CHAPTER 1

INTRODUCTION

There are several alkaloid derivatives which are used as pharmaceutical agents. They have served, and continue to serve, as important tools in the elucidation of key pharmacological effects, physiological responses and biochemical mechanisms. Several data are presented for the actions of alkaloids with numerous receptors and ion channels. Alkaloids have been important in considering to be the potential for drug discovery and development for the future. Within the plant kingdom, alkaloids are not evenly or ubiquitously distributed. According to recent data from the NAPRALERT^{sm} database, alkaloids are distributed in 7231 species of higher plants in 1730 genera within 186 plant families involving Caricaceae (Cordell et al., 2001).

Various parts of *Carica papaya* L. (*C. papaya*)(Caricaceae) have been used in tradition medicine in different parts of the world. Many reports have shown the pharmacological properties of *C. papaya* ranging from antimicrobial (Giordani et al., 1991), antioxidant (Osato et al., 1993), diuretic (Sripanidkulchai et al., 2001) and antihypertensive (Eno et al., 2000) activities. It can be used to treat various reproductive disorders (Cherian, 2000). *C. papaya* contains many biologically active compounds in which the alkaloid is an important group. Carpaine has been demonstrated to be the major alkaloid found in leaves and seeds of this plant. This 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 that the absolute conclusion. Until 1965, the quest for the absolute configuration of carpaine ($C_{28}H_{50}N_2O_4$) seems to be concluded by the recent work of Coke and Rice (reviewed by Burdick, 1971).

While the structure of carpaine was proposed, the pharmacological effects of carpaine were also reported. Carpaine and pseudocarpaine have a dose-dependent action on

the heart depression (Hurnick et al., 1978). Studies with crude extract of *C. papaya* leaves have a marked dose dependent action on reducing blood pressure and heart rate, the intestinal strips show cessation of movement, the uterus marked relaxation, the bronchioles dilatation (Tuffley and Williams, 1951), respiratory depression (reviewed by Gupta et al., 1990) and central muscle relaxation (Gupta et al. 1990). Carpaine has been demonstrated its hypotensive and vasodilatating activity on the cardiovascular system in intact animal (Mulkijanyan et al., 1991). In addition, our previous investigations have shown the ability of crude alkaloid to cause uterine relaxation. These studies have shown that the crude alkaloid of *C. papaya* caused inhibition of KCl (56.3 mM) and $CaCl_2$ induced contractions on isolated rat uterus. It is indicated that the extract may act on the smooth muscle directly. Crude alkaloid extract inhibited not only the contraction induced by both KCl and $CaCl_2$ but also inhibited the contraction produced by oxytocin, acetylcholine and $PGF_{2\alpha}$ in a concentration-dependent manner (Keereevong, 2002). It is possible that carpaine affects the contractile response which is mediated by calcium and produces relaxation in smooth muscle. However, the extract used in the previous investigation was a crude extract and likely to contain many compounds such as alkaloids, cardiac glycoside (Gupta et al., 1990,) and flavonoids (Runnie et al., 2004). At this stage it is not possible to state which of these alkaloids from *C. papaya* is responsible for the spasmolytic activity. Although, many researchers have demonstrated many pharmacological actions of carpaine, the studies that describe the mechanism of action of carpaine are still limited. Recently, crude alkaloids of *C. papaya* have been proposed to act by interfering with the calcium influx via L-type Ca^{2+} channel in uterus (Keereevong, 2002). In this regard, the process of relaxation requires a decrease in intracellular Ca^{2+} concentration. The mechanisms are implicated in the removal cytosolic Ca^{2+} including inhibition of Ca^{2+} influx, membrane hyperpolarization due to activation of K^+ channels, intracellular cAMP increase, protein kinase inhibition and NO production could be involved in the effect of carpaine. It is of interest, therefore, to study further on this effect using isolated rat uterus.