STUDY ON ANTIPROLIFERATIVE ACTIVITY OF *Hypsizygus tessellatus* AND *Flammulina velutipes* EXTRACTS ADSORBED ON SULPHATED ZIRCONIA NANOPARTICLES AGAINST BREAST CANCER CELL LINES

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SUPERVISOR'S DECLARATION

We hereby declare that we have checked this thesis, and, in our opinion, this thesis is adequate in terms of scope and quality for the award of the degree of Doctor of Philosophy.

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I hereby declare that the work in this thesis is based on my original work except for quotations and citations which have been duly acknowledged. I also declare that it has not been previously or concurrently submitted for any other degree at Universiti Malaysia Pahang or any other institutions.

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C.I. Ukaegbu.
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ABSTRAK

Dalam kajian ini, aktiviti '*in vitro*' biologi air, metanol, aseton, dan ekstrak etil asetat dari dua jenis *Hypsizygus tessellatus* (Buna shimeji coklat dan Bunapi shimeji putih) dan *Flammulina velutipes* (Enoki) telah dikaji. Topi dan batang cendawan telah diekstrak dengan pelarut yang berbeza dan telah dicirikan secara kimia dari segi jumlah kandungan fenol (TPC), jumlah kandungan flavonoid (TFC), aktiviti antioksidan (terhadap DPPH dan FRAP) dan pengklasifikasian fitokimia menggunakan UPLC-QTOF/MS (berdasarkan aktiviti antioksidan). Kemudian, "multiple correspondence analysis" (MCA) telah dilakukan ke atas fitokimia yang diekstrak menggunakan pelarut daripada cendawan. Kemudian, aktiviti antiproliferative ke atas bahagian berpotensi dijalankan terhadap dua garisan sel kanser payudara (MCF-7 dan MDA-MB-231) dengan menggunakan kaedah MTT. Siasatan lanjut telah dijalankan ke atas aktiviti antiproliferative bagi ekstrak cendawan yang dijerap pada nanopartikel zirconia sulfat (SZN). Keputusan kajian ini menunjukkan topi cendawan ekstrak mempunyai lebih TPC dan TFC berbanding ekstrak stem. Ekstrak topi Enoki mengandungi TPC dan TFC yang lebih tinggi berbanding ekstrak topi Buna shimeji dan Bunapi shimeji. Susunan melalui pemerhatian ke atas cendawan mengikut aktiviti antioksidan daripada ekstrak adalah: Enoki > Bunapi shimeji > Buna shimeji, dan untuk pelarut: air > methanol > aseton > etil asetat. TPC bagi ekstrak menunjukkan hubungan positif dengan aktiviti antioksidan keseluruhan analisis MCA itu menunjukkan hubungan yang positif antara pelarut pengekstrakan dan fitokimia yang diekstrak daripada cendawan. Kajian antiproliferatif daripada ekstrak menggunakan dua garisan sel kanser (MCF-7 dan MDA-MB-231) menunjukkan garisan sel kanser mempunyai tahap sensitiviti yang tinggi ke atas ekstrak air dan metanol Enoki dan topi Bunapi shimeji. Antara kesemua ekstrak, ekstrak topi Enoki dengan air menunjukkan aktiviti antiproliferative yang tertinggi terhadap MCF-7 (nilai IC_{50} antara 14.42 - 24.84 μg/mL) dan MDA-MB-231 (nilai IC_{50} antara 151.57 - 227.99 μg/mL) selepas 72 h. SZN juga menunjukkan tahap yang agak aktiviti antiproliferative yang tinggi terhadap bahagian-bahagian sel kanser pada kepekatan yang dikaji manakala sel-sel Normal (normal) kurang sensitif kepada (julat nilai IC_{50} daripada 130.7 - 134.1 μg/mL) SZN berbanding MCF-7 sel (IC_{50} julat nilai 36.5 - 37.0 μg/mL) dan MDA-MB-231 sel (IC_{50} nilai julat 68.9 - 70.9 μg/mL). Secara sinergi, penjerapan ekstrak pada SZN menambah baik aktiviti antiproliferatif mereka terhadap garisan sel kanser ($p < 0.05$), akan tetapi ekstrak topi Enoki dengan air menunjukkan aktiviti antiproliferatif yang terbaik selepas penjerapan pada SZN. Secara keseluruhan, ekstrak topi Enoki dan Buna shimeji dengan air dan metanol amat ketara menghalang percambahan '*in vitro'* MCF-7 dan MDA-MB 231, dan ia boleh dikatakan aktiviti antiproliferatif mereka terhadap garisan sel kanser telah dipertingkatkan melalui penjerapan fitokimia pada nanopartikel zirconia sulfat.

ABSTRACT

In this study, the *in vitro* biological activities of water, methanol, acetone, and ethyl acetate extracts of two *Hypsizygus tessellatus* variants (brown Buna shimeji and white Bunapi shimeji) and *Flammulina velutipes* (Enoki) were investigated. The caps and stems of the mushrooms were extracted with different solvents and chemically characterized for total phenolic content (TPC), total flavonoids content (TFC), antioxidant activities (against DPPH and FRAP). Furthermore, the extracted phytochemicals from the mushrooms were identified using Ultra performance liquid chromatography quadrupole time of flight mass spectrometer (UPLC-QTOF/MS). A multiple correspondence analysis (MCA) was performed on the extracted phytochemicals from the mushrooms based on the solvents used during the extraction process. Then, the antiproliferative activity of the potent fractions were evaluated against two breast cancer cell lines (MCF-7 and MDA-MB-231) using MTT assay. Further investigations were carried out on the antiproliferative activity of the mushroom extracts adsorbed on sulphated zirconia nanoparticles (SZN). The results of this study showed the mushroom caps extracts to have more TPC and TFC compared to the stem extracts. Enoki cap extracts contained higher TPC and TFC compared to Buna shimeji and Bunapi shimeji cap extracts. The mushroom order of the observed antioxidant activity of the extracts was: Enoki > Bunapi shimeji > Buna shimeji, and in the solvent order: water > methanol > acetone > ethyl acetate. The TPC of the extracts showed a positive correlation with their antioxidant activities whole the MCA analysis showed a positive correlation between the extraction solvents and the extracted phytochemicals from the mushrooms. The antiproliferative study of the extracts using two cancer cell lines (MCF-7 and MDA-MB-231) showed a considerable level of sensitivity of the cell lines to water and methanol extracts of Enoki and Bunapi shimeji caps. Among the extracts, Enoki caps water extract showed the highest antiproliferative activity against MCF-7 (IC_{50} value ranged from 14.42–24.84 µg/mL) and MDA-MB-231 (IC_{50} value ranged from 151.57 – 227.99 µg/mL) after 72 h. SZN also showed a considerable level of antiproliferative activity against the cancer cell lines at the studied concentrations while the Normal (normal) cells were less sensitive to SZN (IC_{50} value range of 130.7 – 134.1 µg/mL) compared to MCF-7 cells (IC_{50} value range of 36.5 – 37.0 µg/mL) and MDA-MB-231 cells (IC_{50} value range of 68.9 – 70.9 µg/mL). The adsorption of the extracts on SZN synergistically improved their antiproliferative activities against the cancer cell lines ($p < 0.05$), but Enoki caps water extract showed the best antiproliferative activity after adsorption on SZN. Conclusively, water and methanol extracts of Enoki and Bunapi shimeji caps significantly inhibited the *in vitro* proliferation of MCF-7 and MDA-MB 231, and it can be suggested that their antiproliferative activity against the cancer cell lines was enhanced through adsorption of the phytochemicals on the sulphated zirconia nanoparticles.

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LIST OF SYMBOLS

%	Percentage
IC_{50}	50 % inhibitory concentration
µg	Microgram
<	Less than
>	Greater than
±	Plus/minus
*	Multiplication sign

LIST OF ABBREVIATIONS

ATCC	American Type Culture Collection
BC	Buna shimeji caps
BCA	Buna shimeji caps (acetone fraction)
BCEA	Buna shimeji caps (ethyl acetate fraction)
BCM	Buna shimeji caps (methanol fraction)
BCW	Buna shimeji caps (water fraction)
BHA	Beta-hydroxyl acid
BHT	Butylated hydroxytoluene
BPC	Bunapi shimeji caps
BPCA	Bunapi shimeji caps (acetone traction)
BPCEA	Bunapi shimeji caps (ethyl acetate fraction)
BPCM	Bunapi shimeji caps (methanol fraction)
BPCW	Bunapi shimeji caps (water fraction)
BPSA	Bunapi shimeji stem (acetone)
BPC	Bunapi shimeji caps
BS	Buna shimeji stem
BPS	Bunapi shimeji caps
BPSEA	Bunapi shimeji stem (ethyl acetate)
BPSM	Bunapi shimeji stem (methanol)
BSA	Buna shimeji stem (acetone fraction)
BSEA	Buna shimeji stem (ethyl acetate)
BSM	Buna shimeji stem (methanol)
BSW	Buna shimeji stem (water)
CCS	Collision cross section
CNPs	Cerium nanoparticles
CO_2	Carbon dioxide
DA	Diode array
DHT	Dihydrotestosterone
DMEM	Dulbecco’s Modified Eagles Medium
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid

DPPH	1, 1-diphenyl-2-picryl-hydrazil
EC	Enoki cap
ECA	Enoki cap (acetone fraction)
ECEA	Enoki cap (ethyl acetate fraction)
ECM	Enoki cap (methanol fraction)
ECW	Enoki cap (water fraction)
Eq	Equation
ES	Enoki stem
ESA	Enoki stem (acetone fraction)
ESEA	Enoki stem (ethyl acetate fraction)
ESM	Enoki stem (methanol fraction)
ESW	Enoki stem (water fraction)
FBS	Fetal bovine serum
FDA	Food and Drug Administration
FRAP	Ferric reducing antioxidant power
FTIR	Fourier Transform Infrared
GAE	Gallic acid equivalent
h	Hour
H_2O_2	Hydrogen peroxide
LN	Lipid nanoparticle
MBC	Minimum bactericidal concentration
MCA	Multiple correspondence analysis
mg/g	Milligram per gram
MIC	Minimum inhibitory concentration
MRSA	Multi drug resistant Staphylococcus aureus
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium Bromide
NIST	National Institute of Standards and Technology
NK	Natural killer
NPs	Nanoparticles
OD	Optical density
PCA	Principal component analysis
PNPs	Platinum nanoparticles
QE	Quercetin equivalent

RES	Reticuloendothelial system
ROS	Reactive oxygen species
SD	Standard deviation
SEM-EDS	Scanning electron microscopy-energy dispersive spectroscopy
SWCNT	Single-walled carbon nanotubes
SZN	Sulphated zirconia nanoparticles
TCA	Trichloroacetic acid
TDM	Total dry material
TEM	Transmission electron microscopy
TGA	Thermogravimetric analysis
TFC	Total flavonoids content
TNF	Tumor necrosis factor
TPC	Total phenolics content
UPLC-QTOF/MS	Ultra-performance liquid chromatography quadrupole time of flight mass spectrometer
UV	Ultraviolet

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