ANTIMYCOBCATERIUM ACTIVITY OF ALLIUM CEPA TARGETING
ISOCITRATE LYASE, MALATE SYNTHASE AND
TWO-COMPONENT SYSTEM

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ABSTRACT

Tuberculosis is one of the most serious diseases that caused by *Mycobacterium tuberculosis*. In this study, crude, petroleum ether, n-butanol, chloroform and methanol aqueous extracts of *A. cepa* were evaluated for its anti-mycobacterium property against H8000 *M. smegmatis mc²155* targeting on the ICL and MS in the glyoxylate cycle and two-component system. The crude extract showed no inhibition while the petroleum ether extract showed inhibition in the glyoxylate assay targeting ICL and MS but it might not be potent enough to be further developed into an anti-persistent TB drug whereas the chloroform and n-butanol extracts were cytotoxic. In the two-component system, the n-butanol extract showed inhibition but it might not be potent enough to be developed into a new anti-TB drug whereas the petroleum ether and chloroform extracts were cytotoxic. Further purification of the cytotoxic compound from *A. cepa* might help in the development of *A. cepa* into new anti-TB drug.
ANTIMIKOBACTERIA AKTIVITI ALLIUM CEPA YANG SASAR PADA ISOCITRATE LYASE, MALATE SYNTHASE DAN TRANSDUKSI ISYARAT

ABSTRAK

Penyakit tuberkulosis merupakan salah satu penyakit serius yang disebabkan oleh Mycobacterium tuberculosis. Dalam kajian ini, ekstrak mentah, petroleum eter, kloroform, n-butanol dan metanol akues A. cepa dinilai untuk ciri antimikrobakteriannya terhadap H8000 M. smegmatis mc²155 yang sasar pada ICL dan MS dalam pintasan gliosilat dan transduksi isyarat. Ekstrak mentah tidak menunjukkan perencatan. Ekstrak petroleum eter menunjukkan perencatan pada pengujian gliosilat yang sasar pada ICL dan MS tetapi ia mungkin tidak cukup berkesan untuk dikembangkan kepada agen anti-TB manakala ekstrak kloroform dan n-butanol adalah toksik. Dalam transduksi isyarat, ekstrak n-butanol menunjukkan perencatan tetapi ia mungkin tidak cukup berkesan untuk dikembangkan kepada agen anti-TB manakala ekstrak petroleum eter dan kloroform adalah toksik. Penulisan selanjutnya pada kompoun yang toksik daripada A. cepa mungkin akan membantu dalam perkembangan A. cepa kepada agen anti-tubi yang baru.
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CHAPTER 1

INTRODUCTION

1.1 Background

Tuberculosis (TB) is a chronic infectious disease of the lung caused by the bacterium *Mycobacterium tuberculosis*. Once inhale the infected droplets formed when someone coughing which has an active case of the disease, the bacillus will infects the lungs. It can also be spreaded through unpasteurized milk, as animals can be infected with the bacteria also (Lerner et al., 2003).

One-third of the world population (1720 million people) is estimated to have latent infection with *M. tuberculosis* (Smith et al., 2004). Each year there are eight million new TB cases and two million deaths (Zhang, 2006). 1.6 million people died from TB in 2005, equal to an estimated 4400 deaths a day (WHO, 2007).

4.5 million people world-wide are estimated to be co-infected with HIV and tuberculosis, and of these 98% are in developing countries (Sussman, 2002). Coinfection with the human immunodeficiency virus (HIV) significantly increases the
risk of developing TB. Countries with a high prevalence of HIV, particularly those in sub-Saharan Africa, have seen an increase in the number of TB cases, with reported incidence rates increasing two- or threefold in the 1990s (WHO, 2003).

The infection will only be chronic when the bacteria become active and attack the lungs. Patients infected with the disease will suffer from fatigue, loss of weight, night fevers and chills, and persistent coughing with sputum-streaked blood. The infection is virulent and can spread to other parts of the body. Treatment is needed to prevent the condition from being fatal (Lerner et al., 2003).

One of the hallmarks of tuberculosis is the persistent phase of infection (Smith et al., 2004). *M. tuberculosis* is recalcitrant to treatment by conventional anti-TB drugs (Girling, 1989). Emergence of multi-drug resistant TB (MDR-TB) is caused by the long-term therapies lasting between 6 and 9 months with isoniazid and rifampin (Duncan et al., 2000; Mckinney et al., 1998). The MDR-TB is resistant to at least one first-line or primary anti-TB drugs (isoniazid, rifampin, streptomycin, ethambutol and pyrazinamide), as well as some of the second-line drugs (ethionamide, cycloserine, thiacetazone and the quinolones) (Manjula et al., 2002; Duncan et al., 2000).

Bacteria needs to induce the glyoxylate cycle to gain glucose when the C₂ compounds, such as ethanol and acetate, are the only sources of carbon (Lorenz et al., 2002). Isocitrate lyase (ICL) and malate synthase (MS) enzymes in the glyoxylate pathway in *Mycobacterium* serve as drug targets for persistent infection (Smith et al., 2003). The ICL enzyme plays an important role as it catalyzes the hydrolyzation of six-carbon isocitrate into two-carbon glyoxylate and four-carbon succinate (Bentrup et
Then, malate synthase enzyme catalyzes the formation of four-carbon malate by the condensation of two-carbon acetyl-CoA and glyoxylate. As bacteria cannot survive without the glyoxylate cycle, the detection of the active component which can inhibit the activities in the *M. tuberculosis* is very important for the development of antimicrobial drugs (Lorenz *et al*., 2002).

Two-component system is signal-transducing ATPase that use energy releases from ATP hydrolysis to produce responses to changing environmental conditions (Hoch *et al*., 1995). There were 11 two-component systems in *M. tuberculosis*, the scope of this study was narrowed to those Mg$^{2+}$ ion-dependent. When the Mg$^{2+}$ ion in the external environment of the bacteria is low, the two component system will be turned on which lead to the virulence of the bacteria (Stock *et al*., 1995).

The two-component system has a specific sensor kinase and a response regulator protein which will response to external stimulus (Koretke *et al*., 2000). The sensor protein detects signal from the environment, autophosphorylates and transmits the phosphoryl group to the response regulator. Then, the activated response regulator will regulate the transcriptions of proteins (Barett *et al*., 1998). The fact that the two-component system is essential for bacterial survival and virulence makes it attractive candidates for anti-TB drug design (DiRita *et al*., 1989; Miller *et al*., 1989; Deretic *et al*., 1991).

The extracts of *Allium cepa* possessed activity in anti-mycobacterium screening as reported by Ch'ng, 2007 and Teoh, 2007. It is most commonly known as onion which produces strong odour, strong taste and has some medicinal uses. *A. cepa*
can be used to prevent age-dependent changes in the blood vessels, and loss of appetite. Besides, it also contributes to the treatment of bacterial infections such as dysentery, and as diuretic. In addition, it has also been used as an adjuvant therapy for diabetes. *A. cepa* was reported to have applications as antimicrobial, antithrombotic, antitumor, hypolipidaemic, antiarthritic and hypoglycemic agents (Ali *et al.*, 2000).

The methanol aqueous and petroleum ether extracts of *A. cepa* were proven to have inhibition effect in antituberculosis (Ch’ng, 2007; Teoh, 2007). Thus, the study of the *A. cepa* bulb extracts targeting the glyoxylate cycle and two-component system holds the potential to contribute to the development of new anti-TB drugs.

### 1.2 Objectives

The objectives to carry out this study were as below:

i. To prepare extracts and fractions of *Allium cepa*.

ii. To evaluate the activity of *Allium cepa* against depathogenic H8000 *Mycobacterium smegmatis* mc²155 seed culture targeting the ICL and MS enzymes in the glyoxylate cycle.

iii. To evaluate the activity of *Allium cepa* against depathogenic H8000 *Mycobacterium smegmatis* mc²155 seed culture targeting the two-component system.
1.3 Scope of Study

This study focused on the biological activities of inhibitors in the extract of *A. cepa* bulb for persistent latent TB infection targeting the ICL and MS in the glyoxylate cycle and two-component system of *Mycobacterium*. Depathogenic *M. smegmatis mc²155* was used instead of pathogenic *M. tuberculosis* in this study.

*Allium cepa* bulbs were extracted to obtain the crude extract. Then the *A. cepa* crude extract was evaluated for its biological activity against H8000 *Mycobacterium smegmatis mc²155* targeting the ICL and MS in the glyoxylate cycle and two-component system using agar diffusion screening systems.

*A. cepa* crude extract was then used to run the solvent-solvent extraction to yield petroleum ether, chloroform, n-butanol and methanol aqueous extracts fractions. Each of the extracts fractions were evaluated for their biological activities against H8000 *Mycobacterium smegmatis mc²155* targeting ICL and MS in the glyoxylate cycle and two-component system using agar diffusion screening systems.
CHAPTER 2

LITERATURE REVIEW

2.1 *Allium cepa* (onion)

2.1.1 Systematics and Distribution of *Allium cepa*

*A. cepa* is a member of the large genus *Allium* which contains about 700 species, including economically important vegetables and flowering ornamentals as well as wild species from Europe, Asia, and the Americas (Fenwick *et al.*, 1985). These plants are able to survive under harsh conditions such as winter or dryness because of their bulbs, tubers and rhizomes as shown in Photo 2.1.

![Red onions](photo.jpg)

**Photo 2.1** Red onions.
The plants of the Liliaceae show very different habits and contain various classes of chemical compounds. The classification of the Liliaceae has been discussed for a long time: *A. cepa* has been assigned by Hutchinson to the subfamily Allioideae, belonging to the Amaryllidaceae in year 1959 (Hutchinson, 1959). But as *A. cepa* lack of alkaloids (typical of Amaryllidaceae), the Allioideae was also classified as a member of the Liliaceae. Finally, plants of the genus *Allium* were classified in the independent family of Alliaceae (Dahlgren et al., 1985). Its taxonomy is:

Section: Spermatophyta
Subsection: Angiospermae
Class: Monocotyledonae (= Liliatae)
Subclass: Liliidae
Order: Liliales (= Liliflorae)
Family: Alliaceae
Subfamily: Allioideae
Tribe: Allieae
Subtribe: Alliinae
Genus: Allium

The flavour and odour of *A. cepa* are easily recognized. It grows biennially which produces an underground storage bulb at the end of the first growing season and flowers in the next. It is odourless until the tissue is damaged, at which the volatile and reactive sulphur-containing chemicals that cause its best-known characteristic are generated (Jones et al., 2004). *A. cepa* is important as a food plant
and as a drug in folk medicine. Today, *A. cepa* is cultivated all over the world, especially in moderate climates (Breu, 1996).

### 2.1.2 Description of *Allium cepa*

*A. cepa* is a perennial herb which produces strong smelling when crushed. The bulbs vary in size and shape from type to type. It is often depressed-globose and up to 20 cm in diameter with outer tunics membranous. Besides, it usually stem up to 100 cm tall and 30 mm in diameter and is tapering from inflated lower part. It can reach up to around 40 cm in height and 20 mm in diameter, usually almost semicircular in section and slightly flattened on upper side. In addition, its stamens are exserted and the filaments are about 4–5 mm. Its outer is subulate while the inner is with an expanded base up to 2 mm wide and bearing short teeth on each side (WHO, 1999).

### 2.1.3 General Appearance

*A. cepa* bulb varies in size and shape from cultivar to cultivar. It is usually 2–20 cm in diameter with flattened, spherical or pear shape. It is white or coloured (Bruneton, 1995).

### 2.1.4 Organoleptic Properties

*A. cepa* produces strong odour with alliaceous characteristic. It also produces strong taste. Sweating can be stimulated through crushing or cutting the bulb (WHO, 1999).
2.1.5 Geographical Distribution

*A. cepa* is commercially cultivated worldwide, especially in regions of moderate climate. For example, it is cultivated in Geneva and western Asia (Breu et al., 1994). *A. cepa* is among the oldest of all cultivated plants with its origin in central Asia (Ali et al., 2000).

2.1.6 Major Chemical Constituents in *Allium cepa*

*A. cepa* is a rich source of various compounds and has been thoroughly investigated by phytochemists during the last 100 years. Among the compounds, the most abundant in the *A. cepa* are organosulphur compounds. These compounds are such as the amino acids cysteine and methionine, the S-alk(en)yl-substituted cysteine sulphoxides and the \( \gamma \)-glutamylcysteine peptides. There are four S-alk(en)yl-cysteine sulphoxides that have been detected in *A. cepa* which are (+)-S-methyl-, (+)-S-propyl-, trans-(+)-S-(1-propenyl)-L-cysteine sulphoxide and cycloalliin (WHO, 1999).

The cysteine sulphoxides that are released from the compartments will contact with the alliinase enzyme in adjacent vacuoles when the onion bulb is crushed. The alliinase enzyme will catalyze the metabolism of S-alk(en)yl-L-cysteine sulphoxides to sulphenic acids. Hydrolysis and immediate condensation of the highly reactive sulfenic acids will produce the volatile sulphur compounds which will contribute to the lachrymatory pungency, typical smell, taste and pharmacological actions of *A. cepa* extracts (Suzuki., 1962).
Approximately 90% of the soluble organosulphur compounds that are present as γ-glutamylcysteine peptides (which are not acted on by alliinase) contributes to the taste quality of *A. cepa* and the formation of potentially pharmacologically active ingredients in *A. cepa* extracts. The γ-glutamylcysteine peptides function as storage reserve and contribute to the germination of seeds (Randle *et al.*, 1995).

The volatile sulphur-containing compounds that are present in the *A. cepa* are such as zwiebelanes, cepaenes, the mono-, di- and trisulphides that are produced from the thiosulphinates, which contributes to the characteristic *A. cepa* flavour and (Z)-propanthial-S-oxide which will further dimerize to (Z,Z)-d,l-2,3-dimethyl-1,4-butanthiol-S,S'-dioxide (Breu *et al.*, 1996). The formation of the volatile sulphur compounds in *A. cepa* extracts are showed in Figure 2.1.
Figure 2.1 The formation of the volatile sulphur compounds in A. cepa extracts (WHO, 1999).

2.1.7 Medicinal Uses of Allium cepa in Folk Medicine

A. cepa contributes in the treatment of bacterial infections such as dysentery and as a diuretic (Kapoor, 1990; Bruneton, 1995). It also has been reported to be able to treat ulcers, wounds, scars, keloids and asthma (Dorsch et al., 1991; Sharma et al., 1979).
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