectal cancer, BMC Cancer 19(1) (2019) 629.
[134] L.-K. Zhang, S. Du, X. Wang, Y. Jiao, L. Yin, Y. Zhang, Y.-Q. Guan, Bacterial cellulose based composites enhanced transdermal drug targeting for breast cancer treatment, Chemical Engineering Journal 370 (2019) 749-759.
[135] A.K. HPS, C.K. Saurabh, A. Adnan, M.N. Fazita, M. Syakir, Y. Davoudpour, M. Rafatullah, C. Abdullah, M. Haafiz, R. Dungani, A review on chitosan-cellulose blends and nanocellulose reinforced chitosan biocomposites: Properties and their applications, Carbohydrate polymers 150 (2016) 216-226.
[136] L. Li, T.L. ten Hagen, M. Bolkestein, A. Gasselhuber, J. Yatvin, G.C. van Rhoon, A.M. Eggermont, D. Haemmerich, G.A. Koning, Improved intratumoral nanoparticle extravasation and penetration by mild hyperthermia, J. Control. Release 167(2) (2013) 130-137.

[137] Y. Matsumura, H. Maeda, A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs, Cancer Res. 46(12 Part 1) (1986) 6387-6392.
[138] D. Zheng, Y. Deng, Y. Xia, Y. Nan, M. Peng, X. Wang, J. Yue, Fabrication and Performance of a Spherical Cellulose Nanocrystal-based Hydrophobic Drug Delivery Vehicle using Rubber Wood, BioResources 14(4) (2019) 7763-7774.
[139] K. Abe, H. Yano, Comparison of the characteristics of cellulose microfibril aggregates of wood, rice straw and potato tuber, Cellulose 16(6) (2009) 1017-1023.
[140] T.S. Anirudhan, J. Nima, P.L. Divya, Synthesis, characterization and in vitro cytotoxicity analysis of a novel cellulose based drug carrier for the controlled delivery of 5-fluorouracil, an anticancer drug, Applied Surface Science 355 (2015) 64-73.
[141] J. Supramaniam, R. Adnan, N.H.M. Kaus, R. Bushra, Magnetic nanocellulose alginate hydrogel beads as potential drug delivery system, Int. J. Biol. Macromol. (2018).
[142] S.K. Mallapragada, N.A. Peppas, P. Colombo, Crystal dissolution-controlled release systems. II. Metronidazole release from semicrystalline poly (vinyl alcohol) systems, Journal of Biomedical Materials Research: An Official Journal of The Society for Biomaterials and The Japanese Society for Biomaterials 36(1) (1997) 125-130.
[143] S.F. Plappert, F.W. Liebner, J. Konnerth, J.-M. Nedelec, Anisotropic nanocellulose gel–membranes for drug delivery: Tailoring structure and interface by sequential periodate–chlorite oxidation, Carbohydrate polymers 226 (2019) 115306.
[144] G. Sarkar, J.T. Orasugh, N.R. Saha, I. Roy, A. Bhattacharyya, A.K. Chattopadhyay, D. Rana, D. Chattopadhyay, Cellulose nanofibrils/chitosan based transdermal drug delivery vehicle for controlled release of ketorolac tromethamine, New Journal of Chemistry 41(24) (2017) 15312-15319.
[145] M. Yusefi, K. Shameli, H. Jahangirian, S.-Y. Teow, H. Umakoshi, B. Saleh, R. Rafiee-Moghaddam, T.J. Webster, The Potential Anticancer Activity of 5-Fluorouracil Loaded in Cellulose Fibers Isolated from Rice Straw, International Journal of Nanomedicine 15 (2020) 5417-5432.
[146] Z. Hedayatnasab, F. Abnisa, W.M.A.W. Daud, Review on magnetic nanoparticles for magnetic nanofluid hyperthermia application, Materials & Design 123 (2017) 174-196.
[147] M.A. Agotegaray, V.L. Lassalle, Silica-Coated Magnetic Nanoparticles: An Insight into Targeted Drug Delivery and Toxicology, Springer2017.
[148] A. Salunkhe, V. Khot, S. Patil, S.A. Tofail, J. Bauer, N.D. Thorat, MRI guided magneto-chemotherapy with high-magnetic-moment iron oxide nanoparticles for cancer theranostics, ACS Applied Bio Materials 3(4) (2020) 2305-2313.
[149] N.D. Thorat, R.A. Bohara, S.A. Tofail, Z.A. Alothman, M.J. Shiddiky, M.S. A Hossain, Y. Yamauchi, K.C.W. Wu*, Superparamagnetic Gadolinium Ferrite Nanoparticles with Controllable Curie Temperature–Cancer Theranostics for MR-Imaging-Guided Magneto-Chemotherapy, European Journal of Inorganic Chemistry 2016(28) (2016) 4586-4597.
[150] N. Wang, X. Cheng, N. Li, H. Wang, H. Chen, Nanocarriers and their loading strategies, Advanced healthcare materials 8(6) (2019) 1801002.

[151] A. Dabbagh, Z. Hedayatnasab, H. Karimian, M. Sarraf, C.H. Yeong, H.R. Madaah Hosseini, N.H. Abu Kasim, T.W. Wong, N.A. Rahman, Polyethylene glycol-coated porous magnetic nanoparticles for targeted delivery of chemotherapeutics under magnetic hyperthermia condition, International Journal of Hyperthermia 36(1) (2019) 104-114.
[152] I.O. Wulandari, V.T. Mardila, D.D.H. Santjojo, A. Sabarudin, Preparation and characterization of chitosan-coated Fe3O4 nanoparticles using ex-situ co-precipitation method and tripolyphosphate/sulphate as dual crosslinkers, IOP Conference Series: Materials Science and Engineering, IOP Publishing, 2018, p. 012064.
[153] L. Jiang, F. Chai, Q. Chen, Soft magnetic nanocomposite microgels by in-situ crosslinking of poly acrylic acid onto superparamagnetic magnetite nanoparticles and their applications for the removal of Pb (II) ion, European Polymer Journal 89 (2017) 468-481.
[154] H. Su, X. Han, L. He, L. Deng, K. Yu, H. Jiang, C. Wu, Q. Jia, S. Shan, Synthesis and characterization of magnetic dextran nanogel doped with iron oxide nanoparticles as magnetic resonance imaging probe, International journal of biological macromolecules 128 (2019) 768-774.
[155] N. Malhotra, G. Audira, J.-R. Chen, P. Siregar, H.-S. Hsu, J.-S. Lee, T.-R. Ger, C.-D. Hsiao, Surface modification of magnetic nanoparticles by carbon-coating can increase its biosafety: Evidences from biochemical and neurobehavioral tests in zebrafish, Molecules 25(9) (2020) 2256.
[156] A. Peigneux, F. Oltolina, D. Colangelo, G.R. Iglesias, A.V. Delgado, M. Prat, C. Jimenez-Lopez, Functionalized biomimetic magnetic nanoparticles as effective nanocarriers for targeted chemotherapy, Particle & Particle Systems Characterization 36(6) (2019) 1900057.
[157] S. Ullah, K. Seidel, S. Türkkan, D.P. Warwas, T. Dubich, M. Rohde, H. Hauser, P. Behrens, A. Kirschning, M. Köster, Macrophage entrapped silica coated superparamagnetic iron oxide particles for controlled drug release in a 3D cancer model, Journal of Controlled Release 294 (2019) 327-336.
[158] H.-Y. Cho, T. Lee, J. Yoon, Z. Han, H. Rabie, K.-B. Lee, W.W. Su, J.-W. Choi, Magnetic oleosome as a functional lipophilic drug carrier for cancer therapy, ACS applied materials & interfaces 10(11) (2018) 9301-9309.
[159] Y.-J. Wang, P.-Y. Lin, S.-L. Hsieh, R. Kirankumar, H.-Y. Lin, J.-H. Li, Y.-T. Chen, H.-M. Wu, S. Hsieh, Utilizing Edible Agar as a Carrier for Dual Functional Doxorubicin-Fe3O4 Nanotherapy Drugs, Materials 14(8) (2021) 1824.
[160] E. Christodoulou, M. Nerantzaki, S. Nanaki, P. Barmpalexis, K. Giannousi, C. Dendrinou-Samara, M. Angelakeris, E. Gounari, A.D. Anastasiou, D.N. Bikiaris, Paclitaxel magnetic core–shell nanoparticles based on poly (Lactic acid) semitelechelic novel block copolymers for combined hyperthermia and chemotherapy treatment of cancer, Pharmaceutics 11(5) (2019) 213.
[161] B. Dutta, S. Checker, K. Barick, H. Salunke, V. Gota, P. Hassan, Malic acid grafted Fe3O4 nanoparticles for controlled drug delivery and efficient heating source for hyperthermia therapy, Journal of Alloys and Compounds (2021) 160950.
[162] V. Hovhannisyan, K. Siposova, A. Musatov, S.-J. Chen, Development of multifunctional nanocomposites for controlled drug delivery and hyperthermia, Scientific reports 11(1) (2021) 1-10.

[163] J.-t. Jang, J.W. Jeoung, J.H. Park, W.J. Lee, Y.J. Kim, J. Seon, M. Kim, J. Lee, S.H. Paek, K.H. Park, Effects of Recovery Time during Magnetic Nanofluid Hyperthermia on the Induction Behavior and Efficiency of Heat Shock Proteins 72, Scientific reports 7(1) (2017) 1-9.
[164] J. Kurian, B. Lahiri, M.J. Mathew, J. Philip, High magnetic fluid hyperthermia efficiency in copper ferrite nanoparticles prepared by solvothermal and hydrothermal methods, Journal of Magnetism and Magnetic Materials (2021) 168233.
[165] Z. Ferjaoui, E. Jamal Al Dine, A. Kulmukhamedova, L. Bezdetnaya, C. Soon Chang, R. Schneider, F. Mutelet, D. Mertz, S. Bégin-Colin, F. Quilès, Doxorubicin-loaded thermoresponsive superparamagnetic nanocarriers for controlled drug delivery and magnetic hyperthermia applications, ACS applied materials & interfaces 11(34) (2019) 30610-30620.
[166] X. Yao, X. Niu, K. Ma, P. Huang, J. Grothe, S. Kaskel, Y. Zhu, Graphene quantum dots-capped magnetic mesoporous silica nanoparticles as a multifunctional platform for controlled drug delivery, magnetic hyperthermia, and photothermal therapy, Small 13(2) (2017) 1602225.
[167] B. Chen, J. Xing, M. Li, Y. Liu, M. Ji, DOX@ Ferumoxytol-Medical Chitosan as magnetic hydrogel therapeutic system for effective magnetic hyperthermia and chemotherapy in vitro, Colloids and Surfaces B: Biointerfaces 190 (2020) 110896.
[168] C. Tapeinos, A. Marino, M. Battaglini, S. Migliorin, R. Brescia, A. Scarpellini, C.D.J. Fernández, M. Prato, F. Drago, G. Ciofani, Stimuli-responsive lipid-based magnetic nanovectors increase apoptosis in glioblastoma cells through synergic intracellular hyperthermia and chemotherapy, Nanoscale 11(1) (2019) 72-88.
[169] M. Norouzi, V. Yathindranath, J.A. Thliveris, B.M. Kopec, T.J. Siahaan, D.W. Miller, Doxorubicin-loaded iron oxide nanoparticles for glioblastoma therapy: A combinational approach for enhanced delivery of nanoparticles, Scientific reports 10(1) (2020) 1-18.
[170] R. Mannu, V. Karthikeyan, N. Velu, C. Arumugam, V.A. Roy, A.-I. Gopalan, G. Saianand, P. Sonar, K.-P. Lee, W.-J. Kim, Polyethylene glycol coated magnetic nanoparticles: Hybrid nanofluid formulation, properties and drug delivery prospects, Nanomaterials 11(2) (2021) 440.
[171] A.R.K. Sasikala, A.R. Unnithan, Y.-H. Yun, C.H. Park, C.S. Kim, An implantable smart magnetic nanofiber device for endoscopic hyperthermia treatment and tumor-triggered controlled drug release, Acta Biomater. 31 (2016) 122-133.
[172] M. Radmansouri, E. Bahmani, E. Sarikhani, K. Rahmani, F. Sharifianjazi, M. Irani, Doxorubicin hydrochloride-Loaded electrospun chitosan/cobalt ferrite/titanium oxide nanofibers for hyperthermic tumor cell treatment and controlled drug release, International journal of biological macromolecules 116 (2018) 378-384.
[173] A.R.K. Sasikala, R.G. Thomas, A.R. Unnithan, B. Saravanakumar, Y.Y. Jeong, C.H. Park, C.S. Kim, Multifunctional nanocarpets for cancer theranostics: remotely controlled graphene nanoheaters for thermo-chemosensitisation and magnetic resonance imaging, Scientific reports 6(1) (2016) 1-14.
[174] G.K. Thirunavukkarasu, K. Cherukula, H. Lee, Y.Y. Jeong, I.-K. Park, J.Y. Lee, Magnetic field-inducible drug-eluting nanoparticles for image-guided thermo-chemotherapy, Biomaterials 180 (2018) 240-252.

[175] J.t. Jang, J. Lee, J. Seon, E. Ju, M. Kim, Y.I. Kim, M.G. Kim, Y. Takemura, A.S. Arbab, K.W. Kang, Giant magnetic heat induction of magnesium-doped γ-Fe2O3 superparamagnetic nanoparticles for completely killing tumors, Advanced Materials 30(6) (2018) 1704362.
[176] M.S. Moorthy, S. Bharathiraja, P. Manivasagan, K.D. Lee, J. Oh, Crown ether triad modified core–shell magnetic mesoporous silica nanocarrier for pH-responsive drug delivery and magnetic hyperthermia applications, New Journal of Chemistry 41(19) (2017) 10935-10947.
[177] W. Pon-On, T. Tithito, W. Maneeprakorn, T. Phenrat, I.-M. Tang, Investigation of magnetic silica with thermoresponsive chitosan coating for drug controlled release and magnetic hyperthermia application, Materials Science and Engineering: C 97 (2019) 23-30.
[178] G. Kandasamy, A. Sudame, P. Bhati, A. Chakrabarty, D. Maity, Systematic investigations on heating effects of carboxyl-amine functionalized superparamagnetic iron oxide nanoparticles (SPIONs) based ferrofluids for in vitro cancer hyperthermia therapy, Journal of Molecular Liquids 256 (2018) 224-237.
[179] R. Kumar, A. Chauhan, B.K. Kuanr, A robust in vitro anticancer activity via magnetic hyperthermia mediated by colloidally stabilized mesoporous silica encapsulated La0. 7Sr0. 3MnO3 core-shell structure, Colloids Surf. Physicochem. Eng. Aspects 615 (2021) 126212.
[180] S. He, H. Zhang, Y. Liu, F. Sun, X. Yu, X. Li, L. Zhang, L. Wang, K. Mao, G. Wang, Maximizing specific loss power for magnetic hyperthermia by hard–soft mixed ferrites, Small 14(29) (2018) 1800135.
[181] F. Reyes-Ortega, Á.V. Delgado, E.K. Schneider, B. Checa Fernández, G.R. Iglesias, Magnetic nanoparticles coated with a thermosensitive polymer with hyperthermia properties, Polymers 10(1) (2018) 10.
[182] D. Nieciecka, J. Celej, M. Żuk, A. Majkowska-Pilip, K. Żelechowska-Matysiak, A. Lis, M. Osial, Hybrid system for local drug delivery and magnetic hyperthermia based on SPIONs loaded with doxorubicin and epirubicin, Pharmaceutics 13(4) (2021) 480.
[183] Z. Hedayatnasab, A. Dabbagh, F. Abnisa, W.M.A.W. Daud, Synthesis and In-vitro Characterization of Superparamagnetic Iron Oxide Nanoparticles Using a Sole Precursor for Hyperthermia Therapy, Materials Research Bulletin (2020) 110975.
[184] Z. Hedayatnasab, A. Dabbagh, F. Abnisa, W.M.A.W. Daud, Polycaprolactone-Coated Superparamagnetic Iron Oxide Nanoparticles for In Vitro Magnetic Hyperthermia Therapy of Cancer, European Polymer Journal (2020) 109789.
[185] H.A. Albarqi, L.H. Wong, C. Schumann, F.Y. Sabei, T. Korzun, X. Li, M.N. Hansen, P. Dhagat, A.S. Moses, O. Taratula, Biocompatible nanoclusters with high heating efficiency for systemically delivered magnetic hyperthermia, ACS nano 13(6) (2019) 6383-6395.
[186] K. Parekh, A. Bhardwaj, N. Jain, Preliminary in-vitro investigation of magnetic fluid hyperthermia in cervical cancer cells, Journal of Magnetism and Magnetic Materials 497 (2020) 166057.
[187] F. Oltolina, A. Peigneux, D. Colangelo, N. Clemente, A. D'Urso, G. Valente, G.R. Iglesias, C. Jiménez-Lopez, M. Prat, Biomimetic Magnetite Nanoparticles as

Targeted Drug Nanocarriers and Mediators of Hyperthermia in an Experimental Cancer Model, Cancers 12(9) (2020) 2564.
[188] A. Garanina, I. Kireev, O. Zhironkina, O. Strelkova, A. Shakhov, I. Alieva, V. Davydov, S. Murugesan, V. Khabashesku, A. Majouga, Long-term live cells observation of internalized fluorescent Fe@ C nanoparticles in constant magnetic field, Journal of nanobiotechnology 17(1) (2019) 1-10.
[189] H.S. Huang, J.F. Hainfeld, Intravenous magnetic nanoparticle cancer hyperthermia, International journal of nanomedicine 8 (2013) 2521.
[190] Y. Oh, M.S. Moorthy, P. Manivasagan, S. Bharathiraja, J. Oh, Magnetic hyperthermia and pH-responsive effective drug delivery to the sub-cellular level of human breast cancer cells by modified CoFe2O4 nanoparticles, Biochimie 133 (2017) 7-19.
[191] J.E. Hall, M.E. Hall, Guyton and Hall textbook of medical physiology e-Book, Elsevier Health Sciences2020.
[192] A. Ruiz, Y. Hernandez, C. Cabal, E. Gonzalez, S. Veintemillas-Verdaguer, E. Martinez, M. Morales, Biodistribution and pharmacokinetics of uniform magnetite nanoparticles chemically modified with polyethylene glycol, Nanoscale 5(23) (2013) 11400-11408.
[193] H. Arami, K.M. Krishnan, Intracellular performance of tailored nanoparticle tracers in magnetic particle imaging, Journal of applied physics 115(17) (2014) 17B306.
[194] A. Albanese, P.S. Tang, W.C. Chan, The effect of nanoparticle size, shape, and surface chemistry on biological systems, Annu. Rev. Biomed. Eng. 14 (2012) 1-16.
[195] M. Yu, J. Zheng, Clearance pathways and tumor targeting of imaging nanoparticles, ACS nano 9(7) (2015) 6655-6674.
[196] H.M. El-Zeiny, M.R. Abukhadra, O.M. Sayed, A.H. Osman, S.A. Ahmed, Insight into novel β-cyclodextrin-grafted-poly (N-vinylcaprolactam) nanogel structures as advanced carriers for 5-fluorouracil: Equilibrium behavior and pharmacokinetic modeling, Colloids Surf. Physicochem. Eng. Aspects 586 (2020) 124197.
[197] M. Yusefi, K. Shameli, Z. Hedayatnasab, S.-Y. Teow, U.N. Ismail, C.A. Azlan, R.R. Ali, Green synthesis of Fe 3 O 4 nanoparticles for hyperthermia, magnetic resonance imaging and 5-fluorouracil carrier in potential colorectal cancer treatment, Research on Chemical Intermediates (2021) 1-20.
[198] M. Yusefi, P. Kia, S.N.A.M. Sukri, R.R. Ali, K. Shameli, Synthesis and Properties of Chitosan Nanoparticles CrossLinked with Tripolyphosphate, Journal of Research in Nanoscience and Nanotechnology 3(1) (2021) 46-52.
[199] K. Tao, H. Dou, K. Sun, Facile interfacial coprecipitation to fabricate hydrophilic amine-capped magnetite nanoparticles, Chemistry of materials 18(22) (2006) 5273-5278.
[200] M. Ma, Y. Zhang, W. Yu, H.-y. Shen, H.-q. Zhang, N. Gu, Preparation and characterization of magnetite nanoparticles coated by amino silane, Colloids and Surfaces A: physicochemical and engineering aspects 212(2-3) (2003) 219-226.
[201] D.-L. Zhao, P. Teng, Y. Xu, Q.-S. Xia, J.-T. Tang, Magnetic and inductive heating properties of Fe3O4/polyethylene glycol composite nanoparticles with core–shell structure, Journal of Alloys and Compounds 502(2) (2010) 392-395.

[202] Ç.Ö. Ay, A.S. Özcan, Y. Erdoğan, A. Özcan, Characterization of Punica granatum L. peels and quantitatively determination of its biosorption behavior towards lead (II) ions and Acid Blue 40, Colloids and Surfaces B: Biointerfaces 100 (2012) 197-204.
[203] O. Akinjogunla, N. Asamudo, M. Okon, P. Nya, Fourier Transform Infrared Spectroscopic Analysis, Phytochemical Constituents and Anti-staphylococcal Efficacies of Aqueous Leaf Extracts of Baphia nitida and Annona muricata, Nigerian Journal of Pharmaceutical and Applied Science Research 7(3) 39-46.
[204] T.J.I. Edison, M. Sethuraman, Biogenic robust synthesis of silver nanoparticles using Punica granatum peel and its application as a green catalyst for the reduction of an anthropogenic pollutant 4-nitrophenol, Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 104 (2013) 262-264.
[205] J.R. Franca, M.P. De Luca, T.G. Ribeiro, R.O. Castilho, A.N. Moreira, V.R. Santos, A.A. Faraco, Propolis-based chitosan varnish: drug delivery, controlled release and antimicrobial activity against oral pathogen bacteria, BMC complementary and alternative medicine 14(1) (2014) 478.
[206] H.d.S. Barud, A.M. de Araújo Júnior, S. Saska, L.B. Mestieri, J.A.D.B. Campos, R.M. De Freitas, N.U. Ferreira, A.P. Nascimento, F.G. Miguel, M.M.d.O.L. Vaz, Antimicrobial Brazilian propolis (EPP-AF) containing biocellulose membranes as promising biomaterial for skin wound healing, Evidence-based complementary and alternative medicine 2013 (2013).
[207] A.C. Moţ, R. Silaghi-Dumitrescu, C. Sârbu, Rapid and effective evaluation of the antioxidant capacity of propolis extracts using DPPH bleaching kinetic profiles, FT-IR and UV–vis spectroscopic data, Journal of Food Composition and Analysis 24(4-5) (2011) 516-522.
[208] M. GUTIERREZ-GONÇALVES, M. MARCUCCI, Atividades antimicrobiana e antioxidante da própolis do estado do Ceará, Revista Fitos 4(1) (2009) 81-86.
[209] R.N. Oliveira, M.C. Mancini, F.C.S.d. Oliveira, T.M. Passos, B. Quilty, R.M.d.S.M. Thiré, G.B. McGuinness, FTIR analysis and quantification of phenols and flavonoids of five commercially available plants extracts used in wound healing, Matéria (Rio de Janeiro) 21(3) (2016) 767-779.
[210] Y. Amemiya, A. Arakaki, S.S. Staniland, T. Tanaka, T. Matsunaga, Controlled formation of magnetite crystal by partial oxidation of ferrous hydroxide in the presence of recombinant magnetotactic bacterial protein Mms6, Biomaterials 28(35) (2007) 5381-5389.
[211] C. Sun, J.S. Lee, M. Zhang, Magnetic nanoparticles in MR imaging and drug delivery, Advanced drug delivery reviews 60(11) (2008) 1252-1265.
[212] B.I. Kharisov, H.R. Dias, O.V. Kharissova, A. Vázquez, Y. Pena, I. Gomez, Solubilization, dispersion and stabilization of magnetic nanoparticles in water and non-aqueous solvents: recent trends, RSC Advances 4(85) (2014) 45354-45381.
[213] S. Sisodiya, L.R. Wallenberg, E. Lewin, O.F. Wendt, Sonogashira coupling reaction over supported gold nanoparticles: Influence of support and catalyst synthesis route, Applied Catalysis A: General 503 (2015) 69-76.
[214] L.H. Reddy, J.L. Arias, J. Nicolas, P. Couvreur, Magnetic nanoparticles: design and characterization, toxicity and biocompatibility, pharmaceutical and biomedical applications, Chemical reviews 112(11) (2012) 5818-5878.

[215] A. Kolhatkar, A. Jamison, D. Litvinov, R. Willson, T. Lee, Tuning the magnetic properties of nanoparticles, International journal of molecular sciences 14(8) (2013) 15977-16009.
[216] S. Yu, G.M. Chow, Carboxyl group (–CO 2 H) functionalized ferrimagnetic iron oxide nanoparticles for potential bio-applications, Journal of Materials Chemistry 14(18) (2004) 2781-2786.
[217] U.E. Illangakoon, D.-G. Yu, B.S. Ahmad, N.P. Chatterton, G.R. Williams, 5-Fluorouracil loaded Eudragit fibers prepared by electrospinning, Int. J. Pharm. 495(2) (2015) 895-902.
[218] N. Singh, G.J. Jenkins, R. Asadi, S.H. Doak, Potential toxicity of superparamagnetic iron oxide nanoparticles (SPION), Nano reviews 1(1) (2010) 5358.
[219] I.C. Radu, A. Hudita, C. Zaharia, B. Galateanu, H. Iovu, E. Tanasa, S. Georgiana Nitu, O. Ginghina, C. Negrei, A. Tsatsakis, Poly (3-hydroxybutyrate-CO-3-hydroxyvalerate) PHBHV biocompatible nanocarriers for 5-FU delivery targeting colorectal cancer, Drug delivery 26(1) (2019) 318-327.
[220] M. Hessien, M. Rashad, R. Zaky, E. Abdel-Aal, K. El-Barawy, Controlling the synthesis conditions for silica nanosphere from semi-burned rice straw, Materials science and engineering: B 162(1) (2009) 14-21.
[221] P. Lu, Y.-L. Hsieh, Preparation and characterization of cellulose nanocrystals from rice straw, Carbohydrate Polymers 87(1) (2012) 564-573.
[222] R.-L. Wu, X.-L. Wang, Y.-Z. Wang, X.-C. Bian, F. Li, Cellulose/soy protein isolate blend films prepared via room-temperature ionic liquid, Ind. Eng. Chem. Res. 48(15) (2009) 7132-7136.
[223] W. Chen, H. Yu, Y. Liu, P. Chen, M. Zhang, Y. Hai, Individualization of cellulose nanofibers from wood using high-intensity ultrasonication combined with chemical pretreatments, Carbohydrate Polymers 83(4) (2011) 1804-1811.
[224] X. Chen, J. Yu, Z. Zhang, C. Lu, Study on structure and thermal stability properties of cellulose fibers from rice straw, Carbohydrate polymers 85(1) (2011) 245-250.
[225] F. Jiang, Y.-L. Hsieh, Chemically and mechanically isolated nanocellulose and their self-assembled structures, Carbohydrate polymers 95(1) (2013) 32-40.
[226] A. Basta, V. Fierro, H. El-Saied, A. Celzard, 2-Steps KOH activation of rice straw: an efficient method for preparing high-performance activated carbons, Bioresource technology 100(17) (2009) 3941-3947.
[227] J.P. de Oliveira, G.P. Bruni, K.O. Lima, S.L.M. El Halal, G.S. da Rosa, A.R.G. Dias, E. da Rosa Zavareze, Cellulose fibers extracted from rice and oat husks and their application in hydrogel, Food Chem. 221 (2017) 153-160.
[228] N. Zainuddin, I. Ahmad, H. Kargarzadeh, S. Ramli, Hydrophobic kenaf nanocrystalline cellulose for the binding of curcumin, Carbohydrate polymers 163 (2017) 261-269.
[229] S. Daneshfozoun, M. Abdullah, B. Abdullah, Preparation and characterization of magnetic biosorbent based on oil palm empty fruit bunch fibers, cellulose and Ceiba pentandra for heavy metal ions removal, Industrial Crops and Products 105 (2017) 93-103.
[230] G. Kadry, Comparison between gelatin/carboxymethyl cellulose and gelatin/carboxymethyl nanocellulose in tramadol drug loaded capsule, Heliyon 5(9) (2019) e02404.

[231] K. Zhu, T. Ye, J. Liu, Z. Peng, S. Xu, J. Lei, H. Deng, B. Li, Nanogels fabricated by lysozyme and sodium carboxymethyl cellulose for 5-fluorouracil controlled release, Int. J. Pharm. 441(1-2) (2013) 721-727.
[232] J. Bhandari, H. Mishra, P.K. Mishra, R. Wimmer, F.J. Ahmad, S. Talegaonkar, Cellulose nanofiber aerogel as a promising biomaterial for customized oral drug delivery, International journal of nanomedicine 12 (2017) 2021.
[233] S. Pragati, S. Ashok, S. Kuldeep, Recent advances in periodontal drug delivery systems, International journal of drug delivery 1(1) (2009).
[234] H. Tibolla, F.M. Pelissari, M.I. Rodrigues, F.C. Menegalli, Cellulose nanofibers produced from banana peel by enzymatic treatment: Study of process conditions, Industrial crops and products 95 (2017) 664-674.
[235] A. Kadam, R.G. Saratale, S. Shinde, J. Yang, K. Hwang, B. Mistry, G.D. Saratale, S. Lone, D.-Y. Kim, J.-S. Sung, Adsorptive remediation of cobalt oxide nanoparticles by magnetized α-cellulose fibers from waste paper biomass, Bioresource technology 273 (2019) 386-393.
[236] K. Srasri, M. Thongroj, P. Chaijiraaree, S. Thiangtham, H. Manuspiya, P. Pisitsak, S. Ummartyotin, Recovery potential of cellulose fiber from newspaper waste: An approach on magnetic cellulose aerogel for dye adsorption material, Int. J. Biol. Macromol. 119 (2018) 662-668.
[237] P. Li, Z. Yang, Y. Wang, Z. Peng, S. Li, L. Kong, Q. Wang, Microencapsulation of coupled folate and chitosan nanoparticles for targeted delivery of combination drugs to colon, J. Microencaps. 32(1) (2015) 40-45.
[238] A.M. Khalid, M. Hossain, N. Ismail, N.A. Khalil, V. Balakrishnan, M. Zulkifli, A.N.A. Yahaya, Isolation and Characterization of Magnetic Oil Palm Empty Fruits Bunch Cellulose Nanofiber Composite as a Bio-Sorbent for Cu (II) and Cr (VI) Removal, Polymers 13(1) (2021) 112.
[239] Z. Izadiyan, K. Shameli, M. Miyake, H. Hara, S.E.B. Mohamad, K. Kalantari, S.H.M. Taib, E. Rasouli, Cytotoxicity assay of plant-mediated synthesized iron oxide nanoparticles using Juglans regia green husk extract, Arabian Journal of Chemistry 13(1) (2020) 2011-2023.
[240] B. Bahrami, T. Behzad, A. Zamani, P. Heidarian, B. Nasri-Nasrabadi, Optimal design of ozone bleaching parameters to approach cellulose nanofibers extraction from sugarcane bagasse fibers, J. Polym. Environ. 26(10) (2018) 4085-4094.
[241] A. Gupta, G. Tiwari, R. Tiwari, R. Srivastava, A. Rai, Enteric coated HPMC capsules plugged with 5-FU loaded microsponges: a potential approach for treatment of colon cancer, Brazilian Journal of Pharmaceutical Sciences 51(3) (2015) 591-605.
[242] B.A. Evans, M.D. Bausch, K.D. Sienerth, M.J. Davern, Non-monotonicity in the influence of nanoparticle concentration on SAR in magnetic nanoparticle hyperthermia, Journal of Magnetism and Magnetic Materials 465 (2018) 559-565.
[243] S. Panja, S. Maji, T.K. Maiti, S. Chattopadhyay, A smart magnetically active nanovehicle for on-demand targeted drug delivery: where van der waals force balances the magnetic interaction, ACS applied materials & interfaces 7(43) (2015) 24229-24241.
[244] T. Doane, C. Burda, Nanoparticle mediated non-covalent drug delivery, Adv. Drug Del. Rev. 65(5) (2013) 607-621.

[245] Y. Li, H. Pang, Z. Guo, L. Lin, Y. Dong, G. Li, M. Lu, C. Wu, Interactions between drugs and polymers influencing hot melt extrusion, Journal of Pharmacy and Pharmacology 66(2) (2014) 148-166.
[246] J. Liao, H. Huang, Review on magnetic natural polymer constructed hydrogels as vehicles for drug delivery, Biomacromolecules 21(7) (2020) 2574-2594.
[247] W. Xue, X.-L. Liu, H. Ma, W. Xie, S. Huang, H. Wen, G. Jing, L. Zhao, X.-J. Liang, H.M. Fan, AMF responsive DOX-loaded magnetic microspheres: transmembrane drug release mechanism and multimodality postsurgical treatment of breast cancer, Journal of Materials Chemistry B 6(15) (2018) 2289-2303.
[248] D. Niedzwiecki, R.M. Hasson, H.J. Lenz, C. Ye, M. Redston, S. Ogino, C.S. Fuchs, C.C. Compton, R.J. Mayer, R.M. Goldberg, A study of thymidylate synthase expression as a biomarker for resectable colon cancer: Alliance (cancer and leukemia group B) 9581 and 89803, The oncologist 22(1) (2017) 107.
[249] Q. Chen, Z. Zong, X. Gao, Y. Zhao, J. Wang, Preparation and characterization of nanostarch-based green hard capsules reinforced by cellulose nanocrystals, International Journal of Biological Macromolecules 167 (2021) 1241-1247.
[250] K. Mondal, S. Sakurai, Y. Okahisa, V.V. Goud, V. Katiyar, Effect of cellulose nanocrystals derived from Dunaliella tertiolecta marine green algae residue on crystallization behaviour of poly (lactic acid), Carbohydrate Polymers 261 (2021) 117881.
[251] E. Qua, P. Hornsby, H. Sharma, G. Lyons, Preparation and characterisation of cellulose nanofibres, Journal of Materials Science 46(18) (2011) 6029-6045.
[252] S.-C. Pech-Cohuo, G. Canche-Escamilla, A. Valadez-González, V.V.A. Fernández-Escamilla, J. Uribe-Calderon, Production and modification of cellulose nanocrystals from Agave tequilana weber waste and its effect on the melt rheology of PLA, International Journal of Polymer Science 2018 (2018).
[253] M. Abyadeh, A.A.K. Zarchi, M.A. Faramarzi, A. Amani, Evaluation of factors affecting size and size distribution of chitosan-electrosprayed nanoparticles, Avicenna journal of medical biotechnology 9(3) (2017) 126.
[254] M. Mozafari, A. Pardakhty, S. Azarmi, J. Jazayeri, A. Nokhodchi, A. Omri, Role of nanocarrier systems in cancer nanotherapy, J. Liposome Res. 19(4) (2009) 310-321.
[255] P.Y. Aw-Yong, P.H. Gan, A.O. Sasmita, S.T. Mak, A. Ling, Nanoparticles as carriers of phytochemicals: Recent applications against lung cancer, Int. J. Res. Biomed. Biotechnol 7 (2018) 1-11.
[256] K. Greish, J. Fang, T. Inutsuka, A. Nagamitsu, H. Maeda, Macromolecular therapeutics, Clinical pharmacokinetics 42(13) (2003) 1089-1105.
[257] H. Maeda, Toward a full understanding of the EPR effect in primary and metastatic tumors as well as issues related to its heterogeneity, Adv. Drug Del. Rev. 91 (2015) 3-6.
[258] M. Danaei, M. Dehghankhold, S. Ataei, F. Hasanzadeh Davarani, R. Javanmard, A. Dokhani, S. Khorasani, M. Mozafari, Impact of particle size and polydispersity index on the clinical applications of lipidic nanocarrier systems, Pharmaceutics 10(2) (2018) 57.
[259] A. Rehman, S.M. Jafari, Q. Tong, T. Riaz, E. Assadpour, R.M. Aadil, S. Niazi, I.M. Khan, Q. Shehzad, A. Ali, Drug nanodelivery systems based on natural polysaccharides against different diseases, Advances in Colloid and Interface Science (2020) 102251.

[260] B. Sun, M. Zhang, J. Shen, Z. He, P. Fatehi, Y. Ni, Applications of cellulose-based materials in sustained drug delivery systems, Curr. Med. Chem. 26(14) (2019) 2485-2501.
[261] Z. Hanif, F.R. Ahmed, S.W. Shin, Y.-K. Kim, S.H. Um, Size-and dose-dependent toxicity of cellulose nanocrystals (CNC) on human fibroblasts and colon adenocarcinoma, Colloids Surf. B. Biointerfaces 119 (2014) 162-165.
[262] K.P. MR, P.R. Iyer, Antiproliferative effects on tumor cells of the synthesized gold nanoparticles against Hep2 liver cancer cell line, Egyptian Liver Journal 10(1) (2020) 1-12.
[263] M. Vinci, S. Gowan, F. Boxall, L. Patterson, M. Zimmermann, C. Lomas, M. Mendiola, D. Hardisson, S.A. Eccles, Advances in establishment and analysis of three-dimensional tumor spheroid-based functional assays for target validation and drug evaluation, BMC Biol. 10(1) (2012) 1-21.
[264] A.S. Nunes, A.S. Barros, E.C. Costa, A.F. Moreira, I.J. Correia, 3D tumor spheroids as in vitro models to mimic in vivo human solid tumors resistance to therapeutic drugs, Biotechnol. Bioeng. 116(1) (2019) 206-226.
[265] B.K. Bozoğlan, O. Duman, S. Tunç, Preparation and characterization of thermosensitive chitosan/carboxymethylcellulose/scleroglucan nanocomposite hydrogels, International journal of biological macromolecules 162 (2020) 781-797.
[266] Z. Hussain, H. Katas, M.C.I.M. Amin, E. Kumolosasi, F. Buang, S. Sahudin, Self-assembled polymeric nanoparticles for percutaneous co-delivery of hydrocortisone/hydroxytyrosol: an ex vivo and in vivo study using an NC/Nga mouse model, Int. J. Pharm. 444(1-2) (2013) 109-119.
[267] S.K. Thomas, P.S. Begum, C. Midhun Dominic, N.V. Salim, N. Hameed, S.M. Rangappa, S. Siengchin, J. Parameswaranpillai, Isolation and characterization of cellulose nanowhiskers from Acacia caesia plant, J. Appl. Polym. Sci. 138(15) (2021) 50213.
[268] R. Abou Gabal, D. Shokeir, A. Orabi, Cytotoxicity and Hemostatic One Step Green Synthesis of Iron Nanoparticles Coated with Green Tea for Biomedical Application, Trends in Sciences 19(3) (2022) 2062-2062.
[269] E.S. Cutrim, A.A. Vale, D. Manzani, H.S. Barud, E. Rodriguez-Castellon, A.P. Santos, A.C. Alcântara, Preparation, characterization and in vitro anticancer performance of nanoconjugate based on carbon quantum dots and 5-Fluorouracil, Materials Science and Engineering: C 120 (2021) 111781.
[270] M. Mondéjar-López, A. Rubio-Moraga, A.J. López-Jimenez, J.C.G. Martínez, O. Ahrazem, L. Gómez-Gómez, E. Niza, Chitosan nanoparticles loaded with garlic essential oil: A new alternative to tebuconazole as seed dressing agent, Carbohydrate Polymers 277 (2022) 118815.
[271] M. Jia, X. Zhang, J. Weng, J. Zhang, M. Zhang, Protective coating of paper works: ZnO/cellulose nanocrystal composites and analytical characterization, Journal of Cultural Heritage 38 (2019) 64-74.
[272] N. Li, H. Zhang, Y. Xiao, Y. Huang, M. Xu, D. You, W. Lu, J. Yu, Fabrication of cellulose-nanocrystal-based folate targeted nanomedicine via layer-by-layer assembly with lysosomal pH-controlled drug release into the nucleus, Biomacromolecules 20(2) (2019) 937-948.
[273] T. Kumar, M. Chandrasekar, K. Senthilkumar, R. Ilyas, S. Sapuan, N. Hariram, A.V. Rajulu, N. Rajini, S. Siengchin, Characterization, thermal and antimicrobial

properties of hybrid cellulose nanocomposite films with in-situ generated copper nanoparticles in Tamarindus indica Nut Powder, Journal of Polymers and the Environment 29(4) (2021) 1134-1142.
[274] S.E. Favela-Camacho, E.J. Samaniego-Benítez, A. Godínez-García, L.M. Avilés-Arellano, J.F. Pérez-Robles, How to decrease the agglomeration of magnetite nanoparticles and increase their stability using surface properties, Colloids Surf. Physicochem. Eng. Aspects 574 (2019) 29-35.
[275] M. Samy, S.H. Abd El-Alim, A. Amin, M.M. Ayoub, Formulation, characterization and in vitro release study of 5-fluorouracil loaded chitosan nanoparticles, International Journal of Biological Macromolecules 156 (2020) 783-791.
[276] M.A.C.M. Haniffa, K. Munawar, C.Y. Chee, S. Pramanik, A. Halilu, H.A. Illias, M. Rizwan, R. Senthilnithy, K.R.R. Mahanama, A. Tripathy, Cellulose Supported Magnetic Nanohybrids: Synthesis, Pysicomagnetic Properties and Biomedical Applications-A Review, Carbohydrate Polymers (2021) 118136.
[277] M.K. Jeddi, M. Mahkam, Magnetic nano carboxymethyl cellulose-alginate/chitosan hydrogel beads as biodegradable devices for controlled drug delivery, International journal of biological macromolecules 135 (2019) 829-838.
[278] J. Liao, H. Huang, Smart pH/magnetic sensitive Hericium erinaceus residue carboxymethyl chitin/Fe3O4 nanocomposite hydrogels with adjustable characteristics, Carbohydrate Polymers 246 (2020) 116644.

LIST OF PUBLICATIONS

Web of Science Indexed Journals

1. **M. Yusefi**, M.L.-K. Soon, S.-Y. Teow, E.I. Monchouguy, B.N.H. Mooneerah, Z. Izadiyan, H. Jahangirian, R. Rafiee-Moghaddam, T.J. Webster, K. Shameli, Fabrication of cellulose nanocrystals as potential anticancer drug delivery systems for colorectal cancer treatment, International Journal of Biological Macromolecules (2022). **(Q1, IF: 6.953)**

2. **M. Yusefi,** M.S. Lee-Kiun, K. Shameli, S.-Y. Teow, R.R. Ali, K.-K. Siew, H.-Y. Chan, M.M.-T. Wong, W.-L. Lim, K. Kuča, 5-fluorouracil loaded magnetic cellulose bionanocomposites for potential colorectal cancer treatment, Carbohydrate Polymers (2021) 118523. **(Q1, IF: 9.381)**

3. **M. Yusefi,** H.-Y. Chan, S.-Y. Teow, P. Kia, M. Lee-Kiun Soon, N.A.B.C. Sidik, K. Shameli, 5-Fluorouracil Encapsulated Chitosan-Cellulose Fiber Bionanocomposites: Synthesis, Characterization and In Vitro Analysis towards Colorectal Cancer Cells, Nanomaterials 11(7) (2021) 1691. **(Q1, IF: 5.076)**

4. **M. Yusefi,** K. Shameli, Z. Hedayatnasab, S.-Y. Teow, U.N. Ismail, C.A. Azlan, R. Rasit Ali, Green synthesis of Fe_3O_4 nanoparticles for hyperthermia, magnetic resonance imaging and 5-fluorouracil carrier in potential colorectal cancer treatment, Research on Chemical Intermediates 47(5) (2021) 1789-1808. **(Q2, IF: 2.914)**

5. **M. Yusefi,** K. Shameli, O.S. Yee, S.-Y. Teow, Z. Hedayatnasab, H. Jahangirian, T.J. Webster, K. Kuča, Green synthesis of Fe_3O_4 nanoparticles stabilized by a Garcinia mangostana fruit peel extract for hyperthermia and anticancer activities, International Journal of Nanomedicine 16 (2021) 2515. **(Q1, IF: 6.400)**

6. **M. Yusefi,** K. Shameli, R.R. Ali, S.-W. Pang, S.-Y. Teow, Evaluating anticancer activity of plant-mediated synthesized iron oxide nanoparticles using Punica granatum fruit peel extract, Journal of Molecular Structure 1204 (2020) 127539. **(Q2, IF: 3.196)**

7. **M. Yusefi,** K. Shameli, H. Jahangirian, S.-Y. Teow, H. Umakoshi, B. Saleh, R. Rafiee-Moghaddam, T.J. Webster, The potential anticancer activity of 5-fluorouracil loaded in Cellulose fiber isolated from rice straw, International journal of nanomedicine 15 (2020) 5417. **(Q1, IF: 5.115)**

Scopus Indexed Journals

8. **M. Yusefi**, R.B.R. Ali, E.C. Abdullah, K. Shameli, Analysis on Physiochemical Properties of Cellulose Fiber from Rice Straw Waste, IOP Conference Series: Materials Science and Engineering, IOP Publishing, 2020, p. 012038.

Non-indexed Journals

9. **M. Yusefi**, P. Kia, S.N.A.M. Sukri, R.R. Ali, K. Shameli, Synthesis and Properties of Chitosan Nanoparticles Cross-Linked with Tripolyphosphate, Journal of Research in Nanoscience and Nanotechnology 3(1) (2021) 46-52.

10. **M. Yusefi**, K. Shameli, P. Kia, H. Hamrayev, Facile Fabrication of Polysaccharide Nanocomposites Using Ionic Gelation Method, Journal of Research in Nanoscience and Nanotechnology 3(1) (2021) 37-45.

11. **M. Yusefi**, K. Shameli, S.N.A.M. Sukri, Magnetic Nanoparticles in Hyperthermia Therapy: A Mini-Review, Journal of Research in Nanoscience and Nanotechnology 2(1) (2021) 51-60.

12. **M. Yusefi,** O.S. Yee, K. Shameli, Bio-mediated production and characterisation of magnetic nanoparticles using fruit peel extract, Journal of Research in Nanoscience and Nanotechnology 1(1) (2021) 53-61.

13. **M. Yusefi,** K. Shameli, Nanocellulose as a Vehicle for Drug Delivery and Efficiency of Anticancer Activity: A Short-Review, Journal of Research in Nanoscience and Nanotechnology 1(1) (2021) 30-43.

14. **M. Yusefi,** K. Shameli, A.F. Jumaat, Preparation and properties of magnetic iron oxide nanoparticles for biomedical applications: A brief review, Journal of Advanced Research in Materials Science 75(1) (2020) 10-18.