Pharmacological and Biological Activities

A great number of natural products, especially alkaloids, which exhibit a range of biological activities including acetylcholineestrease inhibition and antineoplastic, cardiovascular and immunostimulating activities have been isolated from plants of the family Amaryllidaceae (Jin, 2007,2009). Of the six alkaloids from *Crinum delagoense*, tested for cytotoxicity, only lycorine and 6-hydroxycrinamine were active against BL-6 mouse melanoma cells (Nair *et al*., 1998). Crinafolidine and crinafoline were found to produce significant reduction in the viability and *in vivo* growth of S-180 ascites tumour cells. Ungeremine was found to exhibit significant inhibitory activity against a number of test-tumour systems. Criasbetaine also showed significant antitumour activity *in vitro* P-388 (ED_{50} 0.82 μg ml^{-1} and KB (ED_{50} 1.2 μg ml^{-1}) tests and also caused cytolysis of Sarcoma 180 ascites tumour cells (SCL, 20.48 ± 1.14; normal spleen cells, SCL 7.05 ± 0.72) (Tram *et al*., 2002a). Palmilycorine and lycorine significantly inhibited the viability of ascites tumour cells, whereas the glycosidic alkaloids promoted their growth (Ghosal *et al*., 1985b). Epoxyambelline, at concentrations of 5 μg ml^{-1} moderately activated mouse spleen lymphocytes. A mixture of epoxyambelline and ambelline (1:1), at the same concentration, produced pronounced activation of the spleen lymphocytes. Lycorine inhibited the induction of MM46 cells death by calprotectin and also inhibited the suppressive effect of calprotectin on target DNA synthesis at a half-effective concentration 0.1-0.5 μg ml^{-1} (Tram *et al.*, 2002a). Lycorine, crinamine and augustine demonstrated significant cytoxic response in 12 cell lines (Likhitwitayawuid *et al*., 1993a). 4'-Hydroxy-7-methoxy-8-methylflavan, was tested on human leukemic Molt 4-cells and showed an important cytotoxic effect at 42 μg ml^{-1} (Tram *et al*., 2002a).

The bulb of *Hymenocallis littoralis* was found to contain a cytotoxic, isocarbostyril-type biosynthetic product, 7-hydroxy-*trans*-dihydronarciclasine. This compound inhibited the cytopathicity and/or replication of various viruses. Companion cytotoxic constituents of *Hymenocallis littoralis* and *Hymenocallis* sp., were found to be pancratistatin, narciclassine, and 7-deoxynarciclasine. Although there were striking differences in overall potency, some of these compounds shared a highly characteristic differential cytotoxicity profile against the 60 diverse human tumour cell lines. As a group, the melanoma subpanel lines were most sensitive; certain individual lines within other panels (e.g. NSC lung, colon, brain, renal) were as much as a thousand-fold or more sensitive than the less sensitive lines (Pettit *et al*., 1993). The Chinese medicinal plant, *Zephyranthes candida* also contains the cytotoxic constituent (*trans*-dihydronarciclasine) with an ED_{50} 3.2 x 10^{-1} μg/mL (Pettit *et al*., 1990). Pancratistatine, undergoing preclin development as an anticancer, was isolated from several *Hymenocallis* species (Pettit *et al*., 1995a,b). Kaya and Gözler (2005) studied the cytotoxicity of *Galanthus nivalis* subsp. *cilicicus* and stated that they displayed meaningful IC_{50} values. The methanolic extracts of species from the genera *Galanthus* and *Leucojum* were found to possess cytotoxic effects on the human carcinoma and acute myeloid leukemia cells (Jokhadze *et al*., 2007). Amaryllidaceae isocarbostyril alkaloids and their derivatives as promising antitumour agents have been reviewed by Ingrassia *et al*. (2008).

Crinamine, isolated from *Crinum jagus*, showed strong antibacterial activity (Adesanya *et al*., 1992). Lycorine, one of the main alkaloids of the Amaryllidaceae family, was found to be responsible for the pronounced antiviral activity of the crude extracts from the roots and leaves of *Clivia miniata* Regel (Ieven *et al*., 1982). The antiviral activity of some Amaryllidaceae alkaloids on herpes simplex virus was reported. The antiviral activity of the alkaloids was due to the inhibition of multiplication and not to the direct inactivation of extracellular viruses (Renard-Nozaki *et al*., 1989). *Lycoris radiata* agglutinin showed antiviral activity to Herpes simplex virus II (HSV-II) and the IC_{50} was 5-10 μg/mL (Chang *et*

al., 2005). Narciclasine, lycoricidine, pancratistatine, 7-deoxypancratistatine, and acetates, isonarciclasine, *cis*-dihydronarciclasine, *trans*-dihydronarciclasine, their 7-deoxy analogs, lycorines and pretazettine exhibited consistent *in vitro* activity against all 3 flaviviruses and against the bunyaviruses, Punta Toro and Rift Valley fever virus. Activity against sandfly fever virus was only observed with 7-deoxy analogs. Pancratistatine and 7-deoxypancratistatine demonstrated activity in mice infected with Japanese encephalitis virus but only at near toxic concentrations. However, this represents a rare demonstration of chemotherapeutic efficacy (by a substance other than an interferon inducer) in a Japanese-encephalitis-virus-infected mouse model (Gabrielsen *et al*., 1992).

The anticholinesterase activity of the alkaloid galanthamine and its derivatives has been reported (Umarova *et al*., 1966b). Acetylcholinesterase activity of *dl*-narvedine (narwedine) was higher than *d*-narvedine (both isolated from *Ungernia sewerzowi*) (Umarova *et al*, 1966a). Twenty-three Amaryllidaceae alkaloids having several different ring types were evaluated for their acetylcholinesterase (AChE) inhibitory activity. The alkaloid 1-*O*-acetyllycorine (IC_{50}: 0.96 ± 0.04) showed significant AChE inhibitory activity. In addition, crinine (IC_{50}: 461 ± 14), crinamidine (IC_{50}: 300 ± 27), epivittatine (IC_{50}: 239 ± 9), 6-hydroxycrinamine (IC_{50}: 490 ± 7), *N*-desmethyl-8α-ethoxypretazettine (IC_{50}: 234 ± 13), *N*-desmethyl-8β-ethoxypretazettine (IC_{50}: 419 ± 8), lycorine (IC_{50}: 213 ± 1) and 1,2-di-*O*-acetyllycorine (IC_{50} : 211 ± 10) had weak activity (Elgorashy *et al*., 2004). Of the alkaloids of *Crinum glaucum* and *Crinum jagus*, hamayne (**40**), from *Crinum glaucum* was found to possess the most cholinesterase inhibitory properties (Houghton *et al*., 2004). Both antioxidant and acetylcholinesteasic activities of *Hippeastrum morelianum*, *Hippeastrum psittacinum* and *Hippeastrum santacatarina* have been reported. The antioxidant activity of lycorine indicated an IC_{50} value of 0.326 mM (Giordani *et al*., 2008). *Leucojum aestivum* (summer snowflake) is used for the extraction of galanthamine, an acetylcholinesterase inhibitor for the treatment of Alzheimer's disease (Georgieva *et al*., 2007).

Digitalis-like effects of *Crinum amabile* (Wasicky and Hardebeck, 1952), *Crinum pretense* and *Hippeastrum solandriflorum* (Wasicky, 1953) have been reported. The mannan fraction isolated from *Ungernia ferganica* displayed high hypolipidemic activity in intact animals as well as in animals with experimental hyperlipidimia (Rakhimov *et al*., 1996). The two fructans, isolated from *Liriope spicata* var. *prolifera* caused a significant decrease of the fasting blood glucose and a significant improvement on glucose tolerance in type 2 diabetic mice (Wu *et al*., 2009).

The alkaloid ungerine, isolated from the bulbs of *Ungernia sewerzowii* prolonged the anesthetic effect of heanal, thiopentanal, Nembutal and chloral hydrate, intensified the pain-relieving effect of morphine and promedol, and relieved convulsions induced by corazole (Zakirov *et al*., 1966). The aqueous extract of *Crinum giganteum* possesses sedative properties. In rats it prolonged the duration of pentobarbital sleeping time and in mice reduced spontaneous motor activity, decreased the exploratory activity and attenuated amphetamine-induced stereotype behavior (Amos *et al*., 2003). Narwedine, isolated from *Ungernia sewerzowii* possesses antinarcotic effect (Bazhenova *et al*., 1967). Narwedine, an alkaloid from *Ungernia minor* briefly and slightly decreased the arterial pressure and had no effect on rhythm and frequency of heart contractions nor on respiration (Abdumalikova *et al*., 1966). Lycorine and Augustine showed moderate antimalarial activity against *Plasmodium falciparum*. Lycorine also showed mild activity against *Tripanozoma brucei rhodesiense*. Cripowelline A from *Crinum powellii* had insecticidal activity against diamond black moth on cabbage plants; 0.1 % (w/w) water solution of cripowelline A showed total effectiveness for 7 days (Tram *et al*., 2002).