ANTI-PROLIFERATIVE POTENTIAL OF *Eleutherine bulbosa* (Mill.) Urb. BULB EXTRACTED UNDER OPTIMISED CONDITION ON THREE-DIMENSIONAL RETINOBLASTOMA CELL CULTURE MODEL (WERI-Rb-1)

By

'AMMAR AKRAM BIN KAMARUDIN

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

July 2022

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DEDICATION

A little gift for:

My beloved parents:
Mr. Kamarudin Napiah & Mrs. Nooryah Hassan

My brothers and sisters:
Mrs. Nurhazirah Tasnim, Mr. Ridzuan, Mrs. Durrani Tasnim, Mr. Ammar Asyraf & Ms. Nurhani Tasnim

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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Chair : Norhaizan Mohd Esa, PhD
Institute : Bioscience

According to the Malaysia National Cancer Registry (2007-2011), ocular cancer has been listed among the most prevalent cancers in children after leukaemia, brain and nervous system, lymphoma, as well as bone. A paucity of scientific evidence on the mode of retinoblastoma inhibition remains a great challenge. A folklore medicine locally used among the Dayak community, "Bawang Dayak" or scientifically known as *Eleutherine bulbosa* bulb has been chosen as a potential alternative remedy to inhibit the growth of retinoblastoma. Therefore, the main objective of this study is to scrutinise the new insights on anti-proliferative potential of *E. bulbosa* bulb extract against the mode of retinoblastoma inhibition. The optimisation of the phenolic extraction using response surface methodology was carried out and the results revealed that the temperature of 48 °C; time of 70 min; solid-liquid ratio of 10 g in 146 mL was the best for phenolic extraction. High Performance Liquid Chromatography (HPLC) analysis revealed that eight bioactive compounds were successfully quantified such as gallic acid, chlorogenic acid, rutin, quercetin, epicatechin gallate, eleutherin, kaempferol, and myricetin. The results of the cytotoxic study revealed a potent IC_{50} value of 15.7 ± 2.7 µg/mL compared to cisplatin with 3.6 ± 2.2 µg/mL. The acridine orange/ propidium iodide (AO/PI) dual staining illustrated a significant apoptotic cell death, manifesting apoptotic features such as membrane blebbing, chromatin condensation, and secondary necrosis. In the meantime, Annexin V-FITC portrayed early and late apoptosis as well as cell cycle arrestment in Sub G0/G1 and G0/G1 phases on WERI-Rb-1 cells upon treatment. The apoptosis was further confirmed with qPCR analysis, demonstrating an upregulation of Bax, Bad, p53, Caspase 3, Caspase 8, and Caspase 9. The downregulation of Bcl-2, Bcl-xL, Nrf-2, and HO-1 genes confirmed the apoptotic and antioxidant related pathways were involved in the mode of retinoblastoma inhibition. To further elucidate and compare its anti-proliferative potential, 3D cell culture studies were conducted to investigate the effect of *E. bulbosa* ethanolic bulb extract on apoptotic mechanism and its relation to the antioxidant pathway. The cytotoxic assay was conducted by Resazurin

sodium salt and demonstrated an increased IC_{50} value of 45.7 ± 1.7 µg/mL and 26.6 ± 6.0 µg/mL for *E. bulbosa* ethanolic bulb extract and cisplatin, respectively. The morphological assessments through 4', 6-diamidino-2-phenylindole (DAPI) and PI double staining as well as scanning electron microscope (SEM) displayed the onset of apoptosis on the 3D retinoblastoma treated cells. The results of gene and protein expressions exhibited that the ratio of pro-survival and pro-apoptotic genes and proteins such as Bcl-2, Bcl-xL, Bax, and Bad were upregulated, suggesting that the extracellular matrix (ECM) hindered the drug penetration resulting in apoptotic resistance. However, the activation of caspase cascades like Caspase 3, 8, and 9 by *E. bulbosa* ethanolic bulb extract confirmed the intrinsic apoptotic mechanism pathway. Of note, the upregulation of antioxidant proteins for instance Nrf-2 and SOD-1 promotes the proliferation of WERI-Rb-1 cells and leads to tumour resistance due the presence of ECM. Surprisingly, the HO-1 protein was downregulated and may be potentially inhibited the growth of retinoblastoma upon treatment by mediating more reactive oxygen species (ROS). Taken together, these findings suggested that the ethanolic bulb extract of *E. bulbosa* may be potential anti-proliferative agent for retinoblastoma cancer as it portrayed selective killing properties in 3D WERI-Rb-1 cells as opposed to cisplatin. Besides, it provides a fundamental understanding on the inhibition of 3D retinoblastoma cancer cells as it mimics more tissue resemblance to in vivo conditions.

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

POTENSI ANTI-PROLIFERATIF BEBAWANG *Eleutherine bulbosa* (Mill.) Urb. DI BAWAH KEADAAN OPTIMUM KE ATAS TIGA-DIMENSI RETINOBLASTOMA SEL KULTUR MODEL

Oleh

'AMMAR AKRAM B. KAMARUDIN

Julai 2022

Pengerusi : Norhaizan Mohd Esa, PhD
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Menurut Pendaftaran Kanser Kebangsaan Malaysia (2007-2011), kanser okular telah disenaraikan antara kanser paling lazim di kalangan kanak-kanak selepas leukemia, otak dan sistem saraf, limfoma, serta tulang. Kekurangan bukti saintifik ke atas cara perencatan retinoblastoma kekal sebagai cabaran besar. Perubatan tradisional yang digunakan secara tempatan dalam kalangan masyarakat Dayak iaitu "Bawang Dayak" atau dikenali secara saintifik sebagai bebawang *Eleutherine bulbosa* telah dipilih sebagai rawatan alternatif yang berpotensi menghalang pertumbuhan retinoblastoma. Oleh itu, objektif utama kajian ini adalah untuk mendalami potensi anti-proliferatif ekstrak bebawang *E. bulbosa* terhadap mod perencatan retinoblastoma. Pengoptimuman ekstrak fenolik menggunakan kaedah permukaan tindak balas (RSM) telah dijalankan dan keputusan menunjukkan bahawa suhu 48°C; masa 70 min; nisbah pepejal-cecair 10 g dalam 146 mL adalah yang terbaik bagi pengekstrakan fenolik. Analisis Kromatografi Cecair Berprestasi Tinggi (HPLC) mendedahkan lapan sebatian bioaktif telah berjaya diidentifikasi seperti asid gallik, asid klorogenik, rutin, kuersetin, epicatechin gallate, eleutherin, kaempferol, dan miricetin. Keputusan potensi sitotoksik yang kuat telah ditunjukkan dengan nilai IC_{50} sebanyak 15.7 ± 2.7 µg/mL berbanding cisplatin dengan 3.6 ± 2.2 µg/mL. Pewarnaan dwi AOPI menggambarkan kematian sel apoptosis yang ketara, menunjukkan ciri apoptosis seperti pengembangan membran, pemeluwapan kromatin dan nekrosis sekunder. Sementara itu, Annexin V-FITC menggambarkan apoptosis awal dan lewat serta penahanan kitaran sel di fasa Sub G0/G1 dan G0/G1 dalam WERI-Rb-1 setelah rawatan. Selanjutnya, apoptosis disahkan melalui analisis qPCR, menunjukkan peningkatan pengawalseliaan Bax, Bad, p53, Caspase 3, Caspase 8, dan Caspase 9. Pengurangan gen Bcl-2, Bcl-xL, Nrf-2, dan HO-1 mengesahkan penglibatan apoptosis dan antioksida. Bagi mendalami dan membandingkan potensi anti-proliferatif dengan lebih lanjut, kajian sel kultur 3D telah dijalankan untuk menyiasat kesan ekstrak etanol bebawang *E. bulbosa* pada mekanisme

apoptosis dan kaitannya dengan antioksida. Ujian sitotoksik telah dijalankan melalui natrium Resazurin menunjukkan peningkatan nilai IC_{50} masing-masing sebanyak 45.7 ± 1.7 µg/mL dan 26.6 ± 6.0 µg/mL bagi ekstrak etanol bebawang *E. bulbosa* serta cisplatin. Penilaian morfologi melalui pewarnaan berganda 4', 6-diamidino-2-phenylindole (DAPI) dan PI serta mikroskop pengimbasan elektron (SEM) memaparkan permulaan apoptosis pada sel 3D retinoblastoma yang dirawat. Keputusan gen dan protein menunjukkan nisbah gen dan protein 'pro-survival' dan pro-apoptosis seperti Bcl-2, Bcl-xL, Bax, dan Bad didapati meningkat menunjukkan bahawa ekstrasellular matriks (ESM) menghalang penembusan rawatan dan menyebabkan rintangan apoptosis. Walau bagaimanapun, pengaktifan caspase seperti Caspase 3, 8, dan 9 oleh ekstrak etanol bebawang *E. bulbosa* mengesahkan mekanisme dalaman apoptosis. Selain itu, pengawalseliaan protein antioksida contohnya Nrf-2 dan SOD-1 meningkat, memberi kesan terhadap rintangan tumor dan menggalakkan proses proliferasi dengan kehadiran ESM. Menariknya, kawal selia protein HO-1 menurun dan mungkin berpotensi menghalang pertumbuhan retinoblastoma setelah rawatan dengan menghasilkan lebih banyak spesies oksigen reaktif (ROS). Secara keseluruhannya, ekstrak etanol bebawang *E. bulbosa* boleh dicadangkan sebagai agen anti-proliferatif yang berpotensi bagi kanser retinoblastoma kerana ia menunjukkan sifat membunuh yang terpilih dalam sel 3D WERI-Rb-1 berbanding cisplatin. Kajian ini menyediakan kajian asas pada perencatan sel kanser 3D retinoblastoma kerana ia menggambarkan lebih banyak persamaan tisu terhadap persekitaran in vivo.

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"*In the name of Allah, the Most Gracious and the Most Merciful*"

This thesis is written as a reflection of my bittersweet journey, seeking for His limitless knowledge over the past few years. The odyssey to find knowledge reminded me of those elucubrate moments of working relentlessly with my fellow comrades. I owed a great debt of appreciation to countless number of individuals in order to achieve my dream. Alhamdulillah, finally I reached the finishing line.

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Sincerely;
Dr. Ammar Akram Kamarudin
Class of 2022

This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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This is to confirm that:

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2D	Two-dimensional
3D	Three-dimensional
ABTS	2,2′-azinobis (3-ethylbenzo thiazoline-6-sulphonic acid) disodium salt
AOPI	Acridine orange propidium iodide
ANOVA	Analysis of variance
APAF-1	Apoptotic protease-activating factor-1
ARPE-19	Retinal pigmented epithelium
BCA	Bicinchoninic acid
Bcl-2	B-cell lymphoma 2
BSA	Bovine serum albumin
DAPI	4', 6-diamidino-2-phenylindole
Caspase	cysteine aspartyl-specific proteases
cDNA	Complementary deoxyribonucleic acid
CO_2	Carbon dioxide
DISC	Death-inducing signalling complex
DMEM	Dulbeccos's modified essential medium
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DoE	Design of Experiment
DPPH	2,2-diphenyl-1-picrylhydrazyl
ECM	Extracellular matrix
FADD	Fas-associated death domain
FBS	Fetal bovine serum
g	Gram

GAPDH	Glyceraldehyde 3-phosphate dehydrogenase
h	Hour
HPLC	High performance liquid chromatography
HRP	Horseradish peroxidase
HtrA2	Omi/high-temperature requirement protein A
IC	Inhibitory concentration
i.e.	Id est
LOF	Lack of fit
mg	Milligram
min	Minute
mL	Millilitre
mM	Milli Molar
MNCR	Malaysia National Cancer Registry
MTT	(3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide)
NED	National Eye Database
ng	Nanogram
nm	Nanometre
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
Nrf-2	Nuclear factor erythroid 2-related factor 2
PBS	Phosphate buffered saline
PCR	Polymerase chain reaction
Ppm	Part per million
PVDF	Polyvinylidene difluoride
qPCR	Quantitative real time polymerase chain reaction
RIPA	Radioimmunoprecipitation
ROCK-1	Rho-associated serine/threonine kinase protein

ROS	Reactive oxygen species
RNA	Ribonucleic acid
RPMI	Roswell Park Memorial Institute
RSM	Response Surface Methodology
RT-qPCR	Reverse transcriptase quantitative polymerase chain reaction
SDS-PAGE	Sodium dodecyl sulphate-polyacrylamide gel
SEM	Scanning electron microscope
SI	Selectivity index
SMAC	Second mitochondria-derived activator of caspase
TBST	Tris buffered saline Tween 20
TNF	Tumour necrosis factor
TRADD	TNF receptor-associated death domain
TRAIL	TNF-related apoptosis-inducing ligand
Trolox	6-hydroxy-2, 5, 7, 8-tetra-methylchroman 2- carboxylic acid
UV	Ultraviolet
µL	Microlitre
WERI-Rb-1	Retinoblastoma
XIAP	X-linked inhibitor of apoptosis protein
%	Percentage

CHAPTER 1

INTRODUCTION

1.1 Background

Retinoblastoma (Rb) is a genetically rare ocular cancer instigated by a bi-allelic mutation of the retinoblastoma gene (RB1), originating from the retinal cells (Dimaras et al., 2015). Paediatrics are more vulnerable than geriatrics, with most cases happening among children with the age of less than 5 years old (Fabian et al., 2018). The annual occurrence of retinoblastoma per country is estimated around 8, 000 new cases with an incidence rate between 1 in 16, 000 to 18, 000 live births (Seregard et al., 2004; Haggerty et al., 2004; Broaddus et al., 2009; Dimaras et al., 2015). The prognosis and the survival rate of Rb patients pivoted on the early diagnosis and treatments received (Ancona-Lezama et al., 2020). In developed countries, the goal of the treatment focuses on the globe salvation and vision preservation (Broaddus et al., 2009; Ancona-Lezama et al., 2020). However, low- and middle-income countries (LMIC) countries have major treatment crises as the majority of the children display late-stages of the advanced tumour at presentation (Kao et al., 2002; Prasad Sah et al., 2013; Gichigo et al., 2015; Goolam et al., 2018). According to Reddy and Anusya (2010), the late presentation of advanced retinoblastoma in Malaysia is due to awareness deprivation among the public. In several cases, parents do not accept the reality that their children were diagnosed with a fatal intraocular tumour and they prefer treatments from the traditional healers, which surprisingly ineffective (Reddy et al., 2010). Besides that, technological and social issues are also perturbing in LMIC regions as compared to developed countries (Chawla et al., 2017). The global burden of Rb encompasses of 43% (3452 of 8099 children) in countries such as India (1486), China (1103), Indonesia (277), Pakistan (260), Bangladesh (184), and the Philippines (142) (Usmanov and Kivelä, 2014). Due to the explosive population growth in the Asia-Pacific region, Dimaras et al. (2012) proposed that Rb has globally triumphed over uveal melanoma as the most prevalent ocular malignancy. With the contemporary trend unveiled, the global burden of Rb is forecasted to escalate by 100 cases annually (Jain et al., 2019).

The management of Rb is still exigent within the remit of ocular oncology. The ultimate goal is to save life, followed by vision salvage (Andersch et al., 2019). Eye preservation is advisable in the case of a localised tumour, which has multiple treatment options such as brachytherapy and local intra-arterial chemotherapy (Andersch et al., 2019). For a massive tumour, systemic chemotherapy would be recommended to reduce the initial tumour size before subsequent treatment options could be prescribed. Like any other cancer, Rb, on the other hand, could disseminate through the optic nerve into the central nervous system and also via sclera, resulting in distant metastatic sites like lymph nodes, bones, and liver (Schaiquevich et al., 2022). In this case, high doses of combinative chemotherapy drugs like vincristine, etoposide, and

carboplatin are less effective as they could impact the quality of life due to the aggressive drug effects (Dunkel et al., 2000; Kremens et al., 2003; Gombos et al., 2007; Maus and June, 2016). Therefore, the urge for alternative and complementary treatment options are warranted.

In search for an alternative treatment, cell-based assays are the essential pillars in drug discovery and development process (Joseph et al., 2018). Mammalian cell cultures provide a solid foundation for deeper exploration of tissue physiology and pathophysiology outside the organisms (Joseph et al., 2018). For over a century, the traditional monolayer 2D cell culture technique has been widely utilised for cellular responses in drug discovery. Up until now, the method is still applicable and has successfully strengthened our understanding on drug mechanisms of action; however, they still have significant drawbacks that require amendments. The primary limitation involves fully grown cells on a culture flask that is made up of stiff platform, rendering them unnatural growth kinetics and cell attachments (Kapałczyńska et al., 2018). As a result, natural microenvironment of the particular cells is not fully represented, which could render misleading data. Most drugs fail during the clinical stage of phases II and III because of the abysmal drug efficacy and safety problems (Arrowsmith and Miller, 2013). It is suggested that the reduced attenuation of drug responses is caused by unfitted preclinical testing i.e. in vitro models that offer insufficient information associated with drug efficacy and safety issues (Kapałczyńska et al., 2018). Hence, new technologies in preclinical testing are rapidly evolving, making improvements for a better in vitro cell culture model that resembles in vivo environment, the three-dimensional (3D) cell culture model (Joseph et al., 2018). The technique is designed to improve the cellular structures and physiology for better mimicry of tissues and organs specific microarchitectures (Ballav et al., 2021).

Cancer remains a perplexing disease for many years, with several strategies conducted to maximise the effectiveness of treatment outcomes (Mitra and Dash, 2018). In view of this, natural products are vigorously explored to fathom the intricate mechanism within cancer. Since immemorial time, natural products have been the mainstay of folklore medicine in treating various ailments. Phytochemicals act directly on the specific molecular targets i.e. genes and proteins, or indirectly by stabilising the conjugates that may affect the metabolic pathways (Saldanha and Tollefsbol, 2012). The shreds of evidence from the past studies displayed that myriad of natural compounds have anti-cancer activities, which could be used as a functional treatment approach through various mechanisms (Li et al., 2013; Zheng et al., 2016; Zhou et al., 2016; Grosso et al., 2017). However, the number of explored natural products for their therapeutic benefits, particularly plants, are still scarce (Ickes et al., 2003; Noor Rain et al., 2007). Notably, polyphenols are the potential candidate for the anti-cancer drug discovery, with a broad range of small molecules to highly polymerised secondary metabolites (Manach et al., 2004). They present abundantly in foods and beverages such as vegetables, fruits, herbs, tea, and wine (Fu et al., 2010; Zhou et al., 2016; Deng et al., 2013).

Thus, extraction plays imperative role in acquiring polyphenols with therapeutic activities. The extraction of polyphenols largely relies on the polarity of the solvent, extraction time, and method as it influences the qualitative and quantitative constitution of the compounds (Rodríguez-Pérez et al., 2015). Organic solvents such as methanol, acetone, hexane, and chloroform are pertinent for extraction as it determines the active component in a particular plant but, significantly toxic for human health (Li et al., 2006). Thus, ethanol is widely chosen for its green solvent quality that could dissolve polar and non-polar compounds efficiently. Besides that, phenolic compounds have different polarities that vary significantly, and the development of a single, optimum extraction is necessary (Garcia-Salas et al., 2010). Conventional optimization is unavailing as it complies one-variable-at-a-time approach, which could potentially miss the interaction effects between parameters and the response of interests (Ibrahim and Elkhidir, 2011). Hence, response surface methodology (RSM), a useful mathematical tool is used to evaluate multiple responses simultaneously, with less labour-intensive management for better extraction reproducibility (Azahar et al., 2017).

Locally known as bawang Dayak or bawang hutan, *Eleutherine bulbosa* Mill. bulb is an herbaceous, perennial flowering plant from the Iridaceae family that is broadly cultivated in Southern America, the African region, and Indonesia (Kusuma et al., 2010; Insanu et al., 2014). In Indonesia, it is widely cultivated across sulphuric land, within 600 to 2000 m above the sea level of Kalimantan Island (Ieyama et al., 2011). The bulb is famous among the local tribe of Kalimantan, the Dayaks, where it is traditionally used to treat diabetes, breast cancer, hypertension, stroke, sexual disorders, as well as to enhance the production of breast-milk (Ieyama et al., 2011). Naphthalene, anthraquinone, and naphthoquinone are the key constituents of *E. bulbosa* bulb which demonstrated various pharmacological responses such as anti-microbial, anti-inflammatory, anti-hypertension, anti-cancer, anti-diabetic, and anti-melanogenesis activity (Kusuma et al., 2010; Insanu et al., 2014). However, studies on the pharmacological activity of *E. bulbosa* bulb are still minimal, primarily on anti-cancer properties.

1.2 Research problems

The prevalence of retinoblastoma cases are arising over the years. It is a genetically rare type of ocular cancer that requires significance attention as their treatments are challenging and involves invasive approaches. Due to the lack of public awareness and parental denial issues, late presentation of advance Rb is a commonplace in Malaysia (Reddy and Anusya, 2010). In view of this, combinative chemotherapies such as etoposide, carboplatin, and vincristine are given to the patients. However, these treatments are less efficient and may aggravate the side effects such as nausea, diarrhoea, fatigue, as well as fever. Invasive procedure such as enucleation is commonly practiced to prevent metastatic secondary cancers however, it does not eliminate tumour recurrence (Yang et al., 2018). Thus, new anti-cancer compound with safe and good efficacy is warranted to treat retinoblastoma.

Eleutherine bulbosa Mill. bulb or locally known as Bawang Dayak is one of the most undervalued plants, traditionally used to treat diabetes, breast cancer, hypertension, stroke, sexual disorders, and production of breast-milk among the Dayak people (Ieyama et al., 2011). Naphthalene, anthraquinone, and naphthoquinone are the key constituents of *E. bulbosa* bulb that are responsible for its anti-microbial, anti-inflammatory, anti-hypertension, anti-cancer, anti-diabetic, and anti-melanogenesis properties (Kusuma et al., 2010; Insanu et al., 2014). However, the studies on the anti-cancer properties are still minimal, which is worth to explore as it exhibits potent anti-cancer activity on breast cancer.

To understand the mechanism of the retinoblastoma inhibition, the development of a cell-based model should be selected appropriately to resembles the real tumour microenvironment. The 2D cell culture model has been used since the early 1900s, however, it promotes uneven growth kinetics on a stiff planar, causing unnatural tumour microenvironment (Cukierman et al., 2001). Using this model, the potential drug efficacy would be affected and the data might be misleading to in vivo and clinical studies. Thus, focus has been shifted to the 3D cell culture system as the technique is designed to improve the cellular structures and physiology for better mimicry of tissues and organs specific microarchitectures (Ballav et al., 2021).

1.3 Significance of research

This study highlights the importance of curative treatment for retinoblastoma through a reliable 3D cell culture model using plant resources, bawang Dayak as an alternative medicine. This study offers a substantial understanding of the native behaviour for cell growth and in vivo tissue resemblance, which could highly minimise animal testing. Since animal testing is the subject of heated debate over these past few years, stringent ethical requirements are necessary, and most of the animal-right extremists and anti-vivisectionists request a total abolishment of animal use in research. Besides that, the efficacy of a potential chemotherapeutic drug such as *E. bulbosa* bulb could be scrutinised optimally using a 3D cell culture approach. Moreover, secondary metabolites derived from the plant usually displays selective cytotoxic capability upon cancer cells, resulting in minimal side effects of chemotherapeutic drugs on healthy cells. Besides, a convenient yet economical method for phenolics extraction of *E. bulbosa* bulb using a green solvent, ethanol could be established. The most significant purpose of using natural resources is due to their cost-effectiveness and relative abundance in nature.

1.4 Hypothesis

It is hypothesised that the optimised extraction of *E. bulbosa* ethanolic bulb extract demonstrates selective cytotoxicity on 2D and 3D model of retinoblastoma cancer cells. It is also postulated that the extract is a potent inhibitor of retinoblastoma cancer cells through the activation of the antioxidant

defence system that could trigger the apoptotic genes and proteins related pathways.

1.5 Objectives

General objective: To investigate the in vitro effect of *E. bulbosa* ethanolic bulb extracted under optimised extraction condition on the retinoblastoma cancer cells via apoptosis and antioxidant signalling pathways.

Specific objectives:

1. To optimise the extraction condition of phenolic compounds from *E. bulbosa* bulb using response surface methodology and obtain its bioactive constituents using high-performance liquid chromatography (HPLC) analysis.

2. To investigate the effects of the optimise *E. bulbosa* ethanolic bulb extract as a chemotherapeutic potential on apoptotic-induced 2D monolayer culture of retinoblastoma cancer cells and its underlying mechanisms.

3. To develop a 3D retinoblastoma cell culture model extracted from the rat tail tendon and observe the effects of *E. bulbosa* ethanolic bulb extract on the morphological changes of the developed 3D retinoblastoma cell culture.

4. To investigate the anti-cancer effects of *E. bulbosa* ethanolic bulb extract on the 3D retinoblastoma cell culture model through regulation of apoptotic and antioxidant related genes and proteins.

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