SYNTHESIS AND CHARACTERIZATION OF NANOZEOLITE NaY AND ITS POTENTIAL AS ALTERNATIVE ADJUVANT THERAPY FOR CANCER

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

Faculty of Biosciences and Medical Engineering
Universiti Teknologi Malaysia

NOVEMBER 2016

To my loving husband

Wan Khairil Reza bin Wan Kamaludin

and my precious sons

Wan Muhammad Faiz
Wan Muhammad Ilyas
Wan Muhammad Raziq
Wan Muhammad Aqmal
Wan Muhammad Ishaq

ACKNOWLEDGEMENT

Alhamdulillah, praises to Allah the Almighty for His blessings along the journey to complete the research and in writing this thesis.

I would like to use the opportunity here to express my sincere appreciation to my main supervisor, Dr. Salehhuddin bin Hamdan, for his wisdom, kind words and support all through my study years under him. I would also like to convey my deepest gratitude to my co-supervisor, Dr. Nik Ahmad Nizam bin Nik Malek for all his help, guides and motivations to keep me on track all the time.

A big thank you to all my laboratory mates and the university staff for your contributions of ideas and expertise. I shall treasure the good company and memories we shared along the way. This journey was not that lonely after all.

Last but not least, a special token to my family members for their full understanding and unconditional support whenever I need them. Without them, I am nowhere near where I am today.

May Allah bless all of you with happiness, good health and success in this world and the hereafter. Thank you very much.

ABSTRACT

The efficacy of zeolite as anticancer adjuvant is unclear, but natural zeolite clinoptilolite has been proven to have antiproliferation activity against cancer cells. This research investigated the potential of synthetic nanozeolite as anticancer adjuvant *in vitro*. Initial study proved the antiproliferation abilities of zeolite NaY (Zeo-NaY), commercial zeolite Y (CBV300) and beta (CP814E) against six types of cancer cells through 3-(4,5-dimethythiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. The aim of this research was to synthesize nanozeolite NaY (Nano-NaY) with higher antiproliferation activity and tolerance to gastrointestinal condition using organotemplate-free method and rice husk ash (RHA) as the silica source. The newly-synthesized Nano-NaY was characterized by X-ray diffraction (XRD), Fourier transform infra-red (FTIR) spectroscopy, field emission scanning electron microscopy (FESEM), transmission electron microscopy (TEM) and surface area analysis. Structural stability of Nano-NaY was tested in simulated gastric fluid (SGF) and intestinal fluid (SIF) at different concentrations by monitoring its characteristic and elemental composition (Al^{3+}, Si^{4+}). Elemental composition (Ca^{2+}, Mg^{2+}) of nanozeolite-treated media were analyzed before and after preparation. Cytotoxicity of Nano-NaY was tested by MTT assay against colon cancer cells (HT-29) and normal liver cells (WRL-68). Pure Nano-NaY was successfully synthesized with the particles sized from 220 nm to 470 nm, and 788 m^2/g surface area. Incubation of 30 mg/ml Nano-NaY in simulated gastrointestinal fluid (SGIF) resulted in slight dealumination of the Nano-NaY, but its structure remained stable. Reduction of Ca^{2+} and Mg^{2+} concentrations (35-85%) from nanozeolite-treated media suggested adsorption of the cations by Nano-NaY through ionic exchange mechanism. Antiproliferation activity and cytotoxicity of Nano-NaY were dependent on its micropore surface area ($S_{micropore}$), with initial half maximal inhibitory concentration (IC_{50}) against HT-29 recorded at 1.26 mg/ml. The cytotoxicity against WRL-68 after incubation in SGIF was low (IC_{50} = 650 mg/ml). Thus, Nano-NaY might have the potential as an alternative adjuvant therapy for colorectal cancer.

ABSTRAK

Keberkesanan zeolit sebagai pembantu antikanser belum diketahui, tetapi zeolit semulajadi telah dibuktikan mempunyai aktiviti antiproliferasi terhadap sel kanser. Penyelidikan ini mengkaji potensi nanozeolite sintetik sebagai pembantu antikanser secara *in vitro*. Kajian awal membuktikan kebolehan antiproliferasi zeolit NaY (Zeo-NaY), zeolit Y komersil (CBV 300) dan zeolit beta komersil (CP814E) terhadap enam jenis sel kanser melalui ujian 3, (4,5-dimetilthiazol-2-yl)-2,5-diphenil tetrazolium bromida (MTT). Tujuan kajian ini adalah untuk mensintesis nanozeolit NaY (Nano-NaY) yang mempunyai aktiviti antiproliferasi dan toleransi kepada keadaan di dalam gastrointestin dengan menggunakan kaedah tanpa-templat-organik dan abu sekam padi (RHA) sebagai sumber silika. Pencirian Nano-NaY yang baru ini dibuat melalui kaedah difraksi sinar-X (XRD), spektroskopi inframerah transformasi Fourier (FTIR), mikroskopi pancaran pengimbasan electron (FESEM), mikroskopi transmisi electron (TEM) dan analisis luas permukaan. Kestabilan struktur Nano-NaY kemudiannya diuji di dalam simulasi cecair gastrik (SGF) dan simulasi cecair intestin (SIF) pada kepekatan yang berbeza dengan memerhatikan ciri-ciri dan komposisi elemen (Al^{3+}, Si^{4+}) di dalam cecair-cecair tersebut. Komposisi elemen (Ca^{2+}, Mg^{2+}) bagi media yang dirawat dengan nanozeolit dianalisa sebelum dan selepas penyediaan. Kesitotoksikan Nano-NaY pula diuji melalui ujian MTT terhadap sel kanser kolon (HT-29) dan sel normal hati (WRL-68). Nano-NaY tulen telah berjaya disintesis dengan partikel bersaiz dari 220 nm hingga 470 nm, dan keluasan permukaan sebanyak 788 m^2/g. Inkubasi Nano-NaY sebanyak 30 mg/ml di dalam cecair simulasi gastrointestin (SGIF) menyebabkan sedikit dealuminasi pada Nano-NaY, tetapi strukturnya kekal stabil. Pengurangan kepekatan Ca^{2+} and Mg^{2+} (35-85%) daripada media yang dirawat dengan nanozeolit mencadangkan penjerapan kation-kation tersebut oleh Nano-NaY melalui mekanisme pertukaran ion. Aktiviti antiproliferasi dan sitotoksisiti Nano-NaY bergantung kepada luas permukaan liang-mikro ($S_{liang\text{-}mikro}$), dengan kepekatan perencatan separuh maksima (IC_{50}) ke atas HT-29 direkod pada 1.26 mg/ml. Sitotoksisiti ke atas WRL-68 selepas inkubasi di dalam SGIF adalah rendah (IC_{50} = 650 mg/ml). Dengan itu, Nano-NaY mempunyai potensi sebagai satu terapi alternatif yang mungkin bagi kanser kolorektal.

TABLE OF CONTENT

LIST OF TABLES

LIST OF FIGURES

LIST OF SYMBOLS

%	-	Percentage
*	-	Asterisk
<	-	Less than
±	-	Plus minus sign (confidence interval or error)
≤	-	Less than or equal to
°C	-	Degree Celsius
µl	-	Microliter
Å	-	Angstrom
Al	-	Aluminium
Al_2O_3	-	Aluminium oxide
Al^{3+}	-	Aluminium ion
AlO_4	-	Aluminate
C	-	Carbon
Ca	-	Calcium
Ca^{2+}	-	Calcium ion
cm^{-1}	-	Reciprocal centimeter (wavenumber)
CO_2	-	Carbon dioxide
g	-	Gram
g/cm^3	-	Gram per cubic centimeter
H_2O	-	Water
K	-	Potassium
KBr	-	Potassium bromide
keV	-	Kilo electron volt
KH_2PO_4	-	Potassium dihydrogen phosphate
kV	-	Kilo Volt
M	-	Molar
m^2/g	-	Meter square per gram

mA	-	MiliAmpere
mg/kg/day	-	Miligram per kilogram per day
mg/L	-	Miligram per liter
mg/ml	-	Miligram per mililiter
Mg^{2+}	-	Magnesium ion
ml	-	Mililiter
N_2	-	Nitrogen gas
Na	-	Sodium
$Na_2HPO_4.7H_2O$	-	Sodium phosphate dibasic heptahydrate
Na_2O	-	Sodium oxide
Na_2SiO_3	-	Sodium silicate
$NaAl(OH)_4$	-	Sodium aluminate (hydrated)
$NaAlO_2$	-	Sodium aluminate (anhydrous)
$NaHCO_3$	-	Sodium hydrogen carbonate
NaOH	-	Sodium hydroxide
nm	-	Nanometer
O	-	Oxygen
O-H	-	Hydroxyl
ppm	-	Part per million
rpm	-	Rotation per minute
Si	-	Silicon
Si^{4+}	-	Silicon ion
SiO_4	-	Silicate
V	-	Volt
Zn^{2+}	-	Zinc ion
ZnO	-	Zinc oxide
α	-	Alpha
θ	-	Theta
λ	-	Lambda (wavelength)

LIST OF ABBREVIATIONS

*BEA	-	Beta polymorph A disordered framework
A549	-	Alveolar epithelial cell line
ANA	-	Analcime framework
ATSDR	-	Agency for Toxic Substances and Disease Registry
BET	-	Brunauer, Emmett and Teller
BxPC-3	-	Pancreatic adenocarcinoma cell line
Caco-2	-	Pancreatic carcinoma cell line
CHO-K1	-	Chinese hamster ovary cell line
DF	-	Dilution factor
DMEM	-	Dulbecco's modified essential medium
EA.hy926	-	Umbilical vein cell line
EDS	-	Energy dispersive spectroscopy
EDX	-	Energy dispersive x-ray
EMT	-	Elf Mulhouse Two framework
ERK	-	Extracellular signal-regulated kinases
FAU	-	Faujasite framework
FBS	-	Fetal bovine serum
FESEM	-	Field emission scanning electron microscopy
FTIR	-	Fourier transform infra-red
G_0	-	Gap 0 (Interphase)
G_1	-	Gap 1 (Interphase)
G_2	-	Gap 2 (Interphase)
GIS	-	Gismondine framework
HCl	-	Hydrochloric acid
Hef522	-	Diploid fibroblast cell line
HEK-293	-	Human embryonic kidney cell line
HeLa	-	Cervical carcinoma cell line

Hep-2	-	Laryngeal carcinoma cell line
HEU	-	Heulandite framework
HPV	-	Human papillomavirus
HT-29	-	Colorectal adenocarcinoma cell line
i.v.	-	Intravenous
IC_{50}	-	Half maximal inhibitory concentration
ICP-OES	-	Inductively coupled plasma – optical emission spectrometry
IL	-	Interleukin
IPCS	-	International Programme on Chemical Safety
IR	-	Infrared
IUPAC	-	International Union of Pure and Applied Chemistry
IZA	-	International Zeolite Association
LD_{50}	-	Half maximal lethal dose
LDH	-	Lactate dehydrogenase
LTA	-	Linde type A framework
LTL	-	Linde type L framework
M	-	Mitosis
MCF-7	-	Breast adenocarcinoma cell line
MDA-MB-231	-	Breast adenocarcinoma cell line
MDA-MB-468	-	Breast adenocarcinoma cell line
MiaPaCa-2	-	Pancreatic carcinoma cell line
Min	-	Minute
MTT	-	Methyl tetrazolium thiazol
$NF_{\kappa}B$	-	Nuclear factor kappa light chain enhancer of activated B cells
OECD	-	Organization for Economic Co-operation and Development
OS	-	Overall survival
OSDA	-	Organic structure directing agent
PBS	-	Phosphate buffer saline
PI	-	Propidium iodide
PKB/Akt	-	Protein kinase B
PS	-	Phosphatidylserine

QOL	-	Quality of life
RAW 264.7	-	Murine macrophage cell line
RHA	-	Rice husk ash
ROS	-	Reactive oxygen species
RPMI	-	Roswell Park Memorial Institute medium
S	-	Synthesis of DNA (Interphase)
SBU	-	Secondary building unit
SD	-	Standard deviation
SEM	-	Scanning electron microscopy
SEM	-	Standard error mean
SGF	-	Simulated gastric fluid
SGIF	-	Simulated gastrointestinal fluid
SIF	-	Simulated intestinal fluid
SW620	-	Pancreatic carcinoma cell line
TBU	-	Tertiary building unit
TEM	-	Transmission electron microscopy
THP-1	-	Monocytic leukemia cell line
TMA	-	Tetramethylammonium
TMABr	-	Tetramethylammonium bromide
TMAOH	-	Tetramethylammonium hydroxide
TNF	-	Tumor necrosis factors
TNM	-	Tumor Node Metastasis
UPMU	-	University Laboratory Management Unit
UTM	-	Universiti Teknologi Malaysia
UV	-	Ultra violet
XRD	-	X-ray diffraction
β-NADH	-	Beta-nicotinamide adenine dinucleotide hydrate

LIST OF APPENDICES

CHAPTER 1

INTRODUCTION

1.1 Background of Research

Cancer refers to the condition of an uncontrolled growth of cells which will invade and destroy the cell functions, particularly the main organs. It has been one of the major cause of deaths in the world. There are many factors that may contribute to the rise of cancer cases such as genetic hereditary, tobacco, unhealthy diet, lack of physical activities, ultraviolet (UV), radiation and prolonged exposures to carcinogens (Vogelstein and Kinzler, 2004; Ezzati *et al.,* 2005; Sankpal *et al.,* 2012). Historically, surgery was the only way to treat cancer but now it is limited to certain cases like primary tumor treatment, metastases resection and staging purposes.

Cancer staging is essential in order to identify the extent of the disease and in selecting the best treatment regime for the patient. The most common staging system is the tumor node metastasis (TNM) system (Edge and Compton, 2010). Cancer diagnosis and staging is normally confirmed by biopsy. The samples obtained will be sent to the laboratory where they will be examined, processed and stained using immunohistochemistry method. A pathologist will generate a cytology and histopathology report before the oncologist can decide and initiate the necessary treatment.

There are many available choices of treatment nowadays besides surgery such as chemotherapy, radiotherapy, targeted therapy, hyperthermia, stem cell transplant and photodynamic therapy. The choice of treatments, however, depends on the type of cancer and its classification (World Health Organization, 2008; Ministry of Health Malaysia, 2002 and 2003). Combined treatments may be arranged through neoadjuvant therapy or adjuvant therapy to ensure the effectiveness of the main treatment. Neoadjuvant therapy is normally given prior to surgery in order to shrink the tumor beforehand. On the other hand, adjuvant therapy is a systemic therapy that is given to the patients after the main treatment particularly for those with a high risk of recurrence. The objective is to prevent tumor cells progression and boost the immune system so the patients will be able to live long and comfortable life despite the disease.

Even with ample choices given, there are restrictions to the available treatments. One example is the possibility of recurrence after surgery (Snyder and Greenberg, 2010), meaning that cancer may come back after treatment at the same site (local) or at a different site (distant). Another major concern is drug resistance in chemotherapy through adaptation of the tumor cells to the given drugs (Casanovas, 2012). Cancer treatment by radiotherapy is useful for localized cancer but may affect the normal cells nearby, while treatments by hyperthermia and stem cell transplant have yet to prove their effectiveness in clinical studies. With all the limitations at hand and no definite cure as yet, the use of adjuvant therapy is very much relied on, although it means that patients have to suffer the immediate side effects or the delayed late toxicity. Therefore, a research on new potential anticancer adjuvant that possesses good anticancer activity with fewer side effects or toxicity is very much anticipated.

Zeolite was first discovered by Cronstedt in 1756 with the discovery of stilbite (Breck, 1974). The term zeolite comes from two Greek words, "*zeo*" (to boil) and "*lithos*" (stone). Zeolite is an aluminosilicate with a relatively open framework due to its porous structure. The zeolite framework consists of Si-O tetrahedral complex and at some places in the framework the Si^{4+} is replaced by Al^{3+}. This results in a negative framework charge which is due to the deficiency of an electron

at the Al-O tetrahedral (Maesen and Marcus, 2001). Charge-compensating cation from the alkali or alkaline earth metals enters the pore to maintain the electroneutrality of the overall zeolite framework. However, the molecules entering the pore would be selectively sieved by the size of each molecule. These unique properties contribute to the major function of zeolites as catalysts, ion exchangers and adsorbents with vast application in many industries. Thus, this research investigated on the potential of using a newly-synthesized nanozeolite NaY in biomedical application as an alternative adjuvant therapy for cancer.

1.2 Problem Statements

The revelation of natural zeolite, clinoptilolite, as an anticancer adjuvant that is able to inhibit the growth of cancer cells and promotes longer lifespan with low side effects is appreciated (Pavelic *et al.*, 2001). However, natural zeolites contain impurities from the open environment. Variation in the mineral composition of the natural zeolite may result in diverse levels of anticancer activity which will make dosage determination difficult. Therefore, a purification process of natural zeolites is necessary before any biomedical application. Unfortunately, it does not ensure complete extraction of the unwanted minerals (Tomasevic-Canovic, 2005). Unless a complete preliminary characterization is made and the zeolite material is standardized, the use of natural zeolites in biomedical application should be reconsidered as natural zeolites are poor materials to begin with (Colella, 2011).

A possible alternative to natural zeolites is the synthetic zeolites. Synthetic zeolites will ensure standardization in the matter of purity, size distribution, cationic composition and the production procedures. Synthesis of zeolite generates zeolites that are engineered to the desired form and provides rooms for modification in order to enhance the capability of the zeolites for the intended application. For example, decreasing the size of the zeolites to nanoscale will create larger surface area, expose more active sites and reduce diffusion path lengths, thus, will increase the activity of the zeolites (Mintova *et al.*, 2013). Napierska *et al.* (2009) had proven the inverse relationship between particle size and cytotoxicity of monodisperse silica

nanoparticles. Most methods for the preparation of synthetic nanozeolites, however, require the use of huge quantity of organic templates which is not environmentally friendly and costly. Modification through green methods by fine controlling the nucleation and adjusting the growth steps through chemical or physical conditions may help to reduce the use of environmental hazards in the synthesis process (Mintova *et al.*, 2013; Ng *et al.*, 2012a).

The use of rice husk ash (RHA) as silica source alternatively promotes waste materials to wealth (Della *et al.*, 2002). More than 90% of amorphous silica can be obtained from the combustion of rice husk at high temperature (600°C) along with elimination of carbon and organic components found in rice husk (Yusof *et al*., 2010). As proven by Yusof *et al*. (2010) through thermogravimetric analysis, RHA that was prepared from plug flow reactor or furnace (RHA-PFC) has very low impurities when compared to RHA prepared by the open burning method (RHA-OB). RHA-PFC showed minor total weight loss after ignition (≈ 12%) whereas RHA-OB recorded a higher amount of total weight loss (50%) after ignition, indicating that there were less impurities in RHA-PFC than in RHA-OB and thus, RHA-PFC was suitable to be used as the source of silica for the synthesis of highly pure zeolites. Hence, in this research, the aim was to synthesize pure nanozeolite NaY that has higher anticancer activity than the currently available synthetic zeolites as an alternative to the natural zeolite clinoptilolite, using an organic template-free method and RHA as the silica source, which is more environmentally friendly and cheaper in cost.

Each type of zeolites has different Si/Al ratio. Zeolite with a low Si/Al ratio would have a high negative charge due to the high number of aluminium, and thus a high number of exchangeable cations in the extraframework (Meinander, 2014). It was hypothesized that the mechanism for zeolite antiproliferation activity against the cancer cells might be related to the adsorption of serum components since the activity was detected only in the presence of serum (Katic *et al*., 2006). As an adsorbent, the mechanism for the adsorption of cations by zeolites is through ion exchange (Meinander, 2014). Therefore, zeolites with low ratio of Si/Al were selected as they have higher cation exchange capacity compared to zeolites with high

Si/Al ratio (Breck, 1974). Besides that, the pore size of the zeolites was also considered. Zeolites with large pores such as zeolites X and Y (0.6-0.8 nm) would allow large molecules to be adsorbed into their pores while zeolite with small pore size such as zeolite A (0.35-0.45 nm) might prevent large molecules from entering its pore (Flanigen, 2001; Breck, 1974). Zeolites in the sodium form would give an advantage due to the low electronegativity of the sodium ion, which means it could be easily replaced by other cations (Meinander, 2014).

The efficacy of the application through oral consumption is of the main concern once the selected nanozeolite is synthesized. The nanozeolite is expected to be unstable in the acidic environment of the stomach due to the alkaline nature of the nanozeolite. The structure of the nanozeolite may collapse as the extraframework cations of the nanozeolite would be replaced by the hydronium ions and followed by dealumination (Colella, 2011). On the other hand, the basic condition of the intestinal tract would favor the dissolution of nanozeolite releasing the silicate and aluminate from the nanozeolite framework (Colella, 2011). It is also important to ensure that the application of zeolite will not interfere with the biological environment that will affect the physiological aspect. Thus, the challenge is to attain the concentration that is structurally stable, tolerable to the gastrointestinal condition and capable of inhibiting the proliferation of cancer cells. In order to ensure the stability of the zeolite structure, zeolite NaY (Si/Al: 1.5-3.0) was selected instead of zeolite NaX (Si/Al: 1-1.5) or zeolite NaA (Si/Al: 1), due to its higher Si/Al ratio. Dissolution or disintegration of the framework is highly dependent on the Si/Al ratio of the zeolite, where zeolites with higher Si/Al ratio such as zeolite Y were found to be more stable in acidic solution compared to zeolites with low Si/Al such as zeolite A (Hartman and Fogler, 2007).

The antiproliferative activity of nanozeolites is normally cell type-dependent and dose-dependent (Petushkov *et al.*, 2009). They were found to be non-toxic to the cells at low concentrations (Laurent *et al.*, 2013), but cytotoxicity at concentrations above 0.5 mg/ml had been reported (Thomassen *et al.*, 2012). Therefore, the question whether the antiproliferative activity of the synthesized nanozeolite will remain after passing through the gastrointestinal tract is an additional concern. A

study by Kavak and Ulku (2013) showed an insignificant decrease in the antiproliferative activity of digested zeolite. Thus, a slight decrease in the antiproliferation activity would be expected, but most importantly the synthesized nanozeolite must have low toxicity against the normal cells for it to function as an anticancer adjuvant alternative to the clinoptilolite.

1.3 Objectives of Research

The main objective of this research is to characterize and determine the potential of a synthetic nanozeolite as an alternative adjuvant therapy for cancer. These are the four sections of the main objective:

1. To screen selected synthetic zeolites (CBV300, CP814E and Zeo-NaY) for antiproliferative activity.
2. To synthesize and characterize synthetic nanozeolite (Nano-NaY).
3. To study the effects of the synthesized nanozeolite (Nano-NaY) after incubation in simulated gastrointestinal fluid.
4. To study the antiproliferation ability and cytotoxicity of the synthesized nanozeolite (Nano-NaY) before and after incubation in simulated gastrointestinal fluid.

1.4 Scope of Research

The research was focused on the characterization of a synthetic nanozeolite (Nano-NaY) for biomedical application as an alternative adjuvant in cancer therapy. A preliminary study was performed using commercial synthetic zeolites Y (CBV300) and beta (CP814E) at different concentrations to screen for the antiproliferative ability of the zeolites against cancer cells via *in vitro* proliferation test. Another zeolite Y (Zeo-NaY) that was previously synthesized using RHA as the silica source was also included in the testing. Established cell lines of the cervical carcinoma (HeLa), pancreatic adenocarcinoma (BxPC-3), breast adenocarcinoma (MDA-MB-231, MDA-MB-468, and MCF-7), colorectal

adenocarcinoma (HT-29) and Chinese hamster ovary (CHO-K1) were used to measure the range of anticancer activity by the synthetic zeolites against the cell lines. All the synthetic zeolites were initially characterized to confirm their identity and purity.

The first scope started with the synthesis of a synthetic nanozeolite and ended with the study on the structural and morphological stability of the synthesized nanozeolite in the simulated gastrointestinal fluid. A novel nanozeolite NaY (Nano-NaY) was synthesized using RHA (prepared from plug flow reactor) as the silica source through an organic template-free method. Several modifications were made to a previous hydrothermal method. Different forms of RHA were used and optimization of the aging time, as well as the crystallization temperature, were performed in order to reduce the particle size of the final product. The final product attained was then characterized for identification.

Subsequently, the stability of Nano-NaY in gastrointestinal condition was studied using simulated gastric fluid (SGF) and simulated intestinal fluid (SIF). The pH of both simulated fluids was measured prior to and after the incubation with Nano-NaY. Samples of Nano-NaY from both of the simulated fluids were taken for characterization and samples from both simulated fluids were also taken for elemental analysis. The Nano-NaY was then incubated in simulated gastrointestinal fluid (SGIF) by incubating the nanozeolites in SGF and SIF subsequently. This was performed in order to mimic the actual gastrointestinal condition before performing further tests using the Nano-NaY that had been immersed in SGIF (NanoNaY-SGIF).

The second scope covers the study on the potential of the synthesized Nano-NaY for biomedical application, started with the preparation of nanozeolite-treated media and ended with the antiproliferative activity and cytotoxicity study of the nanozeolite via *in vitro* proliferation test. Nanozeolite-treated media was prepared by mixing Nano-NaY with the cell culture media. Dulbecco's modified essential medium (DMEM) was used to cultivate the normal liver cell lines (WRL-68) while Roswell Park Memorial Institute medium (RPMI) was used to cultivate the colorectal adenocarcinoma cell lines (HT-29). Samples of the Nano-NaY after being used to

treat DMEM (NanoNaY-DMEM) and samples of the Nano-NaY after being used to treat RPMI (NanoNaY-RPMI) were taken for characterization. Both nanozeolite-treated media were also sent for elemental analysis. The procedures were repeated for NanoNaY-SGIF with the samples labeled as NanoNaY-SGIF-DMEM and NanoNaY-SGIF-RPMI.

Antiproliferation activity of the Nano-NaY and NanoNaY-SGIF against HT-29 and toxicity against WRL-68 were tested using the MTT assay and LDH assay. The half maximal inhibitory concentration (IC_{50}) of both Nano-NaY and NanoNaY-SGIF were then calculated and analyzed. The amount of LDH released were also calculated and analyzed.

1.5 Significance of Research

The research was performed with the aim to synthesize, characterize and study the potential of a synthetic nanozeolite as an alternative to clinoptilolite for the application as an anticancer adjuvant with improvement in purity, crystallinity and antiproliferation activity. The efficiency of the synthetic nanozeolite as anticancer adjuvant was then assessed by studying its stability in simulated gastrointestinal fluid and measuring its cytotoxicity via *in vitro* tests. Figure 1.1 shows the contribution of the research in the vicinity of all the research for cancer treatments.

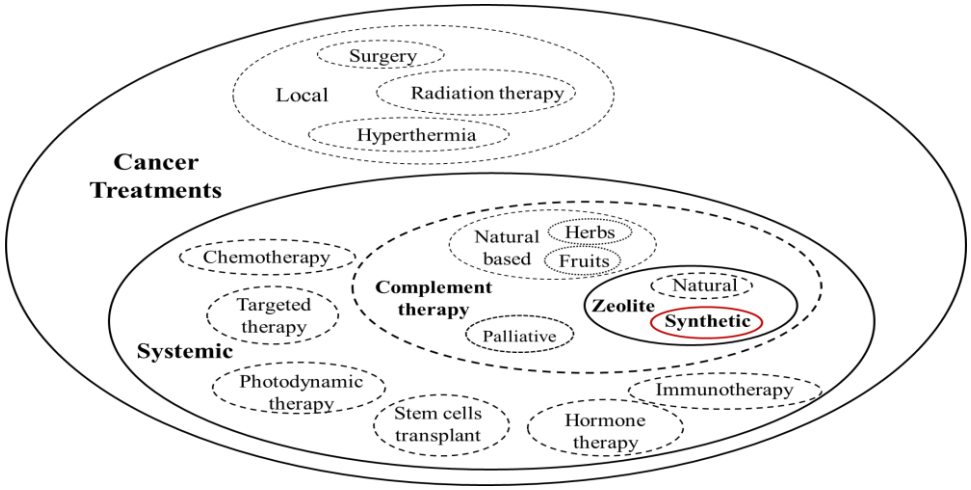

Figure 1.1 Contribution of the research

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