BIOCOMPATIBLE, ADSORPTIVE AND ANTIBACTERIAL POLYSULFONE HOLLOW FIBRE MEMBRANE INCORPORATED WITH SILICA ALPHA MANGOSTIN FOR UREMIC TOXINS REMOVAL

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ABSTRACT

Kidney failure patients rely on haemodialysis treatment to survive. However, unlike the kidney, this treatment cannot remove protein bound uremic toxins effectively and its long exposure to dialysis fluid poses risk of bacterial contamination. Hence, the main objective of this study is to develop a biocompatible, adsorptive and antibacterial polysulfone (PSf) based dual-layer hollow fibre (DLHF) membrane for efficient uremic toxins removal. In the first phase of the study, a silica nanoparticle with adsorption property was hybrid with α-mangostin via sol-gel technique, to enhance its biocompatibility. The synthesized nanoparticle had the Santa Barbara Amorphous-15 (SBA-15) mesoporous silica characteristic with particle size range of 15-25 nm, as confirmed by Fourier transform infrared spectroscopy (FTIR), particle size analysis, X-ray powder diffraction (XRD) and transmission electron microscopy (TEM). An adsorption study of a protein bound uremic toxin, namely p-cresol, and an antioxidant activity study were conducted, where the effect of α-mangostin addition was investigated. Silica nanoparticle showed the highest p-cresol adsorption capacity of 198 mg/g, followed by silica nanoparticles containing 5 wt% α-mangostin (186 mg/g) and 2 wt% α-mangostin (179 mg/g), respectively. Silica nanoparticle with 5 wt% α-mangostin prolonged the blood clotting time by 21.5% and inhibited the formation of reactive oxygen species by 36% compared to silica nanoparticle. The addition of 5 wt% α-mangostin enhanced the antioxidant property and maintained the good p-cresol adsorption capacity of silica nanoparticle. In the second phase of the study, 2 wt% silica and 1-2 wt% silica/α-mangostin nanoparticles were incorporated into PSf membrane, individually, where their effects on the surface properties, the adsorption capacity and the biocompatibility of the membrane were determined. Results showed that the membrane incorporated with 2 wt% silica/α-mangostin nanoparticle had a reduced water contact angle by 12.5%, indicating its improved surface hydrophilicity. Besides, the incorporation of silica/α-mangostin nanoparticle enhanced the p-cresol adsorption capacity of the membrane by 20.9% with the value of 56 mg/g. The silica/α-mangostin also improved the scavenging activity of hydrogen peroxide and nitrogen oxide by 61.8% and 36%, respectively and inhibited the formation of human complement fragment 5a (C5a) by 27.3%. In the final phase of the study, DLHF membranes consisting different combinations of inner and outer layers were prepared. 2 wt% of silica and activated carbon (AC) was incorporated in the outer layer of the membrane, individually, to impart antibacterial property to the membrane. Compared to the single layer hollow fibre membrane, the DLHF membranes showed 6-8% improvement of bovine serum albumin (BSA) rejection. DLHF membrane with the combination of silica/α-mangostin nanoparticle in the inner layer and AC in the outer layer possessed the highest removal of urea and creatinine throughout the 4-hour filtration. The silica/α-mangostin nanoparticle promoted the membrane's interaction with urea and creatinine via chemisorption. Moreover, the AC in the outer layer of DLHF membrane successfully filtered bacteria via bacteria entrapment. The membrane displayed the highest antibacterial capability against *Escherichia coli* and *Staphylococcus aureus*, by having an antibacterial rate of 68% and 75%, respectively. The biocompatible and adsorptive DLHF membrane was successfully developed for safe and effective removal of uremic toxins in haemodialysis application.

ABSTRAK

Pesakit buah pinggang bergantung pada rawatan hemodialisis untuk terus hidup. Namun, tidak seperti buah pinggang, rawatan ini tidak dapat membuang toksin uremik terikat protein dengan berkesan dan pendedahannya yang lama terhadap cecair dialisis menimbulkan risiko pencemaran bakteria. Oleh itu, objektif utama kajian ini adalah untuk membangunkan membran gentian berongga dwi-lapisan (DLHF) berasaskan polisulfon (PSf) yang bioserasi dan menjerap untuk penyingkiran toksin uremik. Pada fasa pertama kajian, nanozarah silika ditambahkan dengan α-mangostin semasa sintesisnya melalui teknik sol-gel, untuk meningkatkan biokeserasiannya. Nanozarah yang disintesis mempunyai ciri silika berliang meso Santa Barbara Amorphous-15 (SBA-15) dengan julat saiz zarah sebanyak 15-25 nm, seperti yang disahkan oleh spektroskopi inframerah transformasi Fourier (FTIR), analisis saiz zarah, difraksi serbuk sinar-X (XRD) dan mikroskop elektron transmisi (TEM). Kajian penjerapan toksin uremik terikat protein, iaitu p-kresol, dan kajian aktiviti antioksidan dilakukan, dimana pengaruh penambahan α-mangostin diselidiki. Nanozarah silika menunjukkan muatan penjerapan p-kresol tertinggi sebanyak 198 mg/g, diikuti oleh nanozarah silika yang mengandung 5 wt% α-mangostin (186 mg/g) dan 2 wt% α-mangostin (179 mg/g). Nanozarah silika dengan 5 wt% α-mangostin memanjangkan masa pembekuan darah sebanyak 21.5% dan menyekat pembentukan spesies oksigen reaktif sebanyak 36% berbanding dengan nanozarah silika. Penambahan α-mangostin meningkatkan sifat antioksidan dan mengekalkan keupayaan penjerapan p-kresol yang baik pada nanozarah silika. Pada fasa kedua kajian, nanozarah silika dan silika/α-mangostin dimasukkan ke dalam membran PSf, secara individu, dimana kesannya terhadap sifat permukaan, muatan penjerapan dan biokeserasian membran ditentukan. Hasil kajian menunjukkan bahawa membran yang dimasukkan dengan 2 wt% nanozarah silika/α-mangostin mempunyai sudut sentuh air yang berkurang sebanyak 12.5%, menunjukkan peningkatan hidrofilik permukaannya. Selain itu, kemasukan nanozarah silika/α-mangostin meningkatkan muatan penjerapan p-kresol membran sebanyak 20.9% dengan nilai 56 mg/g. Silika/α-mangostin juga meningkatkan aktiviti hapus sisa hidrogen peroksida dan nitrogen oksida, masing-masing sebanyak 61.8% dan 36% dan menyekat pembentukan C5a sebanyak 27.3%. Pada fasa akhir kajian, membran DLHF yang terdiri daripada kombinasi lapisan dalam dan luar yang berlainan telah disediakan. 2 wt% silika dan karbon aktif (AC) dimasukkan ke dalam lapisan luar membran, secara individu, untuk memberikan sifat antibakteria pada membran. Berbanding dengan membran gentian berongga lapisan tunggal, membran DLHF menunjukkan peningkatan penolakan albumin serum bovin (BSA) sebanyak 6-8%. Membran DLHF dengan kombinasi nanozarah silika/α-mangostin di dalam lapisan dalam dan AC di dalam lapisan luar mempunyai penyingkiran urea dan kreatinin tertinggi sepanjang 4 jam penapisan. Nanozarah silika/α-mangostin menggalakkan interaksi membran dengan urea dan kreatinin melalui penjerapan kimia. Selain itu, AC di dalam lapisan luar membran DLHF berjaya menapis bakteria melalui pemerangkapan bakteria. Membran tersebut menunjukkan keupayaan antibakteria tertinggi terhadap *Escherichia coli* dan *Staphylococcus aureus*, masing-masing dengan kadar antibakteria sebanyak 68% dan 75%. Membran DLHF yang bioserasi dan menjerap berjaya dibangunkan untuk penyingkiran toksin uremik yang selamat dan berkesan dalam aplikasi hemodialisis.

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LIST OF ABBREVIATIONS

Ab	-	Antibody
AC	-	Activated Carbon
AFM	-	Atomic Force Microscopy
APTES	-	(3-Aminopropyl) Triethoxysilane
APTT	-	Activated Partial Thromboplastin Time
ATCC	-	American Type Culture Collection
BET	-	Brunauer-Emmet-Teller
BSA	-	Bovine Serum Albumin
C5a	-	Human Complement Fragment 5a
CFU	-	Colony Forming Unit
DER	-	Dope Extrusion Rate
dH_2O	-	Distilled Water
DLHF	-	Dual-Layer Hollow Fibre
EBPG	-	European Best Practice Guidelines
EDX	-	Energy-Dispersive X-ray Spectroscopy
EU	-	Endotoxin Units
EtOH	-	Ethanol
FESEM	-	Field Emission Scanning Electron Microscopy
FTIR	-	Fourier Transform Infrared
HRP	-	Horseradish Peroxidase
HPLC	-	High Performance Liquid Chromatography
IUPAC	-	International Union of Pure and Applied Chemistry
LB	-	Luria-Bertani Broth
LPS		Lipopolysaccharides
MHA	-	Mueller-Hinton Agar
MBC	-	Minimum Bacterial Concentration
MIC	-	Minimum Inhibition Concentration
NA	-	Nutrient Agar
NB	-	Nutrient Broth
NMP	-	N-Methyl-2-Pyrrolidone

PBS	-	Phosphate Buffer Saline
PSf	-	Polysulfone
PPP	-	Platelet Poor Plasma
PRP	-	Platelet Rich Plasma
PT	-	Prothrombin Time
PVP	-	Polyvinylpyrrolidone
ROS	-	Reactive Oxygen Species
SAED	-	Selective Area Electron Diffraction
SAL	-	Sterility Assurance Level
SBA-15	-	Santa Barbara Amorphous
SEM	-	Scanning Electron Microscopy
SLHF	-	Single-Layer Hollow Fibre
SNP	-	Sodium Nitroprusside
TEM	-	Transmission Electron Microscopy
TEOS	-	Tetraethyl Orthosilicate
UF	-	Ultrafiltration
UV	-	Ultraviolet
QC	-	Quality Control
XRD	-	X-ray Power Diffraction

LIST OF SYMBOLS

A	-	Number of bacterial colonies on MHA agar plate from the solution containing bacteria
A_e	-	Effective surface area
B	-	Number of bacterial colonies on MHA agar plate from the permeate of tested membrane
b	-	Langmuir constant
C		Solute clearance
C_e	-	Equilibrium concentration
C_f	-	Concentration of feed
C_i	-	Initial concentration
C_o	-	Initial concentration
C_P	-	Permeate concentration
K_F	-	Freundlich constant
m	-	Mass
n	-	Number of trials
P	-	Pressure
q_e	-	Equilibrium adsorption capacity
Q_{max}	-	Maximum adsorption capacity
R	-	Rejection
R^2	-	Correlation coefficient
R_a	-	Average surface roughness
t	-	Time
V	-	Volume

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CHAPTER 1

INTRODUCTION

1.1 Research Background

Kidney failure has been affecting more than 750 million people worldwide and in Malaysia this disease has increased progressively each year with an average of 13.2% annual increase of treated kidney failure from 2003 to 2016 (Division *et al.*, 2018). End stage renal disease (ESRD) patients are the people whose kidney has partly or completely lost its function, and because of that, they need to do dialysis or kidney transplant to sustain their life. Approximately 98.7% of ESRD patients choose haemodialysis procedure as their prominent treatment as the chance for having a kidney transplant is very slim (Ministry of Health Malaysia, 2018). Malaysian Dialysis and Transplant Report estimated that by 2020, more than 51,000 patients on dialysis in Malaysia (Ministry of Health Malaysia, 2018).

In the past five decades, haemodialysis treatment kept on evolving in sustaining kidney patient health. Membrane technology has been used to mimic the renal function and prolong the patient's life (Kim *et al.*, 2015; Eswari and Naik, 2020). Tens of thousands of hollow fibre membrane, whose properties determine the quality of the blood filtered, are potted inside a membrane module known as haemodialyser, which is the heart of haemodialysis treatment (Ma, Khan and Hussain, 2019). The implementation of membrane technology in blood purification applications has been vital (Ronco and Clark, 2018). Blood purification is achieved by regulating impure blood flow through the lumen of hollow fibre membrane while an electrolyte solution, namely dialysate flows in a counter-current direction outside the membrane (Baldwin *et al.*, 2016). Due to the concentration difference, uremic toxins like urea, creatinine etc. are filtered out from the blood through the porous structure of the membrane into the dialysate while water and electrolytes like sodium chloride from the dialysate move into the blood (Eswari and Naik, 2020). In addition, the membrane facilitates the

filtration without the loss of important blood proteins such as human serum albumin (Tsuchida and Minakuchi, 2011). The desirable characteristics of hollow fibre membranes for haemodialysis application include high flux, excellent selectivity and good biocompatibility (Eswari and Naik, 2020).

Since the first invention of haemodialyser back in 1943 by Willem Kolff, biocompatibility issue has become a major concern (Gautham *et al.*, 2013; Pandit, Planell and Navarro, 2013). Haemodialyser is repeatedly used and even a small event that repeatedly occur each time may cause undesirable side effects such as chronic inflammation (Yamashita and Sakurai, 2015). Interactions may occur between blood and the membranes as the membranes are not inert, subsequently leading to alterations in blood elements (Felgueiras *et al.*, 2018). Blood interaction with the membranes could also lead to the development of protein adsorption (Kyriakides, 2015; Felgueiras *et al.*, 2018). When protein adsorption occurs, body immune system will activate the defence mechanism and develop events such as thrombosis, infection, and inflammation (Mariani *et al.*, 2019; Labarrere, Dabiri and Kassab, 2020; Prasadh, Ratheesh and Wong, 2020). Biocompatibility of haemodialysis membranes is mainly affected by these interactions.

Even though various types of haemodialyser have been developed, CKD patients are still facing with multiple clinical complications such as heart disease, bone disease, amyloidosis and nerve damage (Arnold *et al.*, 2016). These diseases have been associated with the existence of the small molecule uremic toxins in the patients especially in cardiovascular events. Cardiovascular disease has been responsible for approximately half of the deaths of haemodialysis patients. The presence of small and middle molecule uremic toxins problems in blood can be solved using a high flux haemodialyser which consists of membranes with bigger pore size and increased applied convection. However, the increase in applied convection does not improve the removal of protein bound uremic toxins. Due to its affinity to protein, this class of uremic toxins is hardly removed using conventional haemodialysis membranes. It is also found that most protein bound uremic toxins are carcinogenic and could affect the renal patient's mortality (Dhondt *et al.*, 2000). To date, many studies focused on removing protein bound uremic toxins using sorbent hemoperfusion. This method

utilises adsorption process using nano porous adsorbents, in direct contact with blood, to remove the uremic toxins (Park *et al.*, 2016). However, most adsorbents are bio-incompatible as they promote platelet activation and thus increase the risk of blood clotting (Park *et al.*, 2019).

Biocompatibility of the materials used to prepare haemodialysis membrane is paramount to prevent from producing adverse health effects to the renal patients. Bio-incompatibility between membrane polymer and blood sample will cause a rapid adsorption of protein onto the membrane surface due to the hydrophobicity of polymeric and eventually platelets coagulation will occur on the surface of membrane. Besides, membrane fouling can happen due to the adsorption of non-polar solutes and hydrophobic bacteria on the membrane surface. This fouling problem will reduce the lifetime expectancy of the membrane. Thus, in this study, the polymeric membrane was modified by blending with hydrophilic polymer such as polyvinylpyrrolidone (PVP) and incorporating inorganic particles to overcome the limitations of polymeric membrane.

Furthermore, haemodialysis patients are exposed to approximately 300 – 600 L of water (dialysate) a week during the haemodialysis treatment (Coulliette and Arduino, 2013). This high exposure to water increases the possibility of contamination to waterborne pathogens during the treatment. Hence, the quality of dialysate is one of the important factors that needs to be taken seriously. Bacterial endotoxin in dialysate may pass through haemodialysis membrane into the patient's blood and cause a silent chronic microinflammation to the kidney patients. The interaction between endotoxin and blood may potently initiate the activation of pro-inflammatory cytokines from monocyte (Abe *et al.*, 2017). High concentration of cytokines (Interleukin-1, Interleukin-6 and TNF-alpha) may induce acute and chronic side effects to the haemodialysis patients.

Recently, there were few attempts to utilise mixed matrix membrane (MMM) for haemodialysis application. The incorporation of inorganic nanomaterial in polymeric membrane has shown promising results in terms of the separation characteristic and performance. Silica nanoparticle is biocompatible, chemically

stable, and highly adsorptive. Based on a review done by Weber *et al.* (2018), a small portion of silica adsorbed to the surface of erythrocytes without altering the cell membrane or morphology (Weber *et al.*, 2018). Furthermore, silica has been widely used in cosmetics as well as food additives. Hybrid silica and other organic/inorganic materials have also been safely used in various applications including enzyme encapsulation.

1.2 Problem Statement

The advancement in the development of haemodialysis membrane has provided better removal of uremic toxins for end-stage renal disease patients. The manipulation of the pore size and permeability of the membrane producing high flux hemodialyzer that are able to remove widest range of uremic toxins by allowing high fluid flow and convective transport. Urea normal level in the blood for a healthy person, in general is approximately around 7 – 20 mg/dL (Amin *et al.*, 2014). Meanwhile, the normal range for creatinine in the blood is approximately around 0.84 – 1.21 mg/dL. In addition, accumulation of p-cresol in blood has been associated not only in the progression of chronic kidney disease, but also in the development of cardiovascular disease among haemodialysis patients. Elevated concentration of these uremic toxins indicated impaired kidney function (Kaysen, 2001; Meijers *et al.*, 2008). At the same time, there are proteins that need to be retained during haemodialysis ranging from size 64-66 kDa (Tanaka *et al.*, 2014). Clearance of these uremic toxins and retention of protein through semi-permeable haemodialysis membrane need to be achieved. However, there are concern in the use of high flux hemodialyzer as water pathogens can enter from the dialysate into the blood by back filtration (convective transfer) and back diffusion (movement down the concentration gradient). In conventional haemodialysis centre setting, dialysate undergo water treatment and ultrafilter/endotoxin-retentive filter to remove bacteria and endotoxin by using a positively charged filter surface and size exclusion prior delivery to the hemodialyzer. The delivery of dialysate into hemodialyzer can either be indirect or direct system. Indirect system is preferable and safer as the water constantly circulate through reverse osmosis treatment and ultrafilter, even when the machines are in not use. While direct

delivery system is one way system and water become stagnant when the machines are in not use. Consequently, stagnant water contributes to the formation of microbiological biofilm. Unfortunately, poor dialysate delivery system of using direct system and poor maintenance in some developing countries are unavoidable.

In recent years, some strategies to retained and removed endotoxin from the dialysate have been studied by using sorbent or adsorptive membrane. Dialysate passed through these adsorptive filters before entering the hemodialyzer. Based on the study done by Das et al., activated carbon also showed good bactericidal or killing percentage against the commonly available waterborne pathogen *Escherichia coli* (around 43%) even without incorporation of any metals in it (Cai *et al.*, 2017; Geremia, Bansal and Stamatialis, 2019). However, direct contact of activated carbon with blood may induce bio-incompatibility of the membrane (Tijink, Wester, Sun, Saris, L. A. M. Bolhuis-Versteeg, *et al.*, 2012a). Therefore, the idea of developing dual-layer hollow fibre (DLHF) membrane which consist of AC on the membrane outer layer was proposed (Fahmi *et al.*, 2018) to prevent direct contact of AC with blood. The membrane will be thick and high concentration of AC with antibacterial properties was concentrated on the outer layer of the membrane to inhibit the bacteria or endotoxin transfer. Geometrical structure of membrane fibre plays an important role in the ability of the membrane to inhibit bacteria or endotoxin transfer. A study done by Henrie et. al. stated that there is presence of endotoxin in the blood circuit sample of mostly available haemodialysis membrane in the market except for thick-wall membrane (Henrie *et al.*, 2008).

To achieve both biocompatible membrane with better clearance of uremic toxins and prevention of bacterial penetration into blood compartment, DLHF membranes with different outer layer composition was developed. Novel biocompatible silica/α-mangostin nanoparticle was incorporated into the inner layer of the membrane to enhance the biocompatibility of the membrane when in contact with blood while maintaining its adsorption capacity. Silica is a good adsorbent towards both urea and creatinine. Hiue et al. showed that silica (modified mesoporous silica SBA-15) has the adsorption capacity for urea and creatinine, 1644.7 and 181.7 mg/g, respectively (Hieu *et al.*, 2021). Hassankhani et al. proved that silica nanoparticle has

no hematological, histopathological or biochemical alterations in various organs. However, 10 – 15 nm silica nanoparticles are able to exert toxic effects (Hassankhani *et al.*, 2014). Thus, some modification on the silica nanoparticles with alpha mangostin was done to enhance its biocompatibility (Kankala, Lin and Lee, 2020). Alpha mangostin is a bioactive compound that can be extracted from mangosteen pericarp (Ghasemzadeh *et al.*, no date). It has various pharmacological activities, including antioxidant, anticancer, anti-inflammatory, and antimicrobial (Ngawhirunpat *et al.*, 2010; Aizat, Jamil and Ahmad-hashim, 2019). The presence of this bioactive compound at the membrane surface can enhance the biocompatibility of the membrane, hence minimizing the biocompatibility issues of haemodialysis membrane. AC were incorporated in the outer layer of the membranes and bacteria filtration for the membrane was done. To avoid delamination of DLHF membrane, PSf polymer was used as the main polymer for both inner and outer layer of the membrane. The morphological structure, performances of the membrane to remove uremic toxins (urea and creatinine) and the bacteria filtration capability of the membrane were evaluated and compared to single layer hollow fibre membrane. A summary of this whole study is shown in Figure 1.1.

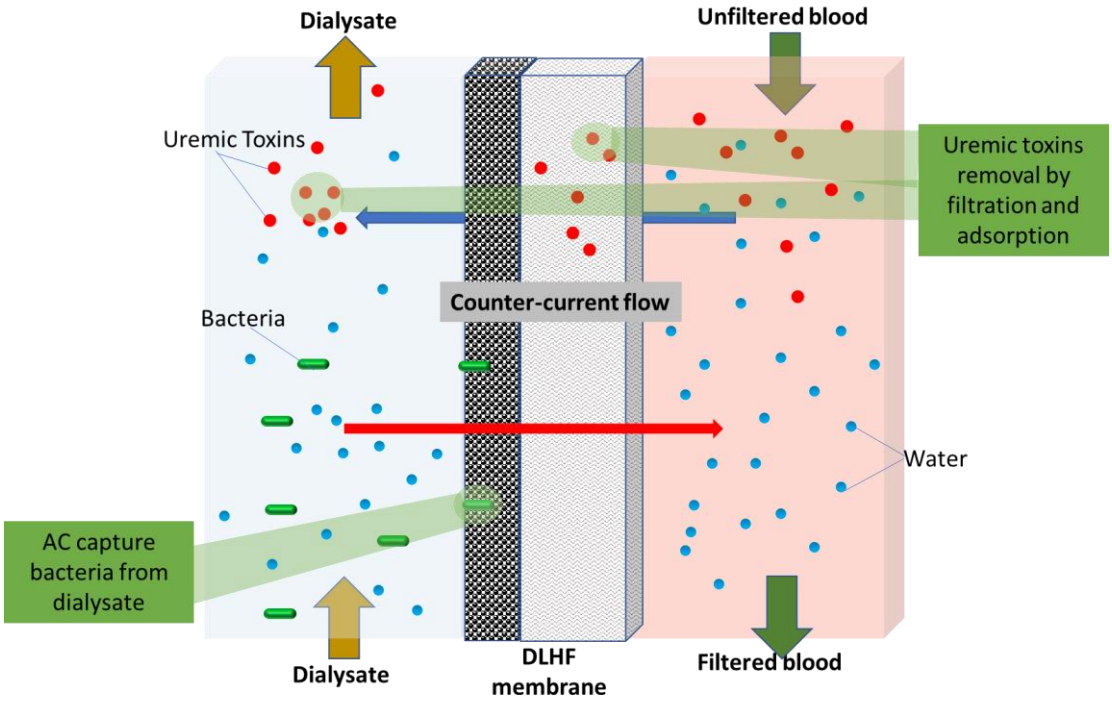

Figure 1.1 Illustration showing the summary of the whole study

1.3 Research Objectives

The main objective of this study is to fabricate a biocompatible, adsorptive and antibacterial PSf based DLHF membrane embedded with inorganic particles via a single-step co-extrusion technique for haemodialysis application. The specific objectives of this study are:

(a) To assess the effect of silica nanoparticle modification with α-mangostin at various concentrations on the nanoparticle biocompatibility and adsorption capacity towards p-cresol.

(b) To investigate the effect of silica and modified silica nanoparticles addition on the separation performance, adsorption capacity and biocompatibility of the resultant single layer hollow fibre (SLHF) membrane.

(c) To examine the effect of different combinations of inner and outer layer compositions on the dialysis performance and antibacterial property of the resultant DLHF membrane.

1.4 Scopes of the Study

(a) Studying the effect of silica nanoparticle modification with α-mangostin at various concentrations on the nanoparticle biocompatibility and adsorption capacity towards p-cresol.

   i. Synthesising silica nanoparticle via sol-gel process and modifying the silica nanoparticle during the process via the addition of 2 and 5 wt% α-mangostin to form silica/α-mangostin nanoparticle.

   ii. Characterising silica and silica/α-mangostin nanoparticles by analysing the chemical functionality, particle size and surface charge measurement, crystalline structure, pore and surface analysis, surface/cross-section morphology and elemental composition.

iii. Conducting the adsorption isotherm studies of p-cresol on the silica and silica/α-mangostin nanoparticles by varying the initial p-cresol concentration (0-250 mg/L) and studying the effect of contact time (0-24 hours) on the p-cresol adsorption capacity.

iv. Determining the biocompatibility of silica and silica/α-mangostin nanoparticles by analysing the nitric oxide (NO) and hydrogen peroxide (H_2O_2) scavenging activities and the blood clotting time.

(b) Investigating the effect of silica and modified silica nanoparticles addition on the separation performance, adsorption capacity and biocompatibility of the resultant SLHF membrane.

i. Preparing several dope solutions containing 18 wt% PSf, 3 wt% PVP and different loadings of silica or silica/α-mangostin nanoparticles (0, 1 and 2 wt%) using N-methyl-2-pyrrolidone (NMP) as solvent.

ii. Fabricating SLHF membranes of different nanoparticles (silica and silica/α-mangostin) via the dry-wet spinning technique at 50 cm air gap distance, 8 ml/min inner dope extrusion rate (DER), 8 ml/min bore fluid flow rate and 4 rpm take-up speed.

iii. Examining the morphology of SLHF membranes by scanning electron microscopy (SEM), surface hydrophilicity using contact angle goniometer, water permeability and bovine serum albumin (BSA) rejection.

iv. Evaluating the separation performance of SLHF membranes in terms of urea and creatinine removal by filtration at the pressure of 0.5 bar using crossflow filtration system.

v. Determining the adsorption capacity of SLHF membranes on p-cresol by varying the initial p-cresol concentration (0-250 mg/L) and studying the effect of contact time (0-24 hours).

vi. Conducting the dynamic adsorption-filtration performance of SLHF membranes for p-cresol removal by filtration of 500 ppm p-cresol solution at 0.5 bar for 20 minutes time intervals.

vii. Evaluating the biocompatibility of SLHF membranes based on the results of platelet adhesion, NO and H_2O_2 scavenging activity, and human complement fragment 5a (C5a) activation.

(c) Examining the effect of different combinations of inner and outer layer compositions on the dialysis performance and antibacterial property of the resultant DLHF membrane.

i. Preparing inner dope solutions containing 18 wt% PSf, 3 wt% PVP, and the optimised silica/α-mangostin nanoparticle composition, and several outer dope solutions containing 18 wt% PSf, 5 wt% PVP and 2 wt% different types of inorganic particle (silica or activated carbon), using NMP as solvent.

ii. Fabricating DLHF membranes with different combinations of inner and outer layer compositions via one-step co-extrusion technique using a triple orifice spinneret at 50 cm air gap distance, 8 ml/min inner dope extrusion rate (DER), 1 ml/min outer DER, 8 ml/min bore fluid flow rate and 4 rpm take-up speed.

iii. Characterising the DLHF membranes in terms of morphology, surface hydrophilicity, water permeability and BSA rejection.

iv. Conducting 4 hours of dialysis experiment on the DLHF membranes using a feed solution containing a mixture of red blood cell, 0.9% saline solution, 1500 ppm urea, 1000 ppm creatinine, 500 ppm p-cresol and 500 ppm BSA.

v. Evaluating the antibacterial property of the DLHF membranes by in-vitro filtration using dialysate contaminated with approximately 1 – 2 x 10^8 CFU/mL bacterial culture of *E. coli* and *S. aureus* as feed.

1.5 Significance of the Study

The rationale of this research is to explore the development of biocompatible and adsorptive membranes for haemodialysis application. This study would have brought upon a huge importance towards multiple fields of research which includes nanotechnology, membrane technology and nephrology. The primary outcome of the research would benefit the scientific community in the sense of filling in the knowledge gap in those fields. The employment of biocompatible organic-inorganic nanofiller in hemodialysis membrane for instance could progressively diversify its potential in this biomedical-device application. The ingenious approach which combined both unique properties of inorganic nanoparticle and versatility of polymer as a host showed great potential to combat the biocompatibility issues commonly faced by polymeric membranes. In addition, the research on haemodialysis membranes in Malaysia is still at early stages and there is no large-scale initiative to utilise local experts in membrane technology for haemodialysis application. Hence, this novel invention is believed to become a steppingstone which could provide a valuable information for membranologists and lead the way to further study. The aftermath of the research will also benefit the ESRD patients by providing a biocompatible haemodialysis membrane that is capable and reliable to perform exceptional blood purification with minimal adverse effect. Therefore, this research's long-term target is to develop a locally made dialyser equipped with a highly efficient membrane to sustain the current demand, especially in Malaysia. Triggered by the general necessities of serving the social community, the study would attract companies that manufacture or supply medical equipment as a platform to patent and market the product.

1.6 Organisation of Thesis

The thesis consists of 7 chapters altogether. Chapter 1 outlines brief information on the current issues that are related to haemodialysis and the purpose of conducting this research. The objectives, scopes and the significance of this study have also been highlighted in this chapter. Chapter 2 includes a comprehensive review on

how membrane works in haemodialysis treatment, haemodialysis membrane compatibility with blood and current membrane technology in removing uremic toxins for haemodialysis application. Chapter 3 describes all the materials, experimental set ups, working procedures and characterisation methods that were used in this study.

Results and discussion were elaborated in Chapter 4 – Chapter 6. Chapter 4 discusses the effect of silica nanoparticle modification via the incorporation of 2 wt% and 5 wt% α-mangostin, on the p-cresol adsorption capacity and the in-vitro biocompatibility of the nanoparticle. The optimum α-mangostin weight percent was selected and was used to fabricate the SLHF membranes in Chapter 5. Chapter 5 focusses on the effect of silica and modified silica nanoparticles addition on the separation performance, adsorption capacity and biocompatibility of the SLHF membranes. The optimum SLHF membrane composition was then used for the preparation of DLHF membrane inner layer in Chapter 6. The development of DLHF membranes consisting different combinations of inner and outer layers were prepared in Chapter 6. The effect of silica and activated carbon incorporation in the outer layer on the dialysis performance and antibacterial property of the DLHF membranes were addressed. To conclude this thesis, the general conclusion of this study and some recommendations for future work have been listed in Chapter 7.

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LIST OF PUBLICATIONS

Journal with Impact Factor

1. **Mansur, S**., Othman, M. H. D., Ismail, A. F., Kadir, S. H. S. A., Goh, P. S., Hasbullah, H., Ng, B. C., Abdullah, M. S. (2016). Investigation on the effect of spinning conditions on the properties of hollow fiber membrane for hemodialysis application. Journal of Applied Polymer Science, 133(30), pp. 1–12.
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2. **Mansur, S**., Othman, M. H. D., Ismail, A. F., Kadir, S. H. S. A., Goh, P. S., Hasbullah, H., Ng, B. C., Abdullah, M. S., Kamal, F., Abidin, M. N. Z. Retno, A. L. (2019). Synthesis and characterisation of composite sulphonated polyurethane/polyethersulfone membrane for blood purification application. Journal of Materials Science and Engineering C, 99, pp. 491–504.
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3. **Mansur**, S., Othman, M., Abidin, M., Ismail, A., Abdul Kadir, S., Goh, P., Hasbullah, H., Ng, B., Abdullah, M. and Mustafar, R., 2021. Enhanced adsorption and biocompatibility of polysulfone hollow fibre membrane via the addition of silica/alpha-mangostin hybrid nanoparticle for uremic toxins removal. *Journal of Environmental Chemical Engineering*, 9(5), p.106141.
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1. **Mansur, S**., Othman, M. H. D., Ismail, A. F., Kadir, S. H. S. A., Goh, P. S., Hasbullah, H., Ng, B. C., Abdullah, M. S., Kamal, F. (2018). Study on the effect of pvp additive on the performance of psf / pvp ultrafiltration hollow fiber membrane, Malaysian Journal of Fundamental and Applied Science, 14(3), pp. 343–347. **(Indexed by SCOPUS)**

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2. **Mansur, S**., Othman, M. H. D., Ismail, A. F., Kadir, S. H. S. A., Goh, P. S., Hasbullah, H., Ng, B. C., Abdullah, M. S., Abidin, M. N. Z., Asraf, M. H. (2021). Bacteria entrapment by co-adsorptive biocompatible dual-layer hollow fibre haemodialysis membrane. Journal of Taiwan Institute of Chemical Engineering.

Book Chapter

1. Ismail, A. F., Abidin, M. N. Z., **Mansur, S**., Zailani, M. Z., Said, N., Raharjo, Y., Rosid, S. M., Othman, M. H. D., Goh, P. S., Hasbullah, H. (2018). Hemodialysis membrane for blood purification in *Handbooks in Separation Science: Membrane Separation Principles and Applications from Material Selection to Mechanisms and Industrial Uses*, 283-309, ISBN: 978-0-12-812815-2. **(ELSEVIER)**