CHAPTER I

INTRODUCTION

Piperine (1-piperoyl piperidine) is a principal alkaloid present in various piper species of *Piperaceae* family, including *Xylopia brasilliensis* fruits and *Rhododendron fauriae* leaves (Kawakuchi et al., 1942; Costa, 1963; Lewis, 1977). Among the piper species, black pepper and white pepper which derived from Piper nigra and long pepper (Piper longum Linn.) are commonly used to make the food tasty and to stimulate appetite in many regions of the world, particularly those in Asia, Central and Latin America, and Africa. Piper fruit contains approximately 6-9 % piperine (Viehoever and Cohen, 1938). It has been reported that the daily intake of black pepper as computed from the average composition and consumption of curry powder, a regular form of spice mixture consumed in certain sections of population in India, is about 17 mg/kg body weight of an adult (Srinivasan and Satyanarayana, 1981).

Piperine is a very weak base or alkaloid, has the formula $C_{17}H_{19}O_3N$ (see Fig.1), molecular weight 285.16, has a density of 1.193 and are optically inactive. This compound is insoluble in cold water and only slightly soluble in hot water. It is soluble in chloroform, ether, benzene and is soluble up to 6.7 % in alcohol at 23 C. (Viehoever and Cohen, 1938).

PHARMACOLOGICAL ACTIONS OF PIPERINE

Piperine has been used not only as food additive (as pungent

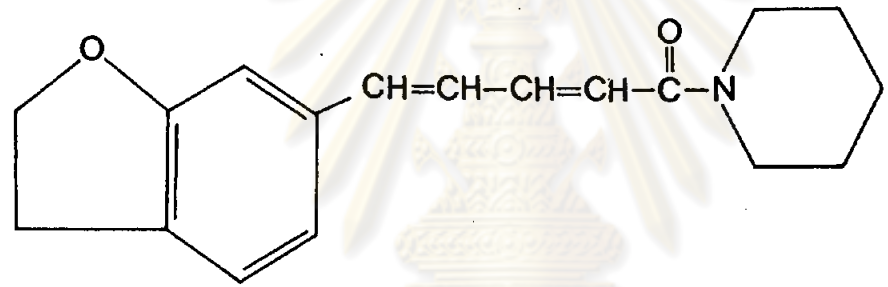

Figure 1 Chemical structure of piperine.

agent) but also medicinally. Some reports claimed that petroleum ether extract of black pepper and long pepper are employed in folklore medicine for treatment of asthma, bronchitis, dysentery, pyrexia, insomnia and tuberculosis (Kitikar and Basu, 1944; Chopra, 1955).

Pharmacological investigation of piperine was first reported by Stecher (1960); the diverse pharmacological actions including hypnotic, carminative, analgesic and antipyretic activities were noted. Further investigations have demonstrated that piperine also has anticonvulsant activity (Chow, 1974; Pei and Tao, 1974). Several reports were presented in support of this pharmacological action (Pei et al., 1979, 1980; Zhang et al., 1980; Chow, 1981). As a result, piperine was used in the clinic to treat epilepsy, and its therapeutic effect evaluated. From clinical observation piperine has been proved effective and is being widely used as antiepileptic agent in China. Although piperine has been used widely for the treatment of epilepsy, the mechanism of its anticonvulsant action is unclear. However, some neurochemical studies demonstrated that the anticonvulsant activity of piperine may involve central serotonergic system (Pei et al., 1983; Liu et al., 1984).

Recently, systemic pharmacological action of piperine was reported by Lee et al. (1984). The authors found that this compound elicited diverse pharmacological activities: CNS depressant activity characterized by antagonism against electroshock seizure and by muscle relaxant activity in mice, antipyretic activity in typhoid vaccinated rabbits, analgesic activity as evaluated by tail clip pressure and writhing syndrome in mice, and antiinflammatory activity in carrageenin-induced edema in rats.

TOXICOLOGICAL INFORMATIONS

Over the past several decades, numerous investigators have demonstrated that piperine was an effective insecticide. Dry fruits of black peper and its extracts (piperine) have been reported to be toxic to the housefly, Musca domestica L. (Harville et al., 1943; Synerholm et al., 1945), to be used as protectant of yellow-eye bean to bean weevil, Acanthoscelides obtectus (Say) (Lathrop and Keirstead, 1946), and as synergists to pyrethrins (Nakayama, 1950; Su, 1977). Furthermore, piperine could react with nitrite in many animal species to form nitrosamine which is a carcinogen. Most interestingly, was the observation that this reaction could occur in human stomach if the drug was to come in contact with nitrite from the saliva or from such nitrite-containing food as cured meats (Lijinsky et al., 1973; Lijinsky, 1976; Andrews et al., 1978).

Singh et al., (1973) studied acute toxicity of piperine in mice and rats. Piperine caused a significant increase in spontaneous motor activity (SMA) when give i.v. at a dose of 10 mg/kg. Further increase in dosage of piperine successively produced clonic and tonic convulsion terminating in the death of the animals. These has been confirmed by Piyachaturawat et al. (1983) in which the LD_{50} value of i.v., i.p., s.c., i.g. and i.m. administration of piperine induced the excitation and convulsion in rats, mice and hamsters. In addition, subacute toxicity of piperine was also investigated in rats receiving piperine i.g., at a dose of 100, 250, 300 and 500 mg/kg body wt. once a day, for 7 consecutive days. Piperine at the dose of 500 mg/kg body wt./day induced hemorrhagic ulceration in gastrointestinal tract, urinary bladder and adrenal gland.

VARIOUS BIOLOGICAL PROPERTIES

Biological investigation of piperine was first reported by Viehoever and Cohen (1937), in Daphnia placed in meuseum jar three - quaters filled with saturated piperine. The authors found that this compound produced excitatory movements of sex organ and depressed heart rate. Subsequently, the central stimulant activity of piperine was studied in frogs, mice and dogs. Kulshestha et al. (1969, 1971) and Singh et al. (1973) demonstrated that piperine produced respiratory stimulation in smaller and convulsions in larger doses. The respiratory stimulation in dogs was central in origin as it occurred even in debuffered dogs. Piperine antagonized the respiratory depression produced by morphine or pentobarbitone sodium. The convulsions induced by piperine were blocked by phenobarbitone, trimethadione and ethosuximide while phenytoin, mephenesin and trihexyphenidyl were found to be ineffective. In frogs, the convulsions induced by piperine were abolished by medullay ablation. These findings suggest medulla oblongata as the principal site of action.

Effects of piperine on cardiovascular system were reported by Szolcsanyi and Janossy (1977). Intravenous administration of piperine in anesthetized cats and rats produced effects of the Bezold-Jarisch reflex (apnea, bradycardia and hypotension). In cats, intravenous injection of piperine elicited no Bezold-Jarisch reflex after bilateral vagotomy; instead pressor effect and tachycardia were obtained. In contrast, 5 mg/kg of intravenously administered piperine produced only insignificant effect in anesthetized dogs (Singh et al., 1973).

There are few incomplete studies on gastrointestinal tract and respiratory system. Bartho and Szolcsanyi (1978) studied the effects of pungent agents such as piperine and pungent congeners of capsaicin

on the isolated guinea-pig ileum. They found that pungent agents produced contraction of the longitudinal muscle strip. These contractile responses could be antagonized by tetrodotoxin. In addition, capsaicin at low concentration ($1x10^{-7}$ g.per ml) could act either from the serosal surface or from the lumen of the gut to facilitate the peristaltic reflex. The author then assumed that pungent agents have a powerful stimulating effect on peristalsis by activating a local chemoreflex. Also, piperine produced contraction of the isolated guinea pig tracheal strip. Tetrodotoxin, hyocine and hexamethonium caused no inhibition of the response while chronic denervation prevented it. From these results, the authors conclude that the response to piperine is mediated by tetrodotoxin-resistant terminal portions of cholinergic nerves (Szolcsanyi, 1983).

Recently, the antifertility effect of piperine was investigated by Piyachaturawat et al. (1983). Piperine at the dose of 12.5 mg/kg, twice a day, effectively inhibited pregnancy in mice when given by either intraperitoneal or oral route of administration at both pre-and post-implantation periods. At the same dose level which interrupted pregnancy, piperine did not affect the estrous cycle. Neither uterotropic, antiestrogenic nor antiprogestational property was observed. Additionally, piperine also inhibited uterine contraction both in vivo and in vitro. The authors therefore suggested that the antifertility activity of piperine did not operate through any hormonal actions or uterotonic activity. Most recently, Micevych et al. (1983) and Jhamandas et al. (1984) reported that intrathecal injection of piperine resulted in marked losses of substance P in spinal cord.

From the literature reviewed, it can be noted that although piperine has long been used in many regions of the world, little is

known about its biological activity. In particular, the actions of piperine on the cardiovascular system have received little attention. The cardiovascular effects of piperine in previous studies was partially observed (Szolcsanyi and Janossy, 1971). In this study the author decided to investigate the circulatory effect and the cardiac action of piperine both in vivo and in vitro. The results obtained from this study may be important for further studies.