CHAPTER ONE
INTRODUCTION

Cancer is a major health problem worldwide. It accounts for 7.6 million or 13% of all deaths from a total of 58 million mortalities worldwide in 2005 (Globocan Database, 2002). More than 70% of cancer deaths occurred in low and middle income countries. It is more worrying when it is projected that the estimated number of mortality caused by cancer is going to rise to about 9 million in 2015 and approximately 12 million in 2030 (Facts about Cancer, World Health Organization, 2009). In Malaysia, cancer is the fourth leading cause of deaths (Lim, 2002). A total of 21,773 cancer cases were diagnosed in Peninsular Malaysia in 2003 with colorectal cancer (16.5%) and breast cancer (29.9%) being the most common cancers among male and female populations respectively. In addition, there is an increasing trend of incidence rate with age (National Cancer Registry, 2006).

Current treatments that are available for cancers in Malaysia are surgery, radiotherapy, chemotherapy, hormonal therapy, immunotherapy and symptomatic and supportive therapy. These treatments are expected to play important roles in cancer management (Lim, 2002). Nonetheless, the present treatment regimens face major challenges including selectivity and drug resistance, which are yet to be overcome till today.

Photodynamic therapy (PDT), also known as photo-chemotherapy, is emerging as a relatively new treatment modality for premalignant and malignant cancers as well as some non-malignant diseases of skin and eye. Photodynamic therapy is advantageous because it involves the use of a drug (photosensitiser) which selectively accumulates in tumor tissues more than the surrounding normal tissues which then activate the drug via delivery of a light source with specific wavelength to the targeted areas. The

procedures significantly promote the efficacy of treatment as well as minimize systemic side effects which are commonly observed in other treatment options.

Most of the photosensitisers that are approved for clinical applications or currently in clinical trials are either originated or partially derived from the structures found in natural resources. This includes Photofrin®, the first generation photosensitiser that was derived from haematoporphyrin (blood) (Stenberg and Dolphin, 1998); chlorophyll-based compounds from higher plants, algae as well as microbes including chlorins, purpurins and bacteriochlorophylls. Many of these natural occurring photosensitisers have excellent pharmacological applications. In addition, the discovery of non-tetrapyrrolic photosensitisers such as hypericin from *Hypericum perforatum* (Stavropoulos *et al.*, 2006) and hypocrellin from *Hypocrella bambusae sacc*. (Estey *et al.*, 1996) has also indicated the potential of sourcing photosensitisers with unique structures in nature.

1.1 Research hypotheses

The diversity in marine ecosystem creates a unique chemical ecology. Amongst the marine organisms, marine algae are well known for a broad array of photosynthetic and non-photosynthetic pigments. This encourages us to explore possibilities of sourcing potential photosensitisers from marine algae which are yet to be fully explored.

The hypotheses of this project are as follows:

Null hypothesis (H_o): Seaweeds of Malaysia do not produce photosensitising compounds that have the potentials to be developed as PDT agents.

Research hypothesis (H_1): Seaweeds of Malaysia produce photosensitising compounds that have the potentials to be developed as PDT agents.

1.2 Research objectives

The aim of this study is to screen for bioactive compounds isolated with anti-cancer activity from the selected Malaysian seaweeds, for their potentials to be developed as PDT agents. The specific objectives are to:

(i) Obtain methanolic extracts from selected seaweeds from Port Dickson, west coast Peninsular Malaysia

(ii) Screen the methanol extracts obtained from the selected seaweeds for cytotoxicity against promyelocytic leukemia cells (HL60) incubated in the dark and after light treatment

(iii) Conduct bioassay-guided fractionation of the crude extracts of the selected photo-cytotoxic seaweeds to yield bioactive compounds

(iv) Isolate and identify the active principles using ^{1}H NMR and mass spectrometry

The approaches used to achieve the objectives of this study are shown in Figure 1.1.

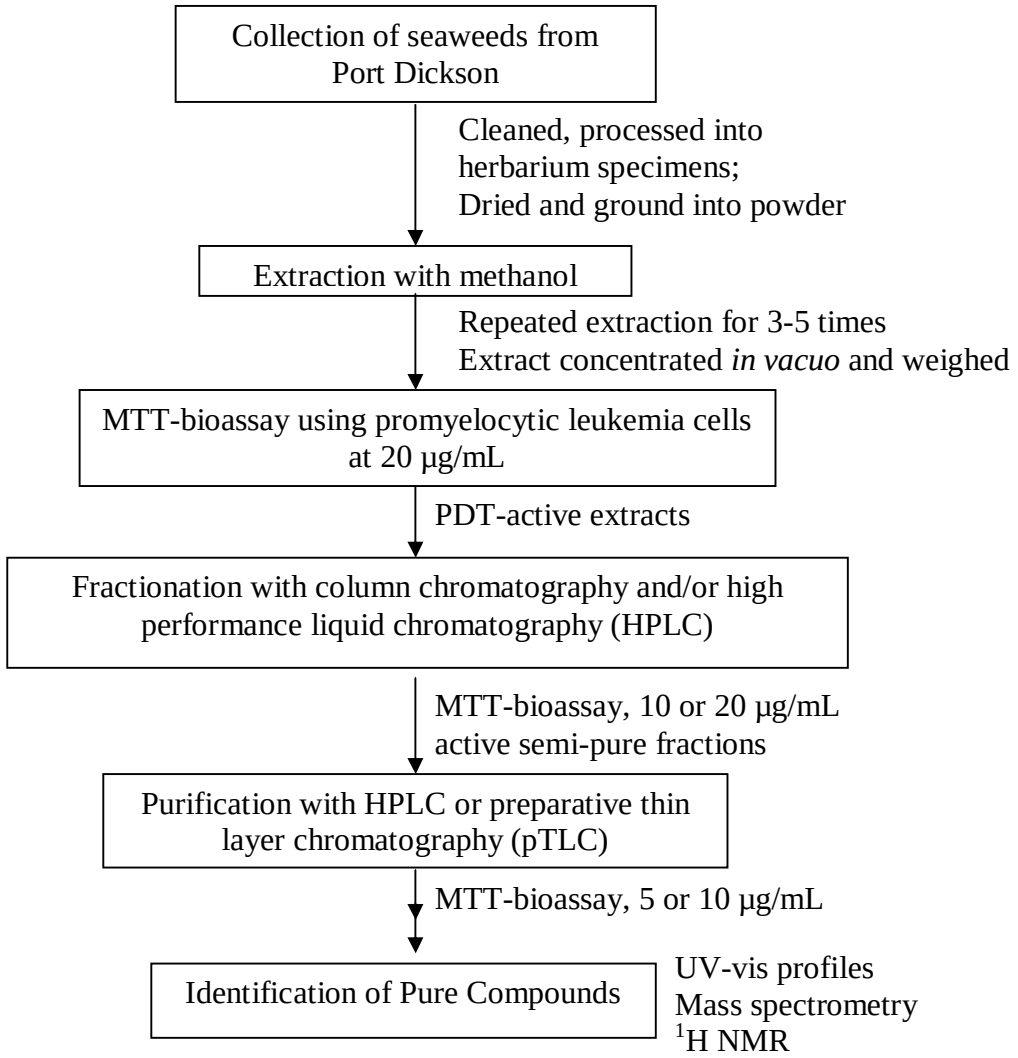

Figure 1.1: Outline of approaches used to achieve in the objective of this study