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EVALUATION OF ANTIOXIDANT AND CYTOTOXIC ACTIVITIES OF AQUEOUS EXTRACTS FROM Donkioporiella mellea MYCELIA

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By

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

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Master of Science

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April 2021

Chair : Sumaiyah Abdullah, PhD
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Lately, people have started consuming vitamins, dietary supplements, functional food and nutraceutical products in their diet regularly as a source of enhancers. The demand for health-improving food and beverage from natural resources has increased. Polypore mushrooms contain various bioactive compounds that have medicinal alternatives. Traditional Chinese medicine and indigenous people have widely used polypore mushrooms as herbal remedies since yesteryears. In Malaysia, only a small number of common polypore mushrooms has been acknowledged for pharmacological value. New local polypore species was discovered namely, *Donkioporiella mellea*. *D. mellea* has identical botanical morphology like other polypore mushrooms with medicinal properties. Somehow, no scientific publication has a record on the potential of *D. mellea*. Polypore has several growth stages in a complete growth cycle like mycelia, pinhead and fruiting body. As other growth stages of mushroom, mycelia have been reported for pharmaceutical potential. Mycelia can be obtained through suspension culture. Suspension culture promises potential advantages of higher mycelial production in a compact space and shorter time with lesser chances of contamination. Mushroom complete media (MCM) is a suspension media used to culture the mycelium of various polypore mushrooms. This media provides a favourable condition for polypore. However, the total production of mycelia is at a low level. The mycelium growth formation depends on carbon (C) and nitrogen (N) as its primary nutrient sources, which play an important role in mycelial production's yield and efficiency. Therefore, some modification of suspension culture was done as an alternative in obtaining higher mycelial biomass accumulation of *D. mellea*. The suspension culture media was optimised at 22g/L glucose and 3 g/L yeast extract with mycelial production was 8203.33 ± 110.247 mg/L. The antioxidant properties of *D. mellea* were evaluated through several antioxidant assays; 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging ability, beta-carotene (β-carotene) linoleate model system and cupric-reducing ion capacity (CUPRAC). Each analysis was tested at serial dilution concentration of extract (0.01, 0.02, 0.04, 0.08, 0.16, 0.31, 0.63, 1.25, 2.5, 5 and 10 mg/ml).

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Hot aqueous extract of *D. mellea* showed good scavenging activity compared to cold aqueous extract with EC_{50} values 2.9 ± 1.986 and 3.3 ± 1.326 mg/ml, respectively. Meanwhile, the cold aqueous extract has good antioxidant activity in protecting β-carotene compared to hot aqueous extract with EC_{50} value 0.31 ± 0.754 and 1.25 ± 0.963 respectively. Both *D. mellea* extracts showed same CUPRAC ability with CUPRAC value 1.791 ± 0.046 and 1.821 ± 0.053 at 0.08 mg/ml respectively. The biocompatibility of *D. mellea* and human body was discovered by cytotoxicity test through 3-[4,5-dimethylthiazole-2-yl]-2,5-diphenyltetrazolium bromide (MTT) assay. The cytotoxicity activity of *D. mellea* extract was tested on normal human lung fibroblast (MRC5) and human lung carcinoma (A549). The cytotoxic evaluation was done in serial dilution concentration of extracts (1.95, 3.9, 7.8, 15.625, 31.25, 62.5, 125, 250, 500 and 1000 µg/ml). Aqueous extracts of *D. mellea* exhibited selective cytotoxicity potential with selective index (SI); 8.71 And 3.14 for hot and cold aqueous extract, respectively. Hot and cold aqueous extracts of *D. mellea* have mild anti-cancer properties against A549 at 500 µg/ml with the percentage of inhibition were 15.67 ± 1.93 and 50.24 ± 2.23 respectively. In general, the findings proved that *D. mellea* has potential and more biological evaluation needed for stimulating research advancement in mycological studies.

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PENILAIAN TERHADAP AKTIVITI ANTIOKSIDA DAN SITOTOKSIK BAGI EKSTRAK AIR DARIPADA MISELIA *Donkioporiella mellea*

Oleh

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Mutakhir ini, orang ramai mula mengambil vitamin, makanan tambahan kesihatan dan produk nutraseutikal dalam diet harian mereka sebagai penambah baikan sistem imunisasi badan. Permintaan terhadap makanan dan minuman kesihatan yang berasaskan alam semulajadi semakin mendapat sambutan ramai. Cendawan polipor mempunyai pelbagai kandungan bioaktif yang digunakan sebagai perubatan alternatif. Perubatan tradisional masyarakat cina dan orang asli telah menggunakan cendawan polipor sebagai herba sejak zaman dahulu lagi. Di Malaysia, terdapat sejumlah kecil cendawan polipor yang diangkat mempunyai nilai farmakologi. Terdapat satu species polipor tempatan yang baru ditemui bernama *Donkioporiella mellea*. Spesies *D. mellea* ini mempunyai ciri-ciri botani yang sama dengan cendawan polipor lain yang digunakan dalam perubatan akan tetapi sebarang penerbitan saintifik tentang potensi cendawan ini tidak dilaporkan. Cendawan polipor mempunyai beberapa tahap pertumbuhan dalam kitaran hidupnya yang lengkap. Seperti tahap pertumbuhan cendawan yang lain, miselia cendawan dilaporkan mempunyai nilai farmaseutikal. Miselia cendawan boleh dikumpulkan melalui pengkulturan cendawan menggunakan media cecair. Media cecair menjanjikan pelbagai kebaikan antaranya boleh didapatkan diruangan yang terhad dalam masa yang singkat dengan kadar pencemaran yang rendah. Media cendawan lengkap (MCM) merupakan media cecair yang sering digunakan untuk membiakkan miselia cendawan polipor. Namun begitu, ia mempunyai jumlah pengeluaran miselia yang rendah. Pembentukan miselia cendawan bergantung kepada sumber nutriennya terutamanya carbon (C) dan nitrogen (N) yang mana memainkan peranan penting dalam penghasilan miselia. Oleh itu, sedikit modifikasi bagi media cecair telah dijalankan sebagai langkah pengumpulan biojisim miselia dengan jumlah yang tinggi bagi spesies *D. mellea*. Media cecair telah dioptimumkan pada kadar 22 g/L glukosa dan 3 g/L ekstrak yis dengan jumlah miselianya ialah 8203.33 ± 110.247 mg/L. Nilai antioksida cendawan spesies *D. mellea* telah dinilai melalui beberapa ujikaji antioksida iaitu kebolehan menyingkirkan radikal bebas 2,2-diphenyl-1-picrylhydrazyl (DPPH), uijian sistem

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model beta-carotene (β-carotene) linoleate dan aktiviti penurunan ion cupric (CUPRAC). Setiap analisis dijalankan dalam pencairan kepekatan bersiri (0.01, 0.02, 0.04, 0.08, 0.16, 0.31, 0.63, 1.25, 2.5, 5 and 10 mg/ml). Ekstrak air panas bagi spesies *D. mellea* mempunyai kebolehan menyingkirkan radikal bebas yang baik berbanding ekstrak air sejuk dengan nilai EC_{50} masing-masing ialah value 2.9 ± 1.986 and 3.3 ± 1.326 mg/ml. Sementara itu, ekstrak air sejuk mempunyai potensi antioksida yang baik dalam melindungi β-carotene didalam sistem model berbanding ekstrak air panas dengan nilai EC_{50} masing-masing ialah 0.31 ± 0.754 dan 1.25 ± 0.963. Kedua-dua ekstrak air bagi spesies *D. mellea* ini mempunyai kebolehan CUPRAC yang sama dengan nilai CUPRAC masing- masing 0.791 ± 0.046 and 1.821 ± 0.053 pada kepekatan 0.08 mg/ml. Keserasian antara ekstrak spesies *D. mellea* dan tubuh badan manusia dinilai melalui ujian toksik pada sel menggunakan ujian 3-[4,5-dimethylthiazole-2-yl]-2,5-diphenyltetrazolium bromide (MTT). Ativiti ini diuji dengan menggunakan sel normal (MRC5) dan sel kanser (A549) paru-paru manusia. Kadar toksik ekstrak cendawan spesies *D. mellea* telah dijalankan pada pencairan kepekatan bersiri (1.95, 3.9, 7.8, 15.625, 31.25, 62.5, 125, 250, 500 and 1000 µg/ml). Hasil kajian mendapati bahawa kedua-dua ekstrak air cendawan spesies *D. mellea* ini bersifat selektif terhadap sel-sel yang diuji dengan indeks selektifnya (SI) ialah 8.71 dan 3.14 untuk ekstrak air panas dan ekstrak air sejuk. Ekstrak air panas dan ekstrak air sejuk bagi spesies *D. mellea* mempunyai sifat anti kanser yang ringan dalam melawan sel A549 pada kepekatan 500 µg/ml dengan peratusan perencatan sel bagi setiap ekstrak adalah 15.67 ± 1.93 and 50.24 ± 2.23. Secara umumnya, penyelidikan ini telah membuktikan bahawa cendawan spesies *D. mellea* merupakan spesies yang berpotensi dan memerlukan lebih banyak lagi penilaian biologi untuk dijalankan bagi merangsang kemajuan penyelidikan dalam bidang mikologi.

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Declaration by Members of Supervisory Committee

This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
- supervision responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) are adhered to.

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TABLE OF CONTENTS

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LIST OF TABLES

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LIST OF FIGURES

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LIST OF ABBREVIATIONS

et al.	and others
%	Percentage
˚C	Degree celcius
g	gram
µg	microgram
mg	milligram
ml	mililiter
L	liter
µL	microlitre
mM	Micro molar
M	Molar
MCM	Mushroom complete media
DPPH	2,2-Diphenyl-1-Picrylhydrazyl
CUPRAC	Cupric reducing antioxidant
TBHQ	Tetr-butyl-hydroquinone
Nc	Neocuproine
NH_4Ac	Ammonium acetate
ANOVA	Analysis of variance
$CuCl_2$	Copper chloride
KH_2PO_4	Potassium dihydrogenphosphate
K_2HPO_4	Dipotassium phosphate
$MgSO_4$	Magnesium sulphate
CO_2	Carbon dioxide

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RPMI	Roswell Park Memorial Institute
FBS	Fetus Bovine Serum
MTT	3-(4,5-Dimethylthiazol-yl)-,5-Diphenytetrazolium Bromide
BSC	Biosafety cabinet
DMSO	Dimethyl Sulfoxide
PBS	Phosphate buffer saline
CCM	Complete culture media
rpm	Revolutions per minute
DNA	Deoxyribonucleic acid
ITS	Internal transcribed spacer
bp	Base pair
PCR	Polymerase chain reaction
BLAST	Basic local alignment search tool
MEGA	Molecular Evolutionary Genetics Analysis
PDA	Potato dextrose agar
mm	milimeter
C	Carbon
N	Nitrogen

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CHAPTER 1

INTRODUCTION

Pandemic has taught us the importance of being healthy and fit. Infectious diseases remain one of the major threats to human health throughout the world. The ability of infection tolerance depends on an individual's immune system, where lower immunity puts the person in high-risk condition. These days, healthy consciousness among society has awakened and greatly impacted the importance of being healthy and fit. Everyone has adopted a healthy, active lifestyle in their family and community. Recently, the demand for health-improving food and beverage has increased parallel with the rising cost of health care, increased life expectancy and the desire for higher life quality (Tur and Bibiloni, 2016). Food items with nutritional value ingredients have become a growing concern among people. People started consuming vitamins, dietary supplements, functional food, and nutraceutical products in their diet regularly as a source of enhancers to maintain a balance in the calorie intake and the nutrients to improve the body's biological functions (Dudeja and Gupta, 2017; Elkhatib, 2020).

Today, plenty of natural product has good potential to boost up the human body's immune system. Natural product contains various specific components as good as synthetic pharmaceutical vitamins and supplements, which influence the health and well-being of the consumer. As time changes, people start looking for a new supplement alternative from natural products as their primary health care substitute. Natural products are chemical compounds derived from live organisms where present a good chance for direct curative effect and discovery of main compounds that provide effective medications (Ahmed *et al., 2019*). Today, various research study emphasise on common producers of natural products within different groups of organisms including, animals, plants, marine microorganisms, fungi, bacteria, and actinobacteria as sources of supplement and nutraceutical products (Selim *et al*., 2012; Rahi and Malik, 2016; Ahmad *et al*., 2019).

Recently, mushrooms have received attention for their health-giving qualities as valuable health food used in complementary and alternative medicine (Rathee *et al*., 2012; Ayeka, 2018). Since the beginning of time, mushrooms have been well known for their nutritional and therapeutic values. They have been used as traditional medicines and routine remedies by ancient Chinese and indigenous people (Palacios *et al*., 2011; Joshi *et al.,* 2014; Jayachandran *et al*., 2017). Now, mushroom usage has expanded in pharmaceuticals, nutraceuticals and cosmeceuticals for human consumption (Rathore *et al*., 2017). Current estimation of mushroom constituents at least 12,000 species worldwide where about 35 mushrooms species were cultivated commercially and 200 wild species used for medicinal purposes (Beulah *et al*., 2013). Mushrooms have been acknowledged as a curative and prevention due to their biological components. There are various biological components in mushrooms, such as

phenylpropanoids, terpenoids, furans, polysaccharides, unsaturated fats, amino acids, mineral elements, and antioxidants molecules (Chen *et al*., 2019). These biological components have the ability to regulate biological activities, as reported by pharmacological studies. Mushrooms have a number of biological and pharmacological activities, including anti-inflammatory, immunomodulatory, antioxidative, antimicrobial, antiviral, anticancer, antithrombotic, hypoglycemic, hypotensive, hypolipidemic, anti-atherosclerotic, anti-carcinogenic, anti-cholesterol, anti-hemorrhagic hepatoprotective and neuroprotective effects (Rathore *et al*., 2017; Chen *et al*., 2019).

The polypore mushrooms are a group of terrestrial fungi of the phylum Basidiomycota (Basidiomycetes). Most of the well-known species that have excellent medicinal value are from a group of polypores. Polypore mushrooms are typically fruit bodies that inhabit wooden surfaces with perennial growth habitats. Some polypores are severe forest pathogens that act as wood decays, while the rest are useful for their medicinal properties (Dai, 2007; Dai *et al*., 2009; Rajchenberg and Robledo, 2013). Polypores are the primary source of biologically active natural products among the diverse fungal phylum Basidiomycota species. In European regions, numerous studies acknowledge five polypores as part of the European mushroom heritage, namely *Laetiporus sulphureus*, *Fomes fomentarius*, *Fomitopsis pinicola*, *Piptorus betulinus* and *Laricifomes officinalis* (Grienke *et al*., 2014). In Asian countries such as Japan, Korea and China, the species of *Phellius linteus* has been regarded as a traditional Chinese medicine with a 2000-year long history being used in medicinal applications for treatments of hemorrhaging, hemostasis and disease related to female menstruation (Chen *et al*., 2016; Chen *et al*., 2019). Besides *Phellinus*, Malaysia also has documented several medicinal species of mushrooms endowed with medicinal properties such as *Ganoderma lucidum*, *Lignosus rhinocerotis* (Tiger milk mushroom), *Lentinus* spp., *Hericium erinaceum* (Monkey head mushroom), and others (Lau *et al*., 2013; Jamil *et al*., 2018; Sairi *et al*., 2020).

A new mushroom species had been discovered under the group of polypores identified as *D. mellea* (Qin *et al*., 2016). Although polypore mushrooms have various pharmacological effects, researchers have yet to explore the potential of *D. mellea.* To date, there has no record of any scientific publication on biological activities toward this species. Most bioactive compounds found in polypore mushrooms have antioxidants properties which play an essential role in human and animal physiology (Palacios *et al*., 2011; Joshi *et al.,* 2014; Jayachandran *et al*., 2017). Antioxidants are used as additives in food products due to their ability to prolong the shelf life of foods by scavenging free radical damage against oxidative degradation reactions (Barros *et al*., 2007; Oh *et al*., 2008). These antioxidant molecules also inhibit or delay cellular damage, preventing free radical damage and chronic diseases (Hu, 2000; Nimse and Pal, 2015). Polyphenolic compounds in polypore mushrooms are able to counteract oxidative damage by inhibiting or quenching free radicals and reactive oxygen species (Smith *et al*., 2015). The therapeutic values discovered in polypore mushrooms due to their antioxidant properties result in varying biological activities (Omar *et al*., 2011; Dundar *et al*., 2015).

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Besides, polypore mushrooms also contain bioactive compounds that have potential inhibiting cancer cells, such as hispolon and polysaccharide. As proven in several studies found that hispolon of *P. linteus* has exhibited therapeutic efficacy against various cancer cells such as colorectal, melanoma, leukemia, nasopharyngeal, breast, epithelial and glioblastoma cancer cells (Chen *et al*., 2019). Polysaccharides of *P. linteus* can inhibit human colorectal carcinoma cell and human liver cancer cells, and they could also reduce the adverse side effect of drugs in colon cancer cells (Yu *et al.,* 2018; Chen *et al*., 2019). While Beta-glucan (β-glucan) from the polysaccharide group of mushrooms has an immunomodulatory potential. Today, plenty of natural organisms contain potential medicinal alternatives as a form of medication or are able to produce a synergism effect in treating cancer without adverse side effects. Mushroom, a class of fungi, is a natural organism that has medicinal potential for pharmacology. As reported in previous studies, there are several types of mushrooms embodying the ability to target cancer cells, such as *Phellinus, Ganoderma lucidum, Lignosus rhinocerotis, Fomes fomentarius, Piptoporus betulinus, Cordyceps militaris, Grifola frondosa, Hericium erinaceus,* and *Antrodia* (Patel *et al*., 2012; Grienke *et al*., 2014; Liu *et al*., 2019). Hence, this study attempts to unveil another potential polypore mushroom.

Most of the mushroom extract was obtained from the fruit body of the mushroom. However, mycelia were reported to have a good pharmacological potential as a fruiting body of mushroom (Gründemanna *et al*., 2020). Mushrooms can be propagated through a vegetative way in which a new mushroom grows from a fragment of the parent mushroom. There are two ways of cultivation techniques known as substrate culture or suspension culture. Propagation through the substrate culture is vital in obtaining the fruiting bodies, whereas suspension culture cultivates mycelia and culture broth (Lee *et al*., 2008)). However, both propagation methods differ in harvesting times. Traditional growth of polypore mushrooms through substrate culture takes around six months and above to produce the fruiting bodies in favourable conditions longer than (Lee *et al*., 2008). On top of that, the cultivation requires specialised facilities and high costs (Hur, 2008). Meanwhile, suspension culture cuts the harvesting time to only 14 days. Additionally, it promises potential advantages of higher mycelial production in a compact space and shorter time with lesser chances of contamination (Yang and Liau, 1998; Friel and McLoughlin, 2000; Kim *et al*., 2002). Thus, researchers recognise mycelium as an alternative method by applying suspension culture, which is of considerable significance and value in promoting the exploitation and utilisation of rapid growth and mass production compared to fruiting bodies (Cui *et al*., 2006; Chen *et al*., 2016). Mushroom complete media (MCM) is a suspension media that had been used to culture mycelium of polypore mushroom as this media provides favourable conditions for polypore mushrooms such as *Phellinus* sp., *Ganoderma* sp. and *Lignosus rhinocerus* (Kim *et al*., 2002; Hurr, 2008; Jeong *et al*., 2009, Lai *et al*., 2011). However, the total production of mycelia is at a low level (Kim *et al*., 2002; Lai *et al*., 2011). Carbon and nitrogen play an important role that influences the yield and efficiency of mycelial production, also crucial in protein and fat formation in mushroom mycelium (Kurbanoglu *et al*., 2004). The mycelium growth formation depends on carbon (C) and nitrogen (N) as its primary nutrient sources. The optimisation of

suspension culture as an alternative in obtaining higher mycelial biomass accumulation of *D. mellea* needs to be considered as a primary procedure.

The biocompatibility between *D. mellea* and the human body needs to be clarified through a predominant biological evaluation. According to ISO10993, cytotoxicity tests must be performed as a tool to determine the suitable or non-toxic bioactive compound introduced to the human body (Shafiee *et al*., 2021). This step is crucial to ensure the safety of further research and clinical use. This study investigates the potential of a new local polypore, *D. mellea,* in terms of potentials as a new bioresource as stimulating research advancement in mycological and nutraceutical studies.

Therefore, the objectives of this study are:

i. To optimise suspension culture for mycelial biomass accumulation of *D. mellea*.

ii. To evaluate the antioxidant activity of hot and cold aqueous extracts of *D. mellea*.

iii. To determine the cytotoxicity of *D. mellea* on A549 (human lung carcinoma)

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