ELSEVIER

Journal of Ethnopharmacology 78 (2001) 15–26

Journal of ETHNO-PHARMACOLOGY

www.elsevier.com/locate/jethpharm

Crinum species in traditional and modern medicine

C.W. Fennell *, J. van Staden

Research Centre for Plant Growth and Development, School of Botany and Zoology, Faculty of Science and Agriculture, University of Natal-Pietermaritzburg, Private Bag X01, Scottsville, 3209, South Africa

Received 5 February 2001; received in revised form 19 June 2001; accepted 29 June 2001

Abstract

Crinums are large, showy plants with umbels of lily-like flowers. They are found in tropical and subtropical regions throughout the world, where, for centuries, they have been used traditionally to cure ailments and diseases. Sometimes they are prescribed for the same medicinal purpose. This would suggest that they contain a common ingredient. Phytochemical analysis has recently yielded a vast array of compounds, including more than 150 different alkaloids. These are of the Amaryllidaceae type, whose most noted effects are: analgesic, anticholinergic, antitumour and antiviral. Even though much has been reported on the medicinal properties of *Crinum*, only an estimated 20% of the species worldwide are represented in these analyses, as reviewed in this paper.

Keywords: *Crinum*; Amaryllidaceae; Ethnobotany; Phytochemistry

1. Introduction

Crinum species produce tunicate bulbs that, at certain times of the year, are dormant. But "few plants are more striking than this stately Amaryllid" (McFarland et al., 1948) when the heavy umbels of lily-like flowers later appear. With this apparent disappearance and then reappearance, it is no wonder that the plants entered into folklore. The 130 species of *Crinum* (Verdoorn, 1973; Bryan, 1989) have a pantropical distribution, with the centre of diversity south of the Sahara (Fangan and Nordal, 1993). They are, therefore, found in regions where there is a long history of traditional plant usage. They were esteemed by herbalists who used them for all manner of ills. While the knowledge survived for centuries through apprenticeship to traditional healers, early missionaries, colonial botanists and Victorian plant hunters were among the first to document it (Bryant, 1966; Watt and Breyer-Brandwijk, 1962). More recently it has attracted the attention of medical science. Yet the disappearance of plants at the hands of bulb enthusiasts and gatherers who collect for the thriving markets of medicinal plants, may mean a loss to the pharmaceutical industry of US$25 billion (Scott, 1993). Concerns for the protection of plant diversity and the preservation of indigenous knowledge, therefore, has led to an increase in the publication of ethnobotanical research (Cotton, 1996). However, few attempts have been made to synthesize the information available. Therein lies the potential for new drug discoveries using ethnobotanical leads and taxonomic revision using phytochemical data (Lewis, 1997). The following is a review of the medicinal uses of *Crinum* species: both in traditional medical practices and as sources of pharmacologically active compounds. Already the genus has yielded more than 170 different compounds, most of which are alkaloids. These have shown significant analgesic, antitumour and antiviral activity. Since only 27 species have been investigated phytochemically, there is much scope for future screening programmes. Phytochemical profiles of individual species may help resolve some of the taxonomic confusion (Fangan and Nordal, 1993), which exists because the genus has not been revised over its entire distribution range (Snijman and Linder, 1996).

2. Ethnobotany

Reports in the literature suggest widespread use of *Crinum* species in treating a variety of ailments (Table 1). In some cases the plants were and are used in different countries for the same medicinal purposes.

* Corresponding author.

0378-8741/01/$ - see front matter
PII: S0378-8741(01)00305-1

Table 1
The ethnobotany of *Crinum* species

Crinum spp.	Use	Country	Reference
C. amabile	Emetic, rheumatism, earache	Vietnam	Pham et al., 1998
C. asiaticum	Anodyne	Malaya	Beckstrom-Sternberg et al., 1994
	Antidote	Somoa	Beckstrom-Sternberg et al., 1994
	Antidote (arrow poison)	Java	Beckstrom-Sternberg et al., 1994
	Bilious		Beckstrom-Sternberg et al., 1994
	Carbuncle	China	Beckstrom-Sternberg et al., 1994
	Chafing	Malaya	Beckstrom-Sternberg et al., 1994
	Diaphoretic	Southeast Asia and Polynesia, Egypt	Etkin, 1986; Beckstrom-Sternberg et al., 1994
	Dysuria	Java	Beckstrom-Sternberg et al., 1994
	Edema	Java	Beckstrom-Sternberg et al., 1994
	Emetic	Southeast Asia and Polynesia, Egypt, Somoa and Malaya	Etkin, 1986; Beckstrom-Sternberg et al., 1994
	Expectorant		Beckstrom-Sternberg et al., 1994
	Fever	Malaya	Beckstrom-Sternberg et al., 1994; Ahmad, 1996
	Headache	Malaya	Beckstrom-Sternberg et al., 1994; Ahmad, 1996
	Ipecac	India	Beckstrom-Sternberg et al., 1994
	Laxative		Beckstrom-Sternberg et al., 1994
	Lumbago	Malaya	Beckstrom-Sternberg et al., 1994; Ahmad, 1996
	Orchitis	Malaya	Beckstrom-Sternberg et al., 1994
	Sores	Malaya	Beckstrom-Sternberg et al., 1994
	Swelling	Malaya	Beckstrom-Sternberg et al., 1994; Ahmad, 1996
	Tonic		Beckstrom-Sternberg et al., 1994
	Tumour (stomach)	Zaire, Indochina	Beckstrom-Sternberg et al., 1994
	Whitlow	India	Beckstrom-Sternberg et al., 1994
	Wound	Philippines	Beckstrom-Sternberg et al., 1994
	Yaws (preventative)	Java	Beckstrom-Sternberg et al., 1994
C. bracteatum	Whitlow	India	Beckstrom-Sternberg et al., 1994
C. bulbispermum	Abscesses and sores	South Africa	Watt and Breyer-Brandwijk, 1962
	Aching joints	South Africa (Zulu & Tswana)	Roberts, 1990
	Backache	South Africa	Watt and Breyer-Brandwijk, 1962
	Binding for dressings	South Africa	Watt and Breyer-Brandwijk, 1962
	Charm	South Africa (Zulu, Xhosa, Sotho); Lesotho	Jacot Guillarmod, 1971; Hutchings, 1989; Beckstrom-Sternberg et al., 1994
	Colds	South Africa Lesotho, Southern Sotho	Githens, 1949; Roberts, 1990; Beckstrom-Sternberg et al., 1994
	Coughs	Southern Sotho	Roberts, 1990
	Earache	South Africa	Watt and Breyer-Brandwijk, 1962
	Gynaecological remedy	South Africa (Zulu, Xhosa, Sotho)	Hutchings, 1989
	Haemorrhoids	Southern Sotho	Watt and Breyer-Brandwijk, 1962; Roberts, 1990
	Kidney and bladder infections (increase urine flow)	South Africa (Tswana)	Watt and Breyer-Brandwijk, 1962
	Lactogogue	Lesotho	Beckstrom-Sternberg et al., 1994
	Malaria	South Africa	Watt and Breyer-Brandwijk, 1962
	Reduce swelling of swollen joints and sprains	South Africa	Watt and Breyer-Brandwijk, 1962
	Scrofula	South Africa, Southern Sotho	Githens, 1949; Roberts, 1990
	Varicosities	South Africa (Zulu)	Watt and Breyer-Brandwijk, 1962
	Wounds	Southern Sotho	Roberts, 1990
C. cochinchinense	Diaphoretic	Madagascar	Githens, 1949
	Emetic	Madagascar	Githens, 1949
C. defixim	Burns		Beckstrom-Sternberg et al., 1994
	Carbuncle		Beckstrom-Sternberg et al., 1994
	Poison		Beckstrom-Sternberg et al., 1994
	Whitlow		Beckstrom-Sternberg et al., 1994
C. deflexum	Whitlow	India	Beckstrom-Sternberg et al., 1994
C. delagoense	Urinary tract infections	South Africa (Zulu and Xhosa)	Hutchings et al., 1996

Table 1 (*Continued*)

Crinum spp.	Use	Country	Reference
	Swellings of the body	South Africa (Zulu and Xhosa)	Hutchings and Johnson, 1986
	Veterinary treatment of retained placenta, milk loss, low milk production, healthy calves, weight loss in cattle	South Africa (Zulu)	Hutchings, 1989; Cunningham & Zondi, 1991
C. erubescens	Asthma	Haiti	Beckstrom-Sternberg et al., 1994
	Bronchitis	Haiti	Beckstrom-Sternberg et al., 1994
	Cardiotonic	Haiti	Beckstrom-Sternberg et al., 1994
	Emetic	Dominican Republic	Beckstrom-Sternberg et al., 1994
	Expectorant	Haiti	Beckstrom-Sternberg et al., 1994
	Malaria	Haiti	Beckstrom-Sternberg et al., 1994
	Resolvent	Haiti	Beckstrom-Sternberg et al., 1994
C. firmifolium	Parasitic skin diseases	Madagascar	Razafimbelo et al., 1996
C. flaccidum	Starch for gruel	Australia	Usher, 1974
C. foetidum		Botswana (Kalahari or !kô Bushmen)	Heintz and Maguire, 1992
C. giganteum	Ceremonies and festivals	Mexico (Sierra Norte)	Leszczynska-Borys, 1995
	Leprosy	Congo	Githens, 1949; Watt and Breyer-Brandwijk, 1962
C. jagus	Anticonvulsant	Nigeria	Adesanya et al., 1992
	Open sores	Nigeria	Adesanya et al., 1992
	Veterinary	Cameroon	Bizimana, 1994
C. kirkii	Indigestion	East Africa	Githens, 1949
	Purgative	Tanganyika/Tanzania	Watt and Breyer-Brandwijk, 1962
	Rat poison	Tanganyika/Tanzania	Watt and Breyer-Brandwijk, 1962
	Sores (wash)	Kenya (Bondei)	Watt and Breyer-Brandwijk, 1962; Bastida et al., 1995
	Making shamba boundaries	Kenya	Bastida et al., 1995
C. latifolium	Earache		Usher, 1974; Beckstrom-Sternberg et al., 1994
	Fistula	India (Santal)	Beckstrom-Sternberg et al., 1994
	Rheumatism	India	Usher, 1974; Beckstrom-Sternberg et al., 1994
	Rubefacient	India	Beckstrom-Sternberg et al., 1994
	Tubercle	India (Santal)	Beckstrom-Sternberg et al., 1994
	Tumour	Indochina	Beckstrom-Sternberg et al., 1994
	Whitlow	India	Beckstrom-Sternberg et al., 1994
C. longiflorum	Poison	USA	Beckstrom-Sternberg et al., 1994
C. macowanii	Acne	South Africa	Pujol, 1990
	Veterinary treatment of retained placenta, milk loss, low milk production, healthy calves, weight loss in cattle	South Africa (Zulu)	Cunningham and Zondi, 1991; Bizimana, 1994
	Backache	Zimbabwe	Gelfand et al., 1985; Duri et al., 1994
	Bandages and poultices	Southern Africa	Hutchings et al., 1996
	Blood cleansing and increased supply	Zimbabwe, South Africa	Gelfand et al., 1985; Pujol, 1990
	Boils	South Africa	Pujol, 1990
	Emetic	Zimbabwe	Gelfand et al., 1985; Duri et al., 1994
	Fever	South Africa	Pujol, 1990
	Glandular swelling	South Africa	Pujol, 1990
	Kidney and bladder diseases	South Africa	Pujol, 1990
	Lactation (humans and animals)	Zimbabwe	Gelfand et al., 1985; Duri et al., 1994; Mavi, 1994
	Pus diseases	South Africa	Pujol, 1990
	Skin complaints, e.g. rashes	South Africa (Zulu, Xhosa, Sotho)	Pujol, 1990; Hutchings et al., 1996
	Sores	South Africa	Pujol, 1990
	Swelling and urinary tract problems	South Africa (Zulu)	Hutchings et al., 1996
	Venereal disease	Zimbabwe	Gelfand et al., 1985
C. macrantherum	Emetic	New Guinea	Beckstrom-Sternberg et al., 1994
	Wounds	New Guinea	Beckstrom-Sternberg et al., 1994
C. moorei	Veterinary treatment of retained placenta, milk loss, low milk production, healthy calves, weight loss in cattle	South Africa (Zulu)	Hutchings, 1989; Cunningham and Zondi, 1991

Table 1 (*Continued*)

Crinum spp.	Use	Country	Reference
C. paludosum	Cattle feed	South Africa and Namibia	Verdoorn, 1973
C. pratense	Intestinal diseases (diarrhoea and dysentry)	India	Prance et al., 1994
C. scabrum	Leprosy	Congo	Githens, 1949
Crinum species	Antidote to magical poisons	New Guinea Highlands	Etkin, 1986
	Antiperiodic		Githens, 1949
	Astringent		Githens, 1949
	Cancer	South Africa (Zulu)	Albrecht et al., 1996
	Colds		Githens, 1949
	Dyspepsia	New Guinea	Beckstrom-Sternberg et al., 1994
	Emetic		Le Maout and Decaisne, 1873
	Febrifuge		Githens, 1949
	Leprosy		Githens, 1949
	Micturition	South Africa (Zulu)	Watt and Breyer-Brandwijk, 1962; Bryant, 1966
	Pregnancy (before)	South Africa (Zulu)	Cunningham and Zondi, 1991
	Rheumatic fever	South Africa	Watt and Breyer-Brandwijk, 1962; Bryant, 1966
	Scrofula	South Africa (Zulu)	Githens, 1949; Watt and Breyer-Brandwijk, 1962; Bryant, 1966
	Sores	New Guinea Highlands	Etkin, 1986
	Stomachache	New Guinea	Beckstrom-Sternberg et al., 1994
	Tanning leather	Southern Africa (Bushmen of the Kalahari)	Van der Post and Taylor, 1984
	Tonic		Githens, 1949
	Tumours	Asia and America	Le Maout and Decaisne, 1873
	Vomitting (induction)	New Guinea Highlands	Etkin, 1986
C. yuccaeflorum	Rubefacient (topically irritating)	West Africa	Githens, 1949
C. zeylanicum	Cataplasm	Dominican Republic	Beckstrom-Sternberg et al., 1994
	Malaria	Dominican Republic	Beckstrom-Sternberg et al., 1994
	Pectoral	Dominican Republic	Beckstrom-Sternberg et al., 1994
	Poison	Moluccas	Le Maout and Decaisne, 1873

One of the earliest recorded uses of *Crinum* is as a violent emetic. The preparation was made from the mucilage of the bulb and was combined with a bitter gum resin (Le Maout and Decaisne, 1873). In Asia and America the bulbs were used to 'hasten the ripening of indolent tumours' while *C. zeylanicum* was used in the Moluccas as a violent poison (Le Maout and Decaisne, 1873).

C. asiaticum is known throughout southeast Asia and Polynesia as an emetic and diaphoretic (Etkin, 1986). Both the leaves and bulbs are used (Usher, 1974).

According to Roberts (1990), *C. bulbispermum* is a favourite medicinal herb. The southern Sotho use the leaves and sliced or crushed bulbs to make a strong brew for treating colds, coughs, and as an external application or wash for wounds, scrofula and haemorrhoids. A drawing poultice for abscesses and suppurating sores is also made from the bulbs. These may be roasted by the Zulu and Tswana and applied to aching joints. Rheumatism and backache are treated in a similar way. The Zulus bind the roasted bulb to varicosities using the leaves which, because of their strap-like shape, are also used to bind dressings in place. The flowers are bound over swollen joints and sprains to soothe and help reduce swelling. Several tribes are reported to use the juice squeezed from the base of the leaves to cure earache (Watt and Breyer-Brandwijk, 1962; Roberts, 1990). Sometimes pieces of roasted bulb are placed behind the ear or over the ear to ease the pain. Roberts (1990) reports that some tribes make a brew of the leaves which they believe to be an effective treatment for malaria. This same brew is drunk by the Zulu as a treatment for rheumatic fever (usually half a cup chopped leaves in one cup boiling water, strained after standing for 5 min). The Tswana drink a brew of crushed leaf bases and stalks to increase the flow of urine in bladder and kidney infections. The sliced bulb is also warmed and applied over the kidneys to ease discomfort (Roberts, 1990). Hutchings, (1989) records its use as a Zulu, Xhosa and Sotho gynaecological remedy and charm. An infusion of unspecified plant parts is taken during pregnancy to ensure an easy delivery (Hutchings et al., 1996). In Lesotho, *C. bulbispermum* is used as a medicine to increase milk flow. It is also planted outside huts to act as a charm against evil (Jacot Guillarmod, 1971). In India, the roasted bulb is used as a rubefacient in the treatment of rheumatism. Crushed and toasted bulbs are used for

haemorrhoids and applied to sores and abscesses to cause suppuration (Watt and Breyer-Brandwijk, 1962).

Crinum delagoense bulbs are used in Zulu and Xhosa traditional medicine, to prepare a decoction for treating swellings and urinary tract problems (Hutchings et al., 1996).

In Australia, the aborigines obtain starch from the bulbs of *C. flaccidum* to eat as a kind of gruel (Usher, 1974).

C. giganteum Andr. is a Congo leprosy remedy. In Mexico it is known by the common name Lirio and is used as a ceremonial species during festivities of the Sierra Norte (Leszczynska-Borys, 1995).

C. jagus is used as a veterinary medicinal plant in Cameroon (Bizimana, 1994). In Nigeria, however, it is used to treat open sores and in anticonvulsant preparations (Adesanya et al., 1992).

In Tanganyika the fruit and inner bulb scales of *C. kirkii* and other *Crinum* species are used as a purgative and the outer bulb scales as a rat poison. The Bondei use the water in which these bulb scales have been soaked as a wash for children with sores (Watt and Breyer-Brandwijk, 1962).

Crinum macowanii plants are used by traditional medical practitioners in Zimbabwe to treat backache. The bulb is boiled and a compress is applied to the painful area. Bulbs are also used in the preparation of emetics and infusions to increase lactation in animals and humans (Mavi, 1994). The powdered bulb is made into a porridge to treat venereal diseases. When inhaled, the smoke is believed to increase the blood supply (Gelfand et al., 1985; Duri et al., 1994). Preparations of *C. macowanii* also appear to be used by the Zulu, Xhosa and Sotho for swellings, urinary tract problems (Hutchings et al., 1996) and skin complaints. The Xhosa use the fluid from the bulb to soothe itchy skin rashes (Hutchings and Johnson, 1986). Pujol (1990) cites a number of principal uses for *C. macowanii*, namely: pus diseases, blood cleansing, kidney and bladder diseases, glandular swelling, fever, infected sores, boils and acne. The plant fibres are used in southern Africa as poultices and bandages (Hutchings et al., 1996).

The Zulu use *C. moorei* bulbs in a decoction which is taken for swellings and urinary tract problems (Hutchings et al., 1996).

C. pratense is used in Indian medicine for intestinal diseases such as diarrhoea and dysentery (Prance et al., 1994).

Six species of the Natal Lily or *Crinum* are used for colds, leprosy and scrofula (Githens, 1949; Watt and Breyer-Brandwijk, 1962; Bryant, 1966). Bryant, in a book entitled 'Zulu medicine and medicine men' (1966), describes the treatment for scrofula which included a mixture of *umDuze* (*Crinum* spp.; Bryant, 1905) and other roots. These were chopped, pounded and boiled in a small quantity of water to form a decoction of blood-purifying drugs, called an *imBhiza*. A dessertspoonful was taken every morning and evening. Githens (1949) also includes several *Crinum* species in a list of plants containing alkaloids used as tonics, febrifuges, antiperiodics and astringents. The Zulu people use *Crinum* bulbs in medicines for the treatment of rheumatic fever and difficulty in micturition (Watt and Breyer-Brandwijk, 1962). To allay the pains of rheumatic fever, a decoction of *Gunnera perpensa* roots and Natal Lily bulbs is taken (Bryant, 1966). Difficulty in urination is treated with a mixture of *G. perpense* and *Crinum* roots. These are either chopped or pounded and boiled in water to make a decoction (Bryant, 1966). Before pregnancy, Zulu women prepare an *isihlambezo* of *Crinum* bulbs, *G. perpensa* and *Rhoicissus tridentata* (*isihlambezo*). Cunningham and Zondi (1991) report that a similar preparation is used to treat the retained placenta in cows. According to Zulu folklore, *Crinum* species are used in combination with *Eucomis*, *Boweia*, *Xanthozylum* and *Becium* as a form of chemotherapy for cancer (Albrecht et al., 1996). The juice of *Crinum* bulbs is known to be used by the Bushmen of the Kalahari who rub the juice into animal skins to make them soft and flexible (Van der Post and Taylor, 1984). *Crinum* spp. are used medicinally by the indigenous people of the New Guinea Highlands. The plants are consumed as a medicinal meal and with *Lobelia alata* to induce vomiting. They may be applied to sores and the juice used as an antidote to 'nami' and other scorceries effected through ingestion of magical poisons (Etkin, 1986).

The use of Crinums extends to animal treatment. *Crinum* species, including *C. delagoense*, *C. macowanii* and *C. moorei* are used by the Zulus to treat weight loss, low milk production, milk loss, healthy calves and in the treatment of retained placenta among cattle (Hutchings, 1989; Cunningham and Zondi, 1991).

It is estimated that 64% of the total world population depends on traditional medicine for their primary health care (Cotton, 1996). In Africa, where there is a severe shortage of qualified personnel in modern medicine (Mammem and Cloete, 1996) and imported pharmaceuticals are expensive (Scott, 1993), this figure is even higher. Here, 80% of the people rely on plant remedies prescribed by traditional healers (Hamilton, 1993). Most black South Africans (75%) regularly consult traditional medical practitioners (Streak, 1995). The Zulus believe that the plant-based medicines have power (amandla) and so traditional medical practices must also be seen in an historical and cultural perspective (Cunningham, 1984).

3. Pharmaceutical use

Although once regarded as of little relevance to contemporary drug discovery, traditional remedies are now proving to be an important source of potentially

therapeutic drugs (Cox and Balick, 1994). In fact, three quarters of the 120 plant-based drugs in common use were discovered by following leads provided by traditional medicine in various parts of the world (Scott, 1993). Today the ethnobotanical approach to drug discovery is perhaps the most productive strategy in screening some 265,000 flowering plant species as indigenous usage provides powerful clues to a plant's biological activity (Cox and Balick, 1994). A single South African pharmaceutical company, for example, screened 600 traditional medicines and found that 80% were pharmacologically active (Streak, 1995).

The ethnobotanical use of *Crinum*, as with many other medicinal plants, can be explained on the basis of chemical and physiological studies. In most cases these confirm the therapeutic value of the plants. However, where plants have not been studied chemically, a plant's potential pharmaceutical value can be assumed if it is used widely, i.e. in different geographical regions for the same purpose. When different species are used for the same healing properties, it may be that they contain a common ingredient (Githens, 1949).

3.1. Amaryllidaceae alkaloids in Crinum species and their pharmacological effects

The reason why Crinums are used for medicinal purposes and in a number of countries for similar reasons, is possibly due to their alkaloidal constituents, which in some instances are common to a variety of species. The alkaloids are classically grouped as the Amaryllidaceae alkaloids because of their limited taxonomic distribution. Waller and Nowacki (1978) report that only the Amaryllidaceae have alkaloids of the norbelladine type and that derivatives of norbelladine—an intermediate en route to the majority of Amaryllidaceae alkaloids—can be used as taxonomic characters for the determination of plant relationships among the Amaryllidaceae (Waller and Nowacki, 1978).

Over 100 alkaloids of the Amaryllidaceae type have been found—almost all in the last 20 years (Cordell, 1981; Robinson, 1981). New Amaryllidaceae alkaloids, as well as others that have been isolated for the first time from different species, have been the subject of an annual review by Grundon and then Lewis from 1984 to 2000. These have also been comprehensively reviewed by Hoshino (1998). Special mention has been made of the alkaloids of South African amaryllids in a review by Viladomat and coworkers (1997). Interest in alkaloids of pharmaceutical importance, such as galanthamine, has stimulated attempts to produce the compounds in vitro (Sellés et al., 1997a,b, 1999) although yields are still on the low side (Lewis, 1999). Novel Amaryllidaceae alkaloids have also been isolated from the culture fluid of callus cultures (Lewis, 1993).

Crinum species contain the phenanthridine alkaloids like *Galanthus* and *Narcissus* (Spoerke and Smolinske, 1990). Amine, carboline, isoquinoline, lactone and other uncharacterised alkaloids are also reported to occur in *Crinum* species (Glasby, 1991). A list of the trivial names of *Crinum* alkaloids, their distribution and biological activities are reviewed by Ghosal et al. (1985). A variety of new alkaloids have since been reported, while others have been isolated for the first time from other species (Bentley, 1986; Beutner and Frahm, 1986; Elgorashi and Van Staden, 2001; Elgorashi et al., 1999, 2001a,b; Grundon, 1984, 1985, 1987, 1989; Lewis, 1990, 1992, 1993, 1994, 1996, 1997, 1998, 1999, 2000; Likhitwitayawuid et al., 1993; Razafimbelo et al., 1996; Machocho et al., 1998; Nair et al., 1998, 2000; Pham et al., 1998; Ramadan et al., 2000; Velten et al., 1998; Viladomat et al., 1997).

Bulbs contain the highest concentrations of alkaloids. The epidermis of the outer scale leaves appears to be particularly rich while the mucilage-filled raphide cells, which occur in all parts of the plant, are also said to contain much alkaloid (Frohne and Pfänder, 1984).

It has been suggested that the *Crinum* alkaloids play a role in the protective and repair mechanisms of the plant. According to Ghosal et al. (1990), the alkaloids appear to assist in the biosynthesis of some other compounds that are required for repair and cell to cell communication. They are, therefore, also thought to serve as intra- and interspecific signals. Ghosal et al. (1990) found that the uncontrolled surge of alkaloids, following stress, impaired the biosynthesis of carotenoids and ascorbic acid. Injury also enhanced the synthesis of cAMP and caused lycorine to be transformed to oxidized metabolites. Carotenoids were transformed to xanthophylls (Ghosal et al., 1990).

The Amaryllidaceae alkaloids exhibit a range of biological activity, both pharmacological and microbiological (Pham et al., 1998). Among the most noted effects are: analgesic, central nervous system, antitumour, antiviral (Lewis, 1990) and anticholinergic (Pham et al., 1998). This has stimulated further pharmacological screening of the alkaloids (Lewis, 1994) which more recently showed activity against HIV (Pham et al., 1998).

3.1.1. Analgesic activity and nervous system effects

Alkaloids of this family act on the central nervous system (Wildman, 1960). Their resemblance to the morphine and codeine skeletons (Ghosal et al., 1985) may account for their analgesic activity, e.g. caranine ($C_{16}H_{17}NO_3$), crinine ($C_{16}H_{17}NO_3$), galanthamine ($C_{17}H_{21}NO_3$) (Wildman, 1960). Their mode of action and duration of effect are, in fact, comparable to that of morphine e.g. galanthine ($C_{18}H_{23}NO_4$) (Cordell, 1981). Narwedine ($C_{17}H_{19}NO_3$) has been found to potentiate the pharmacological effects of caffeine, carbazole, arecoline and nicotine, and narwedine and vittatine ($C_{16}H_{17}NO_3$) the analgesic effect of morphine. Haemanthidine ($C_{17}H_{19}NO_5$) and lycorine ($C_{16}H_{17}NO_4$)

are analgesics with activity greater than that of aspirin (Lewis, 1998). The alkaloids of the phenenthridine, lycorenine and pretazettine groups have the advantage over other alkaloids in that they are less toxic (Ghosal et al., 1985). Lycorine acts as a cerebral convulsant (Githens, 1949).

Galanthamine ($C_{17}H_{21}NO_3$), one of the more common alkaloids in the Amaryllidaceae family, has been prominent in the popular and scientific press (Lewis, 1996). The alkaloid shows reversible anticholinesterase (Ghosal et al., 1985; Martin, 1987) and muscarinic activity (Lewis, 1996) and is showing promise as a treatment for nervous diseases (Harborne and Baxter, 1993; Greenblatt et al., 1999), paralysis syndrome (Lewis, 1999; Greenblatt et al., 1999), schizophrenia and other forms of dementia (Sramek et al., 2000) as well as Alzheimer's disease (Greenblatt et al., 1999).

Galanthamine acts in a similar manner to other Alzheimer's drugs by replenishing acetylcholine levels in brain areas lacking cholinergic neurones (Eichhorn et al., 1998). This it does by binding to the active site of the brain enzyme acetylcholinesterase (Greenblatt et al., 1999). In addition, it stimulates pre- and postsynaptic nicotinic receptors which can, in turn, increase the release of neurotransmitters like acetylcholine and glutamate (Sramek et al., 2000), thus directly stimulating neuronal function. The stimulation of nicotinic receptors is also suggested to protect against β-amyloid toxicity (Sramek et al., 2000). In theory, the release of additional acetylcholine is of benefit to the patient, although its usefulness has yet to be clinically proven (Sramek et al., 2000). Its dual mode of action (Greenblatt et al., 1999), coupled with the evidence that galanthamine has reduced side effects, make it a promising candidate for the treatment of Alzheimer's disease (Greenblatt et al., 1999) and for designing improved potency drugs. However, given that galanthamine, at present, does not offer advantages in efficacy, safety or convenience over related products, it is its stimulation of nicotinic receptors and potential benefits thereof, that offer exciting prospects for further clinical research (Sramek et al., 2000).

In early clinical trials galanthamine stabilized patients' symptoms for up to one year (Bonner, 1995). More recently it has been shown to improve cognitive function and have a beneficial effect on behavioural symptoms, provided that the treatment is administered early (Sramek et al., 2000). Improvement in daily living is also associated with its usage (Sramek et al., 2000). As a consequence, the United States, EU and Switzerland have approved the use of galanthamine (Reminyl®) for the symptomatic treatment of mild-to-moderate Alzheimer's disease (Sramek et al., 2000) although this has, as yet, not been granted in Canada, Australia and South Africa (Sramek et al., 2000).

Another noteworthy pharmacological action of galanthamine is its ability to amplify the nerve-muscle transfer (Ghosal et al., 1985). This is achieved by reversing non depolarizing neuromuscular block and restoring synaptic transmission (Martin, 1987). In Eastern Europe it has long been used as a reversal agent in anaesthetic practice (Eichhorn et al., 1998). It is also known to inhibit traumatic shock (Martin, 1987) and has been patented for use in the treatment of nicotine dependence (Lewis, 1996). Furthermore, galanthamine acts as a mild analeptic; is as powerful an analgesic as morphine; reduces intraoccular pressure when applied as eye drops and is used to treat several neurological disorders (Eichhorn et al., 1998).

Another alkaloid, galanthine, exhibits powerful cholinergic activity and has therefore attracted much interest in Russia where it is used in the treatment of myasthenia gravis, myopathy and diseases of the central nervous system. Other derivatives of galanthine are being evaluated as central nervous system depressants (Cordell, 1981).

3.1.2. Anticancer activity

Since the time of Hippocrates, crude preparations of several members of the Amaryllidaceae have been used in the treatment of tumours (Wildman, 1960). Of all the Amaryllidaceae alkaloids the only skeletal variety to show anticancer activity is the lycorine type (Wagner et al., 1988). And it is found in a number of *Crinum* species (Ghosal et al., 1985). Lycorine is reported to inhibit the in vivo growth of a murine ascite tumour and reduce the viability of in vitro grown tumour cells (Ghosal et al., 1985). It also reduces cellular activity in femoral bone marrow tissue which results in granulocytic leucopenia and a decrease in the number of erythrocytes (Wildman, 1960). Others have shown that lycorine inhibits the synthesis of DNA and proteins in murine cells (Ghosal et al., 1985). The cytotoxic effects of calprotectin, which induces growth inhibition and apopotic cell death against a variety of tumour cell lines, can be suppressed using lycorine (Yui et al., 1998). Ascorbic acid biosynthesis is also inhibited (Wildman, 1960; Lewis, 1990).

Palmilycorine ($C_{32}H_{47}NO_5$)—a derivative of lycorine—has been isolated from *C. asiaticum* and shown to have an inhibitory effect on the viability of ascites tumour cells (Ghosal et al., 1985 cited by Wagner et al., 1988). Several alkaloids were isolated from the bulbs of *Crinum delagoense* following substantiated reports that an oral intake of an hot water extract of five species, including *C. delagoense*, cured a human cancer (Nair et al., 1998). Only lycorine, the principal constituent of the extract, and 6-hydroxycrinamine ($C_{17}H_{19}NO_5$) were active against BL6 mouse melanoma cells (Nair et al., 1998).

Crinasiatine ($C_{17}H_{19}NO_5$) also has tumour-inhibiting properties (Ghosal et al., 1985 cited by Wagner et al., 1988) while ungeremine ($C_{16}H_{12}NO_3$) is used as an antitumour agent (Grundon, 1984).

Alkaloids with antileukaemic properties include pretazettine ($C_{18}H_{21}NO_5$) and narciclasine ($C_{14}H_{13}NO_7$). Pretazettine shows significant antitumour activity. Together with narciclasine it inhibited HeLa cell growth (Harborne and Baxter, 1993) and is reported to exhibit therapeutic activity in Rauscher leukaemia. Other studies have shown that it is therapeutically effective against advanced Rauscher leukaemia, Ehrlich ascites carcinoma, spontaneous AKR lymphocytic leukaemia and Lewis lung carcinoma (Martin, 1987). And it is one of the most active of the Amaryllidaceae alkaloids against Molt4 lymphoid cells (Weniger et al., 1995). Narciclasine, like other Amaryllidaceae alkaloids (Manske, 1975), is an antimitotic substance that affects cell division at the metaphase stage by terminating protein synthesis (Fuganti, 1975). DNA synthesis is also retarded (Spoerke and Smolinske, 1990). It is related to pancratistatin (Pettit et al., 1995) and shows some promise as an anticancer agent (Harborne and Baxter, 1993).

Other Amaryllidaceae alkaloids are cytotoxic, e.g. the alkaloid augustine ($C_{17}H_{19}NO_4$) from *C. amabile* (Likhitwitayawuid et al., 1993; Viladomat et al., 1995) and crinamine ($C_{17}H_{19}NO_4$) and lycorine (Viladomat et al., 1995). When tested on human and murine tumour cell lines, haemanthidine, hippeastrine ($C_{17}H_{17}NO_5$) and tazettine ($C_{18}H_{21}NO_5$) exhibited cytotoxicity (Antoun et al., 1993). A lycorine type alkaloid, pratorine ($C_{16}H_9NO_3$), and a crinine type alkaloid, 6 α-hydroxybuphanisine ($C_{17}H_{19}NO_4$), from two *Crinum* species, also showed moderate cytotoxic activity when tested on human leukaemic Molt-4-cells (Abd-el-hafiz et al., 1991). Of all the Amaryllidaceae alkaloids, lycorenine ($C_{18}H_{23}NO_4$) is the most cytotoxic against HepG2 hepatoma. Many of the other alkaloids are active against LMTK cells (Weniger et al., 1995). Cytotoxic activity, against murine P388 D1 cells, was also reported for leaf extracts of *C. asiaticum* (Ahmad, 1996).

3.1.3. Immunostimulatory activity

Lycorine-1-*O*-glucoside ($C_{22}H_{27}NO_9H_2O$) has been found to mitogenically activate splenic lymphocytes in mice. Furthermore, it was shown to have a low level of toxicity in albino rats. According to Ghosal et al., 1985, lycorine-1-*O*-glucoside therefore is a potential immunostimulatory agent. 1,2-β-epoxyambelline ($C_{18}H_{21}NO_6$) and ambelline ($C_{18}H_{21}NO_5$) mixed with 1,2-β-epoxyambelline are also reported to activate mouse splenic lymphocytes. The activity for the mixture was comparable with that of a known mitogen, concanavalin A (Ghosal et al., 1985).

3.1.4. Antifertility activity

Lycorine has a marked effect on growth when applied to the testes and ovaries of immature rats. Workers report that cell division only occurred in the secondary spermatocytes and that the cells were multinucleated and large. No cell division was observed in the spermatogonia or primary spermatocytes. No spermatid cells were present in treated animals. Lycorine has a similar effect on the sperm cells of the grasshopper *Acrida lata*. In the ovaries of rats, follicles were found to be smaller and fewer in number (Wildman, 1960). An investigation of the effect of hippadine ($C_{16}H_9NO_3$) on testicular function in rats has shown it to produce reversible inhibition of fertility by acting on the germ cells at an early stage of spermatogenesis (Chattopadhyay et al., 1983).

3.1.5. Anti-infective activity

3.1.5.1. Antibacterial and antifungal activity. Extracts from *C. jagus* bulbs exhibit antibacterial activity. The alkaloid crinamine was isolated from the bulbs and showed strong activity against *Bacillus subtilis* and *Staphylococcus aureus* (Adesanya et al., 1992). In vitro activity against *Candida albicans* was demonstrated for extracts of *C. macowanii* (Gundidza, 1986). Chaumont et al. (1978) tested extracts of *C. moorei* against several fungi pathogenic to man. The alkaloids lycorine, pseudolycorine ($C_{16}H_{19}NO_4$), narciclasine and pretazettine are known to inhibit protein synthesis in eukaryotic cells. In some cases this appears to be achieved by blocking peptide bond formation (Cordell, 1981; Ghosal et al., 1985).

3.1.5.2. Antimalarial activity. Alkaloids isolated from *C. amabile* (Likhitwitayawuid et al., 1993; Viladomat et al., 1995), as well as an unidentified extract from *C. bulbispermum* (Watt and Breyer-Brandwijk, 1962), were found to be active against malaria. Crinamine also exhibits antimalarial activity (Viladomat et al., 1995).

3.1.5.3. Antiviral activity. A study of the effect of Amaryllidaceae alkaloids on the herpes simplex virus demonstrated that alkaloids with a hexahydroindole structure with two hydroxy groups showed most promise. The antiviral activity was due to the inhibition of multiplication (Lewis, 1990).

Lycorine, the principal alkaloid of the Amaryllidaceae, exerts antiviral effects on several RNA and DNA viruses. This is achieved by delaying virus production and decreasing the amount of virus by blocking viral protein synthesis (Ieven et al., 1983), possibly at the level of termination (Vrijsen et al., 1986). In crude extract form, it was shown to inhibit the cytopathogenic effect of one DNA and several RNA viruses in VERO cells (Ieven et al., 1983). Lycorine has shown

pronounced antiviral activity against poliomyelitis, coxsackie and herpes type 1 viruses (Harborne and Baxter, 1993). It has stopped the synthesis of poliovirus, precursors of poliovirus and poliopeptidase (Ghosal et al., 1985). Narciclasine inhibits protein synthesis at the step of peptide bond formation. Pretazettine strongly inhibits the activity of RNA-dependent DNA polymerase (reverse transcriptase), from various oncogenic viruses, by binding to the enzyme (Ghosal et al., 1985). It is used in combination with DNA-binding and alkylating agents in treating Rauscher leukaemia virus. Lewis (1990) suggests that the suppression of cell division, cell elongation and DNA replication may be the causative process for the antiviral activity, although for lycorine, this was shown to be the inhibition of eukaryotic termination (Vrijsen et al., 1986). Pretazettine inhibits both the growth of the Rauscher virus and cellular protein synthesis but does not inhibit cellular DNA and RNA synthesis (Martin, 1987).

An extract from the bulbs of *C. macowanii* was reported to reduce viral cytopathic effects in VERO cells infected with yellow fever virus by 100%. The same extract also caused 70% inhibition of viral cytopathic effects in cells infected with Japanese encephalitis virus. Viral replication was inhibited. No cytotoxic effect was observed (Duri et al., 1994).

3.1.6. Cardiovascular activity

In an extensive screening programme of the Amaryllidaceae alkaloids for cardiovascular activity (Wildman, 1960), a number of *Crinum* alkaloids were shown to exhibit hypotensive activity, e.g. ambelline, caranine, crinamine, crinine, lycorine, narwedine and tazettine. Crinamine is a powerful transient hypotensive agent in dogs. Narwedine was found to increase the amplitude and decrease the frequency of cardiac contractions (Martin, 1987; Harborne and Baxter, 1993). The alkaloids would therefore be of value in reducing blood loss during surgery. Galanthamine is known to cause bradycardia or atrioventricular conduction disturbances (Martin, 1987).

3.1.7. Respiratory system effects

Narwedine increases the amplitude and frequency of respiratory movements (Martin, 1987; Harborne and Baxter, 1993), while crinamine shows respiratory depressant activity (Harborne and Baxter, 1993).

3.1.8. Emetic and diaphoretic activity

Crinum species contain strong emetic and diaphoretic alkaloids (Etkin, 1986). From the few case reports of poisonings in the medical literature, ingestion of the raw bulbs is said to cause nausea, persistent vomiting and diarrhoea (Spoerke and Smolinske, 1990). The small number of recorded human poisonings is most likely due to the low levels of alkaloids in the plants. As yet, the precise mechanism of emesis is not known (Spoerke and Smolinske, 1990).

3.2. Other compounds and their biological effects

A number of other products have been isolated from *Crinum* bulbs and seeds. These include: neokestose (an oligosaccharide; Yasuda et al., 1986), phenolics (El-hafiz et al., 1990; Ramadan et al., 2000), flavonoids (Ali et al., 1981, 1988 [flavans]; Abd-el-hafiz, 1990), mucilage (Abd-el-hafiz, 1990), aliphatic hydroxyketones, methyl palmitate, palmitic acid and stearic acid (Abd-el-hafiz, 1991), keto alcohols (Abd-el-hafiz, 1990), esters, steroids and triterpenoids (Glasby, 1991), organic acids, an haemolytic sapogenin (saponin) and vanillin and coumarin (Watt and Breyer-Brandwijk, 1962). Polysaccharides were found in the bulbs of *C. amabile* and may be connected with the medicinal uses of the bulbs (Murav'-eva and Popova, 1989), while other extracts were shown to have antimutagenic properties (Kalaycioglu and Oner, 1994).

Unidentified extracts of *Crinum* species are slightly effective against experimental malaria (Watt and Breyer-Brandwijk, 1962) while those of *C. glaucum* caused relaxation of the gastrointestinal smooth muscle of guinea pigs (Okpo and Adeyemi, 1998).

Interest has been shown in plant lectins from members of the Amaryllidaceae. Balzarini et al. (1991) found that two plant lectins inhibited infection of MT-4 cells by the human immunodeficiency viruses HIV-1 and HIV-2.

4. Future phytochemical research

Only about 15% of the known plant species have been screened for therapeutic potential. And of these, 1% have been examined exhaustively (Scott, 1993). Members of the Amaryllidaceae continue to yield novel compounds "having interesting biological activity" (Martin, 1987). Yet plants still remain the "sleeping giant of drug development" (Scott, 1993) as pharmaceutical companies are slow to take up the challenge. Thus "isolation of additional alkaloids and further testing may well produce fertile fields for pharmacological research" (Wildman, 1960). Both local and global populations would benefit in terms of improved health care and economics (Cotton, 1996).

Of the 21 South African *Crinum* species, only eight (*C. bulbispermum*, *C. buphanoides*, *C. delagoense*, *C. kirkii*, *C. lugardiae*, *C. macowanii*, *C. moorei* and *C. variabile*) have been investigated for alkaloids. The South African species therefore remain an untapped reservoir of potentially important biologically active compounds. Hybrids are known to contain compounds not present in either parents (John, 1961). Thus the

possibility exists that new hybrids may yield novel compounds. The *Crinum* alkaloids would be of considerable interest to chemists studying the Amaryllidaceae alkaloids, since they are unique to the genus. "At the genus level, it appears that specific alkaloids often are associated with the *Crinum*, *Haemanthus*, *Hymenocallis* and *Narcissus* genera, but no such uniformity is noted in the species of the *Nerine* genus" (Wildman, 1960).

Although Crinums are known to contain alkaloids which, in some cases have been pharmacologically tested, "nothing is known of the effect that *Crinum* based preparations may have on livestock" (Cunningham and Zondi, 1991).

5. Conclusions

Crinum species have long been used to treat illnesses and diseases. Their use extends to all parts of the world, where often the same species is used. Alternatively, traditional medical practitioners may advocate the use of different species in treating the same ailment. This suggests that they possess a certain amount of biological activity. In the few instances where Crinums have been chemically investigated, the isolation of active compounds has confirmed the rationale for the plant's usage. Yet little is known of the phytochemistry of southern African species. This lends impetus to their conservation which is threatened by increasing urbanization and the transformation of medicinal plants into a highly valued commodity.

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