

CHAPTER 1

INTRODUCTION

At present, the search for a new drug which is more effective and less toxic than the ones currently used have been extensively performed throughout the world. Natural products are considered to be a major resource to serve that purposes. Among a diversity of natural products, medicinal plants are still the most favorable for the scientists to explore for a new drug. Papaya (*Carica papaya*, L. Caricaceae) is the one of the most interesting medicinal plant, because it is easily cultivated and widely used as food or dessert (Williams, 1975). Generally, it is cultivated for its ripe fruits, favored by tropical people, as breakfast fruit, and as an ingredient in jellies, preserves, or cooked in various ways (McMarkin, 1996). In addition, it was used as medicinal herb, because various parts of this plant (fruit, leaves, seeds or latex) contain many biologically active compounds. The fruit and also the latex contain proteolytic enzymes, papain, which are now used to help digestion (Macmillan, 1991). Moreover, papain is an ingredient not only in some dentifrices but also in cleansing creams. It is incorporated into "face-lifting" preparation which peel the outer layer of skin, removing blemishes and superficial wrinkles (Morton, 1977). Four alkaloids have been found from alcoholic extracts of *Carica papaya* leaves: carpaine, pseudocarpaine, nicotine and an unidentified alkaloid (reviewed by Gupta et al., 1990). Carpaine is the major alkaloid of *Carica papaya* and occurs in all green parts of the plant (reviewed by Burdick, 1971).

The yield of carpaine from Nigerian *Carica papaya* was 0.0115% of the dried weight of leaves as opposed to 0.2% in Malayan plants (reviewed by Gupta et al., 1990) and the 0.4% in Hawaiian plants (reviewed by Burdick, 1971). Several chemical derivatives of carpaine were reported, such as methyl carpaine, ethyl carpaine, carpaine chloroaurate, carpaine hydrochloride and nitro-carpaine (reviewed by Burdick, 1971). Carpaine alkaloid was first isolated by Greshoff in 1890 (reviewed by Burdick, 1971), when he attributed to the physiological activity of papaya leaves. After that, many chemists proposed the chemical structures of carpaine but they were still to oppose and did not have the absolute conclusion. Until 1969, the quest for the absolute configuration of carpaine seems to be concluded by the recent work of Coke and Rice who proposed the structure of carpaine as a $C_{28}H_{50}N_2O_4$. This chemical structure of carpaine has been an accepted as an absolute configuration until now (reviewed by Burdick, 1971).

While the structures of carpaine were proposed, the pharmacological effect of carpaine was also reported. Its action were quite similar to those of both digitalis and emetine, but without most of their bad side effects (reviewed by Burdick, 1971). Ramaswamy and Sirsi (1960) demonstrated its antituberculosis activity by demonstrating its activity on the inhibition of *Mycobacterium tuberculosis*. Furthermore, carpaine have also been reported to have anti-tumor activity and antihelminthic activity (reviewed by Burdick, 1971). Carpaine and pseudocarpaine have a dose-dependent action on the heart depression (Hurnick et al., 1978), plain muscle is generally depressed. The uterus shows marked relaxation by this alkaloid (reviewed by Burdick, 1971).

To and Kyu (1934) (reviewed by Gupta et al., 1990) reported that carpaine caused respiratory depression, and also might be effective in the treatment of amoebic dysentery. Studies with alcoholic papaya leaves extract, it induced a dose-dependent sedative effect and also induced central muscle relaxation (Gupta et al., 1990). Carpaine was shown to be a peripheral vasodilator and decrease blood pressure in intact animal (Mulkganyan et al., 1991).

As discussed above, the alkaloid carpaine has been demonstrated many beneficial effects and found no serious toxic effect. This would make this substance potentially to be developed as a drug. Unfortunately, the conflicting report on the chemical structure of this substance during 1950 – 1969 might discourage the researcher to delay the investigation on this substance. Although, Coke and Rice (1969) (reviewed by Burdick, 1971), who proposed a chemical structure of carpaine have resolved this confusion, the delay on the research of this alkaloid has continued. Currently, a rapid evolution of the scientific methodology during the last 2-3 decades has given us the knowledge to understand a precise mechanism whereby either endogenous and exogenous substances exert their effects. Although, many researchers have demonstrated many pharmacological actions of carpaine, however, the study which describe the mechanism of action of carpaine is still not proposed elsewhere. This situation has led us to reinvestigate some effects of the alkaloid from this plant, aiming to propose a mechanism of action of the alkaloid extract which has never been mentioned elsewhere.