CHAPTER I

INTRODUCTION

Artocarpus lakoocha Roxb., known in Thai as Mahaad, belongs to the family Moraceae of the order Urticarles. The genus *Artocarpus* consists of about 47 species distributed in Ceylon, India, Pakistan, Burma, Siam, Indo-China, South-China, Malaysia and Solomon Islands. Three species (*A. communis, A. heterophyllus* and *A. integer*) are cultivated throughout the tropics (Kochummen, 1978).

The plants in the genus *Artocarpus* are evergreen trees with milky juice. Leaves are alternate, coriaceous, often very large, entire, lobe or pinnatifid and penninerved. Flowers are monoecious, densely crowded on globose or oblong 1-sexual solitary usually axillary receptacles, often mixed with scales which are often thickened or peltate at the apex. Male flowers are 2-4 lobed perianth or –partite. The lobes are obtuse, valvate or slightly implicate with one erect stamen and no pistillode. Female flowers are tubular perianths, confluent below with the receptacle with the minute mouth. The ovary is straight while the ovule is pendulous. The style is central or lateral while the stigma has entire or lobed receptacle, clothed with the greatly accrescent fleshy perianths and carpels (anthocarps) which have hardened spinescent or truncate or pyramidal or flat apices. Seed is pendulous while the testa are membranous with no albumen. The embryo is straight or incurved while the cotyledons are fleshly equal or unequal and the radical is short and superior (Kirtikar and Basu, 1980).

Artocarpus lakoocha Roxb. is a large deciduous tree reaching 15-18 m in height with a spreading head. The bark is rough, grey in color. The young shoots are thin, densely clothed with a soft grey, tawny or rusty tomentum. Leaves are coriaceous, 10-30 by 5-15 cm, oblong, elliptic or subovate, entire (the young ones sometimes serrate), obtuse cuspidate, glabrous and shining above, softly pubescent beneath. The base is broad or narrow, truncate or rounded. The main nerves are 6-12 paires with reticulate venation between. The petioles are 1.3-2.5 cm long, lanceolate tawny-pubescent.

The flower in axillary globose has shortly pedunculate heads and are bracteole peltate. The male flower has 2-3 sepals, triangular, truncate and puberulous with one stamen and broad filament below. The sepals are tapering upwards with exserted, short, broad, 2-celled anther. The female flowers possess completely united anthocarps. The fruit is 5-7.5 cm in diameter and lobulate, smooth, velvety, yellow. In addition the fruit is edible. The seeds are oblong, few, broad, about 13 mm across (Kirtikar and Basu, 1980)

Since 1957, several phytochemical studies have been performed on *Artocarpus lakoocha* Roxb. (Venkataraman, 1972; Chauhan *et al.*, 1982; Mongolsuk, Robertson and Towers, 1957; Arora *et al.*, 1987; Chatterjee, Sarkar and Rao, 1982; Chauhan and Kumari, 1979; Puntumchai *et al.*, 2004) Several phenolic compounds such as the flavonoids and stilbenoids, together with the mevalonate-derived compounds including steroids and triterpenoids, have been reported (see the Historical Section).

A crude drug known as "Puag-Haad" has been used for anthelmintic and antipruretic properties (Charoenlarp *et al.*, 1981; Charoenlarp *et al.*, 1989). Puag-Haad is a dried aqueous extract of the heartwood of *A. lakoocha*, and its activities come from 2,4,3′,5′-tetrahydroxystilbene. (Farnsworth and Bunyapraphatsara, 1992; Poopyruchpong *et al.*, 1978) In addition, the wood of this plant has been used as construction materials and musical instrument parts, and its fruit is edible with sour and sweet taste (ส่วนพฤกษศาสตร์ป่าไม้, 2542).

Oxyresveratrol (2,4,3′,5′–tetrahydroxystilbene) is a member of the stilbene compounds found in many plants, for example *Artocarpus lakoocha* Roxb. (Moraceae), *Maclura pomifera* (Moraceae) (Djapic *et al.*, 2003), *Morus alba* (Moraceae) (Lorenz *et al.*, 2003) and *Schoenocaulon officinale* (Liliaceae) (Kanchanapoom *et al.*, 2002). The compound is a stronger tyrosinase inhibitor than kojic acid, a well-known whitening agent in skin-care products, suggesting the potential applications of the compound as a skin-whitening agent in cosmetic products or as an anti-browning agent in food of plant origin. In addition, the compound possesses a wide range of other biological activities such as antiviral activity against human immunodeficiency virus (HIV) and herpes simplex virus (HSV), neuroprotective activity, and antioxidative properties

(Likhitwitayawuid, *et al.*, 2005; Breuer, *et al.*, 2006; Lorenz, *et al.*, 2003). This suggests several potential medicinal applications of the compound. The high quantity of oxyresveratrol in the heartwood of *A. lakoocha* provides a source for developing natural-product based useful bioactive compound(s). Although studies on the separation and isolation of oxyresveratrol from *A. lakoocha* have been reported earlier (บุญชู ศรีตุลารักษ์ 2541; บุญชู ศรีตุลารักษ์, วันชัย ดีเอกนามกุล และ กิตติศักดิ์ ลิขิตวิทยาวุฒิ 1998; Venkataraman, 1972; Mongolsuk, Robertson and Towers, 1957;), a more economical and feasible method for large-scale isolation of the compound is needed if the plant is to be developed as an industrial source of the compound. In doing that, a reliable analytical method for the quantitative determination of oxyresveratrol in plant extracts or products is also necessary. A study that is aimed to make use of this compound should also include structure modification studies so that data on structure-activity relationships (SAR) can be obtained. The SAR information may lead to the discovery or design of more potent derivatives.

The purpose of this research is (1) to perform a comparative study on different methods for the isolation of oxyresveratrol from the heartwood of *A. lakoocha*, and (2) to modify the structure of this natural compound for possible improvement of its tyrosinase inhibitory activity. To achieve these goals, the following objectives have been put forward:

1. To develop a simple, reliable and efficient method for the qualitative and quantitative analysis of oxyresveratrol in plant extracts or product(s).

2. To study the methods for the isolation of oxyresveratrol from the heartwood of *A. lakoocha* using several techniques of extraction and separation. The results of the different isolation methods will be compared.

3. To prepare derivatives of oxyresveratrol (about 10 compounds).

4. To evaluate and compare the tyrosinase inhibitory activity of the synthetic analogues for possible structure-activity information.

5. To perform kinetic studies of tyrosinase with obtained oxyresveratrol derivatives which have potent inhibitory activity.

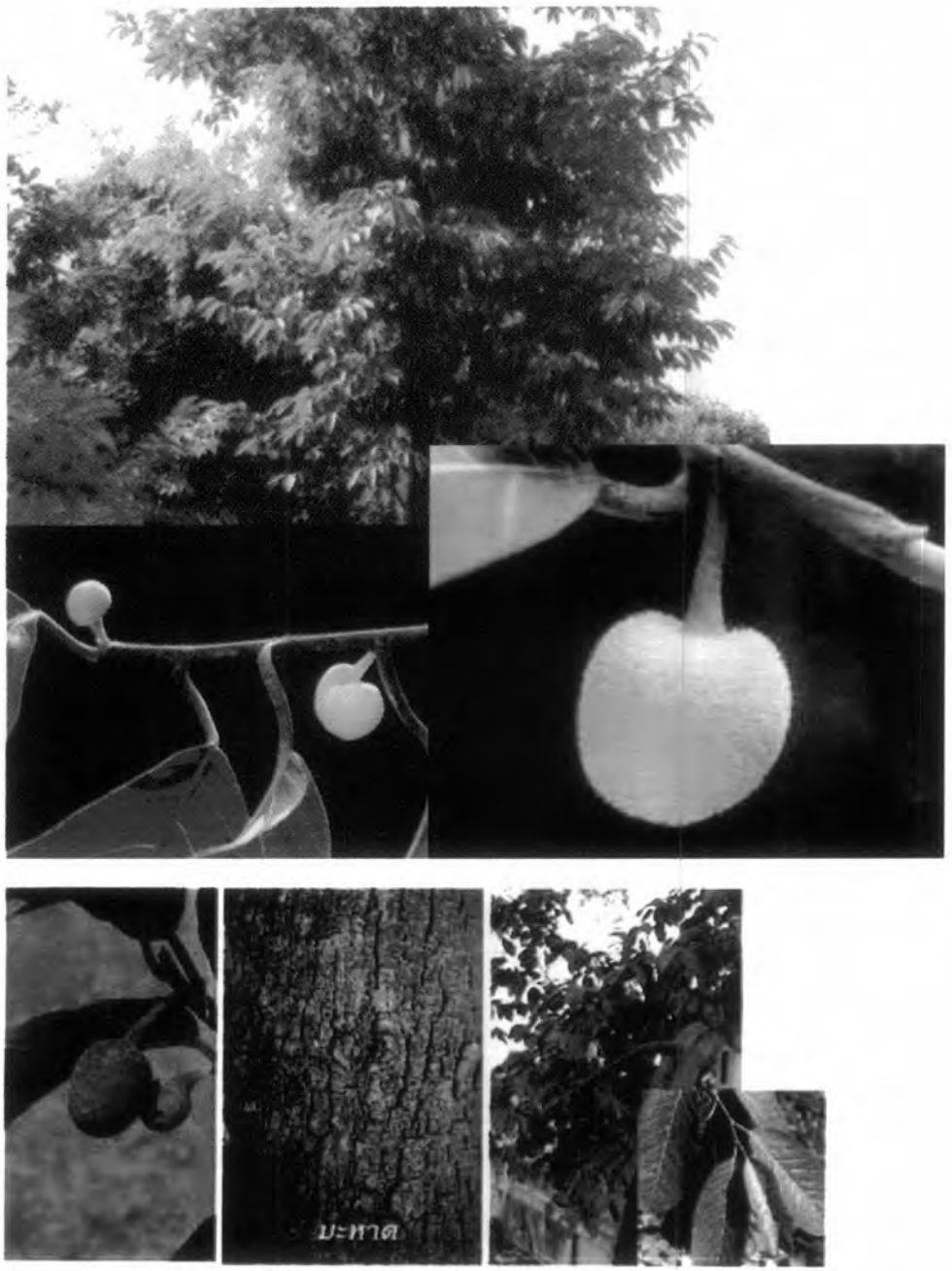

Figure 1: *Artocarpus lakoocha* Roxb.

(Available from http://www.hort.purdue.edu/ newcrop/ncnu02/v5-405.html, http://www.ku.ac.th/AgrInfo/plant/plant2/p75.gif and http://dit.dru.ac.th/herb/pic_herb/mahad.jpg)