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CRINUM; AN ENDLESS SOURCE OF BIOACTIVE PRINCIPLES: A REVIEW. PART V. BIOLOGICAL PROFILE

John Refaat*[1], Mohamed S. Kamel [1], Mahmoud A. Ramadan [2] and Ahmed A. Ali [2]

Pharmacognosy Department, Faculty of Pharmacy, Minia University [1], 61519 Minia, Egypt
Pharmacognosy Department, Faculty of Pharmacy, Assiut University [2], 71515 Assiut, Egypt

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Correspondence to Author:

John Refaat

Pharmacognosy Department, Faculty of Pharmacy, Minia University, 61519 Minia, Egypt

E-mail: johnrefaat82@yahoo.com

ABSTRACT: *Crinum* is a well-known traditional herb belongs to family Amaryllidaceae. Worldwide, different *Crinum* species are commonly used to treat various conditions due to their excellent medicinal values. Members of this genus are also best known biofactories for the unique Amaryllidaceae alkaloids. Due to the significant phytoconstituents produced by this plant as well as their therapeutic potentials, many *Crinum* species have been subjected to extensive chemical, cytological and pharmacological investigations. This part of our comprehensive review work on the chemical and biological profiles of *Crinums* describes the results of biological and toxicological studies conducted on different species. In addition, general analytical conclusions as well as some suggestions for future phytochemical and biological work on *Crinums* are discussed.

INTRODUCTION: Long ago, natural products had attracted considerable phytochemical and pharmacological attention. One of their chief sources is plants which are well-known untapped reservoirs of bioactive substances. In fact, medicinal plants can magically provide us with the key to our leading problem in life; diseases. They also found wide application in pharmaceutical, cosmetic and food industry.

Today, despite of the great advance in synthetic organic chemistry, there is a growing focus on the importance of natural products from plants in solving various health care problems by coupling traditional knowledge with scientific principles. Most used synthetic drugs have got a bad reputation due to their familiar side effects.

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That's why, the development of naturally based potent, less toxic and cost effective drugs is urgent and medicinal plants appear to have these desired comparative advantages.

Amaryllidaceae is a great widely spread family all over the world containing about 90 genera and 1310 species [1]. The genus *Crinum* represents an important sector in family Amaryllidaceae with wide geographical distribution throughout the tropics, subtropics and warm temperate regions of the world [2]. The specific alkaloids produced by these plants have attracted considerable attention due to their interesting pharmacological activities.

In fact, up till now members of Amaryllidaceae continue to yield novel compounds having interesting biological activities and they can be considered a sleeping giant of drug development. Consequently, the previous parts of our review work provided a comprehensive overview of the phytochemical studies of the genus *Crinum* and finally, the current article highlights the possibility of development of this botanical drug into widely used

remedies through a detailed account on various biological reports of different species studied so far as well as their toxicological aspects.

Folkloric significance of *Crinums*: *Crinum* species have a considerable medicinal reputation as potent folkloric remedies. Their use extended from the ancient times to nowadays especially in Africa, tropical Asia and South America. Several *Crinums* are traditionally used as emetics, laxatives, expectorants, tonics, antipyretics, diuretics, diaphoretics, anti-asthmatics, anti-malarial, anti-aging, anti-tumor and lactagogues [3-10]. In addition, they are commonly used in treatment of various painful and inflammatory disorders such as rheumatism, earache, lumbago, edema, headache, swelling, backache, wounds and haemorrhoids [3, 5, 11-13].

Besides, they have important antimicrobial applications in parasitic skin diseases, suppurating sores, abscesses, otitis, tonsillitis, laryngitis, prostatitis, leprosy, anthrax; dysentery and sexually transmitted diseases [3, 7, 12, 14-16]. On the other hand, *Crinums* also found use in veterinary medicine for weight loss, low milk production, milk loss and for retained placenta among cattle [5, 17]. The detailed ethnomedical uses of *Crinums* were previously reviewed by Fennell and Van Staden [18].

Biological activities of *Crinum*: Different biological investigations carried out on various *Crinum* species showed that the total extracts together with many of the isolated compounds exhibited a wide range of interesting activities. The results of these enormous studies strongly account for the wide use of *Crinums* as folkloric medicines.

Analgesic and Anti-inflammatory activities: Pharmacological investigation of the effects of total extracts obtained from different parts of *Crinums* using many algesiometric and inflammatory models showed their potential for treatment of various pains and inflammatory processes. The aqueous extract of *C. giganteum* bulbs (100-200 mg/Kg) significantly inhibited formalin- and acetic acid-induced pain in rats and mice, respectively, in a dose-dependent manner. The effects were comparable to aspirin. In addition, oral administration of the extract (200 mg/Kg) resulted in a marked dose-dependent anti-inflammatory activity in cotton pellet-induced granuloma in rats [8].

Similarly, the aqueous extract of *C. glaucum* bulbs (100-400 mg/Kg, orally) showed significant activities in rat tail flick, mouse writhing and formalin pain models. Moreover, the extract (125-500 mg/Kg, orally) produced a dose-dependent inhibition of carrageenan-induced paw swelling in rats. The results obtained suggested both peripheral and central mechanisms for the analgesic and anti-inflammatory effects of the extract [19].

Ratnasooriya *et al.*, studied the antinociceptive activity of the aqueous leaves' extract of *C. bulbispermum* orally administered to rats using the tail flick, hot plate and formalin tests. The results collectively suggested that the antinociception is mediated both spinally and supraspinally, as well as its effectiveness against phasic and continuous non-inflammatory/inflammatory pain [20].

On the other hand, the chloroform and methanol extracts of *C. asiaticum* leaves (50 mg/Kg, orally) caused significant effect that was stronger than indomethacin on carrageenan-induced paw edema in mice. The anti-inflammatory activity could not be attributed to its anti-bradykinin activities, but may be partly due to its anti-histaminic properties [21, 22]. Consequently, new topical and cosmetic formulations comprising the extract of *C. asiaticum* L. as an active ingredient in an amount effective to treat and alleviate allergy and inflammatory diseases were patented [23].

In another investigation of pain and inflammation relieving properties of *C. augustum* Rox., the alklaine chloroform- and ethyl acetate- soluble fractions (II and III) of the bulbs' total extracts at (400 mg/Kg, orally) showed the highest analgesic effects in mice using the hot plate test, whereas both fractions (II and III) together with the chloroformic fraction (IV) -obtained after saturation with Na_2CO_3 during total extract fractionation- exhibited the highest anti-inflammatory effects in the carrageenan-induced paw swelling in mice at (400 mg/Kg, orally) [24].

Likewise, Lee *et al.* proved that the ethyl acetate fraction of *C. folium* possesses significant analgesic and anti-inflammatory actions by inhibition of prostanoids biosynthesis as one of its mechanism of action [25]. In other studies, the ethanolic bulbs' extract of *C. defixum* Ker Gawl showed significant inhibition of acetic acid-induced writhing and tail

clip-induced algesia [26], while the petroleum ether, dichloromethane, ethanol and 50% methanol extracts of *C. moorei* bulbs showed good inhibition against both COX-1 and COX-2 enzymes [27].

Moreover, the methanolic extract of *C. latifolium* leaves exhibited strong to moderate inhibitory activity to nuclear factor-kappa B (NF-κB) which is an inducible and ubiquitous transcriptional factor required for gene expression of many inflammatory mediators [28]. A significant anti-inflammatory effects of *C. latifolium* leaves' extract were also shown by its potential to suppress indoleamine 2,3-dioxygenase mediated tryptophan degradation in unstimulated- and mitogen-stimulated peripheral blood mononuclear cells at IC_{50} of 241 ± 57 μg/ml and 92 ± 20 μg/ml, respectively [29].

It is worthy mentioned that the previous investigations attributed the observed activities of *Crinums* to their alkaloidal content. Furthermore, studies on the analgesic effects proposed the participation of opioid mechanisms [20], and the resemblance of Amaryllidaceae alkaloids to morphine and codeine skeletons may account for their analgesic activity [30] e.g. caranine, crinine, galanthamine and galanthine [31, 32] . Haemanthidine and lycorine are also analgesics and anti-inflammatory with activities greater than aspirin [33] and indomethacin [34], respectively, while narwedine and vittatine could potentiate the analgesic effects of caffeine and morphine [33].

Effects on Central Nervous System: In 1960, Wildman had reported the action of Amaryllidaceae alkaloids on CNS [31]. One of the most common and important alkaloids of this family is galanthamine which attracted many pharmacological, biochemical and clinical investigations due to its variable central effects [35]. Galanthamine is a tertiary amine and would be expected to be sufficiently lipid-soluble to cross the blood-brain barrier and act on the central nervous system. It exhibited reversible muscarinic and anticholinesterase activities and can be useful as a treatment for nervous diseases, neurological injuries, paralysis syndrome, schizophrenia, mania, and other forms of dementia as well as Alzheimer's disease [35-37]. This alkaloid acts by restocking acetylcholine levels in brain areas lacking cholinergic neurons by binding to the enzyme acetylcholinesterase.

In addition, it stimulates pre- and postsynaptic nicotinic receptors so increases the release of neurotransmitters like acetylcholine and glutamate, and stimulates neuronal function.

Moreover, Galanthamine was shown to have no hepatotoxicity; therefore, it has been approved as its HBr salt for the first time in Bulgaria under the name of Nivalin® in the early 1960s, and later licensed as Razadyne® (formerly Reminyl®) in the United States and some European countries [38].

Furthermore, galanthamine has a central stimulant action. Early reports from Bulgaria and Russia claimed that recovery of consciousness after anesthesia was faster if galanthamine was used instead of neostigmine. This effect has been attributed to either a central stimulant action of galanthamine, or its ability to antagonize the actions of morphine-like analgesics [35]. In addition, Cozanitis and Toivakka concluded from EEG recordings that galanthamine was a mild analeptic, i.e. a central stimulant [39].

In a study of sleep patterns in healthy volunteers, galanthamine HBr (10 or 15 mg, orally) shortened the latency to rapid eye movement sleep, but also increased the number of awakenings [40]. Additional information on central effects of galanthamine could be obtained from case reports in which galanthamine was used to reverse poisoning. It aided recovery after an overdose of the centrally acting muscarinic antagonist hyoscine (scopolamine) [41]. Moreover, it is also known to inhibit traumatic shock and has been patented for use in treatment of nicotine dependence [37].

In the same way, ungeremine and lycorine also exhibited strong anticholinesterase activities. The former was found to be about 6-8 times more potent than galanthamine [38, 42]. Additionally, alkaloidal extracts of *C. jagus* and *C. glaucum* bulbs increased the depressed levels of acetylcholine in the brain associated with Alzheimer's disease. The most active alkaloids isolated were hamayne and lycorine [43], whereas linoleic acid ethyl ester has been identified in the ethanolic extract of *C. powellii* bulbs as the compound responsible for acetylcholinesterase inhibition [44]. On the other hand, in spite of being slightly active when tested for anticholinesterase activity of their leaves' extracts, bulbs and roots of *C. campanulatum, C. graminicola, C. macowanii, C.*

moorei and *C. variabile* contained several compounds with significant inhibitory activity [45]. In another study, lycorine and hamayne were found to reduce the production of amyloid *β*-peptide (A*β*) which can antagonize Alzheimer's progression [46]. On the other hand, galanthine -a lycorine-type alkaloid- found a great importance in treatment of myasthenia gravis, myopathy and CNS diseases due to its cholinergic effects, while, some derivatives of it are being evaluated as CNS depressants.

The aqueous extract of *C. giganteum* (6.25, 12.5 and 25 mg/kg, i.p) was found to have central inhibitory activity (sedative effect). It prolonged the duration of pentobarbital sleeping time in rats and reduced exploratory and spontaneous motor activities, in mice [47]. Similarly, the aqueous leaves' extract of *C. bulbispermum* (1, 1.5 and 3 g/Kg, orally) significantly and markedly impaired the four parameters of rat hold-board test indicating its sedative properties [20]. Narwedine has been found to potentiate the pharmacological effects of caffeine, carbazole, arecoline and nicotine, in laboratory animals [33].

Mesembrine and its analog compounds are serotonin-uptake inhibitors and can be used for treatment of depressive states, psychiatric disorders with anxiety component, alcohol and drug dependence, and obsessive-compulsive disorders [48]. In addition, the crude extract of *C. ornatum* bulbs, lycorine and haemanthamine exhibited dose-dependent anticonvulsant effects using electrical stimulation test in rats [49].

Effects on Cardiovascular system and blood: A number of *Crinum* alkaloids were reported to have hypotensive activity, e.g. ambelline, caranine, crinamine, crinine, lycorine, narwedine, tazettine, ismine and galanthine (50 mg/Kg, in rabbits) [31, 50], while haemanthamine exhibited hypertensive properties [51]. The alkaloid narwedine was found to decrease the frequency of cardiac contractions, while galanthamine is known to cause bradycardia or atrioventricular conduction disturbance [52]. Galanthamine HBr was found to cause a fall in blood pressure in anaesthetized dogs, an effect apparently associated with a transient decrease in respiration [53].

However, i.v. injection of galanthamine HBr (0.2-3 mg/kg) caused an increase in the mean arterial blood pressure which could last for 30 min in anaesthetized rats. The hypertensive action of galanthamine was not affected by ganglion blocking agents [54]. On the other hand, Wasicky had reported that *C. pratense* has *Digitalis*-like effects [55].

The ethyl acetate fraction of *C. folium* was found to have a considerable platelet-aggregation inhibitory effect [25], while the aqueous extract of *C. giganteum* bulbs caused a dose-dependent suppression of total leucocytes count, but an increase in neutrophils percentage was noticed, while monocytes, eosinophils and basophils were not significantly altered [8].

Respiratory system activities: Galanthamine at 3 mg/kg reversed the respiratory depression induced by dextromoramide in urethane-anesthetized rabbits [56]. Narwedine increases the amplitude and frequency of respiratory movements, while crinamine shows respiratory depressant activity [52, 57].

Effects on skeletal and smooth muscles: Galanthamine is said to be widely used as a reversal agent in anesthetic practice in Eastern Europe. It was tested in 40 surgical patients for its ability to reverse neuromuscular blockades induced by alcuronium, pancuronium, gallamine, and tubocurarine. Galanthamine HBr at (5 mg doses to a total of 20 mg, i.v.) successfully reversed the muscular paralysis with all four relaxants, although the rate of recovery was slower than with neostigmine [58].

On the other hand, *C. glaucum* aqueous extract was found to be a non-specific relaxant of the gastrointestinal smooth muscles. It produced a concentration-dependent, non-competitive inhibition of both contractions induced by acetylcholine and calcium chloride on the rat duodenum and contractions of the guinea-pig ileum induced by acetylcholine and histamine at (1-8 mg/mL) and (1-4 mg/mL), respectively. The extract (0.125-2 mg/mL) also, produced a concentration-dependent relaxation of the guinea-pig *Taenia coli*, precontracted with potassium chloride [59]. Similarly, Wiart attributed the vasorelaxing activity of lycorine to the resemblance of Amaryllidaceae alkaloids to isoquinoline alkaloids e.g. papaverine which are known smooth muscle relaxant [60].

Effects on Sexual functions: Hippadine was reported to produce reversible inhibition of fertility by acting on germ cells at early stages of spermatogenesis in rats' tests [61].

Likewise, application of lycorine to the testes and ovaries of immature rats inhibited cell division in the spermatogonia or primary spermatocytes. No spermatid cells were also found in the tested animals, whereas follicles were found to be smaller and less in number in rats' ovaries [31]. Moreover, Ghosal *et al.* reported that ungeremine significantly inhibited testicular metabolism in mice as well [62].

Endocrinological Effects: Galanthamine was found to increase plasma levels of hydrocortisone (cortisol) and ACTH. A single dose of 20 mg (with 0.5 mg atropine) produced a sustained elevation of plasma hydrocortisone from 0.54 to 0.8 µmol/L [63]. It was assumed that such effect is due to the central action of galanthamine, although its mechanism is unknown. Another study reported that galanthamine HBr (0.3 mg/kg, i.v.) caused an increase in adrenocorticotrophic hormone (ACTH) plasma levels in a group of 8 patients undergoing surgery [64].

Antiallergic and Antianaphylactic activities: The aqueous extract of *C. glaucum* was found to inhibit mast cell degranulation in normal and passively sensitized rats induced by dextran and antigen, as well as allergic bronchoconstriction, ileum contractions, and release of mediators from the lungs of sensitized guinea pigs. The effects of the extract observed were comparable to those of sodium cromoglycate. These results may account for its use as an anti-asthmatic in traditional medicine [65, 66].

On the other hand, different combinations of glucan A and phosphatidyllycorine isolated from *C. latifolium* L. produced statistically significant *in vitro* protection against Tween 80-induced degranulation, as well as to sensitized mast cells challenged with an antigen (horse serum). The combination, *in vivo*, also provided protection against compound 48/80-induced degranulation of mast cells [67]. These findings may support the use of *C. latifolium* total extract in treatment of allergic disorders in Ayurvedic medicine.

In addition, lycoriside at (1-20 µg/ml) produced statistically significant protection against Tween 80-induced degranulation *in vitro*, as also to sensitized mast cells challenged with an antigen (horse serum). It also provided protection against compound 48/80-induced degranulation of mast cells when administered *in vivo* (1-5 mg/kg, p.o) [68].

Immunological activities: Aqueous extract of *C. latifolium* showed immunomodulatory properties in human peripheral blood mononuclear cells. Extracts of *C. latifolium* slightly enhance neopterin production in unstimulated peripheral mononuclear cells, whereas an effective reduction of neopterin formation in cells stimulated with concanavalin A (Con A), phytohemagglutinin (PHA), or interferon-gamma (IFN-gamma) was observed [69].

It also promoted human T-lymphocytes *in vitro*, particularly the cell-mediated immune response of $CD4^+$T lymphocytes (T-helper cells) [70]. Moreover, aqueous extracts of *C. latifolium* L. and *Camellia sinensis* showed immunomodulatory properties in human peripheral blood mononuclear cells, whereas extracts of the former seemed to be more effective in reducing neopterin formation in stimulated cells than green and black tea extracts [69].

1,2-*β*-epoxyambelline (5 µg/ml) either alone or in a mixture with ambelline (1:1) activated mouse spleen lymphocytes. The effect was comparable to that of the known mitogen, concanavalin A [71]. Lycorine-1-O-glucoside is a potent immunostimulatory agent and has been found to activate spleen lymphocytes in mice [30]. In contrast, the aqueous extract of *C. giganteum* bulbs showed a pronounced dose-dependent anti-lymphocytic activity in rats [8]. On the other hand, lycorine had been patented as an immunosuppressor and can be useful in suppression of the immune system of mammals for treatment of autoimmune diseases, immune complex diseases, allergic and rheumatic conditions, as well as for prophylaxis against transplant rejections [72].

Cytotoxic and Anticancer activities: Many preparations of *Crinums* have been used as anti-tumors [31]. Recently, a large number of the isolated compounds as well as extracts of different *Crinum* species are known to have potent cytotoxic and anticancer activities. A study by Nair *et al.* reported that lycorine, crinamine and 6-hydroxycrinamine isolated from *C. delagoense* bulbs are active against BL-6 mouse melanoma cells after substantiated reports confirmed the cure of a human cancer after oral intake of the hot aqueous extract of its bulbs [73]. Crinafolidine and crinafoline were found to produce remarkable reduction in the viability and *in vivo* growth of S-180 ascites tumor cells [74].

In addition, criasbetaine, palmilycorine and lycorine showed significant anti-tumor activity *in vitro* and also caused cytolysis of sarcoma 180 ascites tumor cells, but the alkaloidal glycosides enhanced cells growth [75, 76]. Additionally, criasbetaine displayed significant activites against P-388 and KB tests *in vitro*, with ED_{50} of 0.82 and 1.2 μg/ml, respectively [76]. Crinasiatine was also found to exhibit tumor-inhibiting properties [75], whilst ungeremine significantly inhibited the activity of several test-tumor systems [62, 77].

On the other hand, crinamine, lycorine and augustine from *C. amabile* bulbs demonstrated important cytotoxic activities in twelve cell lines [78]. Furthermore, lycorine was reported to inhibit the *in vivo* growth and synthesis of DNA and proteins in murine ascite tumor cells and reduce the viability of *in vitro* grown tumor cells [30]. It also reduces cellular activity in femoral bone marrow, which results in granulocytic leucopenia and erythrocytopenia [31]. Abd El-Hafiz *et al.* reported that 4'-hydroxy-7-methoxyflavan have an important cytotoxic effect at 42 μg/ml while pratorinine and 6-*α*-hydroxy buphanisine showed a moderate activity when tested on human leukaemic Molt 4 cells [79].

Additionally, precriwelline and pretazettine showed remarkable anti-leukaemic activity. The latter is also reported to be effective against Ehrlich ascites carcinoma, lymphocytic leukaemia and Lewis lung carcinoma [52], whereas haemanthamine, crinamine and 6-hydroxycrinamine were moderately active against Rauscher leukaemia [80]. The alkaloid lycobetaine was found to act as a selective topoisomerase IIβ poison. This mechanism causes or at least contributes to the antitumour activity [81].

Of all the Amaryllidaceae alkaloids, lycorenine was found to be the most cytotoxic against HepG2 hepatoma [82]. Isoliquiritigenin was also found to inhibit cell proliferation and induce apoptotic cell death in human hepatoma cells (Hep G2) [83]. Furthermore, Min *et al.* reported that criasiaticidine A, pratorimine and lycorine have *in vitro* cytotoxicity against Meth-A (mouse sarcoma) and Lewis lung carcinoma (mouse lung carcinoma), whereas dihydrolycorine, haemanthamine, lycorine, narci-clasine, pretazettine and pseudolycorine halted protein synthesis in eukaryotic cells by inhibiting peptide bond formation step [30, 32].

In addition, extracts of *C. asiaticum* leaves demonstrated cytotoxic activity against murine P388 D1 cells [11]. Some alkaloids isolated from bulbs of *C. asiaticum* L. var. *sinicum* Baker showed remarkable inhibition against tumor cell lines A549, LOVO, HL-60, and 6T-CEM [85]. Similarly, the ethyl acetate and alkaline ethyl acetate-soluble fractions of *C. asiaticum* L. var. *japonicum* bulbs showed significant cytotoxicity against Lewis lung carcinoma cells [84], whereas hot water extracts of *C. asiaticum* showed strong inhibition of calprotectin-induced cytotoxicity *in vitro* using MM46 mouse mammary carcinoma cells as targets [86]. It was reported that many Amaryllidaceae alkaloids belonging to the crinane-type have selective apoptosis-inducing activity. Biological screening indicated that crinamine and haemanthamine are potent inducers of apoptosis in tumour cells at micromolar concentrations. An alpha C-2 bridge and a free hydroxyl at the C-11 position are important as pharmacophoric requirements for this activity [87].

Crinine, 6-hydroxybuphanidrine and 6-ethoxy buphanidrine showed also antiproliferative effects against human tumor cell lines HL-60 and MDA-MB-231 with crinine being the most active. Hydrogenation of the double bond at C-1 – C-2 leads to activity loss, whereas substitutions at C-6, C-8 and C-11 affect their cytotoxicity [88]. The introduced per os (instead of water) cold-hot aqueous extract from the Vietnamese plant *C. latifolium* L., retarded *in vivo* the growth of chemically induced (by 20-methylcholanthrene) tumours (sarcomas) in rats.

Such inhibition of carcinogenesis has occurred probably due to the influence of immunomodulating and anti-tumour plant alkaloids and other biologically active components in the plant decoctions [89]. Recently, *C. latifolium* showed promise to become one of the leading treatments in the world for prostate and ovarian conditions, including benign prostate hypertrophy (BPH), prostatitis, adenoma, uterine fibroids, ovarian cysts and tumors polycystic ovarian syndrome. It was believed that *Crinum* may enhance the cellular communication so maintaining the balance between cellular proliferation and apoptosis. Lately, it was shown that *Crinum* encourages cells to produce a substance called neopterin, which is responsible for communicating with immune cells calling them into action against foreign invaders and unhealthy or proliferative cells.

This suggests that *Crinum* may not only be valuable for prostate and ovarian conditions, but may also be beneficial for other conditions in which unhealthy, proliferative cells are involved. Another potentially valuable benefit of *Crinum* is that it may be used as a preventative agent, offering protection against prostate and ovarian conditions before they start [9]. These findings were in agreement with the study carried out by Jenny *et al.* which showed dose-dependent inhibitory effects of the aqueous *C. latifolium* extract on cell proliferation of highly metastatic human prostate carcinoma PC3 cells, androgen-sensitive prostate adenocarcinoma LNCaP cells and BPH-1 cells [29].

Antioxidant, Hepatoprotective and Metabolic effects: The ethanolic extract of *C. defixum* Ker Gawl bulbs showed significant dose dependent free radical scavenging property in different *in vitro* models such as DPPH, nitric oxide, superoxide and hydroxyl radical models. The antioxidant activity was attributed to the presence of high phenolic content [26]. Similarly, the 80% methanolic extract of *C. jagus* bulbs possessed a significantly high antioxidant activity in DPPH test, the effect was more pronounced when compared with vitamin C at increased concentrations (50-400 µg/ml) [90]. In addition, good to moderate DPPH radical scavenging and ferric-reducing activities were observed in some extracts of *C. moorei* bulbs [27].

In the same way, the ethanolic extract of *C. ornatum* bulbs as well as some isolated alkaloids e.g. lycorine, haemanthamine and crinamine showed significant DPPH scavenging effects [49]. Equally, the aqueous extract of *C. latifolium* leaves revealed potent *in vitro* antioxidant activity by an oxygen radical absorbance capacity [29]. The aqueous leaves' extract of *C. bulbispermum* also displayed a dose-dependent moderate antioxidant activity (EC_{50}= 203.76 µg/ml) [20]. In a study by Indradevi *et al.*, the ethanolic extract of *C. asiaticum* leaves demonstrated hepatocyte protective nature by attenuating markers of hyperglycemia-mediated oxidative stress and antioxidant competence in hepatic tissues of diabetic rats [91]. A significant decrease in blood sugar, cholesterol, triglycerides, LDL levels and an increase in HDL level were observed. Besides, the activities of AST, ALT, ALP, ACP and LDH enzymes were diminished, whereas the activity of superoxide dismutase, catalase and reduced glutathione was increased by the extract.

Increases in liver lipid peroxides also improved. Similarly, [92], Ilavenil *et al.* showed that *C. asiaticum* L. ethanolic extract and lycorine possess human erythrocyte protective effects against oxidative damage induced by 2-amidinopropane. The effects were attributed to their antioxidant nature. In addition, the aqueous leaves extract of *C. bulbispermum* (3 g/Kg, orally) significantly increased SGOT, SGPT and creatinine levels but did not significantly alter serum urea and haematological parameters (haemoglobin, RBC and WBC counts) [20].

Lately, lycorine exhibited significant hepatoprotective effects against CCl_4-induced oxidative stress in Swiss albino mice at 5 mg/Kg which were comparable to Silymarin. It effectively normalized the increased generation of lipid peroxidation products, high levels of malondialdehyde, glucose, urea, serum bilirubin, and hepatic marker enzymes.

It also normalized the reduction of glutathione, vitamin C content and activities of superoxide dismutase, catalase, glutathione peroxidase, glutathione-*S*-transferase, and glutathione reductase. The histological and ultrastructural observations evidenced that lycorine effectively rescued the hepatocyte from CCl_4-induced oxidative damage without disturbing its cellular metabolic function and structural integrity [93, 94].

Anti-genotoxic activity: (*E*)-N'-[(*E*)-2-butenoyl]-2-butenoylhydrazide from *C. defixum* was found to have anti-genotoxic activity when assayed by onion root tip assay. It imparted a clear dose dependent protective effect against the genotoxic effect of H_2O_2. Furthermore, it was more effective against clastogenic aberrations than physiological aberration at the highest concentration tested (250 ppm) [95].

Antimicrobial activities: The methanolic extract of *C. jagus* possesses antibacterial activity and the alkaloid crinamine isolated from the bulbs showed a strong activity against *Bacillus subtilis* and *Staphylococcus aureus*. On the other hand, lycorine, hamayne and 6-hydroxycrinamine were found to be inactive. Neither the extract nor the isolated alkaloids possessed any antifungal activity [96]. Crinamine and lycorine showed also activity against *Bacillus cereus* and *Pseudomonas aeruginosa* [60]. Extracts of *C. macowanii* demonstrated weak antifungal properties against *Candida albicans in vitro* [97], whereas

Chaumont *et al.*, had reported the activity of *C. moorei* extracts against several fungi pathogenic to man [98]. In addition, the total ethanolic extracts of *C. augustum* bulbs and *C. asiaticum* leaves and their fractions (I-V) showed inhibitory effects on both Gram +ve (*S. aureus*) and Gram -ve (*E.coli*) bacteria at 50 mg/ml, while that on the former was markedly greater.

The total extracts of both plants and their fractions had no inhibitory effects at a concentration of 5 mg/ml, whereas fractions containing alkaloids (II, III and IV) of both plants were the most effective especially at 10 and 50 mg/ml [24]. Ghosal *et al.* also reported a marked antibacterial action of ungeremine against ten bacterial isolates [62]. Moreover, three flavonol glycosides quercetine-3-O-glucoside, kaempferol-3-O-*β*-D-xylopyranosyl(1→3)*β*-D-gluco pyranoside and quercetin-3-O-*β*-D-(6-O-acetyl gluco pyranosyl)(1→3)*β*-D-glucopyranoside were found to be inactive against *S. aureus*, *E.coli* and *P. aeroginosea*, but showed moderate antifungal activity against *Candida albicans in vitro* [99].

In another study, the CH_2Cl_2/MeOH (1:1) leaf extract of *C. purpurascens*, hippadine as well as sitosterol-3-O-*β*-D-glucopyranoside demonstrated antibacterial activity against *P. aeruginosa*, *E. coli*, *K. pneumoniae*, *S. aureus*, *S. typhi* and *S. paratyphi B*, whereas pratorimine did not show any antimicrobial activity against these bacteria strains [100]. Likewise, the ethanolic extract of *C. asiaticum* has a broad spectrum activity against Gram +ve and Gram -ve bacteria. It showed greater activity than the aqueous extract against *K. pneumoniae*, *S. aureus*, *B. subtilis*, *P. aeruginosa* and *E. coli* [101].

Regarding the antiviral activities, it was reported that lycorine exerts powerful antiviral effects on several RNA and DNA viruses such as Coxsackie B_2, poliomyelitis and Herpes type I [57]. This is accomplished by delaying virus production and decreasing the virus amount by blocking viral protein synthesis [102].

Lycorine is also effective against Severe Acute Respiratory Syndrome-associated coronavirus (SARS-CoV) [103]. On the other hand, narciclasine inhibits protein synthesis at the step of peptide bond formation. Pretazettine strongly inhibits the activity of RNA-dependent DNA polymerase from various oncogenic viruses by binding to the enzyme as well [30]. Moreover, Duri *et al.* reported that *C. macowanii* bulbs extract caused 100% reduction of viral cytopathic effects in VERO cells infected with yellow fever virus. The same extract also resulted in 70% inhibition of viral replication and cytopathic effects in cells infected with Japanese encephalitis virus [104]. In addition, the methanolic extract of *C. asiaticum var. japonicum* roots showed significant anti-HIV-1 activity (ED_{50} = 12.5 μg/ml) [105]. Tris phaeridine, lycorine, homolycorine, and haemanthamine showed high antiretroviral activities (IC_{50}= 0.4-7.3 μg/mL) as well [106].

Antiparasitic activity: Four groups of Amaryllidaceae alkaloids (lycorine, crinine, tazettine and galanthamine-types) exhibited antimalarial activity at different potencies when evaluated *in vitro* for their ability to inhibit *Plasmodium falciparum* growth. 6-hydroxy-haemanthamine, haemanthamine and lycorine were found to be the most potent, while galanthamine and tazettine had the least potent activity against *P. falciparum* [107]. Likewise, lycorine, augustine and crinamine from *C. amabile* bulbs showed moderate antimalarial activity against *P. falciparum* [78]. In addition, Nair *et al.* reported that lycorine has a mild *in vitro* activity (IC_{50}= 0.34 μg/ml) against *P. falciparum* (strain NF-54), whereas 4a-dehydroxycrinamabine, crinamidin, macowine and undulatine were inactive [108].

On the other hand, 4a-dehydroxycrinamabine demonstrated a very mild activity (IC_{50}= 11.07 μg/ml) against *Trypanosoma brucei rhodesiense* (strain STIB-900, stage trypomastigotes), the parasite associated with sleeping sickness [108], while 1,2-diacetyllycorine and 3-O-acetylsanguinine from *C. kirkii* bulbs showed activity against *T. brucei rhodesiense*. 3-O-acetylsanguinine also exhibited some activity against *T. cruzi* [109]. Furthermore, crinamine and lycorine were active against *Entamoeba hystolitica* with IC_{50} of 0.53 and 0.23 μg/ml, respectively. Dihydrolycorine has been used as a substitute for emetine in amoebic dysentery due to its protozoacidal effects [110].

Insecticidal and molluscicidal activities: In their search for new bioactive alkaloids from *C. powellii* bulbs, Velten *et al.* isolated two novel insecticidal alkaloids, cripowelline A and B. The aqueous solution of the former (0.1% w/v) revealed a considerable activity against diamondback moth on cabbage plants which lasted for seven days [111].

On the other hand, the aqueous and ethanolic extracts of *C. zeylanicum* were tested against molluscan intermediate hosts of schistosomiasis and fascioliasis. Both extracts showed remarkable mortality rates against *Biomphalaria pfeifferii* (IC_{50}=50 mg/ml) and *Lymnaea natalensis* (IC_{50}=10 mg/ml) [112].

Anti-snake venom activity: The methanolic extract of *C. jagus* bulbs has a significant anti-snake venom activity against *Echis ocellatus* venom. It significantly protected mice from death, myonecrosis and haemorrhage induced by the lethal effects of venoms. The extract showed a very minimal effect against *Naja nigricollis* venom, which is neurotoxic. These results have confirmed the ethnomedical use of the extract for treating snakebite victims among the rural Nigerian population [90, 113].

Antifouling activity: Biofouling or biological fouling is the undesirable accumulation of micro-organisms, plants, algae, and/or animals on wetted surfaces. Settlement of higher organisms such as macroalgae and invertebrates may threaten the survival of individuals of benthic invertebrates. Therefore, benthic invertebrates have developed various defense systems against biofouling, such as biofilm. Accordingly, biofouling on ships hulls, offshore structures or aquaculture equipment represent a major global economic and technical problem.

Antifouling is the process of preventing or removing the accumulation of such biofoulers. Many types of antifoulig agents including organotins (e.g. tributyltin, triphenyltin) as well as copper and its derivative compounds have been found to be toxic to marine organisms. Therefore, the development of environmentally safe antifouling substances is urgently needed [114].

Recently, seven compounds isolated from *C. augustum* Rox. bulbs were evaluated for their antifouling effects using larvae of barnacle *Balanus amphitrite*. Only 6-methoxy-crinamine, crinamine and buphanisine showed significant activity with EC_{50} of 1.8, 1.2 and 0.75 µg/ml, respectively, versus the positive control copper sulphate (EC_{50} = 0.23 µg/ml). In contrast to copper sulphate, the three alkaloids were nearly safe at all the tested concentrations [115].

Other Biological activities: *Crinum*s contain strong emetic and diaphoretic alkaloids. Ingestion of raw bulbs causes nausea, vomiting and diarrhea [5]. Crinamine was found to inhibit hypoxia inducible factor-1 (HIF-1) activity but not activity of hypoxia inducible factor-2. It showed potent dose-dependent inhibition (IC_{50}= 2.7 muM) of HIF-1alpha in a cell-based reporter gene assay, whereas lycorine, norgalanthamine and epinorgalanthamine showed no significant inhibition of HIF-1alpha induced transcriptional activity [116].

Additionally, the 80% methanolic extract of *C. yemense* bulbs showed a potent inhibitory effect on nitric oxide (NO) production in lipopolysaccharide-activated macrophages. Yemenine A, bulbispermine, crinamine, 6-hydroxycrinamine and lycorine also inhibited both NO production and induction of inducible nitric oxide synthase (iNOS) [117]. The pyran derivative, 6-hydroxy-2*H*-pyran-3-carbaldehyde isolated from *C. yemense* was found to be a more potent tyrosinase inhibitor in treatment of hyperpigmentation than kojic acid [118]. Lately, the ethanolic extract of *C. asiaticum* and norgalanthamine showed important potential to promote hair growth via the proliferation of dermal papilla [119].

Bioassay-guided study of the methanol extract of *C. latifolium* yielded 4-senecioyloxymethyl-3,4-dimethoxycoumarin which was found to be a strong inhibitor to the *in vitro* tube-like formation of human umbilical venous endothelial cells (HUVECs), while manifesting no cytotoxicity in tumor cell lines (B16F10, HCT116). In contrast, 5, 6, 3'-trihydroxy-7, 8, 4'-trimethoxyflavone showed a modest inhibitory effect on tube-like formation of HUVECs [120].

Galanthamine has been reported to have blockade effects on ion channels of excitable membranes such as K^+ and Na^+ channels [121]. Unlike tacrine, galanthamine was found to have no affinity for muscarinic or nicotinic cholinoceptors in radioligand binding assays [122]. However, galanthamine (l-10 µM) was found to activate nicotinic acetylcholine receptors in cultured hippocampal neurons. Galanthamine and physostigmine also activated fibroblast cells that had been transfected with the α_4 β_2 form of the neuronal nicotinic receptor [123].

Furthermore, Galanthamine eye drops significantly reduced intraocular pressure in rabbits' eyes. The effect was slow in onset and long-lasting peaking at two hours [124]. On the other hand, lycorine is a powerful inhibitor of growth and cell division in higher plants, algae and yeasts [125], while lycorine-1-O-glucoside and lycoriside are potent promoters of root growth and seed germination in higher plants e.g. *Allium cepa* [75, 126].

Conversely, palmilycorine, lycorine and lycorine-1-O- glucoside were shown to inhibit the emergence of plants' leaves [75]. Furthermore, Niño *et al.* reported that lycorine displayed moderate topoisomerase I inhibitory activity when tested utilizing genetically engineered mutants of the yeast *Saccharomyces cerevisiae* strains RAD+, RAD52Y and RS321 [127]. Lycorine (1 mg/kg) also induced a marked choleretic effect in rats anaesthetized with urethane [128].

Recently, crinumin, a glycosylated serine protease with chymotrypsin-like activity was purified from the latex of *C. asiaticum*. It showed activity over a wide range of pH (4.5-11.5 and optimum at 8.5), temperature (75 °C and optimum at 70 °C) and is also functional against organic solvents and detergents even after prolonged exposure [129].

Toxicological studies: Due to their alkaloidal content, *Crinum* plants are known to be toxic. Raw bulbs ingestion results in nausea, vomiting and diarrhea [5]. In addition, *C. zeylanicum* was used in the Moluccas as a violent poison [130]. As a result, some *Crinum* species were subjected to toxicological studies in order to evaluate their safety. For example, the acute toxicity of the aqueous extract of *C. glaucum* bulbs was studied by Okpo *et al.*. The LD_{50} were 119 mg/Kg, i.p. and 1420 mg/Kg, p.o. in mice [19]. Likewise, the i.p. and oral LD_{50} of *C. giganteum* aqueous extract in mice were found to be 627 and 1468 mg/kg, respectively [47].

In an analogous study on the same extract, the i.p. and p.o. LD_{50} were 627 ± 5.8 and 1486 ± 18.9 mg/Kg in mice, and 520 ± 10.2 and 1023 ± 4.3 mg/Kg in rats, respectively [8]. Similarly, the p.o. LD_{50} of the total ethanolic extract of *C. augustum* bulbs was observed to be 1600 mg/Kg in mice [24].

On the other hand, Ratnasooriya *et al.* evaluated the subchronic toxicity of the aqueous leaves extract of *C. bulbispermum*. The extract induced mild to moderate toxicity in rats which developed diarrhea and postural abnormalities on the second day, and two rats died by the fourth day. Liver and renal toxicities (increase of serum SGOT, SGPT, creatinine and urea) were also reported. The authors attributed this toxicity to the lycorine- and crinine-types of alkaloids present in the extract [20].

Different extracts of *C. bulbispermum* bulbs were tested in a brine shrimp bioassay. The most effective one were the butanol fraction of the acidic extract of the non-flowering bulbs (LD_{50}= 63.1 µg/ml) followed by the ether fraction of the alkaline extract of the flowering bulbs (LD_{50}= 73 µg/ml) [131]. Likewise, the essential oil of *C. ornatum* bulbs was found to be toxic through the brine shrimp assay (LC_{50} = 1.701 µg/ml) [49].

Considering the toxicological studies on the individual compounds, the acute LD_{50} values of galanthamine by various routes were reported to be 18.7 (oral), 8 (i.v.), 14.4 (i.p.) and 6.2 (s.c.) mg/kg in mice [132], while they were 2-4 times higher in rats [133]. Micov and Georgiev reported that daily administration of 1 or 4 mg/kg (equivalent to 0.5 and 2 mg galanthamine HBr) did not cause significant changes in weight, blood count, or in the morphology and histology of brain, liver, kidneys, adrenal glands, heart, and skeletal muscles. In addition, there was no evidence for teratogenicity [134]. Doses from 0.5 µg/kg to one-tenth the LD_{50} were administered orally and s.c. to rats and rabbits. The highest doses had embryotoxic activity on pregnant animals, although they did not produce fetal malformations [133].

CONCLUSION: Since about 1950s, *Crinums* have been subjected to extensive chemical and biological investigations due to their richness in pharmacologically active principles. Phytochemical investigations have resulted in isolation of diverse classes of compounds and have been focused predominantly on alkaloids. About 180 alkaloids belonging to different types of Amaryllidaceae alkaloids have been isolated from *Crinum* species.

In the same way, the enormous cytological, pharmacological and toxicological studies of *Crinums* exhibited a wide range of interesting biological activities. Analgesic, anti-inflammatory, anticholinestrase, CNS, CVS, antiallergic, antiana-phylactic, immunological, anti-tumor, anti-microbial and anti-parasitic activities are the most important reported effects.

Among the various classes of phytocompounds isolated from *Crinums*, alkaloids seem to be the main bioactive constituents. As a result, the above reviewed findings doubtlessly present *Crinum* as an endless source of bioactive principles. This fact can also be substantiated by four evidences. Firstly, only about thirty-five of 130 species have been phytochemically studied, whereas the largest number of species remains out there waiting to be visited. Secondly, hybridization among different species, that is considered a common phenomenon among *Crinums*.

Both the unstudied species and new hybrids open the gate towards isolation of further new compounds. Furthermore, chemical investigation of these unstudied species will be of high chemotaxonomic value to resolve the complicated taxonomic situation within this genus.

The third evidence comes from the lesser attention paid to both the non-alkaloidal and polar constituents, which could open new chemical and biological horizons if studied in the future. Fourthly, from a biological point of view, a large number of different *Crinums'* extracts as well as the purified compounds are still calling for further pharmacological screening. Both positive and new activities are strongly expected. Thus, the aforementioned results undoubtedly recommend *Crinum* and its Amaryllidaceous relatives -especially for their exclusive alkaloidal types- to be considered as candidates for development of new potent drugs, which can provide beneficial solutions against the every day challenging diseases.

REFERENCES:

1. Benson L: Plant Classification. Oxford and I.B.H publishing Co., New Delhi, Bombay, 1970: 793-797.
2. Mabberly DJ: The plant book. Cambridge University Press, 1990.
3. Beckstrom-Sternberg SM, Duke JA and Wain KK: The ethnobotany database. Genome Informatics Group. National Agricultural Library. U.S. Department of Agriculture, Beltsville, MD, 1994.
4. Do Tat L: The Medical Plants and Natural Drugs in Vietnam. Science and Technology Publishing House, Hanoi, 1991.
5. Etkin N: Plants in Indigenous Medicine and Diet: Biobehavioural Approaches. Redgrave, Bedford Hills, New York, 1986.
6. Ghosal S, Rao PH, Jaiswal DK, Kumar Y and Frahm AW: Alkaloids of *Crinum pratense*. Phytochemistry 1981; 20(8):2003-2007.
7. Hutchings A, Scott AH, Lewis G and Cunningham A: Zulu Medicinal Plants, An Inventory. University of Natal Press, Scottsville, Pietermaritzburg, 1996.
8. Kapu SD, Ngwai YB, Kayode O, Akah PA, Wambebe C, and Gamaniel K: Anti-inflammatory, analgesic and anti-lymphocytic activities of the aqueous extract of *Crinum giganteum*. Journal of Ethnopharmacology 2001; 78(1):7-13.
9. Levin S: Traditional Vietnamese herb *Crinum latifolium* shows promise for prostate and ovarian health. International Journal of Immunopharmacology 2001; 1(12): 2143-2150.
10. Tram NT, Titorenkova T, Bankova V, Handjieva N and Popov SS: *Crinum* L. Amaryllidaceae. Fitoterapia 2002; 73(3):183-208.
11. Ahmad M: Cytotoxic activity of the leaf extract of *Crinum asiaticum* Linn. Australian Journal of Medical Herbalism 1996; 8(1):3-6.
12. Chopra RN, Nayar SL and Chopra IC: Glossary of Indian Medicinal Plants. Council Sci. and Ind. Res., New Delhi, 1956.
13. Jayaweera DM: Medicinal plants used in Ceylon. The National Science Council of Sri Lanka, Colombo, 1981.
14. Prance GT, Chadwick DJ and Marsh J: Ethnobotany and the Search for New Drugs. Wiley, Chichester, 1994.
15. Pujol J: Nature Africa. The Herbalist Handbook. African Flora, Medicinal Plants. Jean Pujol Natural Healers Foundation, Durban, 1990.
16. Rasoanaivo P, Petitjean A and Conan JY: Toxic and poisonous plants of Madagascar: an ethnopharmacological survey. Fitoterapia 1993; 64:114-129.
17. Bizimana N: Traditional veterinary practice in Africa. Deutsche Gesellschaft für Technicsche Zusammenarbeit (GTZ), Eschborn, 1994.
18. Fennell CW and Van Staden J: *Crinum* species in traditional and modern medicine. Journal of Ethnopharmacology 2001; 78(1):15–26.
19. Okpo SO, Fatokun F and Adeyemi OO: Analgesic and anti-inflammatory activity of *Crinum glaucum* aqueous extract. Journal of Ethnopharmacology 2001; 78(2):207–211.
20. Ratnasooriya WD, Deraniyagala SA, Bathige SD and Hettiarachchi HDI: Leaf extract of *Crinum bulbispermum* has antinociceptive activity in rats. Journal of Ethnopharmacology 2005; 97(1):123–128.
21. Asmawi MZ, Arafat OM, Amirin S and Eldeen IM: *In vivo* antinociceptive activity of leaf extract of *Crinum asiaticum* and phytochemical analysis of the bioactive fractions. International Journal of Pharmacology 2011; 7(1):125–129.
22. Samud AM, Asmawi MZ, Sharma JN and Yusof APM: Anti-inflammatory activity of *Crinum asiaticum* plant and its effect on bradykinin-induced contractions on isolated uterus. Immunopharmacology 1999; 43(2–3):311–316.
23. Jin KY, Heon KJ, Ho KK, Heui KY and Sil KY: Compositon comprising an extract of *Crinum asiaticum* Linne having anti-allergic and anti-inflammatory activity. European patent office, A61K 36/88, 2007.
24. Refaat J, Mohamed SK, Ramadan MA and Ali AA: Analgesic, anti-inflammatory and antimicrobial activities of *Crinum augustum* Rox. and *Crinum asiaticum* L. Research Journal of Pharmacognosy and Phytochemistry 2011; 3(6): 289-296.
25. Lee SD, Lee SH, Choi SW, Kwon WJ and Kim IH: Pharmacological actions of *Crinum folium*. Korean Journal of Pharmacognosy 1995; 26(2):139–147.
26. Manna AK, Samanta SK, Panda BR and Nanda U: Free radical scavenging and analgesic properties of the bulb of *Crinum defixum* Ker Gawl on experimental animal model. International Journal of Biological and Pharamaceutical Research 2010; 1(2):82–87.
27. Fawole OA, Amoo SO, Ndhlala AR, Light ME, Finnie JF and Van Staden J: Anti-inflammatory, anticholinesterase, antioxidant and phytochemical properties of medicinal plants used for pain-related ailments in South Africa. Journal of Ethnopharmacology 2010; 127(2):235–241.
28. Nam NH and Jae YY: NF-κB Inhibitory activities of the methanol extracts and some constituents therein of some Vietnamese medicinal plants. Scientia Pharmaceutica 2009; 77:389–399.
29. Jenny M, Wondrak A, Zvetkova E, Tram NT, Phi PT, Schennach H, Culig Z, Ueberall F and Fuchs D: *Crinum latifolium* leave extracts suppress immune activation cascades in peripheral blood mononuclear cells and proliferation of prostate tumor cells. Scientia Pharmaceutica 2011 79:323–335.
30. Ghosal S, Saini KS and Razdan S: *Crinum* alkaloids: their chemistry and biology. Phytochemistry 1985; 24(10):2141–2156.
31. Wildman WC: The Alkaloids: Chemistry and Physiology. Edited by R.H.F. Manske, Academic Press, New York, London, Vol. VI, 1960.
32. Cordell GA: Introduction to Alkaloids: A Biogenetic Approach. Wiley, New York, 1981.
33. Lewis JR: Amaryllidaceae and *Sceletium* alkaloids. Natural Products Reports 1998; 15:107–110.
34. Çitoglu G, Tanker M and Gümüsel B: Anti-inflammatory effects of lycorine and haemanthidine. Phytotherapy Research 1998; 12(3):205–206.
35. Harvey AL: The pharmacology of galanthamine and its analogues. Pharmacology and Therapeutics 1995; 68(1):113–128.

36. Greenblatt HM, Kryger G, Lewis T, Silman I and Sussman J: Structure of acetylcholinestrase complexed with (–)-galanthamine at 2.3 Å resolution. FEBS Lett 1999; 463:321–326.
37. Lewis JR: Amaryllidaceae and *Sceletium* alkaloids. Natural Products Reports 1998; 15:107–110.
38. Sener B and Orhan I: Discovery of drug candidates from some Turkish plants and conservation of biodiversity. Pure and Applied Chemistry 2005; 77(1):53–64.
39. Cozanitis DA and Toivakka E: A comparative study of galanthamine HBr and atropine/neostigmine in conscious volunteers. Anaesthesist 1971; 20:416–421.
40. Reimann D, Gann H, Dressing H, Müller WE and Aldenhoff JB: Influence of the cholinesterase inhibitor galanthamine HBr on normal sleep. Psychiatry Research 1994; 51:253–267.
41. Cozanitis DA: Galanthamine HBr, a longer acting anticholinesterase drug, in the treatment of the central effects of scopolamine (hyoscine). Anaesthesist 1977; 26:649–650.
42. Rhee IK, Apples N, Hofte B, Karabatak B, Erkelens C, Stark L, Flippin L and Verpoorte R: Isolation of acetylcholineestrase inhibitor ungeremine from *Nerine bowdenii* by preparative HPLC coupled with on-line to a flow assay system. Biological and Pharmaceutical Bulletin 2004; 27(11):1804-1809.
43. Houghton PJ, Agbedahunsi JM and Adegbulugbe A: Cholinesterase inhibitory properties of alkaloids from two Nigerian *Crinum* species. Phytochemistry 2004; 65(21):2893–2896.
44. Kissling J, Ioset JR, Marston A and Hostettmann K: Bio-guided isolation of cholinesterase inhibitors from the bulbs of *Crinum powellii*. Phytotherapy Research 2005; 19(11):984–987.
45. Jäger AK, Adsersen A and Fennell CW: Acetyl-cholinesterase inhibition of *Crinum* sp. South Africa Journal of Botany 2004; 70(2):323–325.
46. Kwon HC, Cha JW, Park J and : Rapid identification of bioactive compounds reducing the production of amyloid *β*-peptide (Aβ) from South African plants using an automated HPLC/SPE/HPLC coupling system. Biomolecules and Therapeutics 2011; 19(1): 90–96.
47. Amos S, Binda L, Akah P, Wambebe C and Gamaniel K: Central inhibitory activity of the aqueous extract of *Crinum giganteum*. Fitoterapia 2003; 74(1–2):23–28.
48. Gericke NP and Van Wyck BE: US Patent US6, 288, 104, 2001.
49. Oloyede KG, Oke MJ, Raji Y and Olugbade AT: Antioxidant and anticonvulsant alkaloids in *Crinum ornatum* bulb extract. World Journal of Chemistry 2010; 5(1):26–31.
50. Chmeda-Hirschmann G, Astudillo L, Bastida J, Viladomat F and Codina C: DNA binding activity of Amaryllidaceae Alkaloids. Boletin De La Sociedad Chilena De Quimica 2000; 45: 515-518.
51. Bastida J and Viladomat F: Alkaloids of *Narcissus*. In: Medicinal and Aromatic Plants. Industrial Profiles: The Genus *Narcissus* (Hanks G., ed.). Taylor and Francis, London and New York, pp. 141.214, 2002.
52. Martin SF: The Amaryllidaceae Alkaloids. In: Brossi A (ed) The Alkaloids: Chemistry and Pharmacology, 30, Academic Press, San Diego, pp 251–376, 1987.
53. Irwin RL and Smith HJ: The activity of galanthamine and related compounds on muscle. Archives Internationales de Pharmacodynamie et de Therapie 1960; 127:314–330.
54. Chrusciel M and Varagic V: The effect of galanthamine on the blood pressure of the rat. British Journal of Pharmacology 1966; 26:295-301.
55. Wasicky R: *Digitalis*-like effect of *Crinum pratense* and *Hippeastrum solandriflorum* Naunyn Schmiedebergs Archiv for Experimentelle Pathologie und Pharmakologie 1953; 219(4):362–365.
56. Cozanitis DA and Rosenberg P: Preliminary experiments with galanthamine HBr on depressed respiration. Anaesthesist 1974; 23: 302–305.
57. Harborne JB and Baxter H: A Handbook of Bioactive Compounds from Plants. Taylor and Francis, London, 1993.
58. Cozanitis DA: Experiences with galanthamine HBr as curare antagonist. Anaesthesist 1971; 20:226–229.
59. Okpo SO and Adeyemi OO: Effects of *Crinum glaucum* aqueous extract on intestinal smooth muscle activity. Phytotherapy Research 1998; 12(6):413–416.
60. Wiart C: Medicinal Plants of Southeast Asia. Pelanduk Publications (M), Sdn Bhd, Malaysia, 2000.
61. Chattopadhyay S, Chattopadhyay U, Mathur PP Saini KS and Ghosal S: Effects of hippadine, an Amaryllidaceae alkaloid, on testicular function in rats. Planta Medica 1983; 49(4):252–254.
62. Ghosal S, Singh, SK, Kumar Y, Unnikrishnan S amd Chattopadhyay S: The role of ungeremine in the growth-inhibiting and cytotoxic effects of lycorine: evidence and speculation**.** Planta Medica 1988; 54:114–116.
63. Cozanitis DA: Galanthamine HBr vs. neostigmine. A plasma cortisol study in man. Anaesthesia 1974; 29:163–168.
64. Cozanitis DA, Dessypris A and Nuutila K: The effect of galanthamine HBr on plasma ACTH in patients undergoing anaesthesia and surgery. Acta Anaesthesiologica Scandinavica 1980; 24, 166–168.
65. Okpo SO and Adeyemi OO: The anti-allergic effects of *Crinum glaucum* aqueous extract. Phytomedicine 2002; 9(5):438–441.
66. Okpo SO and Adeyemi OO: The antianaphylactic effects of *Crinum glaucum* aqueous extract. Journal of Ethnopharmacology 2002; 81(2):187–190.
67. Ghosal S, Shanthy A, Das PK, Mukhopadhyay M and Sarkar M: Mast cell stabilizing effect of glucan A and phosphatidyllycorine isolated from *Crinum latifolium*. Phytotherapy Research 1988; 2(2): 76–79.
68. Ghosal S, Shanthy A, Mukhopadhyay M, Das PK and Sarkar M: Effect of lycoriside, an acylglucosyloxy alkaloid, on mast cells. Pharm Res 1986; 3(4):240–243.
69. Zvetkova E, Wirleitner B, Tram N, Schennach H and Fuchs D: Aqueous extracts of *Crinum latifolium* L. and *Camellia sinensis* show immunomodulatory properties in human peripheral blood mononuclear cells. Journal of International Immunopharmacology 2001; 1(12): 2143–2150.
70. Tram NT, Zvetkova E, Nikolova E, Katzarova E, Kostov G, Yanchev I and Baicheva O: A novel in vitro and in vivo T-lymphocyte activating factor in *Crinum latifolium* L. aqueous extracts. Experimental Pathology and Parasitology 1999; 3:21–26..
71. Ghosal S, Saini KS and Arora VK: 1,2-*β*-Epoxyambelline, an immunostimulant alkaloid from *Crinum latifolium*. Journal of Chemical Research *(S)* 1984; 7:232–233.
72. Dickneite G, Schorlemmer H and Hans-Harald S: Use of lycorine as an immunosuppressor. US Patent. 06/754, 269 4699912, 1987.
73. Nair JJ, Campbell WE, Gammon DW, Albrecht CF, Viladomat F, Codina C and Bastida J: Alkaloids from *Crinum delagoense*. Phytochemistry 1998; 49(8):2539–2543.
74. Ghosal S and Singh SK: Chemical constituents of Amaryllidaceae. Part 24. crinafoline and crinafolidine, two anti-tumor alkaloids from *Crinum latifolium*. Journal of Chemical Research *(S)* 1986; 3:312–313.
75. Ghosal S, Shanthy A, Kumar A and Kumar Y: Palmilycorine and lycoriside: acyloxy and acylglucosyloxy alkaloids from *Crinum asiaticum*. Phytochemistry 1985; 24(11):2703–2706.
76. Ghosal S, Kumar Y, Singh SK, Kumar A: Chemical constituents of Amaryllidaceae. Part 21. ungeremine and criasbetaine, two anti-tumor alkaloids from *Crinum asiaticum*. Journal of Chemical Research *(S)* 1986; 3:112–113.
77. Zee-cheng R, Yan S and Cheng C: Antileukemic activity of ungeremine and related compounds. Preparation of ungeremine analogs by a practical photochemical reaction. Journal of Medicinal Chemistry 1978; 21(2):199–203.
78. Likhitwitayawuid K, Angerhofer C, Chai H, Pezzuto JM, Cordell GA and Ruangrungsi N: Cytotoxic and antimalarial alkaloids from the bulbs of *Crinum amabile*. Journal of Natural Products 1993; 56(8):1331–1338.
79. Abd El-Hafiz MA, Ramadan MA, Jung ML, Beck JP and Anton R: Cytotoxic activity of Amaryllidaceae alkaloids from *Crinum augustum* and *Crinum bulbispermum*. Planta Medica 1991; 57(5):437–439.
80. Furusawa E, Irie H, Combs D and Wildman WC: Therapeutic activity of pretazettine on Rauscher leukemia: comparison with the related Amaryllidaceae alkaloids. Chemotherapy 1980; 26(1):36–45.
81. Barthelmes HU, Niederberger E, Roth T, Schulte K, Tang WC, Boege F, Fiebig H-H, Eisenbrand G and Marko D: Lycobetaine acts as a selective topoisomerase IIβ poison and inhibits the growth of human tumour cells. British Journal of Cancer 2001; 85(10):1585–1591.
82. Weniger B, Italiano L, Beck JP, Bastida J, Bergoñon S, Codina C, Lobstein A and Anton R: Cytotoxic activity of Amaryllidaceae alkaloids. Planta Medica 1995; 61(1):77–79.

83. Hsu YL, Kuo PL, Lin LT and Lin CC: Isoliquiritigenin inhibits cell proliferation and induces apoptosis in human hepatoma cells. Planta Medica 2005; 71(2):130–134.
84. Min BS, Gao JJ, Nakamura N, Kim YH and Hattori M: Cytotoxic alkaloids and a flavan from the bulbs of *Crinum asiaticum var. japonicum*. Chemical Pharmaceutical Bulletin (Tokyo) 2001; 49(9):1217–1219.
85. Sun Q, Shen Y, Tian J, Tang J, Su J, Liu R, Li H, Xu X and Zhang W: Chemical constituents of *Crinum asiaticum* L. *var. sinicum* Baker and their cytotoxic activities. Chemistry and Biodiversity 2009; 6(10): 1751-1757.
86. Yui S, Mikami M, Kitahara M and Yamazaki M: The inhibitory effect of lycorine on tumor cell apoptosis induced by polymorphonuclear leukocyte-derived calprotectin. Immunopharmacology 1998; 40(2):151–162.
87. McNulty J, Nair J, Codina C, Bastida J, Pandey S, Gerasimoff J and Griffin C: Selective apoptosis-inducing activity of *Crinum*-type Amaryllidaceae alkaloids. Phytochemistry 2007; 68:1068–1074.
88. Berkov S, Romani S, Herrera M, Viladomat F, Codina C, Momekov G, Ionkova I and Bastida J: Antiproliferative Alkaloids from *Crinum zeylanicum*. Phytotherpy Research 2011; 25(11):1686-1692.
89. Tram N, Yanchev I, Zvetkova E, Dineva J, Katzarova E, Kostov G, Svilenov D, Ilieva I and Shalamanov P: Retarded growth of chemically induced with 20-methylcholanthrene tumours in rats under the action of cold-hot aqueous extracts (decoctions) from Vietnamese plant *Crinum latifolium* (L.). Experimental Pathology and Parasitology 2001; 4(7):9–12.
90. Ode OJ, Nwaehujor CO and Onakpa MM: Evaluation of anti-hemorrhagic and antioxidant potentials of *Crinum jagus* bulbs. International Journal of Applied Biology and Pharmaceutical Technology 2010; 1(3):1330–1336.
91. Indradevi S, Ilavenil S, Kaleeswaran B, Srigopalram S and Ravikumar S: Ethanolic extract of *Crinum asiaticum* attenuates hyperglycemia-mediated oxidative stress and protects hepatocytes in alloxan induced experimental diabetic rats. Journal of King Saud University - Science 2011; 24(2): 171-177.
92. Ilavenil S, Kaleeswara B, Sumitha P, Tamilvendanc D and Ravikumar S: Protection of human erythrocyte using *Crinum asiaticum* extract and lycorine from oxidative damage induced by 2-amidinopropane. Saudi Journal of Biological Sciences 2011; 18:181–187.
93. Ilavenil S, Kaleeswaran B and Ravikumar S: Antioxidant and hepatoprotective activity of lycorine against Carbon tetrachloride-induced oxidative stress in Swiss albino mice. Der Pharma Chemica 2010; 2(6):267–272.
94. Ilavenil S, Kaleeswaran B and Ravikumar S: Protective effects of lycorine against carbon tetrachloride induced hepatotoxicity in Swiss albino mice. Fundamental and Clinical Pharmacology 2011; 26(3): 393-401.
95. Bordoloi M, Kotoky R, Mahanta JJ, Sarma TC and Kanjilal PB: Anti-genotoxic hydrazide from *Crinum defixum*. European Journal of Medicinal Chemistry 2008; 44(6):2754-2757.
96. Adesanya SA, Olugbade TA, Odebiyi OO and Aladesanmi JA: Antibacterial alkaloids in *Crinum jagus*. International Journal of Pharmacognosy 1992; 30(4):303–307.
97. Gundidza M: Screening of extracts from Zimbabwean higher plants II: Antifungal properties. Fitoterapia 1986; 57: 111–114.
98. Chaumont JP, De Scheemaeker H and Rousseau J: Antifungal properties of some members of the Amaryllidaceae. Plantes Medicinales et Phytotherapie 1978; 12(2): 157–161.
99. Abou Donia AH, Abou-Ela MA, Hammoda HM and Khashaba AA: Flavonol glucosides from the flowers of *Crinum bulbispermum*. Alexandia Journal of Pharmaceutical Sciences 2005; 19(2):153–157.
100. Nkanwen ER, Gatsing D, Ngamga D, Fodouop SP and Tane P: Antibacterial agents from the leaves of *Crinum purpurascens* herb (Amaryllidaceae). African Health Sciences 2009; 9(4):264–269.
101. Ilavenil S, Kaleeswaran B and Ravikumar S: Evaluation of antibacterial activity and phytochemical analysis of *Crinum asiaticum*. International Journal of Current Research 2010; 1:35-40.
102. Leven M, Van den Berghe D, Vlietinck AJ, Totte J, Dommisse R, Esmans E and Alderweireldt F: Plant antiviral agents. III. Isolation of alkaloids from *Clivia miniata* Regel (Amaryllidaceae). Journal of Natural Products 1982; 45(5):564–573.
103. Li SY, Chen C and Zhang HQ: Identification of natural compounds with antiviral activities against SARS-associated coronavirus. Antiviral Research 2005; 67(1):18–23.
104. Duri ZJ, Scovill JP and Huggins JW: Activity of methanolic extract of Zimbabwean *Crinum macowanii* against exotic RNA viruses *in vitro*. Phytotherapy Research 1994; 8:121–122.
105. Min BS, Kim YH, Tomiyama M, Nakamura N, Miyashiro H, Otake T and Hattori M: Inhibitory effects of Korean plants on HIV-1 activities. Phytotherapy Research 2001; 15(6):481–486.
106. Szlavik L, Gyuris A, Minarovits J, Forgo P, Molnár J and Hohmann J: Alkaloids from *Leucojum vernum* and antiretroviral activity of Amaryllidaceae alkaloids. Planta Medica 2004; 70(9):871–873.
107. Sener B, Orhan I and Satayavivad J: Antimalarial activity screening of some alkaloids and the plant extracts from Amaryllidaceae. Phytotherapy Research 2003; 17(10):1220–1223.
108. Nair JJ, Machocho AK, Campbell WE, Brun R, Viladomat F, Codina C and Bastida J: Alkaloids from *Crinum macowanii* Phytochemistry 2000; 54(8):945–950.
109. Machocho AK, Bastida J, Codina C, Viladomat F, Brun R and Chhabra SC: Augustamine type alkaloids from *Crinum kirkii*. Phytochemistry 2004; 65(23):3143–3149.
110. Machocho A, Chahabra S, Viladomat F, Codina C and Bastida J: Alkaloids from *Crinum stuhlmanii*. Planta Medica 1998; 64(7):679–680.
111. Velten R, Erdelen C, Gehling M, Göhrt A, Gondol D, Lenz J, Lockhoff O, Wachendorff U and Wendisch D: Cripowelline A and Cripowelline B, a novel type of Amaryllidaceae alkaloids from *Crinum powellii*. Tetrahedron Letters 1998; 39(13):1737–1740.
112. Chifundera K, Baluku B and Mashimango B: Phytochemical screening and molluscicidal potency of some Zairean medicinal plants. Pharmacological Research 1993; 28(4): 333–340.
113. Ode OJ and Asuzu IU: The anti-snake venom activities of the methanolic extract of the bulb of *Crinum jagus* (Amaryllidaceae). Toxicon 2006; 48:331–342.
114. Fuestani N: Biofouling and antifouling. Natural Products Reports 2004; 21:94–104.
115. Refaat J, Abdel-Lateff AA, Kamel MS, Ali AA, Ramadan MA, Okino T and Nogata Y: Antifouling alkaloids from *Crinum augustum* (Amaryllidaceae). Pharmacognosy Research 2009; 1(2):43–52.
116. KimYH, Park EJ, Park MH, Badarch U, Woldemichael GM and Beutler JA: Crinamine from *Crinum asiaticum var. japonicum* inhibits hypoxia inducible factor-1 activity but not activity of hypoxia inducible factor-2. Biological and Pharmaceutical Bulletin 2006; 29(10):2140–2142.
117. Abdel-Halim OB, MorikawaT, Ando S, Matsuda H and Yoshikawa M: New crinine-type alkaloids with inhibitory effect on induction of inducible nitric oxide synthase from *Crinum yemense*. Journal of Natural Products 2004; 67(7):1119–1124.
118. Abdel-Halim OB, Marzouk A, Mothana R and Awadh N: A new tyrosinase inhibitor from *Crinum yemense* as potential treatment for hyperpigmentation. Pharmazie 2008; 63(5):405–407.
119. Kim S, Kang J, Kyoung M, Hyun JH, Boo HJ, Park DB, Lee YJ, Yoo ES, Kim YH, Kim YH and Kang HK: Promotion effect of norgalanthamine, a component of *Crinum asiaticum*, on hair growth. European Journal of Dermatology 2010; 20(1):42–48.
120. Nam N H, Kim Y, You YJ, Hong DH, Kim HM and Ahn BZ: New constituents from *Crinum latifolium* with inhibitory effects against tube-like formation of human umbilical venous endothelial cells. Natural Products Research 2004; 18(6):485–491.
121. Krivoi II, Kuleshov VI, Matyushkin DP, Sanotskiĭ VI and Seĭ TP: Miniature end-plate currents of muscular fibres from rat diaphragm under acetylcholinesterase inhibition with galanthamine. Neirofiziologiia 1985; 17:607–614.
122. Sweeney JE, Puttfarcken PS and Coyle JT: Galanthamine, an acetylcholinesterase inhibitor: a time course of the effects on performance and neurochemical parameters in mice. Pharmacology Biochemistry and Behavior 1989; 34:129–137.
123. Pereira EF, Alkondon M, Reinhardt S, Maelicke A, Peng X, Lindstrom J, Whiting P and Albuquerque EX: Physostigmine and galanthamine: probes for a novel binding site on the alpha 4 beta 2 subtype of neuronal nicotinic acetylcholine receptors stably expressed in fibroblast cells. Journal of Pharmacology and Experimental Therapeutics 1994; 270:768–777.
124. Agarwal HC and Gupta SE: Ocular hypotensive effect of galanthamine hydrobromide: an experimental study. Indian Journal of Pharmacology 1990; 22:117–118.
125. Leo De P, Dalessandro G, De Santis A, Arrigoni O: Metabolic responses to lycorine in plants. Plant and Cell Physiology 1973; 14(3):487–496.

126. Ghosal S, Kumar Y and Singh SK: Glucosyloxy alkaloids from *Pancratium biflorum*. Phytochemistry 1984; 23(5):1167–1171.
127. NiñoJ, Hincapié GM, Correa YM and Mosquera OM.: Alkaloids of *Crinum x powellii Album* (Amaryllidaceae) and their topoisomerase inhibitory activity. Zeitschrift für Naturforschung-Section C: Biosciences 2007; 62(3–4):223–226.
128. Cortese I, Renna G, Siro-Brigiani G, Poli G and Cagiano R: Pharmacology of lycorine, Effect on biliary secretion in the rat. Bollettino Societa Italiana di Biologia Sperimentale 1983; 59(9):1261–1264.
129. Singh KA, Kumar R, Rao GR and Jagannadham MV: Crinumin, a chymotrypsin-like but glycosylated serine protease from *Crinum asiaticum*: Purification and physicochemical characterization. Food Chemistry 2010; 119(4):1352–1358.
130. Le Maout E and Decaisne J: A general System of Botany, 1873.
131. Abou-ElaMA, El-Lakany AM and Hammoda HM: Alkaloids from the bulbs of *Crinum bulbispermum*. Pharmazie 2004; 59(11):894–895.
132. Umarova SS, Zakirov UB and Kamilov IK: Comparative evaluation of the pharmacological action of quaternary galanthamine derivatives. Farmakol Alkaloidov Akad Nauk USSR 1965; 2:258–263.
133. Paskov DS: Galanthamine. In: Kharkevich DA (ed) New Neuromuscular Blocking Agents, Vol. 79, Handbook of Experimental Pharmacology, Springer–Verlag, Berlin, 653–672, 1986.
134. Micov V and Georgiev A: The toxicity of the combined preparation Nivalin-P. Eksperimentalna Medidtsina i Morfologiia (Sofia)1986; 25:28–32.

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