UNIVERSITI PUTRA MALAYSIA

BIOLOGICAL ACTIVITIES OF LOCALLY ISOLATED THERMOPHILIC FUNGI

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By

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Faculty : Biotechnology and Biomolecular Sciences

Fungi are organisms of great interest in fermentation processes that culminate in the production of secondary metabolites important in research for new antibiotics, anticancer agents, insecticides, herbicides and others. The discovery and development of antibiotics was one of the most significant medical advances in the twentieth century. Recent researcher trends showed that the discovery of active chemical compounds is to update the effectiveness of drugs that are used in the future, so that, it is necessary to screen new isolated fungi to identify new antimicrobial bioactive compounds. Hence, this research was aimed to study new producers of secondary metabolites from thermophilic fungi and determined their biological properties. Ten thermophilic fungi were chosen out of 30 species isolated locally from Peninsular Malaysia. The investigations of the extracts demonstrated the availability of phenolics (14.61) to (19.64) mg gallic acid equivalent/g which analysed by high performance liquid chromatography (HPLC) and demonstrated the availability of 10 phenolics; pyrogallol, syringic acid, gallic acid, cinnamic acid, salicylic acid, chlorogenic acid, resorcinol, vanillic acid, caffeic acid, and hypophyllanthin, and furthermore the 4 flavonoids (apigenin, daidzein, catechin, and epicatechin). Other 14 fundamental metabolites located by GC-MS included: acetic acid 20.81%, 2,3-Butanediol 42.92%, 2-Furoic acid hydrazide 16.79%, cis-9-Hexadecenoic acid (palmitoleic acid) 10.07%, Isosorbide 5.23%, 9-Octadecenoic acid, methyl ester, (E)- (oleic acid) 22.08%, cis-Vaccenic acid (cis-11-Octadecenoic acid) 13.03%, 1-Naphthalenol, 1,2,3,4-tetrahydro-2,5,8-trimethyl- 9.92%, .alpha.-D-Glucopyranoside, methyl 19.03%, 3,5-Dihydroxy-6-methyl-2,3-dihydro-4H-pyran-4-one 5.27%, 2-Furoic acid, methyl ester 8.76%, Niacinamide 7.75%, 9,12-Octadecadienoic acid, methyl ester (Linoleic acid methyl ester) 4.26% and Pentadecanecarboxylic acid (palmitic acid) 6.78% from all the ten fungal isolates. All methanolic extracts of thermophilic fungi demonstrated a range of antimicrobial activities against both Gram positive and Gram negative pathogenic microorganisms (Inhibition zone: 6.3mm to 25.7mm) at the concentrations of 250, 500 and 1000 µg/disc. Extracts displayed antioxidant activities had a tendency to scavenge the free radicals in the decrease of ferric ion (Fe^{3+}) to ferrous ion (Fe^{2+}) FRAP (50.97 to 79.1%), DPPH (50.62 to 57.48%), ABTS (50.41 to 62.51%) and NO (51.17 to 59.45%) for all

the isolates. Cytotoxicity results demonstrated the capability of methanol extracts from *Myceliopthora thermophila* as a source of anticancer therapeutic agents to breast cancer cells MCF-7 at an IC_{50} concentration of 29.97µg/ml with cell viability 36.66% and cytotoxicity 90.18% against MDBK cell line. For the thermophilic fungus *Myceliophthora thermophila*, the extract concentrate inhibited 50.43% of the inducible nitric oxide synthase in a measurements dose dependent manner at 250µg mL^{-1}, while kept up 91.13% of macrophage RAW 264.7 cell lines induced by LPS/IFN-ɣ demonstrating their obvious anti-inflammatory activity.

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AKTIVITI BIOLOGI TERPENCIL DALAM NEGARA KULAT TERMOFILIK

Oleh

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Kulat adalah organisma kepentingan besar dalam proses penapaian yang berakhir dengan pengeluaran metabolit sekunder yang penting dalam penyelidikan bagi antibiotik baru, agen anti-kanser, racun serangga, racun herba dan lain-lain. Penemuan dan pembangunan antibiotik adalah salah satu kemajuan perubatan paling penting dalam abad kedua puluh. Trend penyelidik baru-baru ini menunjukkan bahawa penemuan bahan kimia aktif adalah untuk mengemaskini keberkesanan ubat yang digunakan pada masa akan datang, supaya, ia adalah perlu untuk melindungi kulat terpencil baru untuk mengenal pasti sebatian bioaktif antimikrob baru. Oleh itu, kajian ini bertujuan untuk mengkaji pengeluar baru metabolit sekunder daripada kulat thermophilic dan ditentukan sifat-sifat biologi mereka. Sepuluh kulat thermophilic dipilih daripada 30 spesies terpencil dalam negara dari Semenanjung Malaysia. Siasatan daripada ekstrak menunjukkan adanya fenolik (14.61) hingga (19.64) mg asid Gallic setaraf / g yang dianalisis oleh kromatografi cecair berprestasi tinggi (HPLC) dan menunjukkan adanya 10 phenolic; Pyrogallol, asid syringic, asid Gallic, asid cinnamic, asid salisilik, asid chlorogenic, resorcinol, asid vanillic, asid caffeic dan hypophyllanthin, dan selain dari itu 4 flavonoid (apigenin, daidzein, catechin, dan epicatechin). Lain 14 metabolit asas terletak di tepi GC-MS termasuk: asid asetik 20.81%, 2,3-Butanediol 42,92%, asid 2-Furoic hydrazide 16.79%, cis-9-Hexadecenoic asid (asid palmitoleic) 10.07%, Isosorbide 5.23%, 9 asid -Octadecenoic, metil ester, (E) - (asid oleik) 22.08%, asid cis-Vaccenic (cis-11-Octadecenoic asid) 13.03%, 1-Naphthalenol, 1,2,3,4-tetrahydro-2,5, 8-trimethyl- 9.92%, .alpha.-D-Glucopyranoside, methyl 19.03%, 3,5-dihydroxy-6-metil-2,3-dihydro-4H-pyran-4-satu 5.27%, asid 2-Furoic, methyl ester 8.76%, Niacinamide 7.75%, 9,12-Octadecadienoic asid, methyl ester (linoleik asid metil ester) 4.26% dan asid Pentadecanecarboxylic (asid palmitik) 6.78% daripada semua sepuluh kulat yang diasingkan. Semua ekstrak metanol kulat thermophilic menunjukkan pelbagai aktiviti antimikrob terhadap kedua-dua Gram mikroorganisma patogen negatif positif dan Gram (zon Perencatan: 6.3 mm untuk 25.7mm) pada kepekatan 250, 500 dan 1000 µg / cakera. Ekstrak dipaparkan akti[iii] oksidan mempunyai kecenderungan untuk keluar mencari radikal bebas dalam penurunan ion ferik (Fe3 +) untuk ion ferus (Fe2 +) FRAP (50,97-79,1%), DPPH (50,62-57,48%), ABTS (50,41-62,51%) dan NO (51,17-59,45%) untuk semua pencilan. Keputusan cytotoxicity

menunjukkan keupayaan ekstrak metanol daripada *Myceliopthora thermophila* sebagai sumber anti kanser agen terapeutik kepada sel-sel kanser payudara MCF-7 pada kepekatan IC50 daripada 29.97µg / ml dengan sel daya maju 36.66% dan cytotoxicity 90,18% berbanding garis sel MDBK. Untuk kulat thermophilic *Myceliophthora thermophila*, pekat ekstrak menghalang 50,43% daripada inducible synthase oksida nitrik dalam cara yang bergantung kepada ukuran dos di 250µg mL-1, manakala disimpan sehingga 91,13% daripada RAW 264,7 bahagian sel macrophage disebabkan oleh LPS/IFN-ɣ mengadakan tunjuk perasaan aktiviti anti-radang jelas mereka.

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10 thermophilic isolates were as: (1) *Aspergillus fumigatus* UPML005; (2) *Rasamsonia composticola*; (3) *Rasamsonia emersonii* UPML010; (4) *Rasamsonia byssochlamydoides* UPML011; (5) *Thermomyces lanuginosus* UPML012; (6) *Eurotiales* sp. UPML15b; (7)*Thermoascus aurantiacus*; (8) *Thielavia terrestris* UPML023; (9) *Myceliophthora thermophila*; (10) *Chaetomium* sp. UPML025.

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LIST OF ABBREVIATIONS

ABTS	2,2'-azinobis(3-ethyl-benzothiazoline-6-sulfonic acid)
$ALCL_3$	Aluminium chloride
approx.	Approximately
bar	A unit of pressure
BHA	Butylate hydroxyanisol
BHT	Butylate hydroxytoluene
bp	Base pairs
°C	Degree centigrades
cfu/ml	Colony forming unit per millilitre
cm^3	Cubic centimeter
$°C\ min^{-1}$	Degree centigrade per minute
CO_2	Carbon dioxide
DMEM	Dulbecco's Modified Eagle's Medium
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DNase	Deoxyribonuclease
dNTPs	Deoxynucleoside triphosphates
DPPH	2,2-diphenyl-1-picryl-hydrazyl
DW	Dry weight
EDTA	Ethylene Diamine Tetraacetic acid
FBS	Foetal Bovine Serum
FDW	Freeze- dried weight
Fe^{2+}	Ferrous
FRAP	Ferric reducing antioxidant power
Fwd_name	Forward name

Fwd_seq	Forward sequence
g	Gram
GAE	Gallic acid equivalent
GC-MS	Gas chromatography mass spectrometry
$HO_2^{\cdot}$	Hydroperoxyl radical
H_2O_2	Hydrogen peroxide
HOCl	Hypochlorous acid
HPLC	High performance liquid chromatography
IC_{50}	Half maximal inhibitory concentration
ID	Identified
IFN-ɣ	Interferon- gamma
iNOS	Nitric oxide synthase
ITS	Internal transcribed spacer regions
kb	Kilo base
$K_3Fe(CN)_6$	Potassium ferricyanide
kV	Kilo volt
L-NAME	L-nitro-arginine methyl ester
LPS	Lipopolysaccharide
M	Molar
mbar	Milli bar
MeOH	Methanol
mg	Milligram
µg	Microgram
µg g^{-1}	Microgram per gram
µg/ml	Microgram per millilitre
mg/L	Milligram per litre
MIC	Minimum inhibitory concentration

min.	Minutes
µl	Microlitre
ml	Millilitre
mL min^{-1}	Millilitre per minute
µm	Micrometer
mm	Millimeter
mM	Milli molar
MTT	3-[4,5-Dimethylthiazol-2-yl]-2.5-diphenyl-tetrazolium bromide
M. WT.	Molecular weight
NA	Nutrient agar
$NaCO_3$	Sodium carbonate
NaOH	Sodium hydroxide
NB	Nutrient broth
NCBI	National centre of biotechnology information
ng	Nanogram
nm	Nanometer
No.	Number
NO	Nitric oxide
$^{\cdot}OH$	Hydroxyl radical
$^1O_2$	Singlet oxygen
$O_2^{\cdot-}$	Superoxide anion
$ONOO^-$	Peroxynitrite
PCR	Polymerase chain reaction
PDA	Potato dextrose agar
pH	Logarithm of hydrogen ion activity
QE	Quercetin equivalent

R^2	A measure of goodness-of-fit of linear regression
RAW-264.7	Murine monocytic macrophage cell line
rDNA	Ribosomal deoxyribonucleic acid
Rev_name	Reverse name
Rev_seq	Reverse sequence
RNA	Ribonucleic acid
ROS	Reactive oxygen species
rpm	Revolving per minute
s	Seconds
SEM	Scanning electron microscopy
± SEM	Standard error of means
sp.	Species
Temp.	Temperature
TF	Thermophilic fungi
TPC	Total phenolic content
u/µl	Unit per microlitre
units/ml	Units per millilitre
UPML	University Putra Malaysia-Laith
v/v	Volume per volume
Ver.	Version
w/v	Weight per volume
%	Percentage
1x	One time
x g	The centrifuge speed unit per minute (Earth gravitational force)

CHAPTER 1

INTRODUCTION

A soil specimen regularly yields a tremendous measure of distinctive types of microorganisms like fungi. The vast majority of fungi are delivering diverse chemical substances to secure and resist against other living beings in the same territory and under comparative ecological conditions. It is accepted that this safety resistance is regularly joined by a predominant creation of bizarre bioactive metabolites.

The fascinating chemicals, distinguished as common natural products, are determined by the fungus and their surroundings that cooperate to produce structural and chemical substances so as to improve survival and aggressiveness (Lee, 2010). In the early history of antibiotics, an assortment of bacterial and fungal strains was researched from temperate locales specimens. At the point when streptomycin was uncovered in 1944, the principle focus turned to streptomycetes. In particular, fungi helped approximately 38% of all isolated microbial products and 17% from unicellular bacterial microorganisms (Berdy, 2005). Hence, as an antimicrobial, fungi have turned out to be a rich source of antibiotics. Meanwhile, fungal bioactive metabolites have been found to be a paramount hotspot of pharmaceuticals bioactive components (Hoffmeister, 2007). In fact, fungi are basic in nature and considered as great natural hotspots for antimicrobial operators (Lindequist *et al*., 2005).

Fungi give an incredible mixture of structural classes and merit researcher's consideration for anticancer medication advancement, as exhibited by a few samples introduced in this study.Thermophilic fungi fit in with the ascomycete's family and develop under high level of temperature (more than 55-60°C) with expanding humidity in tropical and subtropical areas. Those hotness tolerant fungi have an imperative part in a few modern industrial applications. A few species of thermophilics have been viewed as a potential source of catalyst enzymes for degradation. Generally, common fungi pharmacological applications are well known, yet, a great part of the thermophilic fungi pharmaceutical data are rare or remain uncommon in investigative exploration of scientific research.

Phenolic and flavonoid compounds are the real metabolites found in the mushroom, plant endophytic fungi, marine fungi, soil Penicillium, and Aspergillus species of fungi. Among the phenolics, Gallic acid, Pyrogallol and Caffeic acid have commanded research in distinctive fungal species as for their new compound structures and medicinal or pharmaceutical values. As of late, numerous specialists have reported that concentrated extracts of fungi, which held phenolics and flavonoid, demonstrated outstanding antioxidant, anticancer and anti-inflammatory activities.

The thermophilic fungi could be utilised as a part of in vitro to deliver compounds with bioactive effects like antioxidant. The antioxidant activities have anti-inflammatory, anticancer, antibacterial, and antifungal properties.

Thermophilic organisms might be utilised likewise for agrarian and industrial reasons as well. There are many different compounds that help the thermophilic fungi to produce bioactive effects as an alternate source. which could be distinguished and utilised as a natural medicine. Likewise. an anticancer compound taxol had been acquired from fungal endophyte (Stierle *et al.* 1993). This can be further explored to perceive how thermophilic fungi extricate can be utilised for medical purposes.

On the account of thermophilic species of fungi. the bioactive compounds have not been extensively mulled over; in this way. no data is accessible on their extracts regarding their possibility as a source reference of new compounds of bioactivity. Henceforth, the target within the present study was to screen the bioactive compounds of isolated thermophilic fungi methanol extracts and to examine their extracts biotic activities. The data assembled would demonstrate the capability of the tried thermophilic species as a source of bioactive compounds. For the reasons said above, soil microorganisms from Peninsular Malaysian source areas could turn into a source of decision for the identification of new lead compounds regarding medication revelation.

The isolation of thermophilic fungi is not simple enough to follow the old classic isolation methods utilised for the isolation of diverse common mesophilic fungal species. The thermophilic species in the current study are extremely sensitive and troublesome in isolation as a result of extraordinary environment required like high temperature and dampness with high utilizing expense of distinctive particular media to isolate every species and control their appearance in the first run through isolation on the plate specifically from the source specimen.

Identification of thermophilic fungi of interest is not completely led. So, there is a need to concentrate on morphological recognisable proof by utilising advanced microscopically magnifying instruments and SEM Scanning Electron Microscope to assess the itemised macroscopically and microscopically structures of every fungus and contrast them with the information recommended by literature of diverse researchers so as to affirm the fungal morphological identification of our isolated thermophilic fungi.

However, it was vital to affirm their morphological distinguishing proof with support by molecular identification to the species level to be considered as the first report on thermophilic species indicating bioactivity effect which ought to be the starting field of new fungal exploration guide for different scientists as recent natural product sources. This PhD thesis study was carried out to assess the biological activities of methanolic extract of selected thermophilic fungi gathered from an assortment of locally sources from Peninsular Malaysia.

Hence, the specific objectives of this research were:

1. to isolate and preserve locally thermophilic fungi species to high culture purity for the aim of obtaining bioactive effects.

2. to identify the isolated thermophilic fungi morphologically, and molecularly to the species level.

3. to screen the bioactive compounds of the isolated thermophilic fungi methanol extracts utilising the HPLC and GC-MS methods.

4. to assess their methanolic extract bioactivity utilising antibacterial, antifungal, antioxidant, cytotoxicity and anti-inflammatory assays.

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