Delpinoa **45**: 261-268. 2003

Ethnobotanical and phytochemical investigations of southern African Amaryllidaceae

N. R. CROUCH[1], D. A. MULHOLLAND[2], E. NDLOVU[3], T. L. POHL[2], J. CHETTY[2], N. KOORBANALLY[2]

[1, 2]Ethnobotany Unit, National Botanical Institute, PO Box 52099, 4007 Berea Road, South Africa; [2]Natural Products Research Group, Department of Chemistry, University of Natal, 4041 Durban, South Africa; [3]Kwamalulekoes Nursery and Herbalist, PO Box 11409, 3300 Mooi River, South Africa.
crouch@nbidbn.co.za

Abstract. The monocotyledonous family Amaryllidaceae occurs principally in the warm and temperate regions of the world, but is most diverse in southern Africa where about 280 species in 18 genera occur. Amaryllids are usually bulbous, occasionally rhizomatous herbs, and notable for their near-unique production of characteristic isoquinoline alkaloids. Over one hundred and twenty 'Amaryllidaceae alkaloids' have been isolated and characterised from the southern African species. These constituents impart the plants with a non-trivial toxicity, and bioactivities and other physical features that have recommended their incorporation in ethnomedicine. The therapeutic potential of this class of compounds has attracted significant medical interest in, *inter alia*, the fields of anesthesiology, Alzheimer's disease, uterotonic activity, antimalarials, and cancer (cytotoxicity) research. For the *Flora of Southern Africa (FSA)* region some 13 genera and 44 taxa in the Amaryllidaceae have been recorded as traditionally used for medicinal and charm purposes. Included in this number are several that have been recorded as definite or postulated hallucinogens. The Doctrine of Signatures concept has evidently played a role in the selection and adoption of several of these ethnomedicinal subjects. We report on the findings of phytochemical investigations of a selection of Zulu ethnomedicinal Amaryllidaceae species, the known pharmacology of some constituents, and the application and importance of whole plants or plant parts in historical and contemporary traditional medicine.

Key words: Amaryllidaceae, Ethnobotany, Southern Africa, Phytochemistry, Traditional medicine

Worldwide, 850 species of amaryllids in 15 tribes and about 60 genera occur, with centres of diversity in South America (particularly the Andean region), South Africa and the Mediterranean (MEEROW & SNIJMAN 1998). In South Africa about 280 species in 18 genera occur (SNIJMAN 2000). Many of these taxa are ornamentals that have been brought into horticulture over the last 300 years, the most notable being *Clivia miniata* (Lindl.) Regel and *Amaryllis belladonna* L. Amaryllids are usually bulbous, occasionally rhizomatous herbs, and remarkable for their near-unique production of characteristic isoquinoline alkaloids. Over one hundred and twenty 'Amaryllidaceae alkaloids' have been isolated and characterised from the South African species (VILADOMAT *et al.* 1997). Many constituents, including lycorine, occur widely in representatives of the family, and have been pharmacologically investigated.

Four amaryllid taxa (sets) in contemporary use by the Zulu have been highlighted. We report on current and historical usage patterns, popularity in trade, and phytochemical and pharmacological investigations that reveal a rational basis for their incorporation in ethnomedicine.

Brunsvigia radulosa

As one of the most widespread amaryllids in South Africa it is not surprising that *Brunsvigia radulosa* Herb. (syn. *B. cooperi* Baker in Fl. Cap. 6: 207) (Tribe Amaryllideae, Subtribe Amaryllidinae) has been incorporated into traditional medicine across much of its range. In Swaziland where it is known as *lilula* it is used to

straighten bones in children (DLAMINI 1981) and in Lesotho barren women are treated with *B. radulosa* (Sotho name is *lematla*), alone or in combination with other plants (PHILLIPS 1917). This Sotho application may relate to the Doctrine of Signatures principle as the plant resembles the human female pubic region in a manner similar to that shown for *Haemanthus deformis* Hook.f. (Amaryllidaceae) (see below). The Sotho further employ the plant in difficult confinement cases (JACOT GUILLARMOD 1971) and wash divining bones in a decoction of the plant to impart them with greater accuracy (PHILLIPS 1917). LOUBSER & ZIETSMAN (1994) postulated a close link between *B. radulosa* and altered states of consciousness. They interpreted a rock painting at Thaba Bosiu in western Lesotho as a San depiction of this species, and suggested its historic use in inducing hallucinations and trance states. *Brunsvigia radulosa* is not the only amaryllid featured in South African rock art: the well documented hallucinogen *Boophane disticha* (L.f.) Herb. (LAING 1979; DE SMET 1996) has been figured as a coarse rock engraving in Griqualand West (WILMAN 1968).

Based on the report by WATT & BREYER-BRANDWIJK (1962) that an infusion of the bulb of a *Brunsvigia* sp. was applied as an enema by the Zulu for abdominal troubles, CHARLSON (1980) pharmacologically investigated *B. radulosa* for activity arresting the maturation and proliferation of malignant cells. Both *B. radulosa* and the related *Amaryllis belladona* L. showed antineoplastic activity in a mouse P-388 lymphocytic leukaemia assay. Although CHARLSON (1980) demonstrated that lycorine accounted for some of the observed antileukaemic activity in the P-388 mice (3PS, T/C 135% at 75 mg kg^{-1}), the more potent agent was not isolated. Subsequent bioassay-directed fractionation of *A. belladona* bulb extracts by PETTIT *et al.* (1984) led to the isolation and identification of anhydrolycorinium chloride as the principal antineoplastic component (3PS, 64-69% life extension at dose levels of 10-20 mg kg^{-1} *in vivo*, ED_{50} 1.4 g ml^{-1} *in vitro*). PETTIT *et al.* (1984) posited that this same constituent was responsible for the observed 3PS *in vivo* activity of *B. radulosa* extracts. This was subsequently confirmed (CROUCH *et al.* 2002). Even prior to its isolation as a natural product, anhydrolycorinium chloride (isolycorine hydrochloride) had been synthesised and screened by the USA National Cancer Institute's program, showing 3PS T/C 127-153% activity over the dose range 6.25-25 mg kg^{-1} (PETTIT *et al.* 1984). Quarternisation of isoquinoline alkaloids is known to increase their bioactivity (BRUNETON 1999).

A series of phytochemical investigations of *B. radulosa* (DRY *et al.* 1958; LAING & CLARK 1974, CAMPBELL *et al.* 2000; CROUCH *et al.* 2002) have yielded brunsvigine, lycorine, (Fig. 1, ***1***), crinamine (Fig. 1, ***2***), 1-*O*-acetyllycorine, crinine, hamayne, anhydrolycorinium chloride (Fig. 1, ***3***), sternbergine, 1-*O*-acetylnorpluviine, 1-epideacetylbowdensine and anhydrolycorin-6-one.

The current identification of the antineoplastic anhydrolycorinium chloride from *B. radulosa*, the second ever isolation of this compound from a plant, may relate to its ethnomedicinal application in the treatment of abdominal pain. In the Kamberg region of Kwazulu-Natal, this condition is treated with preparations that include *Brunsvigia radulosa*. Bulb material of this taxon is chopped and first dried before placing in cold water which is then boiled. At this point a little more cold water is added, the decoction again brought to the boil and the process repeated five times. To this preparation a small section of the tuber of *Dioscorea dregeana* (Kunth) T.Durand & Schinz may be added. Bark of *Ocotea bullata* (Burch.) Baill. and *Elaeodendron transvaalense* (Burtt Davy) R.H.Archer, and some roots of *Cymbopogon* sp. are introduced to counter the potency of the *Brunsvigia* and *Dioscorea*. Bulbous material of *Scilla natalensis* Planch. or *Eucomis autumnalis* (Mill.) Chitt. may also be included before ingredients are crushed and decocted. Of this preparation, patients are administered two tablespoons thrice daily. At the higher dosage of five tablespoons thrice daily this same preparation may be used to treat psychotic patients; for this condition the *Brunsvigia* material may be optionally substituted with some outer papery bulb scales of *Boophane disticha* (L.f.) Herb. Mentally disturbed patients typically sleep for a couple of hours following this treatment, after which period an improvement should be noticeable.

Despite its use in the treatment of mental disorders, particularly as a substitute for *Boophane disticha*, the authors are unaware of the current use of *B. radulosa* as an hallucinogen; nor is its historical use in this regard definitely known. However, of the approx. 65 Amaryllidaceae of southern Africa that have been investigated phytochemically (VILADOMAT *et al.* 1997), seven have yielded crinamine, including two of the three regional amaryllids considered psychotropic. The other is *Ammocharis coranica* (Ker-Gawl.) Herb. (KOORBANALLY *et al.* 2000). Further, tubers of the Zulu narcotic *Dioscorea dregeana*, used as a sedative (GERSTNER 1941a), have also recently been shown to contain crinamine (MULHOLLAND *et al.* 2002). On the basis of these reports we postulate that crinamine accounts for the psychoactivity which has historically been attributed to *B. radulosa* (LOUBSER & ZIETSMAN 1994).

Clivia species

The genus *Clivia* Lindl. (Tribe Haemantheae) is endemic to southern Africa and is represented by four species of perennial evergreen plants found in moist coastal and inland forests. These are *C. miniata* (Lindl.) Regel (2 varieties), *C. nobilis* Lindl., *C. caulescens* R.A. Dyer and *C. gardenii* Hook., all of which are rhizomatous rather than bulbous herbs possessing several strap-shaped leaves in a distichous arrangement. The chemistries of the first two taxa have been investigated previously and a range of isoquinoline alkaloids found, including a unique set of the homolycorine type e.g. clivonine (Fig. 1, *4*), (VILADOMAT *et al.* 1997). The latter two species have only recently been characterised. All species of the genus *Clivia* are used by traditional healers in southern Africa in the treatment of a number of ailments of a physiological or spiritual origin, and have been implicated in human poisonings. JURITZ (1914) reported on the death in Willowvale in the southern Transkei of a sickly infant treated with *Clivia nobilis*. Further investigations by this author revealed that large quantities of a strong decoction of the plant produced only mildly emetic effects. VEALE *et al.* (1992) considered ethnomedicines based on *C. miniata* to be potentially fatal if taken in large quantities, and noted vomiting, salivation, diarrhoea and depression of the CNS as the main poisoning features. All four species are capable of causing dermatitis (HUTCHINGS *et al.* 1996).

Reports of trade in *C. nobilis* plants in the medicinal plant markets of Kwazulu-Natal (CUNNINGHAM 1988), Witwatersrand (WILLIAMS *et al.* 2000) and Mpumalanga (MANDER 1997) likely refer rather to *C. gardenii* in the former two markets and *C. caulescens* in the latter. *Clivia nobilis* finds its northernmost distribution immediately to the north of the Kei River (extending south to Alexandria) and so is unlikely to have historically been used by the Zulu. In support of the identification of material as *C. gardenii* is the report by WILLIAMS *et al.* (2000) that the common name for genus members in the Witwatersrand trade is *umayime,* in the Zulu vernacular. Additionally, most species (42%) traded at this site are harvested from Kwazulu-Natal (WILLIAMS *et al.* 2000). These authors determined *Clivia* spp. to be among the most commonly available taxa in medicinal plant shops on the Witwatersrand, with over 70% of traders stocking them.

Clivia plants play an important role as protective charms: GERSTNER (1941b) reported that the Zulu use the roots as a sprinkling charm to ward off evil (*intelezi yokuchela*) and as a love-charm emetic. Species of *Clivia* are included as chopped components in intelezi mixes traded in the Durban markets (CUNNINGHAM 1988). The Zulu name *umayime* for *Clivia* spp. has been variously interpreted as "it should stand still" (WILLIAMS *et al.* 1996), or "the young women may stay at home" (GERSTNER 1941b). In both cases the connotation is of the plant preventing evil, of stopping or of making to stay (PUJOL 1993). An example of a protective charm that includes *C. miniata* as a component is detailed by SMITH & CROUCH (1999).

The large range of isoquinoline alkaloids isolated from *Clivia* spp. are generally thought to be responsible for the observed bioactivity of plant extracts. *Clivia miniata* rhizome preparations have been recorded as a remedy for snakebite (BRYANT 1909), specifically for the bite of the puff-adder (SMITH 1893), or associated pain (PUJOL 1993). BRYANT (1909) further listed *C. miniata* as one of the Zulu emetic remedies for

fevers known as *umkhuhlane*. The Xhosa use root decoctions of *C. miniata* for treating both barrenness and urinary complaints (BROSTER 1982). *Clivia caulescens* has also been recorded as ethnomedicinally used by the Swazi, who know the plant as *hlakahla-wemahlatsi* (DLAMINI 1981). The leaves of *C. miniata* are included as a component of *isihlambezo* and *inembe* mixtures, antenatal tonics administered with the aim of ensuring healthy foetal growth, or inducing or augmenting labour (BRYANT 1909; GERSTNER 1941a; VEALE *et al.* 1992; VARGA & VEALE 1997). The preparations typically take the form of aqueous infusions of the leaves. The uterotonic activity of aqueous extracts of *C. miniata* leaves was evaluated using an isolated rat uterus system (VEALE *et al.* 1989). Extracts were shown to possess uterine smooth-muscle stimulant activity which augmented the effects of subthreshold and threshold concentrations of oxytocin. Additionally, the *Clivia* extract elevated the frequency of spontaneous uterine contractions. The inclusion of *Clivia* preparations in antenatal ethnomedications may thus be based on such stimulant effects (VEALE *et al.* 1989). Use of such tonics can result in foetal distress due to uterine hypertonia (VEALE *et al.* 1992), and also an increase in the frequency of meconium-stained liquor passage and caesarian sections (MABINA *et al.* 1997). Rather surprisingly, the active uterotonic compound has been found not to be an alkaloid but linolenic acid (SEWRAM *et al.* 2001).

From *C. caulescens*, hippeastrine, haemanthamine, 11-(*S*)-hydroxyvittatine, lycorine and sternbergine have recently been isolated, and from *C. gardenii*, haemanthamine, and the salts of haemanthidine and tazettine (Fig. 1, ***5***). The free base of tazettine was obtained on treatment of the ammonium salt with NaOH.

Lycorine is a ubiquitous alkaloid with significant bioactivities. These include the inhibition of cell growth and division in higher plants and algae (EVIDENTE *et al.* 1983), inhibition of cyanide-resistant respiration (ARRIGONI *et al.* 1976; EVIDENTE *et al.* 1983), inhibition of protein biosynthesis *in vivo* and activity against RNA and DNA viruses (IEVEN *et al.* 1982, 1983; GHOSAL *et al.* 1985; HARBORNE & BAXTER 1993). Crinamine shows weak brachycardia activity and respiratory depression in dogs (WATT & BREYER-BRANDWIJK 1962). Crinamine has also shown strong cytotoxic and moderate antimalarial activity (LIKHITWITAYAWUID *et al.* 1993).

Ammocharis coranica

Ammocharis coranica (Ker Gawl.) Herb. (Tribe Amaryllideae, Subtribe Crininae), from an African genus of five species (SNIJMAN & LINDER 1996), is one of the most widespread amaryllids of the summer-rainfall region of southern Africa. It is known to the Zulu as *incotho* (HULME 1954), a vernacular term also applied to *Boophane disticha* (L.f.) Herb. (Amaryllidaceae) (GERSTNER 1938) a well-documented hallucinogen, arrow poison and homicidal agent of the region (NEUWINGER 1994; DE SMET 1996; VILADOMAT *et al.* 1997). A healer from the Nongoma District of Zululand reported that *A. coranica* was used as a substitute for *B. disticha* when the latter was unavailable, for the treatment of mentally ill patients. The treatment of hysteria using *Boophane* has earlier been reported (WATT & BREYER-BRANDWIJK 1962; HUTCHINGS *et al.* 1996). The bulb has further been considered a cure for unspecified afflictions resulting from witchcraft (HULME 1954) and (*sensu Ammocharis falcata* Herb.) a useful medicine for cattle (GERSTNER 1938). Across much of its range the outer bulb scales are partially burned in the production of a plastic pitch-like substance which is moulded into traditional headrings for tribal chiefs (POLE EVANS 1938; GERSTNER 1941a) or used as a putty and adhesive (JACOT GUILLARMOD 1971; GIESS & SNYMAN 1986). Extensible cottony threads are recorded as a characteristic feature of bulb scales of members of the tribe Amaryllideae to which *Ammocharis* belongs (SNIJMAN & LINDER 1996).

Although *A. coranica* apparently harbours psychoactive constituents, these have not been pharmacologically characterised. As with *B. radulosa,* it is speculated that crinamine may account for the reputed calming or hypnotic effects. Although CNS effects are attributable to bulb constituents, aerial leaves of *A. coranica* are reputedly grazed by stock (BATTEN & BOKELMANN 1966; PLOWES & DRUMMOND 1990), suggestive of alkaloid localisation in plants.

Phytochemical investigations of this bulbs

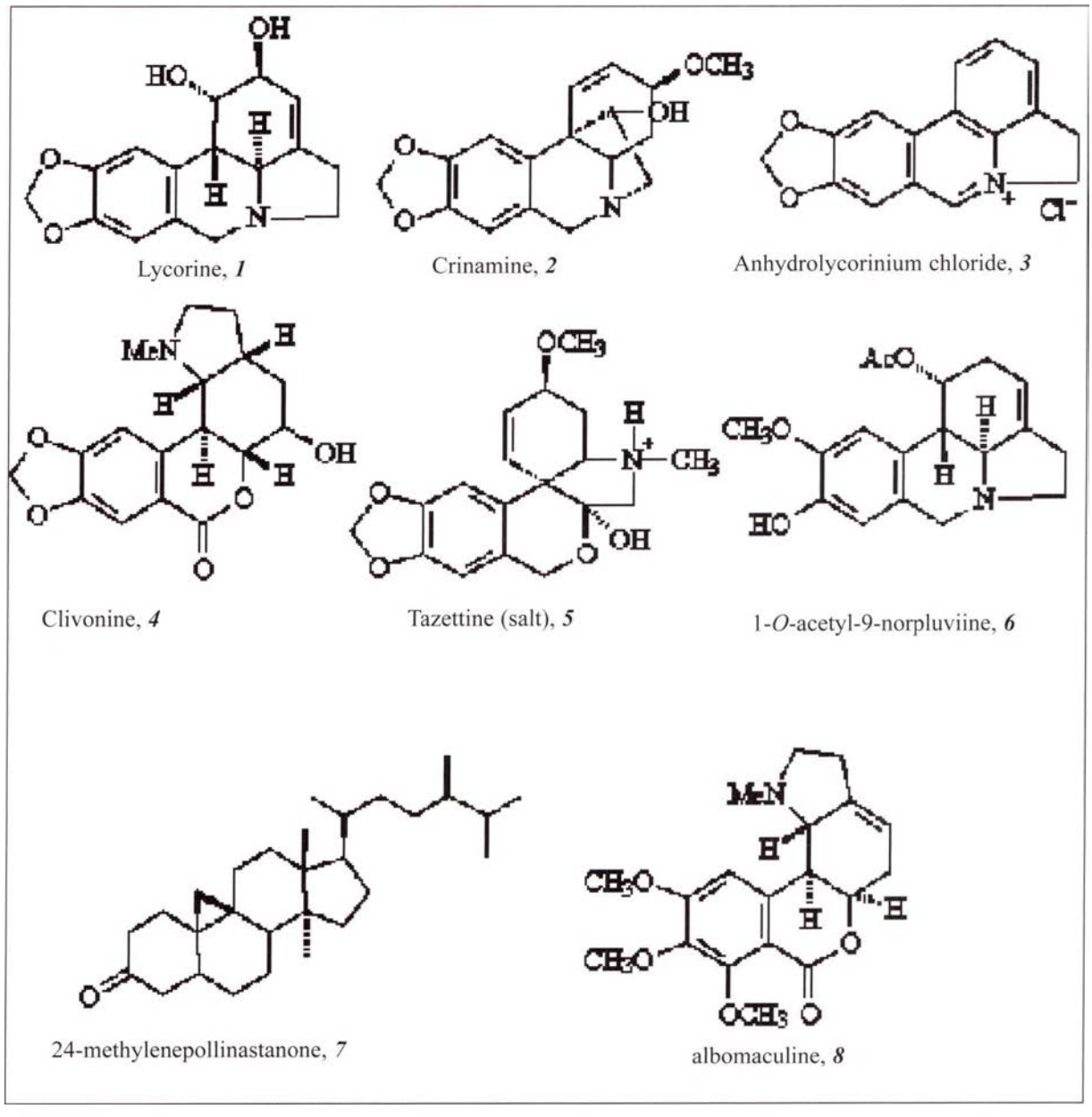

Fig. 1 - Isoquinoline alkaloids and a triterpenoid recently isolated from Zulu ethnomedicinal Amaryllidaceae.

have yielded lycorine, caranine, acetylcaranine, buphanisine, *epi*buphanisine, buphanidrine, ambelline, crinamine, 6-hydroxy-crinamine, *epi*-vittatine, an uncharacterised alkaloid, coranicine, 1-*O*-acetyllycorine, hippadine, 6-α-hydroxypowelline, hamayne and the newly described 1-*O*-acetyl-9-norpluviine (Fig. 1, ***6***). Four cycloartane compounds (triterpenoids): 24-methylenecycloartan-3-β-ol, cycloeucalenol, cycloeucalenone and 24-methylenepollinastanone (Fig. 1, *7*), have also been isolated (KOORBANALLY *et al.* 2000).

Haemanthus species

The bulbous genus *Haemanthus* L. (Tribe Haemantheae) comprises 22 species restricted to southern Africa (SNIJMAN 2000). Amongst these is a distinct closely related group of three species possessing white flowers and an evergreen habit; all are shade loving and occur in the summer rainfall region (SNIJMAN 1984; SNIJMAN & VAN WYK 1993). This set comprises *Haemanthus pauculifolius* Snijman & Van Wyk, *H. albiflos* Jacq. (= *H. albomaculatus* Bak.) and *H. deformis* Hook.f., all

of which are traded in the Zulu ethnomedicinal markets of Durban, South Africa (CUNNINGHAM 1988; PETTIT 1998), the last two as *uzeneke*. *Haemanthus deformis* is known to the Zulu as the 'female' *uzeneke*, distinct from the phallic-like *H. albiflos* Jacq. traded as the 'male' *uzeneke*. In the Eastern Cape the Xhosa use bulb infusions of *H. albiflos* for chronic coughs (BROSTER 1982). Extracts of bulbs of this species have been shown to possess strong antiviral activity (HUSSON *et al.* 1993) and cytotoxicity (VILADOMAT *et al.* 1997), but are reportedly not antibacterial (HUTCHINGS *et al.* 1996).

A total of nine alkaloids of the Amaryllidaceae type were recently isolated from the three *Haemanthus* species investigated. The phytochemical investigation of *H. albiflos* yielded homolycorine, albomaculine (Fig. 1, ***8***), and the quaternary salt of *O*-methyl-lycorenine. Homolycorine was also isolated from *H. pauculifolius* as well as four additional alkaloids: the novel paucamine as a salt, and the quaternary salts of homolycorine, montanine and manthidine. The investigation of *H. deformis* produced three alkaloids, coccinine, montanine and the ammonium salt of manthidine.

Acknowledgements. This research was supported by the National Research Foundation of SA, the University of Natal Research Fund, and the Wellcome Trust (Grant No. 052451). The DEAT is acknowledged for funding MEDBASE, the National Medicinal Plants Database for South Africa.

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