SENOLYTIC AND MITOGENIC ACTIVITIES OF *Moringa oleifera Lam.* LEAF EXTRACT ON CULTURE EXPANDED AND DOXORUBICIN OXIDATIVE STRESS-INDUCED UMBILICAL CORD MESENCHYMAL STEM CELLS

By

MUHAMMAD UMAR ADAMU

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirement for the Degree of Doctor of Philosophy

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DEDICATION

In memory of my late twin sister Zainab Muhammad Adam

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

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August 2022

Chairman : Assoc. Prof. Rajesh Ramasamy, PhD
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Mesenchymal stem cells are potent tools in tissue engineering, regenerative medicine, and drug discovery. The *ex-vivo* expansion of MSCs has become necessary to harvest a desirable number of cells for research or clinical use. However, the *ex-vivo* expansion of MSCs remains a challenge due to decreased cell proliferation due to cellular senescence. Several approaches to mitigate such effects abound, including hypoxia cell culture environment, modification of cell culture surfaces, and the use of small molecules. The use of small molecules is promising because of convenience, cost, and broad applicability compared to other approaches. Interestingly, polyphenols such as quercetin and astragalin are the leading small molecule candidates with senolytic and mitogenic activities that promote laboratory-based cell propagation. Hence, the objective of this study was to evaluate the activity of *Moringa oleifera* leaves ethanolic extract (MOEE), enriched with polyphenols, on proliferation and antisenescence of MSCs.

Moringa oleifera ethanolic leaves extract (MOEE) was subjected to UHPLC/MS and HPLC to identify and quantify constituent polyphenolic compounds. Next, UC-MSCs were generated by explant method and characterized by immunophenotyping and mesodermal differentiation assays. UC-MSCs were subjected to serial passaging and in parallel treated with DOX to induced oxidative stress and, thereafter treated with MOEE for 48 h and 72 h respectively to examine its effects on proliferation, reactive oxygen species generation, apoptosis, stemness, replicative stress and oxidative stress induced senescence as well as gene expressional changes. Cytotoxicity of MOEE was measured by MTT assay while proliferation was assessed by DNA content analysis, cell cycle analysis, and population growth kinetics. Apoptosis assay was measured by annexin-V/PI assay, reactive oxygen species generation (ROS) by 2'7' dichlorofluorescin diacetate (DCFH-DA) assay, stemness was measured by immunophenotyping of hMSCs surface markers, followed by cellular senescence evaluated by β-galactosidase staining and C12FDG assay, while senescence-associated

secretory phenotype was gauged by cytokine bead array (CBA) test. Gene expression of NRF2 and FOXO3a was evaluated by RT-qPCR.

Eight polyphenols were identified by UHPLC/MS among which astragalin and quercetin were quantified by HPLC. Supplementation with graded concentration of MOEE (100, 10, 1, 0.1 μg/mL) for 48 hours profoundly improved the proliferation and viability of culture expanded late passaged UC-MSCs (P7-P10) compared to early passage MSCs (P3-P6) with an IC50 of 840 μg/mL. These findings were corroborated with a decrease in culture-induced early apoptotic cells in the late passage UC-MSCs and increased S-phase cells of the cell cycle. Further, it improves the population growth kinetics in the late passage UC-MSCs, maintain their stemness, and enhances their osteogenic differentiation *via* increase expression of CD73 surface marker. MOEE also decrease the release of interleukin 6, however it does not retard the accumulation of senescent cells in culture expanded late passaged UC-MSCs.

In doxorubicin induced oxidative stress senescence model, administration of MOEE (100, 10, 1, 0.1 μg/mL) for 72 hours improves viability of UC-MSCs in the oxidative stress microenvironment through the scavenging of reactive oxygen species. Similarly, MOEE mitigated cell cycle arrest by enhancing their re-entry to the S-Phase of the cell cycle and prevent apoptosis induced by ROS accumulation. Interestingly, MOEE blocks senescence development in oxidative stress environment (decrease β-galactosidase expression and decrease percentage of senescent cells) as well as the secretion of senescence-associated secretory phenotype: IL-1β, IL-6 and IL-8— known to spread senescence to neighbouring healthy cells. Gene expression studies implicate the involvement of FOXO3a, an antiaging and antioxidant transcription factor, and NRF2, a master regulator of the antioxidant gene as the possible transcriptional factors upregulated by MOEE to exerts its effects in the oxidative stress milieu.

MOEE administration in standard laboratory conditions promotes the proliferation and viability of late passage UC-MSCs, prevents culture-induced apoptosis, and enhances the osteogenic differentiation ability of MSCs. Furthermore, when UC-MSCs are challenged with oxidative stress, MOEE prevents the senescence and apoptosis of MSCs, promotes their entry to the cell cycle, and improves the expression of transcriptional factors that enhance the antioxidative and antisenescence status of UC-MSCs. The laboratory investigation has explored the potential use of MOEE in propagating UC-MSCs; hence it can be further evaluated in GMP conditions to assure safe clinical-scale manufacturing. However, it is vital to ascertain the safe use of MOEE through genetic screening and animal model-based evaluation to conclude their mitogenic and senolytic activities.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

AKTIVITI SENOLITIK DAN MITOGENIK EKSTRAK ETANOLIK DAUN *Moringa oleifera* (MOEE) DALAM PERTUMBUHAN KULTUR SEL INDUK MESENKIMA TALI PUSAT (UC-MSCS) DENGAN TEKANAN OKSIDATIF DOXORUBICIN

Oleh

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Sel induk mesenkima (MSC) merupakan alatan yang penting dalam kejuruteraan tisu, perubatan regeneratif, dan penemuan ubatan baru. Pertumbuhan MSC secara *ex-vivo* adalah diperlukan untuk menuai sejumlah sel yang diingini bagi tujuan penyelidikan atau kegunaan klinikal. Walau bagaimanapun, pertumbuhan MSC secara *ex-vivo* adalah mencabar kerana percambahan sel yang menurun akibat proses penuaan sel. Terdapat beberapa pendekatan untuk mengurangkan kesan tersebut, termasuk penggunaan persekitaran kultur sel hipoksia, pengubahsuaian permukaan kultur sel dan penggunaan molekul kecil. Penggunaan molekul kecil memberi penambahan sel yang menggalakkan dan sesuai digunakan kerana faktor kesesuaian, kos, dan kebolehgunaannya yang luas berbanding dengan pendekatan yang lain. Polifenol seperti kuersetin dan astragalin merupakan contoh molekul kecil dengan aktiviti senolitik dan mitogenik yang mampu menggalakkan percambahan sel dalam makmal. Oleh itu, objektif kajian ini adalah untuk menilai aktiviti ekstrak etanolik daun *Moringa oleifera* (MOEE), yang diperkaya dengan polifenol, terhadap percambahan dan penuaan sel MSC.

Ekstrak etanolik daun *Moringa oleifera* (MOEE) telah dianalisa menggunakan UHPLC/MS dan HPLC untuk mengenal pasti dan mengira komponen sebatian polifenolik. UC-MSC dihasilkan menggunakan kaedah eksplan dan dicirikan menerusi teknik imunofenotaip berserta dengan ujian pembezaan mesoderma. UC-MSC telah disubkultur secara bersiri, selari dengan tekanan oksidatif cetusan DOX dan dirangsang dengan MOEE selama 48 jam dan 72 jam untuk mengkaji kesannya terhadap percambahan, penjanaan spesies oksigen reaktif (ROS), apoptosis, keindukan, tekanan replikatif, penuaan akibat tekanan oksidatif dan perubahan ekspresi gen. Sitotoksisiti MOEE diukur melalui ujian MTT manakala percambahan sel dinilai berdasarkan analisis kandungan DNA, analisis kitaran sel dan kinetik pertumbuhan populasi. Apoptosis diukur dengan ujian annexin-V/PI, penjanaan ROS menggunakan ujian 2'7'

dichlorofluorescin diacetate (DCFH-DA), dan keindukan dinilai menerusi imunofenotaip penanda permukaan hMSC. Penuaan selular dikenal pasti menggunakan pewarnaan β-galactosidase dan ujian C_{12}FDG manakala fenotip rembesan berkaitan dengan penuaan dianalisa dengan ujian manik sitometrik (CBA). Ekspresi gen NRF2 dan FOXO3a telah dinilai menggunakan RT-qPCR.

Astragalin dan kuersetin merupakan antara lapan polifenol yang telah dikenal pasti dan dikira oleh UHPLC/MS. Rangsangan dengan MOEE menggunakan kepekatan berperingkat (100, 10, 1, 0.1 μg/mL) selama 48 jam telah meningkatkan percambahan dan daya maju kultur UC-MSC pasaj lewat (P7-P10) berbanding dengan MSC pasaj awal (P3-P6), dengan IC_{50} sebanyak 840 μg/mL. Penemuan ini disokong dengan penurunan sel apoptosis awal kultur dalam UC-MSC pasaj lewat dan peningkatan sel fasa S dalam kitaran sel. Selain itu, MOEE telah meningkatkan kinetik pertumbuhan populasi dalam UC-MSC pasaj lewat, mengekalkan keindukannya serta meningkatkan pembezaan osteogenik sel melalui peningkatan ekspresi penanda permukaan CD73. MOEE juga mengurangkan pembebasan interleukin 6, namun ia tidak melambatkan pengumpulan sel-sel tua dalam kultur UC-MSC pasaj lewat.

Dalam model penuaan tekanan oksidatif oleh doxorubicin, rangsangan MOEE (100, 10, 1, 0.1 μg/mL) selama 72 jam telah meningkatkan daya maju UC-MSC dalam persekitaran mikro tekanan oksidatif menerusi penghapusan ROS. MOEE juga telah mengurangkan penghentian kitaran sel dengan meningkatkan kemasukan semula sel ke dalam fasa S kitaran sel dan mencegah apoptosis akibat pengumpulan ROS. MOEE menyekat perkembangan penuaan dalam persekitaran tekanan oksidatif (penurunan ekspresi β-galactosidase dan penurunan peratusan sel-sel tua) serta rembesan fenotip berkaitan dengan penuaan seperti IL-1β, IL-6 and IL-8 yang diketahui boleh menyebarkan penuaan kepada sel-sel sihat yang berhampiran. Kajian ekspresi gen menunjukkan penglibatan FOXO3a, sejenis faktor transkripsi anti-penuaan dan anti-oksidan, dan NRF2, sejenis pengawal selia utama gen anti-oksidan, sebagai factor-faktor transkrip yang berkemungkinan besar dipertingkatkan oleh MOEE untuk memberikan impak ke atas persekitaran tekanan oksidatif.

Rangsangan MOEE dalam keadaan makmal piawai menggalakkan percambahan dan daya maju MSC pasaj lewat, menghalang apoptosis disebabkan oleh kultur dan meningkatkan keupayaan pembezaan osteogenik MSC. Walau bagaimanapun, apabila MSC diberikan tekanan oksidatif, MOEE menghalang proses penuaan dan apoptosis MSC, menggalakkan kemasukan sel ke dalam kitaran sel dan meningkatkan ekspresi faktor transkripsi yang meningkatkan status anti-oksidatif dan anti-penuaan UC-MSC. Kajian ini telah meneroka potensi penggunaan MOEE dalam pertumbuhan MSC. Oleh itu, penilaian lebih lanjut dalam keadaan GMP boleh dilaksanakan untuk memastikan pembuatan berskala klinikal. Namun, untuk memastikan penggunaan MOEE adalah selamat, saringan genetik dan penilaian berasaskan model haiwan adalah penting untuk lebih memahami aktiviti mitogenik dan senolitiknya.

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Date: 11 May 2023

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53BP1	Tumour suppressor p53-binding protein one
Aβ1-42	Amyloid-beta 1-42
AdMSCs	Adipose tissue derived MSCs
AIMP3	Aminoacyl-tRNA synthetase-interacting multifunctional protein 3
AKT	Protein kinase B
ALP	Alkaline phosphatase
AMSCs	Amniotic fluid MSCs
ANOVA	Analysis of variance
Apaf-1	Apoptotic peptidase activating factor 1
ARE	Antioxidant response element
AS	Ankylosing spondylitis
ATM	Ataxia telangiectasia mutated protein
BAX	BCL associated X protein
BCL-2	C-cell lymphoma 2
BCL-xL	B-cell lymphoma extra large
BD	Becton and Dickson
BMECs	bovine mammary epithelial cells
BMI1	proto-oncogene polycomb ring finger
BM-MSC	Bone marrow MSC
BV-2	Microglial derived cell from C57/BL6
C_{12}FDG	C_{12} fluorescein-di-β-D-galactopyranoside
CAT	Catalase
CBA	Cytometric bead array
CD105	Cluster of differentiation 105

CD44	Cluster of differentiation 44
CD9	Cluster of differentiation 9
CD90	Cluster of differentiation 90
Cdc42	control protein 42 homologs
CDK 4 and 6	Cyclin-dependent kinase 4 and 6
CDKN1A	Cyclin-dependent kinase inhibitor 1A
CDKN2A	Cyclin-dependent kinase inhibitor 2A
cDNA	Complementary DNA
CNA	Copy number alteration
CoCl2	Cobalt chloride
CoQ10	Co-enzyme Q10
COX1	cyclooxygenase 1
CpG	Cytosine nucleotide adjacent to guanine nucleotide
DAF-16	Ortholog for FOXO family
DEHP	Diethylhexyl phthalate
DMEM-LG	Dulbecco's modified eagle medium-low glucose
DMSO	Dimethyl Sulfoxide
DNA	Deoxyribonucleic acid
DNMT1	DNA methyltransferase 1
DNMT2	DNA methyltransferase 2
DNMT3a	DNA methyltransferase 3a
DNMT3b	DNA methyltransferase 3b
DOX	Doxorubicin
DPI	Diphenyleneiodonium
DPPH	2, 2 diphenyl-1-picrylhydrazyl

DSB	DNA double-strand break
E2F	E2F transcription factor 1
EFNB1	Ephrins
ERα	Estrogen receptor alpha
Erk1/2	Extracellular signal-regulated protein kinase 1 and 2
ERP46	ER-resident protein 46
ERRα	Estrogen-related receptor alpha
EVs	Extracellular vesicles
FBS	Foetal bovine serum
FGF21	Fibroblast growth factor 21
FITC	Fluorescein isothiocyanate
FOXO	Forkhead box
FOXO3a	Forkhead box 3a
FRAP	Fluorescence recovery after photobleaching
G1 phase	Growth phase 1
GAPDH	Glyceraldehyde 3-phosphate dehydrogenase
GATA4	GATA binding protein 4
GFAP	Glial fibrillary acidic protein
γH2AX	H2A histone family member X
GIs	G protein subunit alpha
GPx	Glutathione peroxidase
H1	Histone 1
H2A	Histone 2A
H2B	Histone 2B
H_2O_2	Hydrogen peroxide

H3	Histone 3
H3K27me	Methylate histone 3 at lysine residue 27
H3K9Me2/3	Lysine 9 di-tri methylated histone 3
H4	Histone 4
HaCaT	Human epidermal keratinocytes
HBSS	Hanks balanced salt solution
HDAC1	Histone deacetylase 1
HGPS	Hutchinson-Gilford progeria syndrome
HMGA	High mobility group A
hMSCs	Human mesenchymal stem cells
HO-1	Hemeoxygenase-1
HP1	heterochromatin protein 1
HPLC	High performance liquid chromatography
HUVEC	Human umbilical vein endothelial cells
IDO	Indoleamine 2,3 dioxygenase
IFNβ	Interferon-beta
IGF	Insulin growth factor
IGFBP3	Insulin growth factor binding protein 3
IL-10	Interleukin 10
IL-12p70	Interleukin 12 p70
IL-1β	Interleukin-1 beta
IL-6	Interleukin 6
IL-8	Interleukin 8
iNOS	Inducible nitric oxide synthase
JAK 1	Janus Kinase 1

JNK	Mitogen activated protein kinase 8
Ki-67	Antigen KI-67
KIM-1	Kidney injury molecule 1
KLF4	Kruppel like factor 4
LPA	Lysophosphatidic acid
MBPs	Methyl-CpG-binding proteins
MC3T3-E1	Osteoblast precursor cell line from mouse
MDA	Malonaldehyde
MEM	Minimum essential medium
MFN1	Mitofusin 1
MMP9	Matrix metalloproteinase 9
MnSOD	Manganese superoxide dismutase
MOEE	70% ethanolic leaves extract of *Moringa oleifera*
mTOR	Mammalian target of rapamycin
MVs	Microvesicles
NAD	Nicotinamide adenine dinucleotide
NANOG	Nanog homeobox
NFκβ	Nuclear factor kappa beta
NRLP3	NLR pyrin family
NMNAT3	Nicotinamide adenosyl transferase 3
NOS	Nitric oxide synthase
NRF2	Nuclear factor 2 erythroid factor 2
NSE	Enolase
OCT-4	POU class five homeobox 1
OH	Hydroxyl radical
OPA1	Dynamin-related GTPase

OSIPS	Oxidative stress-induced premature senescence
p16INK4a	Cyclin-dependent kinase inhibitor 2A
p21CIP1	Cyclin-dependent kinase inhibitor 1A
p38MAPK	Mitogen-activated protein kinase 14
p53	Tumour protein P53
PAI	Plasminogen activated inhibitor 2
PBS	Phosphate buffered saline
PcG	Cytochrome P450 family 1 subfamily B member 1
PGC1α	PPARG Coactivator 1 alpha
PI	Propidium Iodide
PI3Kδ	Phosphoinositide 3-kinase delta
PPARα	Peroxisome proliferator-activated receptor alpha
RNA	Ribonucleic acid
ROS	Reactive oxygen species
ROS	Reactive oxygen species
RT	qPCR Real time quantitative polymerase chain reaction (RT-qPCR)
Runx2	RUNX family transcription factor
S phase	synthetic phase
SA-β-gal	Senescence associated b-galactosidase
SAHF	Senescence-associated heterochromatin foci
SASPS	Senescence associated secretory phenotype
SCAPs	Senescence cell anti-apoptotic signals
SH-SH5Y	Human neuroblastoma
SIR 2.1	Serpin family A member 2.1
SIRT1	Sirtuin 1

SIRT3	Sirtuin 3
SIRT6	Sirtuin 6
SKN-1	POU Class 2 Homeobox 3
SK-N-SH	Neuroblastoma cell line
SMAD3	Mothers against decapentaplegic homolog 3
SNAIL	Snail family Transcription Repressor 1
SNV	Single-nucleotide variation
SOX2	Sex determining region Y box 2
STAT	Protein Inhibitor of activated STAT 1
STAT3	Signal transducer and activator of transcription factor 3
SYBR	SYBR green
TGFβ	Transformation growth factor-beta
TIMP-1	TIMP metallopeptidasec1
TIMP2	TIMP metallopeptidase 2
TNFα	Tumour necrosis factor-alpha
tRNA	transfer RNA
TrxG	Trithorax group
UC-MSCs	Umbilical cord-derived mesenchymal stem cells
UCP1	Uncoupling protein 1
UHPLC/MS	Ultra-high-performance liquid chromatography-mass spectrometry
X-Gal	5-Brome-4-chloro-3-indolyl-β-D-galactopyranoside

CHAPTER 1

INTRODUCTION

1.1 General Overview

Mesenchymal stem cells (MSCs) are adult stem cells with self-renewal, mesodermal lineage differentiation ability and immune-modulatory functions (Fonseka et al., 2012; Gao et al., 2017; Lee et al., 2018; Liu et al., 2017; Sanap et al., 2017). They have emerged as a promising tool in cell-based therapy, due to their ease of isolation and more minor ethical concerns (Blázquez-Prunera et al., 2017; Hagenhoff et al., 2016; Kim et al., 2014; Qiu et al., 2018; Wang et al., 2016; Wei et al., 2013). Mesenchymal stem cells are utilised in tissue engineering to replace damaged tissue and facilitate tissue grafting at transplantation sites (Nakagawa et al., 2015; Ren et al., 2019; Wei et al., 2013; Wen et al., 2012). The immune-modulatory effects and the homing ability of MSCs to the site of injury is an active area of research (Bao et al., 2020; Chulpanova et al., 2018; De Witte et al., 2018; Fonseka et al., 2012; Martinez et al., 2017; Merino et al., 2017; Mun et al., 2018; Ramasamy et al., 2012). For example, MSCs homing ability is exploited for delivery of cytotoxic drugs or genes for cancer therapy (Chopra et al., 2019; Hagenhoff et al., 2016; Kalimuthu et al., 2018; Porada & Almeida-Porada, 2010; Qiao et al., 2015; Tran & Damaser, 2015). Thus, up to August 2022, approximately 1,392 clinical trials were registered under the public database (clinicaltrials.gov/) on MSCs therapeutic potentials, clearly underscoring the potential of MSCS in cell-based therapy.

Further, mesenchymal stem cells have been successfully generated from adult tissues such as bone marrow, adipose tissues, dental pulp tissue, and even endometrial tissues as well as perinatal tissues including: umbilical cord, cord blood, amniotic fluid and placenta (Alicka et al., 2019; Choi et al., 2017; Fonseka et al., 2012; Kim et al., 2014; Tong et al., 2011). Although bone marrow and adipose tissue MSCs retrieval and expansion are high (Legzdina et al., 2016; Tong et al., 2011). However, situation such as risky and invasive procedure, as well as short culture period and low proliferation rate limits their accessibility; in contrast umbilical cord tissues derived MSCs possess longer culture period and higher proliferation, partly due to their perinatal origin, thus could serve as an alternative source of MSCs (Seshareddy et al., 2008; Yusoff et al., 2016). Further, umbilical cord is considered a medical waste and will be eventually be discarded after delivery of the newborn, hence alleviating ethical concerns on the number of samples used. Additionally, been of perinatal origin as mentioned earlier, umbilical cord has high retrieval and proliferative rate of UC-MSCs, leading to generation of abundant number of UC-MSCs at earlier passages limiting the number of cords needed for a particular investigation.

However, the low abundance of MSCs in adult tissue necessitates ex vivo expansion before transfusion/transplantation for cellular therapy. For instance, a dose of 1-2 x 106 hMSCs per kg is recommended to be infused for human subjects in clinical trials at

each transfusion session (Gorman et al., 2020; Goto et al., 2018; Huang et al., 2018; Park et al., 2018; Salzig et al., 2016; Schweizer et al., 2019). Nevertheless, during ex vivo expansion, MSCs rapidly assumes a non-replicative state known as replicative senescence or Hayflick limit (Hayflick & Moorhead, 1961; Honda et al., 2020; Squillaro et al., 2019; Suvakov et al., 2019; Yu et al., 2018). Senescence impairs the phenotypic and functional capability of MSCs (Bao et al., 2020; Hladik et al., 2019; Jiang et al., 2017; B. Wang, Liu, et al., 2020a). Furthermore, senescent MSCs secretes pro-inflammatory cytokines, enhancing inflammation and inducing senescence of neighbouring cells *via* paracrine effects (Cárdenes et al., 2018; Hladik et al., 2019; Zhang et al., 2015). Indeed, it has been reported that murine adipose-derived MSCs from older donors induced physical dysfunction in old recipient mice (Wang, Liu, et al., 2020b). Furthermore, this *ex-vivo* observation of MSCs senescence functional alterations might explain the ageing phenomenon observed in aged organisms due to depletion of their stem cells pool. As the organism ages, MSCs undergoes replicative senescence, with the implication of progressive loss of tissue repair and maintenance a characteristic of the ageing process (Behrens et al., 2014; Cárdenes et al., 2018; Khatri et al., 2016; Y. Li et al., 2011; Neri, 2019; Su et al., 2020; Wagner et al., 2019). Delay in fracture healing in an older individual is positively correlated with the amount of senescent MSCs (Wagner et al., 2019; T. Wang et al., 2017).

Another major confounding factor of cellular senescence is oxidative stress. Oxidative stress occurs when there is an imbalance in the production of free radicals/reactive oxygen species and antioxidant enzyme defence system leading to a high level of free radicals/reactive oxygen species. This causes cellular damage, including DNA damage, cell membrane, proteins and organelles damages, which eventually leads to apoptosis or cellular senescence depending on the extent of DNA damage (Denu & Hematti, 2016; Facchin et al., 2018; Park et al., 2017). Thus, oxidative stress has been implicated in ageing and almost all age-related pathology. The effect of oxidative stress on ex vivo MSCs culture have been reported by several investigators (Facchin et al., 2018; Jin et al., 2018; Zhang et al., 2018). In brief, oxidative stress has been shown to cause changes in the physical characteristics of MSCs, such as cell morphology, surface markers expression, cellular granules deposition and functional changes such as their trilineage differentiation potential, stemness, immunomodulation, secretome, gene expression changes as well as increase susceptibility to cellular senescence (Jin et al., 2018; Kong et al., 2019; Liu et al., 2020; Pan et al., 2016a; Sugihara et al., 2020). It is agreed upon that oxidative stress aggravate cellular senescence in late passage ex vivo MSCs culture and MSCs from the older individual (Facchin et al., 2018; Zhang et al., 2018). Thus, it will be interesting to modulate the oxidative stress microenvironment to improve ex vivo expansion of MSCs culture, especially at the late passage where the antioxidant defence system becomes compromised.

The anthracycline-anticancer agent-doxorubicin is an established oxidative stress senescence model in induction of cellular senescence in primary cells. It is able to induce cellular senescence by causing dysregulation of mitochondrial metabolism leading to ROS accumulation, telomere shortening, and expression of cell cycle inhibitors—p16INK4a and p21CIP1, culminating to apoptosis, cell cycle arrest and cellular senescence (Chang et al., 2019; Chen et al., 2018; Piegari et al., 2013). Further, doxorubicin is also able to stimulate the production of senescence associated secretory

phenotype (SASP) (Özcan et al., 2016), thus it is a powerful model in establishing oxidative stress induced premature senescence in primary cells.

Recent studies have demonstrated the abilities of small molecules to relieve tissue culture from senescent cells burden and in aged organisms, increasing longevity and survival a strategy known as senotherapy (Cavalcante et al., 2020; Grezella et al., 2018; Kirkland & Tchkonia, 2020; Roos et al., 2016; Zhang et al., 2020; T. Zhou et al., 2019). Senotherapy involves the use of small molecules that induce senescent cells to undergo apoptosis known as 'senolytics compounds or the use of small molecules that prevent the spread of senescence to adjacent healthy cells, by inhibiting the release of reactive oxygen species and senescence associated secretory phenotype (SASP) (Fang, Yang, et al., 2018; Shin et al., 2016; Xu et al., 2018). For example, Dasatinib, a tyrosine kinase inhibitor, is a senolytic compound that eliminates senescent pre-adipocytes in an *ex-vivo* cultures (Zhu et al., 2015). Similarly, navitoclax and quercetin (a polyphenol compound) were demonstrated to exhibit senolytic activity on senescent cells in MSCs cultures (Grezella et al., 2018). Furthermore, dasatinib and quercetin administration in patients with diabetic kidney disease reduces senescent adipose MSCs burden and decreases the p16INK4a and p21CIP1 expressing cells (Hickson et al., 2019).

Conversely, the senomorphics majorly polyphenols, such as resveratrol, epigallocatechin gallate, curcumin, and the isothiocyanates, R sulphoraphane mitigates the spread of senescence from senescent cells by exerting antioxidant, anti-inflammatory effects on senescent cells as well increase in their oxidative stress defence system including increase expression of NRF-2, PI3K/AKT/pim-1, and SIRT-1, which enhances cellular proliferation, exert cytoprotection and prevent senescence (Choi et al., 2018; Honda et al., 2020; Lei et al., 2016; Shin et al., 2016; Wang et al., 2016). Thus, it becomes intuitive to investigate the plant preparations with rich polyphenolic compounds to test their antisenescence properties and further isolate potent antisenescence compounds that can be of research and clinical significance. In this regard, the plant *Moringa oleifera* becomes relevant. The ethanolic leaves extract of *Moringa oleifera* is endowed with abundant polyphenolic compounds that exert antioxidant, anti-inflammatory, immune modulators, anti-ageing effects (Adamu et al., 2021). *Moringa oleifera*, a tree plant and member of the Moringaceae family, is consumed as part of a regular diet in Southeast Asia, Africa, Latin America, the Caribbean, the Pacific Islands, and India (Jung et al., 2015; Tiloke et al., 2016, p. 201). *Moringa oleifera* roots, leaves, stem bark, seed and flowers have been reported to contain phytochemicals with medical properties (Fernandes et al., 2016; Giacoppo et al., 2016; Jaafaru et al., 2018). It is used traditionally as an anti-diabetic, anti-hypertensive, anti-spasmodic, anti-ulcer, anti-cancer, and anti-ageing, among others (Fernandes et al., 2016; Razis et al., 2014).

1.2 Problem Statement

The cellular senescence of MSCs during *ex-vivo* expansion is an inevitable phenomenon associated with decreased proliferation, differentiation, and general vitality of MSCs. Moreover, the proinflammatory state that is assumed by senescent cells induces the senescence of neighbouring healthy cells *via* a paracrine effect, raising safety concerns of transplanted MSCs that are usually expanded to a clinically relevant cell concentration before their transfusion. Furthermore, oxidative stress serves as contributing confounding factor that induces senescence of MSCs in *ex-vivo* environments, which can be due to normoxic oxygen tension in most traditional CO2 incubators or from culture-induced stressors. In addition, the ubiquitous presence and association of senescence cells in age-associated diseases such as diabetes, osteoarthritis, systemic lupus erythematosus and even tumours warrant the need to develop therapies targeted at eliminating and/or inhibiting the accumulation of senescent cells, thus promoting the restoration of cellular activities and tissue functions.

1.3 Study Justification

Small molecules have demonstrated the capacity to eliminate senescence cells in tissue culture and at organismal level studies, leading to improved cell viability and increased longevity in model organisms. Among the leading small molecules are polyphenolic compounds (quercetin, fisetin, resveratrol etc.), which demonstrate the value in investigating plants with abundant polyphenolic compounds. In this realm, the ethanolic leaf extract of *Moringa oleifera* rich in polyphenols becomes pertinent in the quest to find potent small molecules with senotherapeutic potentials. Moreover, the high consumption of leaves of *Moringa oleifera* in Malaysia, Southeast Asian countries, and Africa as a source of nutrient and a remedy for a variety of ailments further bolster the importance of investigating the senotherapeutic potential of *Moringa oleifera*.

1.4 Null Hypothesis

Supplementation of *Moringa oleifera* leaves ethanolic extract on serially passaged and oxidative stress-induced senescent UC-MSCs does not affect their proliferation and senescence indices.

1.5 Objectives

1.5.1 General Objectives

To probe the mitogenic and senolytic activities of *Moringa oleifera* leaves ethanolic extract (MOEE) on culture expanded and oxidative stress-induced UC-MSCs.

1.5.2 Specific Objectives

a. To identify constituent polyphenols in MOEE

b. To generate and characterised mesenchymal stem cells (MSCs) from the human umbilical cord tissues

c. To assess the influence of MOEE on cell viability, reactive oxygen species generation, cell proliferation, cell growth kinetics, cell cycle progression, apoptosis, stemness and differentiation in culture expanded UC-MSCs

d. To measure the effect of MOEE on cell viability, reactive oxygen species generation, cell cycle progression and apoptosis in oxidative stress-induced senescent UC-MSCs.

e. To evaluate the effect of MOEE on cellular senescence and senescence associated secretory phenotype (SASPS) of culture expanded and oxidative stress-induced senescent UC-MSCs.

f. To gauge the impact of MOEE on antioxidant and antisenescence gene expression in oxidative stress-induced senescent UC-MSCs.

1.6 Research Outlook

The generalized outline of the research thesis is presented, in figure 1.1, and divided into six themes/parts. The first part described the collection, extraction, and standardization of MOEE. Secondly, the umbilical cord's generation and characterization of mesenchymal stem cells (MSCs) was outlined. In the third, effect of MOEE on viability, reactive oxygen species generation, proliferation, growth kinetics, cell cycle progression, apoptosis, stemness marker expression and differentiation in culture expanded UC-MSCs were evaluated.

Fourthly, MOEE effects on cell viability, reactive oxygen species generation, cell cycle progression and apoptosis in oxidative stress induced senescent UC-MSCs was determined. In the fifth, the possibility of MOEE to prevent culture expansion and oxidative stress induced senescence was measured by senescence associated-beta-galactosidase (SA-β-Gal) expression and senescence associated secretory phenotype (SASP) release.

Lastly, gene expression of antioxidant and antisenescence transcriptional factors were gauged in oxidative stress induced senescent UC-MSCs to deduct the plausible mechanism of MOEE in the oxidative stress microenvironment.

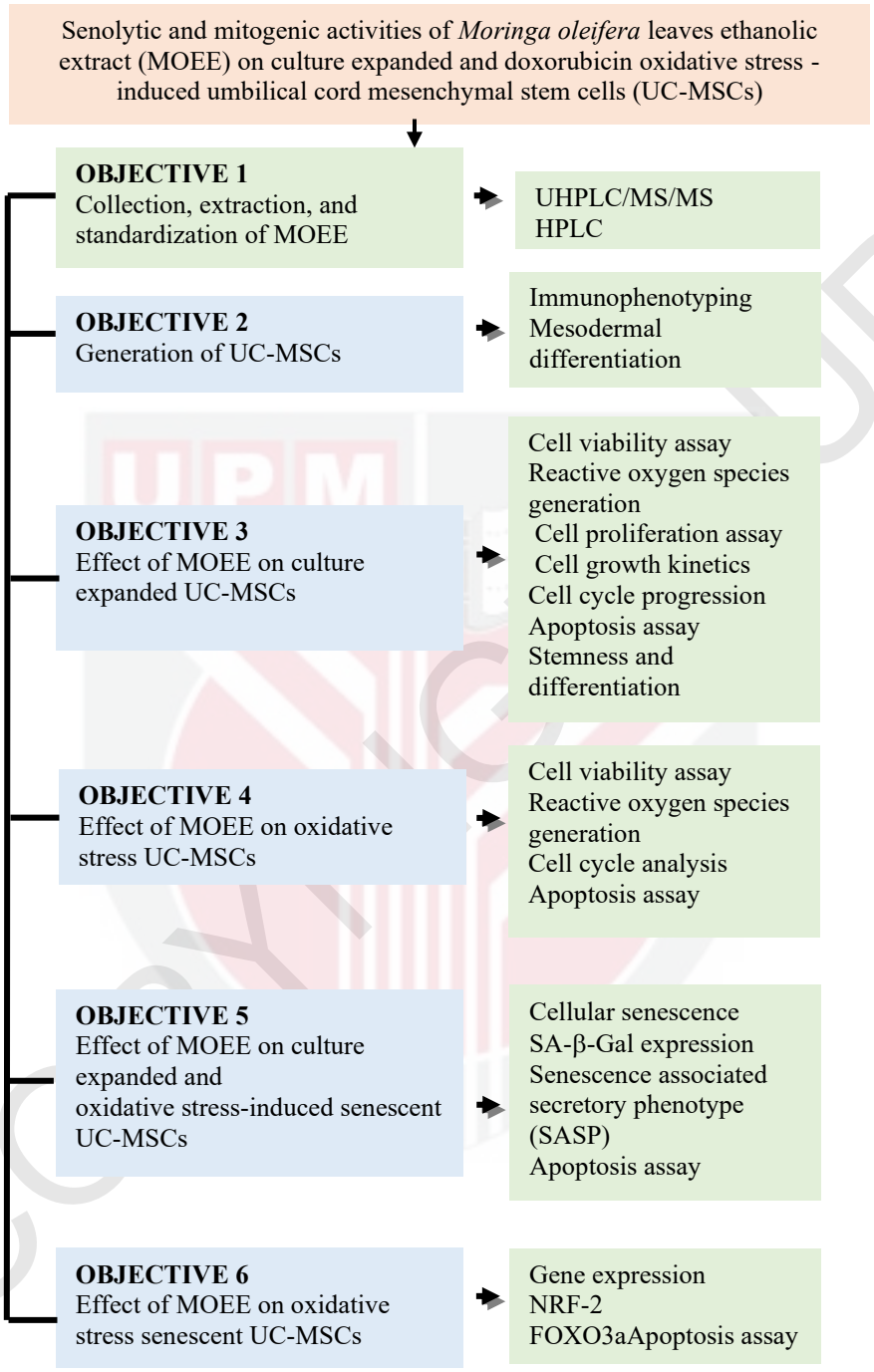

Figure 1.1: A Summarize Chart of the Research Outlook of the Thesis. SA-β-Gal (Senescence associated beta galactosidase, SASP (senescence associated secretory phenotype), MOEE (*Moringa oleifera* leaves ethanolic extract. HPLC (high performance liquid chromatography, UHPLC/MS (Ultra high-performance liquid chromatography, mass spectrometry)

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