EXTRACTION OF ANTI-TUBERCULOSIS PROPERTIES FROM SELECTED MEDICINAL PLANT BY DEEP EUTECTIC SOLVENTS (DES)

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DEDICATION

To my beloved father and mother for their immeasurable support and care. This thesis is also dedicated to my brothers and Sisters who have continually supported and believed in me. I dedicate this thesis especially to my wife, the best in the world, without your support, none of the positive things I have accomplished when we've been together would have been possible. This thesis is as much yours as it is mine. To my wonderful son who is the lights of my life and inspire me every moment of every day.

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ABSTRACT

Globally, the threat of tuberculosis (TB) continues to grow, requiring innovative techniques to find more effective treatment options. Medicinal plants of Malaysia, Middle East, and North Africa (MENA region) following: Algeria, Bahrain, Djibouti, Egypt, Iran, Iraq, Jordan, Kuwait, Lebanon, Libya, Malta, Morocco, Oman, Qatar, Saudi Arabia, Syria, Tunisia, Turkey, United Arab Emirates, Palestine, Yemen, Ethiopia, and Sudan have a significant role in providing new therapeutic remedies. Locals reported that indigenous formulations of some herbs are utilized to treat respiratory disease symptoms relate to TB disease. Deep eutectic solvents (DESs) are considered green solvents and have more significant than traditional solvents in ecosystem. The present study aims to evaluate the potential anti-TB from plants of Malaysia and MENA region extracted by DESs and exploit the traditional medicinal practices of the local people. Aqueous extracts and different types of deep eutectic solvents extracts of 5 kind plant species (*Moringa oleifera* Lam, *Premna odorata* Blanco, *Ocimum basilicum* L, *Rosmarinus officinalis* L and *Eucalyptus camaldulensis)* were screened using different assay against multidrug-resistant (MDR) *Mycobacterium tuberculosis* strain isolated from a clinical sample. The effect of the most active extracts on mycobacterial cells at the cellular level was investigated upon treatment with the crude extracts via time-kill analysis, leakage of compound was absorbing at 280nm. The *in vitro* cytotoxicity of most active extracts was evaluated against Rat Embryonic Fibroblasts (REF) cell line using MTT assay. Phytochemical profiling of the extracts was investigated by using liquid chromatography-mass spectrometry (LC-MS) in order to identify the chemical constituents present in the most active extracts. The findings revealed that DES2: Tailor extract of *R. officinalis* displayed the largest zone of inhibition (DIZ= 17.33 ± 1.15 mm) and exhibited the best antimycobacterial activity with minimum inhibitory concentration (3.12 mg/mL). Followed by DES3: CHGl of *R. officinalis* showed the good minimum inhibitory concentration (MIC= 6.25 mg/mL). DES2: Tailor extract of *R. officinalis* showed the lowest minimum bactericidal concentration (MBC= 12.5 mg/mL). At 3-fold of MIC, DES2: Tailor extract of *R. officinalis* killed the entire bacterial cell within 48 h of exposure by causing the cell lysis and releases of cell constituents when measured cell wall integrity. Cytotoxicity assay revealed that the most active DES extract was non-toxic to the REF cell line. The LC-MS analysis revealed the presence of phytoconstituents like: camphor, α-pinene, quercetin, kaempferol and oleic acid that potentially contribute to the antimycobacterial activity. In conclusion, the results demonstrated that the extracts obtained by DESs have incredible potency in TB treatment and are a greener procedure than conventional extraction solvents. Further studies on the use of DESs of plant extract could lead to the development of new anti-TB drugs.

ABSTRAK

Di peringkat global, ancaman tuberkulosis (TB) terus meningkat, teknik inovatif untuk mencari rawatan yang lebih berkesan amat diperlukan. Tumbuhan ubatan Malaysia, Timur Tengah dan Afrika Utara (rantau MENA) memainkan peranan penting dalam menyediakan ubat terapeutik baharu. Penduduk tempatan juga telah melaporkan bahawa formulasi asli beberapa herba telah digunakan untuk merawat gejala penyakit pernafasan yang berkaitan dengan penyakit TB. Pelarut eutektik dalam (DES) dianggap sebagai pelarut hijau dan lebih penting daripada pelarut tradisional dalam mesra alam. Kajian ini bertujuan untuk mencari potensi tumbuhan anti-TB dari Malaysia dan rantau MENA melalui ekstrak pelarut hijau DESs dan mengeksploitasi amalan perubatan tradisional penduduk tempatan. Ekstrak akueus dan pelbagai jenis ekstrak pelarut eutektik daripada 5 jenis spesies tumbuhan telah disaring menggunakan ujian penyebaran cakera agar untuk mendapat aktiviti antimikobakteria, kepekatan perencatan minimum. Juga diukur secara spektrofotometri pada 570 nm dan kepekatan bakteria minimum terhadap strain Mycobacterium tuberculosis tahan multidrug (MDR) juga diasingkan daripada sampel klinikal. Kesan ekstrak paling aktif pada sel mikobakteria telah disiasat semasa rawatan dengan ekstrak mentah melalui analisis masa-mematikan, kebocoran sebatian menyerap pada 280nm di peringkat sel. Sitotoksisiti in vitro untuk kebanyakan ekstrak aktif telah dinilai terhadap garis sel Embryonic Fibroblasts Tikus (REF) melalui ujian MTT. Pemprofilan fitokimia bagi ekstrak yang telah disiasat menggunakan spektrometri jisim kromatografi cecair (LC-MS) untuk mengenal pasti juzuk kimia yang terdapat dalam ekstrak yang paling aktif. Hasil menunjukkan bahawa DES2: Ekstrak Tailor *R. officinalis* memaparkan zon perencatan terbesar (DIZ= 17.33 ± 1.15 mm) dan menujukkan aktiviti antimikobakteria terbaik dengan kepekatan perencatan minimum (3.12 mg/mL). Diikuti dengan DES1: LGH dan DES3: CHGl of *M. oleifera*, DES3: CHGl of *P. odorata*, DES2: Tailor of *O. basilicum* and DES3: CHGl of *R. officinalis* menunjukkan kepekatan perencatan minimum yang baik (MIC= 6.25 mg/mL) . DES2: Ekstrak Tailor *R. officinalis* menunjukkan kepekatan bakteria minimum yang paling rendah (MBC= 12.5 mg/mL). Pada 3 kali ganda MIC, DES2: Ekstrak Tailor *R. officinalis* membunuh keseluruhan sel bakteria dalam pendedahan selama 48 jam dengan menyebabkan lisis sel dan pelepasan konstituen sel semasa integriti dinding sel diukur. Ujian sitotoksik menunjukkan bahawa ekstrak DES yang paling aktif tidak toksik kepada garis sel REF. Analisis LC-MS mendedahkan kehadiran kandungan fitokimia: camphor, α-pinene, quercetin, kaempferol dan asid oleik yang mempunyai potensi aktiviti antimikobakteria. Kesimpulannya, hasil yang didapati menunjukkan bahawa ekstrak yang diperoleh dari DES mempunyai potensi besar dalam rawatan TB dan merupakan prosedur yang lebih hijau daripada menggunakan pelarut. Kajian lanjut mengenai penggunaan DES dalam ekstrak tumbuhan boleh membawa kepada pembangunan ubat anti-TB baharu.

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LIST OF SYMBOLS AND ABBREVIATIONS

<	-	Less than
%	-	Percentage
°C	-	Degree celcius
>	-	Greater than
≤	-	Less than or equal to
≥	-	Greater than or equal to
µg	-	Microgram
µl	-	Microliter
µm	-	Micrometre
1X	-	1 fold of
2X	-	2 fold of
3X	-	3 fold of
ADC	-	Albumin Dextrose Catalase
AIDS	-	Acquired Immunodeficiency Syndrome
BCG	-	Bacille Calmette Gue´rin
BL-3	-	biosafety level 3
CFU	-	Colony Forming Unit/mL cm – Centimetres
CNS	-	Central Nervous System
DES	-	Deep eutectic solvents
DES1	-	Deep eutectic solvents 1
DES2	-	Deep eutectic solvents 2
DES3	-	Deep eutectic solvents 3
DES4	-	Deep eutectic solvents 4
DIZ	-	Diameter of inhibition zone
DMSO	-	Dimethyl sulphoxide
GC-MS	-	Gas chromatography–mass spectrometry
ChGl	-	Choline Chloride: Glycerol
ChXl	-	Choline Chloride: Xylitol

ChMa	-	Choline Chloride: Malic acid
ChLa	-	Choline Chloride: laevulimic acid
GI	-	Gastrointestinal
H	-	Hour
HIV	-	Human Immunodeficiency Virus
HPLC	-	High Performance Liquid Chromatography
IM	-	Intramuscular
INH	-	Isoniazid
IV	-	Intravenous
JNPC	-	Johor National Park Corporation
LGH	-	Lactic acid, Glucose and Water
MBC	-	Minimum Bactericidal Concentration
MDR	-	Multidrug-Resistant
Mg	-	milligram
MIC	-	Minimum Inhibitory Concentration
Min	-	minute
mL	-	Millilitre
mm	-	millimetre
NA	-	Not active
nm	-	nanometres
OADC	-	Oleic acid, Albumin, Dextrose and Catalase
OD	-	Optical density
PAS	-	Para-Amino Salicylic acid
PYR	-	Pyrazinamide
RIF	-	Rifampin
RNA	-	Ribonucleic acid
Rpm	-	Revolution per minute
RT	-	Retention time
SD	-	Standard deviation
Tailor	-	Glycerol, Xylitol and D-(-)-Fructose
TB	-	Tuberculosis
TDM	-	Trehalose dimycolate
TLC	-	Thin-Layer Chromatography
TLR	-	Toll like receptors

TMM	-	Trehalose monomycolate
TNJER	-	Taman Negara Johor Endau-Rompin
UTHM	-	Universiti Tun Hussein Onn Malaysia
WHO	-	World Health Organization
XDR-TB	-	Extensive drug-resistant

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i) **Dehyab, A. S.,** Bakar, M. F. A., AlOmar, M. K., & Sabran, S. F. (2020). A Review of Medicinal Plant of Middle East and North Africa (Mena) Region as Source in Tuberculosis Drug Discovery. *Saudi journal of biological sciences, 27*(9), 2457.

ii) **Dheyab, A. S.,** Abu Bakar, M. F., AlOmar, M., Sabran, S. F., Hanafi, A. F. M., & Mohamad, A. (2021). Deep Eutectic Solvents (DESs) as Green Extraction Media of Beneficial Bioactive Phytochemicals. *Separations*, *8*(10), 176.

iii) **Dheyab, A. S.,** Ibrahim, A. J. K., Aljumily, E. K., AlOmar, M. K., Bakar, M. F. A., & Sabran, S. F. (2022). Antimycobacterial activity and phytochemical properties of *Eucalyptus camaldulensis* (eucalyptus) extracted by deep eutectic solvents. *Materials Today: Proceedings*, *65*, 2738-2742.

iv) **Dheyab, A. S.,** Kanaan, M. Q., Hussein, N. A., AlOmar, M. K., Sabran, S. F., & Abu Bakar, M. F. (2022). Antimycobacterial Activity of *Rosmarinus officinalis* (Rosemary) Extracted by Deep Eutectic Solvents. *Separations*, *9*(10), 271.

CHAPTER 1

INTRODUCTION

The anti-tuberculosis potential of 5 selected medicinal herbs was described in this study. The components of the selected medicinal plants were extracted using highly standardized deep eutectic solvents in this study. The extracts were bioassayed against a clinical *Mycobacterium tuberculosis* strain with multi-drug resistance utilizing a conventional antimycobacterial test. The effect of the selected plant extracts on mycobacterial cells at the cellular level and their cytotoxicity were also studied. The phytochemical profiling of the selected plant extracts revealed many chemicals that may be responsible for antimycobacterial activity. The claim has been scientifically verified that the extraction of medicinal plants by deep eutectic solvents are much better than traditional solvents and their effect on *Mycobacterium tuberculosis*.

1.1 Research background

Tuberculosis (TB) is a devastating and widespread infectious illness caused by a severe pathogenic bacteria known as *M. tuberculosis*, a member of the Mycobacterium family. This illness is prevalent in various countries throughout the globe because of the varying transmission levels (Abuzeid *et al.*, 2014; Akintola *et al.*, 2013). About two billion individuals, or about one-fifth of the world's population, are believed to be afflicted with tuberculosis (Kandasamy *et al.*, 2018). According to the World Health Organization's (WHO) 2016 estimate, around 10 million people worldwide are afflicted with tuberculosis (TB), and one million of those sick have died as a result of this infectious illness (Organization, 2016). Because of the increased mortality rates of this illness, TB was designated as one of the main causes of death in the African and South-East Asian regions, ranking above HIV/AIDS as one of the top causes of death worldwide (Organization, 2016). In 2015, tuberculosis was considered one of the top 10 causes of death worldwide, and it caused more deaths than HIV/AIDS (AlMatar *et al.*, 2017). The tuberculosis bacteria belong to the Mycobacteriaceae family, and the specific characteristic of tuberculosis bacteria that distinguishes it from other bacteria, whether gram-positive or gram-negative, is the presence of long fatty acid chains in the cell envelope, which is referred to as the mycolic acid layer (Jackson, 2014).

Despite government policies aimed at preventing and controlling tuberculosis, the disease is still regarded as a significant public health problem in Malaysia, despite efforts to combat it (Rafiza, Rampal, and Tahir 2011). TB disease is considered the 5th most common infectious disease in Malaysia, and this conundrum can be attributed to the high amount of universal labourers from many countries, including Indonesia, Myanmar, and Bangladesh, who come to work in the country (Rafiza, Rampal, & Tahir, 2011). Since the 1950s, TB-infected patients have relied on the supply of anti-TB medications, which are split into three groups: Anti-TB medications in the first line, second line, and third line of defence against tuberculosis (Jetan *et al.*, 2010; Keshavjee and Farmer, 2012; Zumla, Nahid, & Cole, 2013). In order to eradicate tuberculosis, modern chemotherapeutic drugs such as isoniazid, rifampicin, ethambutol, streptomycin, and pyrazinamide are utilized. On the other hand, these medications have the undesirable consequence of generating dangerous side effects such as hepatitis, gastroenteritis, and hearing loss in certain people (Altaf *et al.*, 2010; Famewo, Clarke, & Afolayan, 2017).

There are two types of TB resistance: multidrug-resistant TB (MDR-TB), which does not respond to first-line standard treatment, and extensive drug-resistant TB (XDR-TB), which occurs when resistant to second-line TB drugs. MDR-TB is the more serious of the two types of TB resistance. According to 2012 WHO report on monitoring and response to MDR-TB and XDR-TB, 310,000 MDR-TB cases were identified among pulmonary TB patients in 2011, with 84 countries reporting at least one case of XDR-TB. 450,000 people worldwide developed MDR-TB in 2012; 170,000 people died from it. Even though more than half of these cases came from Brazil, China, Russia and India, the overall picture is still alarming (Abdallah & Ali, 2012; Rennie *et al.*, 2011). The difficulties present a unique opportunity to begin investigating novel techniques to treat multidrug-resistant tuberculosis (Robles-Zepeda *et al.*, 2013; Umesiri *et al.*, 2015). As a result, a new anti-TB drug discovery effort should be launched to address the issues mentioned above in previous subsection and demonstrate support for sustainable development and the TB Strategy (Organization, 2016). In light of these adverse side effects of synthetic drugs, the potential efficacy of herbal medicines has piqued the interest of scientists and healthcare providers, who have begun to shift their attention away from synthetic drugs and toward conventional medicinal products for the treatment of certain chronic and infectious diseases (Adaikkappan, Kannapiran, & Anthonisamy, 2012).

Anthropological botany is the study of both people and plants. Plants are a valuable source of traditional medicines and are used for various reasons, including food, fodder, and medicine (Jalil *et al.*, 2012; Tariq *et al.*, 2015). Because of their chemical diversity and crucial role in drug discovery, medicinal plants hold tremendous promise for meeting these needs. These plants have mainly been employed as pure chemicals or as raw materials. Only a few plant species have been thoroughly researched for their therapeutic potential (Gemechu *et al.*, 2013; Kaur and Kaur, 2015). Due to the fact that they are readily available and easily harvested, plants are still being utilized for treatment reasons, namely to manage TB-related clinical signs, by indigenous people all over the world today (Akintola *et al.*, 2013; Bunalema *et al.*, 2014; Jiménez-Arellanes *et al.*, 2014) Plant-based medications have traditionally been used to treat a wide range of infectious diseases all over the world. Approximately 75% of the world's population relies on medicinal plants for their primary health care. TB treatment, in particular, is dependent on the presence of an extensive range of secondary metabolites within them (Jamal *et al.*, 2011; sharma, 2016).

Phytochemical studies of various therapeutic plants have revealed a large number of active natural chemicals; however, few plants have been tested against mycobacteria, and several plants have shown promising results against tuberculosis disease (Kaur and Kaur, 2015). Secondary metabolites of plants, also known as phytochemicals, are chemical compounds found in plants that occur naturally in their environment. This class of chemicals, in contrast to the primary metabolites, does not directly contribute to the growth, proliferation, and development of plants (Ahmed, Arshad, & Khan, 2017). Phytochemicals in plants are closely linked to biological activities, particularly antimycobacterial activity, as these chemicals play a crucial role in describing such activity (Compean and Ynalvez, 2014; Kumar, Banik, & Sharma, 2010).

Malaysia's tropical rainforest is densely planted with various species, including medicinal herbs. There are over 14,500 plant species in Malaysia, of which over 2000 have diverse therapeutic qualities and have a strong potential for commercialization (Ahmad and Othman, 2013; Jamal *et al.*, 2011).

1.2 Problem statements

Among all infectious diseases, tuberculosis is one of the most dangerous killers of adults in the world today. The treatment options offered have the drawback of generating significant side effects such as hepatitis, gastroenteritis, nausea, and hearing loss, amongst other unpleasant side effects. In addition, the pharmaceutical regimen is overly lengthy, lasting anywhere from 6 to 9 months. There are many people who do not stick to the time restriction for therapy because of this reason. As a result, the situation has become more complicated, with *Mycobacterium* modifying resistance to TB medications giving rise to multidrug-resistant TB (MDR-TB) and extended drug-resistant TB (XDR-TB), as well as a pressing need to find new treatments for TB disease strains. Furthermore, the existing anti-TB treatment regimen, which has produced significant side effects in patients for a long time, has necessitated the urgent development of a novel anti-TB drug of plant origin. On the other hand, there are claims for the traditional solvents that have many drawbacks such as long extraction period, toxicity, not ecofriendly, expensive, the requirement of large volume solvent. The selected medicinal plants that have been no actual scientific evaluation of the antimycobacterial activity in these plants extracted by deep eutectic solvents to justify the claim. Deep eutectic solvents (DESs) are expected to be used extensively for the extraction of bioactive compounds from medicinal plants. As a result, a study of these plants in the laboratory is required through extracted by deep eutectic solvents and anti-TB benefits medicinally. The anti-mycobacterial effect agents derived from medicinal plants have been studied extensively in various parts of the world; however, despite Malaysia's rich plant diversity, little attention has been paid to evaluating and detecting anti-mycobacterial activity from Malaysian medicinal plants in the laboratory setting.

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