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Review

Traditional usage, phytochemistry and pharmacology of the South African medicinal plant *Boophone disticha* (L.f.) Herb. (Amaryllidaceae)

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ABSTRACT

Ethnopharmacological relevance: *Boophone disticha* is the most common member of the South African Amaryllidaceae used extensively in traditional medicine of the various indigenous population groups, including the Sotho, Xhosa and Zulu as well as the San. This survey was carried out to identify and highlight areas relevant to the traditional usage of *Boophone disticha*. Pharmacological aspects were examined with the purpose of reconciling these with the traditional usage of the plant. In relation to phytochemical make-up, particular attention was paid on how its alkaloid constitution might corroborate the various biological effects manifested by the plant.

Materials and methods: Information gathering involved the use of four different database platforms, including Google Scholar, ScienceDirect, Scifinder® and Scopus. Arrangement and detailing of this information is as reflected in the various sections of the paper.

Results: Sixteen categories were identified under which *Boophone disticha* finds use in traditional medicine. These were shown to include general usage purposes, such as ‘cultural and dietary’, ‘well-being’, ‘personal injury’, ‘divinatory purposes’, ‘psychoactive properties’ and ‘veterinary uses’. Furthermore, traditional usage was seen to involve six body systems, including functions pertaining to the circulatory, gastrointestinal, muscular, neurological, respiratory and urinary systems. The four remaining categories relate to use for inflammatory conditions, cancer, malaria and tuberculosis. Overall, three areas were discernible in which *Boophone disticha* finds most usage, which are (i) ailments pertaining to the CNS; (ii) wounds and infections; and (iii) inflammatory conditions. In addition, several aspects pertaining to the toxic properties of the plant are discussed, including genotoxicity, mutagenicity and neurotoxicity.

Conclusion: The widespread ethnic usage of *Boophone disticha* has justified its standing as a flagship for the Amaryllidaceae and its relevance to South African traditional medicine. Furthermore, its promising pharmacological and phytochemical profiles have stimulated significant interest in the clinical realm, especially in the areas of cancer and motor neuron disease chemotherapy. These collective properties should prove useful in steering the progress of the plant towards a wider audience.

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Abbreviations: AChE, acetylcholinesterase; AD, Alzheimer’s disease; BW, body weight; CNS, central nervous system; COX, cyclo-oxygenase; IK, indigenous knowledge; LD, lethal dose; MAO, monoamine oxidase; MBC, minimum bactericidal concentration; MIC, minimum inhibitory concentration; MND, motor neuron disease; MTD, minimum toxic dose; OFS, Orange Free State; PD, Parkinson’s disease; SSRI, selective serotonin reuptake inhibitor; T/C index, ratio of treated and control group; TM, traditional medicine

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1. Introduction

The Amaryllidaceae J. St.-Hil. is a large family of bulbous flowering plants comprising roughly 1000 species in 79 genera with a pantropical distribution (Meerow and Snijman, 1998). Andean South America, the Mediterranean and South Africa have been identified as centres of prominence for these monocotyledonous plants (Meerow and Snijman, 1998). Their sphere of influence extends into areas as diverse as agriculture, horticulture, ethnobotany, traditional medicine (TM) and pharmacology (Viladomat et al., 1997; Bastida et al., 2006; Nair et al., 2013). For example, daffodils (Narcissus) are amongst the most commonly sold cut-flower varieties and are thus of significant importance to the floriculture industry (Bastida et al., 2006). Furthermore, several members of the family have intensive usage in the traditional medicinal practices of indigenous peoples around the world (Viladomat et al., 1997; Bastida et al., 2006; Nair et al., 2013). The long history of association of the Amaryllidaceae with TM in the Mediterranean basin can be traced back to the times of Hippocrates and Pliny who recorded diverse medicinal applications of Narcissus (Pettit et al., 1993; Kornienko and Evidente, 2008). Furthermore, archaeological findings at purportedly Inca ruins in South America have indicated that Ismene, Pyrolirion and Stenomessos as depicted on ceremonial drinking vessels may have been a part of popular culture (Vargas, 1981), while San rock paintings of Boophone and Brunsvigia species in South Africa attest to the usage of the Amaryllidaceae by the region's first inhabitants (Dyer, 1950; Van Wyk, 2008).

Roughly one-third of the Amaryllidaceae is found in South Africa, the majority of which are distributed through the Capeflora floral kingdom of the Western Cape (Meerow and Snijman, 1998). Biystematically, members of the South African Amaryllidaceae are almost exclusively to the tribes Amaryllideae, Haemantheae and Cyrtantheae which are three of the 14 recognised tribes in this family (Olivier, 1980; Snijman and Linder, 1996; Meerow and Clayton, 2004). Amaryllidaceae J. St.-Hil. is a monophyletic group consisting of 11 currently recognised genera and approximately 155 species (Snijman and Linder, 1996). Members of the tribe, typified by Crinium, inhabit grassland, savannah and tropical forests in sub-Saharan Africa, but are most speciose in South Africa where habitats include semi-arid dwarf shrublands in the winter rainfall region (Snijman and Linder, 1996). By contrast, the tribe Haemantheae Pax (Hutchinson) consists of five genera (Scadoxus, Haemanthus, Clivia, Gethyllis and Apodanthera) which are distributed through the various regions in South Africa (Meerow and Clayton, 2004). Of the African clades, Cyrtantheae Salisb. is recognised as a tribe unto itself consisting of a single endemic genus, Cyrtanthes (Olivier, 1980).

Apart from its morphological and floral characteristics, the Amaryllidaceae is widely known for its unique alkaloid constituents (Viladomat et al., 1997; Bastida et al., 2006; Jin, 2011; Nair et al., 2013). Chief amongst these secondary metabolites is the alkaloid galanthamine (1) (also referred to as ‘galantamine’) (Scheme 1), a prescription drug in the treatment of Alzheimer's disease (AD) (Greig et al., 2004; Heinrich and Teoh, 2004; Houghton et al., 2006). Having captured a significant share of the multi-billion dollar global market over the past decade, galanthamine, like other acetylcholinesterase (AChE) inhibitor regimens, remains steadfast as a primary choice in the chemotherapeutic approaches to AD (Greig et al., 2004; Heinrich and Teoh, 2004; Houghton et al., 2006). This status is due chiefly to its potent, selective and reversible inhibitory interaction with AChE which is known to play a significant role in the progression of neurodegeneration associated with the pathophysiology of AD (Greig et al., 2004; Heinrich and Teoh, 2004; Houghton et al., 2006). The research and development of galanthamine into a viable contemporary AD drug owes much to TM knowledge evolving out of the usage of Galanthus species, from which galanthamine was first isolated, in the Caucasus region of Eastern Europe (Heinrich and Teoh, 2004).

In terms of structural diversity, Amaryllidaceae alkaloids have been classified into six distinct groups (Viladomat et al., 1997; Bastida et al., 2006; Jin, 2011; Nair et al., 2013). Galanthamine 1, lycorine 2 and crinine 3 are representative of the three major structural-types for these alkaloids (Scheme 1), while homolycorine 4, tazettine 5 and montanine 6 make up the minor series of compounds discernible within the Amaryllidaceae (Viladomat et al., 1997; Bastida et al., 2006; Jin, 2011; Nair et al., 2013). Other less-conspicuous members include degraded, oxidised and truncated variants such as trisphaeridine 7 and ismine 8 (Viladomat et al., 1997; Bastida et al., 2006; Jin, 2011; Nair et al., 2013). All these structures are related as a consequence of their biogenesis from the common amino acid derived precursor norbelladine 9 (Viladomat et al., 1997; Bastida et al., 2006; Jin, 2011; Nair et al., 2013).

In addition to the therapeutic success of galanthamine in the motor neuron disease (MND) arena, other clinical candidates have been identified in the Amaryllidaceae with significant potential for drug development. Of these, the phenanthridones (such as pancratistatin 10) of the lycorine 2 series have attracted most interest as anticancer agents due to their potent and cell line-specific antiproliferative activities and it has been suggested that a commercial target should be made available within the next decade (Kornienko and Evidente, 2008). Thus, with galanthamine 1 and pancratistatin 10 entrenched as veritable leads, the Amaryllidaceae provides a vast resource platform for drug discovery in the cancer, MND and allied disciplines (Viladomat et al., 1997; Bastida et al., 2006; Nair et al., 2013).

Given these interesting biological traits, it is not surprising that the Amaryllidaceae is one of the most common bulbous plants exploited on a global scale in both traditional and mainstream sectors of healthcare (Viladomat et al., 1997; Bastida et al., 2006;
This is also true for the local scene where Amaryllidaceae plants find heavy usage in TM and are consistently amongst the most popular bulbous plants traded on such markets (Hutchings et al., 1996; Louw et al., 2002; Brueton et al., 2008). Amongst the South African Amaryllidaceae contingent, *Boophone disticha* stands out as the most common plant used in both the formal and informal sectors of TM, as well as in local research initiatives (Hutchings et al., 1996; Dold and Cocks, 2002; Louw et al., 2002; Brueton et al., 2008). However, the plant is also known to be one of the several toxic species of the Amaryllidaceae (Van Wyk et al., 2002, 2005). Thus, within the context of South African TM details of the traditional uses, phytochemistry and pharmacology of *Boophone disticha* are afforded herein with the aim of reconciling the traditional aspects of its usage with more recent discoveries in the pharmacology of the Amaryllidaceae.

### 2. Description and distribution

The genus *Boophone* Herb. comprises of only two species: *Boophone disticha* (L.f.) Herb. and *Boophone haemanthoides* F.M. Leight. (Meerow and Snijman, 1998; Williamson, 2012). Now exclusively referred to as *Boophone disticha*, it is distributed along East Africa, ranging from Sudan in the north to the Western Cape Province in the south. In South Africa it is widely occurring with a range covering the northern tropical savannah woodlands to the winter rainfall region of the Western Cape, including the desert-like Karoo biome as well as the Eastern seaboard (Wrinkle, 1984). By contrast, *Boophone haemanthoides* is a rare and threatened species with a restricted territory within the winter rainfall region of South Africa and parts of southern Namibia (Wrinkle, 1984). The generic name *Boophone* is derived from the Greek *bous* (ox) and *phone* (death) while the specific name ‘disticha’ refers to the leaves which are erect in a fan shape. Also known as ‘sore-eye flower’ (‘seerooglelie’ in Afrikaans or ‘incotho’ in Xhosa), *Boophone disticha* is an attractive, deciduous plant which flowers between July and October (Wrinkle, 1984). The large bulbs are covered with a thick layer of papyraceous scales, the skeletal remains of long dried leaves, which rise above soil level and serve to protect the developing flower and newly emerged leaves (Williamson, 2012). The peduncle is stout and carries a dense, rounded ball of numerous red-pink to dark pink flowers with long pedicels which elongate even further and stiffen during maturity to carry the dried seed capsules (Williamson, 2012) (Fig. 1).
3. Taxonomy

Phylogenetic relationships within the Amaryllidaceae have come under intense scrutiny over the past several decades and significant efforts have been directed towards the African tribes Amaryllidaceae, Haemanthaceae and Cyrtanthaceae (Traub, 1963; Olivier, 1980; Dahlgren et al., 1985; Müller-Dobles and Müller-Dobles, 1996; Snijman and Linder, 1996; Meerow and Snijman, 1998; Meerow et al., 1999; Meerow and Snijman, 2001; Meerow and Clayton, 2004). As early as 1963, Traub proposed a two-tier structure for the tribe Amaryllideae based on both vegetative and floral morphological characteristics. Accordingly, subtribe Crineae (Ammocharis Herb., Boophone Herb., Brunsvigia Heist., Crinum L., Cybistetes Müll.-Redh. & Schweick. and Nerine Herb.) was distinguished from subtribe Strumariinae (Carpolyza Salisb., Hessea Herb. and Strumaria Jacq.). Contrary to this subtribal classification, Dahlgren et al. (1985) combined all nine genera listed above together with Amaryllis L. into the single tribe Amaryllidaceae. The 1996 classification of Müller-Dobles and Müller-Dobles re-introduces the subtribal structure to the tribe Amaryllidaceae but in this case with four component subtribes: (i) Amaryllidinae (Amaryllis, Namaquaanula D. and U. M.-D. and Nerine); (ii) Boophoninae (Boophone, Brunsvigia and Crossyne Salisb.); (iii) Strumariinae (Bokkeveldia D. and U. M.-D., Carpolyza, Dewinterella D. and U. M.-D., Gemmaria D. and U. M.-D., Hessea, Strumaria and Tedingea D. and U. M.-D.); and (iv) Crininae (Crinum, Ammocharis and Cybistetes). The revision of the tribe Amaryllidaceae by Snijman and Linder (1996) is widely accepted as the most comprehensive classification to date and reverts back to the initial two-tier structure of Traub (1963) with minor adjustments. Based on morphological, anatomical and cytological data, the tribe was resolved into two monophyletic subtribes: (i) Crininae comprising Ammocharis, Boophone, Crinum and Cybistetes; and (ii) Amaryllidinae comprising Amaryllis, Brunsvigia, Carpolyza, Crossyne, Hessea, Nerine and Strumaria (Snijman and Linder, 1996). Thus, based on these characteristics as well as evidence gleaned from DNA sequence data (Meerow and Snijman, 2001), the placement of the genus Boophone in the tribe Amaryllidaceae has never been in doubt.

4. Conservation status

Given the natural abundance of the Amaryllidaceae in South Africa, its widespread usage in TM, its ornamental value as well as its medicinally significant alkaloid constituents, it is not surprising that these plants feature prominently amongst the manifold challenges posed to the conservation sector. This has been further exacerbated by more recent concerns such as unsustainable usage, unscrupulous collection methods as well as habitat destruction. A recent review of red-listed medicinal plants of South Africa has shown that 42 species of the Amaryllidaceae have been documented in TM, representing 2% of the total medicinal flora (Williams et al., 2013). However, of greater concern is that 26% of the total local Amaryllid population has been classified as 'threatened' or 'near threatened' (Williams et al., 2013). The status of Boophone disticha has been indexed as 'declining' (Williams et al., 2013) which is not unexpected given the extent of its exploitation in TM (Dold and Cocks, 2002). To this end, advances in seed and molecular biology as well as the biotechnology arena have expedited the availability of propagated plants at TM markets to bolster stocks under threat from unsustainable practices (Cheesman, 2013).

5. Traditional usage

The fact that Boophone disticha can be traced back via rock paintings to the original inhabitants of South Africa suggests a long history of association of the plant with the traditional practices of the indigenous peoples of the region (Van Wyk, 2008). This is further substantiated by the discovery of the ~2000 year-old remains of a Khoi-San inhabitant of the Kouga/Baviaanskloof area of the Eastern Cape, found mumified with Boophone disticha scales (Binneman, 1999; Van Wyk, 2008). Furthermore, records of usage of the plant by Cape-Dutch settlers (Watt and Breyer-Brandwijk, 1962) suggest that the application of indigenous knowledge (IK) may have been essential to the medicinal needs of early settlers to the colony. ‘Khoi-San’ is a unifying name for the ‘Khoi’ and ‘San’ tribes of southern Africa, two ethnic groups who share physical and linguistic characteristics distinct from the Bantu majority of the region (Barnard, 1992). Usage of the Amaryllidaceae for medicinal purposes in South Africa is extensive which is reflected by the popularity of these plants on traditional markets of the three most populous tribes of the region (the Sotho, Xhosa and Zulu) (Hutchings et al., 1996; Dold and Cocks, 2002; Louw et al., 2002). For example, Hutchings et al. (1996) documented the usage of 13 different Amaryllid species by traditional healers from various districts within the Zululand area. Of these, eight were for urinary or venereal diseases; six for headache and fever; six for...
swelling, growths and joint ailments; five for skin conditions, bruises, sprains and fractures; four for respiratory problems; three for gastrointestinal disorders; and two for use as internal purifiers (Hutchings et al., 1996). Furthermore, a survey by Dold and Cocks (2002) covering six urban centres in the Eastern Cape Province showed that a minimum of 166 medicinal plants were traded on these markets of the indigenous Xhosa, utilising 525 tonnes of plant material with an estimated value of $3 million annually. In the study, Boophone disticha was listed amongst the most frequently traded plants at these centres (Dold and Cocks, 2002). Another study revealed that Boophone disticha is one of the most commonly traded bulbous plants at the Faraday ‘umuthi’ market in Johannesburg (the largest TM market in South Africa) (Brueton et al., 2008). Given these facts, it is clear that Boophone disticha is the most common of the Amaryllidaceae members exploited across many sectors of TM in South Africa.

For the purpose of this survey, 16 categories (Table 1) were identified under which Boophone disticha finds use in the TM practices of indigenous people of the region. Furthermore, while bulbs were the most common plant part used in TM, leaves, flowers and roots were also utilised but to a lesser extent. In broad terms, Boophone disticha is used for cultural (such as adornment), health and well-being purposes (bulb tonic taken for weakness) as well as for personal injury (wounds, cuts and bruises) (Table 1, entries 1–3). Six categories relating to body system functions were identified, including usage for circulatory, gastrointestinal, muscular, neurological, respiratory, and urinary ailments (Table 1, entries 4–9). Of significance in these categories is the use of bulb scales for treatment of asthma (Watt and Breyer-Brandwijk, 1962; De Beer and Van Wyk, 2011) and the use of bulb infusions for anxiety, depression and age-related dementia (Risa et al., 2004a; Pedersen et al., 2008; Stafford et al., 2008; Neergaard et al., 2008). Interestingly, usage of the plant for respiratory ailments was shown to include both indigenous and European respondents highlighting the cross-cultural significance of the plant. Apart from this Boophone haemanthoides, the only other member of the genus Boophone is also utilised for respiratory illnesses (De Beer and Van Wyk, 2011; Nair et al., 2012b). The widespread usage of Boophone disticha for neurological disorders is well documented and further details of this will be provided in Section 7 of this paper. In relation to specific diseases, Boophone disticha is applicable for treatment of various inflammatory conditions, cancer, malaria and tuberculosis (Table 1, entries 10–13). Details of these functions, especially in cancer chemotherapy, will also be provided in Section 7 of this paper. The three remaining categories pertain to psychoactive, divinatory and Veterinary properties in which the plant finds common usage for therapeutic purposes.

Of the manifold uses of Boophone disticha, its usage as an arrow and dart poison by San communities is most striking (Watt and Breyer-Brandwijk, 1962; Verzár and Petri, 1987; Bisset, 1989; De Smet, 1998). Amongst the varied purposes for which plant toxins have come to be used, their primary function as an auxiliary weapon in the procurement of food has never been disputed (Bisset, 1989; Philippe and Angenot, 2005). In addition, these substances have been widely employed in tribal warfare, as items in inter-tribal trade and as ingredients or sources of medicines (Bisset, 1989; Philippe and Angenot, 2005). In present times it is believed that this practice still continues within some factions of the San people scattered through parts of Namibia and Botswana (Bisset, 1989; De Smet, 1998). Moreover, it is known that the Khoi-San and certain Bantu tribes also once used Boophone disticha for similar purposes, but it is actively contended that the practice descended down from the San (Bisset, 1989; De Smet, 1998). The Khoi-San used bulbs to poison arrows intended for shooting smaller types of game, and they appear to have had a profound knowledge of the bulbs in selecting as more toxic those growing under cover of shade over those in sunnier spots (Watt and Breyer-Brandwijk, 1962). Evidence for this essential cultural practice amongst the San can be seen in arrow heads, known to have been treated with Boophone disticha and taken from the Cape to Berlin in 1806, from which a substance (“haemanthine”) was isolated over one hundred years later (Lewin, 1912a,b; Watt and Breyer-Brandwijk, 1962). Although no trace of the compound remained for comparative studies several decades later, it was nonetheless reputed to be either buphananine 11 or nerbonidine 12 (Bates et al., 1957; Goosen and Warren, 1957; Fales and Wildman, 1961), two known alkaloid constituents of Boophone disticha (refer to Section 6.2). Furthermore, an arrow belonging to the San of the Kalahari, known to have been in possession of the Völkerkunde Museum der Universität Göttingen since 1937, was shown to contain alkaloids characteristic of Boophone disticha 60 years later (Mebs et al., 1996; De Smet, 1998). An in-depth look at the phytochemical makeup of Boophone disticha follows in Section 6.2 of this paper.

Another area where Boophone disticha finds extensive usage is in the practice of circumcision and initiation rituals (Table 1) of the various indigenous tribes of South Africa (Watt and Breyer-Brandwijk, 1962; Verzár and Petri, 1987; De Smet, 1996; Hutchings et al., 1996; Viladomat et al., 1997; Grierson and Afholayan, 1999; Du Plooy et al., 2001; Van Wyk et al., 2008; Philander, 2011). Male circumcision is performed on adolescent or young men for cultural reasons, particularly as an initiation ritual and a rite of passage into manhood (Wilcken et al., 2010). It is a practice common in Sotho, Xhosa and Zulu culture carried out in a non-clinical setting by a traditional healer (an ‘Ngcibi’) with no formal medical training (De Smet, 1996; Foden, 2010; Wilcken et al., 2010). In the townships of Gauteng Province, 10% of males aged 14–24 years and 22% of those aged 19–29 years were reportedly circumcised, in 58–65% of cases by traditional circumcisers (Lagarde et al., 2003). In the same study, it was shown that choice of providers depended on the affiliation to different ethnic groups; for example, 86% of Xhosa participants were circumcised by traditional healers compared with 37% of Tswana men. During the initiation period, Xhosa boys are covered from head to toe with sandstone which gives them the characteristic white colour and live together in a circumcision lodge under strict conditions with sandstone which gives them the characteristic white colour and live together in a circumcision lodge under strict conditions (Foden, 2010). In Sotho tradition, initiates are given food mixed with bulbs of Boophone disticha together with other ingredients which is thought to imbue them with the qualities of their ancestors as well as to make men out of them (De Smet, 1996). The signs of intoxication are regarded as a token that the spirit of manhood had entered their bodies (De Smet, 1996). Furthermore, bulb infusions are used by Sotho and Xhosa boys as an outer dressing for circumcision wounds (Watt and Breyer-Brandwijk, 1962; Verzár and Petri, 1987; De Smet, 1996; Hutchings et al., 1996; Viladomat et al., 1997; Grierson and Afholayan, 1999; Du Plooy et al., 2001; Van Wyk et al., 2008; Philander, 2011). More recently, there have been concerted efforts to popularise the health benefits of medical male circumcision due to its protective effect in model studies of female-to-male transmission of HIV (Wilcken et al., 2010). This not withstanding, traditional male circumcision is not without complications and numerous cases are reported on an annual basis relating to excessive bleeding, infection, delayed wound healing and even death (Wilcken et al., 2010). Given these facts, the popularity of the practice on the cultural landscape as well as the recent availability of male circumcision clinics nationwide, there has been ongoing debate about the integration of this sector of TM into mainstream healthcare in South Africa.
<table>
<thead>
<tr>
<th>Category of use</th>
<th>Description of traditional usage</th>
<th>References</th>
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<tbody>
<tr>
<td></td>
<td>Outer layer of bulbs used to fashion head ring of Swati chief and headman</td>
<td>Botha et al. (2005), Van Wyk et al. (2002, 2005), Watt and Breyer-Brandwijk (1962)</td>
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<td></td>
<td>Leaves are stripped to make fringes which are worn as decorative body ornaments</td>
<td>Hutchings et al. (1996), Watt and Breyer-Brandwijk (1962)</td>
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<td></td>
<td>Bulbs were used as an arrow and dart poison by San and Xhoi-San of the Cape</td>
<td>Bisset (1989), De Smet (1996, 1998), Neuwinger (1994), Verzár and Petri (1987)</td>
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<td></td>
<td>Bulbs known to have caused death by suicide in the OFS</td>
<td>Hutchings et al. (1996), Van Wyk et al. (2002, 2005), Watt and Breyer-Brandwijk (1962)</td>
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<td></td>
<td>Prior to tin utensils, scooped-out bulb was used by Sotho herd boys to warm milk</td>
<td>Watt and Breyer-Brandwijk (1962)</td>
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<td></td>
<td>Zulu use bulb scales to plug ear lobes after piercing</td>
<td>Hutchings et al. (1996)</td>
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<tr>
<td></td>
<td>Cape-Dutch settlers used a sleeping mattress filled with bulb scales to relieve insomnia</td>
<td>Hutchings et al. (1996)</td>
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<td></td>
<td>Chewed dried leaves used to treat alcohol addiction in the Cape</td>
<td>Hutchings et al. (1996)</td>
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<td></td>
<td>Zulu take flower infusions with porridge for dizziness</td>
<td>Hutchings et al. (1996)</td>
</tr>
<tr>
<td>2. Well-being</td>
<td>Dry bulb scales taken for feeling of weakness</td>
<td>Verzár and Petri (1987)</td>
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<td></td>
<td>Fresh bulb water extract is drunk to increase sexual potency</td>
<td>Risa et al. (2004a, 2004b), Stafford et al. (2008)</td>
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<tr>
<td>3. Personal injury</td>
<td>Bulbs are used by most tribes of South Africa (as well as early European settlers to the Cape) for rashes, bruises, burns, cuts, wounds, boils and swelling. The treatment is thought to relieve pain as well as to draw out pus</td>
<td>Cheesman et al. (2012)</td>
</tr>
<tr>
<td></td>
<td>Zulu women roll snuff on a piece of dried bulb scale to improve the efficacy of the snuff</td>
<td>De Beer and Van Wyk (2011), Van Wyk et al. (2008) and Watt and Breyer-Brandwijk (1962)</td>
</tr>
<tr>
<td>4. Gastrointestinal</td>
<td>Leaves are ingested as an internal wash</td>
<td>Hutchings et al. (1996), Watt and Breyer-Brandwijk (1962)</td>
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<td></td>
<td>Bulb decoctions are taken as an emetic and purgative</td>
<td>Hutchings et al. (1996), Watt and Breyer-Brandwijk (1962)</td>
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<td></td>
<td>Bulbs used as enemases by the Sotho, Xhosa and Zulu</td>
<td>Hutchings et al. (1996), Watt and Breyer-Brandwijk (1962)</td>
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<td></td>
<td>Fresh root and bulb decoction used for constipation</td>
<td>Hutchings et al. (1996), Watt and Breyer-Brandwijk (1962)</td>
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<td></td>
<td>Zulu women roll snuff on a piece of dried bulb scale to improve the efficacy of the snuff</td>
<td>De Beer and Van Wyk (2011), Van Wyk et al. (2008) and Watt and Breyer-Brandwijk (1962)</td>
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<td></td>
<td>Bulbs from the Umtentweni area of the KwaZulu-Natal south coast are used in the treatment of ‘fulumfa’ (a type of hysteria)</td>
<td>Neergaard el at. (2009), Pedersen et al. (2008), Sandager el at. (2005), Stafford et al. (2008)</td>
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<td></td>
<td>Bulbs infused drunk to relieve various mental illnesses, including anxiety and depression</td>
<td>Hutchings et al. (1996), Nair et al. (2011), Philander (2011), Van Wyk et al. (2002, 2005), Watt and Breyer-Brandwijk (1962)</td>
</tr>
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<td>10. Inflammatory conditions</td>
<td>Milk in which bulb scales have been macerated was used by Europeans in the Lydenburg district to treat various inflammatory conditions</td>
<td>Botha et al. (2005), Van Wyk et al. (2002, 2005), Watt and Breyer-Brandwijk (1962)</td>
</tr>
<tr>
<td></td>
<td>Moistened bulb scales were also known to be used by early settlers for rheumatic pain</td>
<td>Botha et al. (2005), Van Wyk et al. (2002, 2005), Watt and Breyer-Brandwijk (1962)</td>
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<td></td>
<td>Bulbs are applied for eye conditions as well as healing of infected scars</td>
<td>Botha et al. (2005), Van Wyk et al. (2002, 2005), Watt and Breyer-Brandwijk (1962)</td>
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<td></td>
<td>Weak bulb decoctions administered orally or via enema to Zulu adults for stomach, headache, chest and bladder pain</td>
<td>Botha et al. (2005), Van Wyk et al. (2002, 2005), Watt and Breyer-Brandwijk (1962)</td>
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<tr>
<td></td>
<td>The Manyika apply bulb scales locally for relief from urticaria</td>
<td>Botha et al. (2005), Van Wyk et al. (2002, 2005), Watt and Breyer-Brandwijk (1962)</td>
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<td></td>
<td>Dried leaves moistened with milk or oil is used to treat skin diseases, varicose ulcers and phlebitis</td>
<td>Botha et al. (2005), Van Wyk et al. (2002, 2005), Watt and Breyer-Brandwijk (1962)</td>
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</table>
In addition to the widespread cultural significance of Boophone disticha in areas as diverse as ‘arrow and dart poisons’ as well as ‘initiation and circumcision rituals’, the plant is most widely known for several of its neurological functions such as treatment of hysteria, stress-related ailments, psychosis, anxiety and depression as well as age-related dementia (Watt and Breyer-Brandwijk, 1962; Hutchings et al., 1996; Pedersen et al., 2008; Stafford et al., 2008)(Table 1). Interestingly, a global systematic survey of 143 plants used to treat diseases of the nervous system showed that seven representatives were from the family Amaryllidaceae, including Amaryllis belladonna, Scadoxus puniceus, Galanthus nivalis, Lycoris radiata, Narcissus jonquilla and Narcissus pseudonarcissus, of which the first three are African in origin (Gomes et al., 2009). Furthermore, based on these findings all plants covered in the survey were suggested as being possible complementary or alternative therapies for neurological and neurodegenerative disorders (Gomes et al., 2009). An often overlooked area in this sector is the psychoactive properties of Boophone disticha leading to it being commonly classified as an ‘African hallucinogen’ (De Smet, 1996; Sobiecki, 2008; Foden 2010). In the practice of trance, the Khoi-San believed that the plant could serve as a doorway to the spirit of the dead. Sangomas are also known to take the plant to psychoanalyse their patients, a process they call ‘bioscope’ hence the common name for Boophone disticha (‘bioscope plant’) (De Smet, 1996; Sobiecki, 2008; Foden 2010).

6. Phytochemistry

6.1. Alkaloids of the South African Amaryllidaceae

Although several classes of secondary metabolites are known to occur in the Amaryllidaceae, such as chalcones, flavonoids, lectins, lignans, peptides and terpenoids, it is the isoquinoline alkaloids which have endowed the family with a unique chemical characteristic (Viladomat et al., 1997; Bastida et al., 2006; Nair et al., 2013). These now collectively represent a large and expanding group of alkaloids with a distinct array of structural diversity in which galanthamine 1, lycorine 2 and crinine 3 feature as the three major structural-types (Scheme 1)(Viladomat et al., 1997; Bastida et al., 2006; Jin, 2011; Nair et al., 2013). By contrast, homolykorine 4, tazettine 5 and montanine 6 make up the minor series of compounds while triphaeridine 7 and ismine 8 represent some of the less-conspicuous members (Viladomat et al., 1997; Bastida et al., 2006; Jin, 2011; Nair et al., 2013). All these structures share the same biosynthetic precursor (norbelladine 9) from which they are derived via different sequences of phenolic oxidative coupling (Viladomat et al., 1997; Bastida et al., 2006; Jin, 2011; Nair et al., 2013). To date over 500 of these alkaloids have been identified in Amaryllid species across the globe (Viladomat et al., 1997; Bastida et al., 2006; Jin, 2011; Nair et al., 2013). The South African contingent presently stands at 193 alkaloids, representing roughly 39% of the global complement of structures, which have been isolated from 88 species spanning 14 genera and three tribes (Viladomat et al., 1997; Nair et al., 2013). Furthermore, this number is divisible into the different groups of compounds characteristic of the Amaryllidaceae, including 84 crinanes, 40 lycoranes, 7 galanthamine compounds, 9 tazettine representatives, 27 homolykorine compounds, 10 montanine analogues and 16 miscellaneous alkaloids (Viladomat et al., 1997; Nair et al., 2013). Although crinine alkaloids (such as crinine 3) with 84 representatives are the most populous of the South African Amaryllidaceae, lycorine 2 is by far the most common compound having been isolated on 38 separate occasions i.e. it is present in 43% of plants examined (Viladomat et al., 1997; Nair et al., 2013). Given this statistic alone coupled to the significant array of biological properties demonstrated by lycorine, it is not surprising that the Amaryllidaceae continues to attract widespread interest with the status as a biologically privileged plant family. Furthermore, the commercial success of galanthamine 1, the clinical potential of compounds such as pancratistatin 10 as well as the

Table 1 (continued)

<table>
<thead>
<tr>
<th>Category of use</th>
<th>Description of traditional usage</th>
<th>References</th>
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<tbody>
<tr>
<td>11. Cancer</td>
<td>Bulb extract indicated for this purpose</td>
<td>Botha et al. (2005)</td>
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<tr>
<td>12. Malaria</td>
<td>Bulb extract known to be effective in this treatment</td>
<td>Watt and Breyer-Brandwijk (1962)</td>
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<td>13. Tuberculosis</td>
<td>Zulu in the Umzentweni area of KwaZulu-Natal are known to use bulb decoctions to treat tuberculosis</td>
<td>Watt and Breyer-Brandwijk (1962)</td>
</tr>
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<td>14. Psychoactive properties</td>
<td>(a) Weak bulb decoctions used as a sedative to calm psychotic patients (b) Bulb concoctions taken orally have caused sedation, analgesia, visual hallucinations, unconsciousness, irrational behaviour, talkativeness as well as coma (c) Induce hallucinations for divinatory purposes (d) Used as a narcotic substance (e) Bulbs known to induce trance</td>
<td>Pedersen et al. (2008), Sobiecki (2008) Du Plooy et al. (2001), Neergaard et al. (2009) Van Wyk et al. (2002) Hutchings et al. (1996), Sandager et al. (2005) Neergaard et al. (2009), Stafford et al. (2008)</td>
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<td>15. Divinatory purposes</td>
<td>(a) The Manyika grow the plant outside their huts as a charm to ward off evil dreams, to bring good luck and rain as well as to keep away the ‘mudzimu’ (wandering spirit) after a death (b) Psychoactive properties of the bulbs used to induce trance (c) Used in various divination rituals such as arousing the ancestral spirits and curing demonic possession (d) Thought to symbolise eternal life</td>
<td>Watt and Breyer-Brandwijk (1962) Neergaard et al. (2009), Stafford et al. (2008), Du Plooy et al. (2001), Gadaga et al. (2010), Hutchings et al. (1996), Philander (2011), Van Wyk et al. (2002) Van Wyk (2008)</td>
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<td>16. Veterinary uses</td>
<td>(a) The Xhosa use the bulbs as a remedy for redwater in cattle (b) Cattle are known to browse the plant with impunity (c) It has been suggested that vultures and other carrion birds eat the plant to prevent harm from ingestion of putrid flesh or to sharpen vision</td>
<td>Watt and Breyer-Brandwijk (1962) Verzar and Petri (1987) Watt and Breyer-Brandwijk (1962)</td>
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natural abundance of the Amaryllidaceae in South Africa, where less than a third of the species have been studied, have together galvanised the plant family as a truly viable vehicle for drug discovery.

6.2. Alkaloids from Boophone disticha

Although various compounds such as furfuraldehyde, acetovanillone, chelidonic acid, copper, laevulose, pentatriacontane, a phytosterol, ipuranol and fatty acids were initially reported to be present in bulbs of Boophone disticha (Tutin, 1911a), its alkaloid constituents have subsequently gained prominence due to their important biological properties. Given the long history of usage of Boophone disticha in TM in South Africa, it is not surprising that the plant was amongst the first of the Amaryllidaceae species globally to be examined for alkaloid constituents (Tutin, 1911a,b; Lewin, 1912a,b; Tutin, 1913). Furthermore, the plant serves as a flagship for phytochemical endeavours emanating out of the southern African region. Given the complexity of these structures, the early years of chemical studies on Boophone disticha was understandably arduous. The first phytochemical investigation of the plant was that performed by Tutin (1911a,b) who described the presence of lycorine 2 together with three other unknown alkaloids. Following this, Lewin (1912a,b) isolated a compound loosely referred to as “haemanthine”, which Tutin (1913) maintained was in fact a mixture. However, evidence in support of Lewin’s stance for the chemical individuality of haemanthine was provided by Cooke and Warren (1953) based on elemental analysis, melting points and semi-synthetic derivatisation. By contrast, support for the stance taken by Tutin is reflected in studies carried out several decades later which revealed that “haemanthine” was a component mixture of buphanamine 11 or nerbowdine 12 (Bates et al., 1957; Goosen and Warren, 1957; Fales and Wildman, 1961).

Following on these early investigations, Bates et al. (1957) isolated lycorine 2, buphanamine 11 and buphanidrine 13 from bulbs of Boophone disticha collected at various locations in South Africa, including Bloemfontein, Grahamstown, Pieterniaritzburg and Pretoria. However, to date the most comprehensive phytochemical study carried out on the plant is that of Hauth and Stauffacher (1961) who described the presence of 11 alkaloids in ethanolic bulb extracts, including buphanidrin 13 (19.4%), undulatine 14 (18.6%), buphanisine 15 (16.9%), buphanamine 11 (14.1%), nerbowdine 12 (11.1%), cripine 3 (7.2%), distichamine 16 (5.4%), crinamide 17 (1.2%), acetylnerbowdine 18 (0.6%), lycorine 2 (0.4%) and buphatocene (0.3%) (where percentage values are expressed as relative contribution to total alkaloids). Whereas majority of these compounds have been subsequently verified through physical and spectroscopic means (Viladomat et al., 1997; Nair et al., 2013), the identity of buphatocene remains a mystery to this day. Interestingly, buphanidrine, buphanisine, crinamide and distichamine were also found in Boophone haemanthoides, but at percentages of 46.9%, 23.9%, 7.3% and 21.9%, respectively (Nair et al., 2012b). Further studies of Boophone disticha confirmed the presence of buphanamine, buphanidrin, buphanisine, crinamide and distichamine (Sandager et al., 2005; Neergaard et al., 2009; Cheesman et al., 2012). The most recent phytochemical investigation of Boophone disticha led to the isolation of 6-hydroxycrinamine 19 from a methanolic bulb extract at a concentration of 0.01% dry weight (Adewusi et al., 2012). It is clear from these collective findings that, with the exception of lycorine 2, the alkaloids produced by Boophone disticha are all the crinane series of Amaryllidaceae alkaloids. Furthermore, 6-hydroxycrinamine 19 was the only compound identified belonging to the α-crinane sub-series (Adewusi et al., 2012), the others being characteristic of β-crinane alkaloids (Hauth and Stauffacher, 1961; Sandager et al., 2005; Neergaard et al., 2009; Cheesman et al., 2012). In terms of the structural features of these alkaloids, crinane compounds possess a basic phenanthridine nucleus with varying degrees of oxidation in ring-A, but usually with a methylenedioxy bridge across C-8 and C-9 (as in crinine 11 and buphanisine 15 (Viladomat et al., 1997; Bastida et al., 2006; Nair et al., 2013)). In addition, methoxy substitution at C-7 is common for many analogues across the series, such as buphanidrin 13 and undulatine 14 (Viladomat et al., 1997; Bastida et al., 2006; Nair et al., 2013). In relation to ring-C, oxygen-related substituents are known to occur at all exchangeable positions, including C-1, C-2, C-3 and C-4, and a C-1 to C-2 double bond is common for many derivatives (Viladomat et al., 1997; Bastida et al., 2006; Nair et al., 2013). A distinguishing feature of crinane alkaloids is the presence of the ethano-bridge straddling N-5 and C-10b which may be either α- or β-orientated, leading to the absolute stereochemical configuration at C-4a. In the case of lycorine 2, the C-terminus of the ethano-bridge is at C-4 and C-10b reverts to a tertiary carbon centre (Viladomat et al., 1997; Bastida et al., 2006; Nair et al., 2013). Of the compounds isolated from Boophone disticha, distichamine 16 is most noteworthy for its unique ring-C substitution pattern (Viladomat et al., 1997; Nair et al., 2012a, 2013). In its structure, oxidation has occurred at C-1 in accommodating the keto group and the double bond has shifted to the C-2/C-3 position with concomitant vinylation of the C-3 methoxy group (Viladomat et al., 1997; Nair et al., 2012b). Such a substitution pattern has never been found for any other alkaloid within the crinane series (Viladomat et al., 1997; Nair et al., 2012b). Furthermore, distichamine 16 has never been found outside Boophone and thus reserves the privilege as a distinctive chemotaxonomic marker for the genus (Viladomat et al., 1997; Nair et al., 2012b).

7. Pharmacology

7.1. Antimicrobial activity

Given that Boophone disticha is the most common representative of the Southern African Amaryllidaceae used to treat wounds and infections (Hutchings et al., 1996; Rabe and Van Staden, 1997; Grierson and Afzalayen, 1999; Shale et al., 1999), it is not surprising that some studies have been directed towards gauging its efficacy against bacterial pathogenesis (Heyman et al., 2009; Cheesman et al., 2012). An ethanolic bulb extract of Boophone disticha was active against methicillin-sensitive Staphylococcus aureus with an MIC of 7.25 mg/mL (Heyman et al., 2009). Interestingly, the same extract was shown to be potentially fatal to the pathogen as a minimum bactericidal concentration (MBC) was established at 25.9 mg/mL (Heyman et al., 2009). Further work on Boophone disticha by Cheesman et al. (2012) initially showed bulb extracts to be active against two Gram-positive (Bacillus subtilis and Staphylococcus aureus) and two Gram-negative (Escherichia coli and Klebsiella pneumoniae) strains that made up the microdilution bacterial screen, with IC50s in the range 0.13–0.25 mg/mL. Led by these promising activities, bioassay-guided fractionation then resulted in the isolation of two active crinane alkaloid constituents: buphanidrin 13 and distichamine 16 (Scheme 1) (Cheesman et al., 2012). In the repeat screen, best activities were seen against Staphylococcus aureus, Escherichia coli and Klebsiella pneumoniae with both compounds exhibiting IC50s of 0.063 mg/mL against all Gram-positive pathogens.
three pathogens (correspondent with micromolar values of 200 and 191.5 for buphanidrine \textit{13} and distichamine \textit{16}, respectively) (Cheesman et al., 2012). Both compounds were two-fold less active against \textit{Bacillus subtilis} (IC\textsubscript{50} 0.13 mg/mL) as also seen in the screen against the crude extract (Cheesman et al., 2012). These results, though not as potent as the neomycin standard (IC\textsubscript{50} 0.8 × 10\textsuperscript{-3}–1.6 × 10\textsuperscript{-3} μg/mL) (Cheesman et al., 2012), are nevertheless consistent with previous observations on the low-to-mild antibacterial activities of Amaryllidaceae alkaloids (Viladomat et al., 1997; Elgorashi et al., 2003; Bastida et al., 2006; Nair et al., 2013). Amongst the South African Amaryllidaceae only Boophone disticha is known in TM for treating tuberculosis (Watt and Breyer-Brandwijk, 1962), although no pharmacological studies have been carried out to verify this property.

Information pertaining to the usage of South African Amaryllidaceae plants for fungal infections is sparse in the literature. Although, \textit{Boophone disticha} is not indicated for such purposes, several others, including \textit{Amaryllis belladonna}, \textit{Crinum macowanii} and \textit{Crinum moorei}, have shown antifungal or antiyeast activity (Viladomat et al., 1997). In terms of activities of single compound isolates, lycorine \textit{2} and vittatine \textit{21} were reported with significant activity against \textit{Candida albicans} (MICs of 39 and 31 μg/mL, respectively) (Evidente et al., 2004). In relation to antiviral activity, again the literature is devoid of any mention of the traditional usage of \textit{Boophone disticha} for such purposes. However, the plant has been suggested to be effective against different rhinovirus strains (Viladomat et al., 1997). In regards to activities of individual compounds, lycorine \textit{2} has been shown to be active against a number of viruses (Bastida et al., 2006), including poliomyelitis virus at concentrations as low as 1 μg/mL (Leven et al., 1982). Structure–activity relationship studies involving Herpes simplex virus showed that lycorine exerted its antiviral effect by blocking DNA polymerase activity (Leven et al., 1982). Other compounds of the family which have demonstrated antiviral activity in model studies include homolycorine \textit{4}, tazettine \textit{5}, narciclasine \textit{22} and haemantidine \textit{23} (Scheme 1) (Bastida et al., 2006). In terms of antiparasitic activity of South African Amaryllidaceae plants, only \textit{Amaryllis belladonna} is known to be active against \textit{Plasmodium gallinaceum} (Viladomat et al., 1997). Amongst all these plants, only \textit{Boophone disticha} is known to be used traditionally to treat malaria (Watt and Breyer-Brandwijk, 1962), although no studies have been directed towards gauging the efficacy of plant extracts against the malarial parasite. Of the various groups of Amaryllidaceae alkaloids screened against the malarial parasite, lycorine \textit{2} was the most potent against both chloroquine-sensitive (D10) and chloroquine-resistant (FAC8) strains of \textit{Plasmodium falciparum} with IC\textsubscript{50} 0.6 and 0.7 μg/mL, respectively (Campbell et al., 1998, 2000; Şener et al., 2003).

7.2. Anti-inflammatory activity

‘Inflammation-related conditions’, ‘wounds and infections’ and ‘ailments pertaining to the CNS’ together represent the top three categories under which \textit{Boophone disticha} finds most extensive use in TM in South Africa (Watt and Breyer-Brandwijk, 1962; Verzár and Petri, 1987; De Smet, 1996; Hutchings et al., 1996; Viladomat et al., 1997; Grierson and Afifolany, 1999; Du Plooy et al., 2001; Van Wyk et al., 2008; Philander, 2011). Verification of the usage of the plant for inflammation-related conditions came from cyclo-oxygenase (COX) inhibition studies in which ethanolic bulb extracts of \textit{Boophone disticha} exhibited 55% inhibition against COX-1 (Jäger et al., 1996). In terms of the activities of single compound extractives, lycorine \textit{2} is known to possess anti-inflammatory properties as shown through the carrageenan-induced paw oedema test in mice (Citoglu et al., 1998). At a dosage of 100 mg/kg lycorine induced 20.1% inhibition of oedema in the test subjects compared to 29.1% by the indomethacin control (10 mg/kg) (Citoglu et al., 1998). In addition, crinidine \textit{3} and crinamidine \textit{17}, both known alkaloid constituents of \textit{Boophone disticha} (Hauth and Staffacher, 1961), exhibited mild anti-inflammatory activity as determined through COX inhibition (Elgorashi et al., 2003). To this extent, crinidine \textit{3} and crinamidine \textit{17} at a concentration of 500 μM exhibited respective inhibitory activities of 16% and 10% against COX-1 (Elgorashi et al., 2003). Interestingly, this activity was seen to be selective as COX-2 remained unaffected by similar treatments using either compound (Elgorashi et al., 2003).

7.3. Effects on the central nervous system

7.3.1. Hallucinogenic effects

The use of plants as a source of chemicals with CNS-activating properties is common on the South African cultural landscape. As such, over 300 plant taxa have been identified within this context of TM (Stafford et al., 2008). At least three Amaryllid plants are known from local tradition to be exploited for hallucinatory purposes (De Smet, 1996; Viladomat et al., 1997; Stafford et al., 2008). \textit{Pancratum tenuifolium} is used by the San of the Kalahari to induce visual hallucinations while \textit{Brunsvigia radulosa} is well-known from San culture as a psychoactive plant (Viladomat et al., 1997). In addition, \textit{Boophone disticha} is recognised as a hallucinogenic plant in both San and Sotho traditions (Viladomat et al., 1997; De Smet, 1996; Neuwinger, 1994; Neuwinger and Mebs, 1997; Sobiecki, 2002, 2008; Stafford et al., 2008). It has been suggested that its alkaloid constituents, either as single compounds or additively, are largely responsible for these effects of the Amaryllidaceae (Viladomat et al., 1997; Bastida et al., 2006; Nair et al., 2013). Of the Amaryllidaceae alkaloids, galanthamine \textit{1} (Scheme 1) is best known for its narcotic effects such as induction of “lucid dream” (LD) and “out of body experience” (OBE) as well as its application as a nootropic agent (Harvey, 1995; Heinrich and Teoh, 2004). Of the compounds isolated from \textit{Boophone disticha}, buphanidrine \textit{13} is known to have hyoscine-like activity i.e. it exhibits muscarinic antagonist effects (Viladomat et al., 1997; Nair et al., 2013). Furthermore, since the identity of buphacetine has never been clarified, it could be speculated that this alkaloid may be responsible for the hallucinogenic properties of the plant. In addition, it is possible that all (or some) the alkaloids known from \textit{Boophone disticha} could together function in a synergistic manner to produce the observed hallucinogenic effects. Symptoms of these effects include unconsciousness, dilated pupils, tachycardia, raised blood pressure, slightly raised temperature, laboured respiration, psychosis, drunkenness and visual disturbances as reported by Laing (1979) subsequent to treating patients presenting with \textit{Boophone disticha} intoxication.

7.3.2. Mental disorders

7.3.2.1. Anxiety and stress. In addition to the psychoactive properties of \textit{Boophone disticha}, the plant is also used to treat mental disorders such as anxiety, depression, epilepsy and age-related dementia (Stafford et al., 2008; Gomez et al., 2009). Anxiety disorders are the most common psychiatric illnesses encountered in clinical practice (Pote et al., 2013). Often they are chronic conditions associated with considerable cardiovascular-related morbidity and mortality (Schwartz and Nihalani, 2006). Although information pertaining to the pharmacological basis to the usage of \textit{Boophone disticha} for anxiety and stress is largely absent from the literature, a recent study employed a mouse model to validate this claim (Pote et al., 2013). Maternal separation is a common animal model used to examine the long-term effects of early life experience on subsequent behaviour in adulthood and the development of psychiatric disorders such as anxiety and depression (Pruce and Feldon, 2003). Furthermore, repeated early maternal separation stress is known to produce an
altered effect in cardiovascular response in such models of study (Pryce and Feldon, 2003). In this regard, ethanolic extracts of Boophone disticha were used to gauge the effects on blood pressure and heart rate in adult BALB/c mice subjected to repeated early maternal separation stress (Pote et al., 2013). The results revealed that maternally separated mice treated with a low dose (10 mg/kg/BW/day) of Boophone disticha had the lowest systolic blood pressure, whereas those treated with a high dose (40 mg/kg/BW/day) exhibited the lowest diastolic blood pressure and mean arterial pressure following acute stress in adulthood compared to the control and dizapam treated animals (Pote et al., 2013). These findings suggest that postnatal stress can induce short-term changes in the sensitivity of the cardiovascular system to subsequent stress which can be reduced by treatment with Boophone disticha.

7.3.2.2. Depression. Several antidepressant drugs available in clinical practice, such as citalopram, fluoxetine and paroxetine, exert their effects through selective inhibition of serotonin reuptake and are pharmaceutically classed as selective serotonin reuptake inhibitors (SSRIs) (Nielsen et al., 2004). Mechanistically, such compounds are known to bind to the SSRI binding site on the neuronal serotonin transporter thus inhibiting the transport of serotonin from the synaptic gap back to the neuron (Stahl, 1998). In the competitive binding assay with 3H-labelled citalopram, aqueous leaf and bulb extracts of Boophone disticha resulted in the displacement of more than 50% of the transport protein bound [3H]citalopram at tested concentrations of 5, 1 and 0.1 mg/mL (Nielsen et al., 2004). Buoyed by these findings, bioassay-guided fractionation then led to the isolation of the alkaloids buphanamine 11, buphanidrine 13, buphaniicine 15 and distichamine 16 (Scheme 1) from bulbs of Boophone disticha, which exhibited respective IC50 values of 55, 62, 199 and 65 μM in the serotonin binding assay (Neergaard et al., 2009). In addition, buphanamine 11 and buphanidrine 13 demonstrated affinities to the serotonin transporter in rat brain with IC50 of 1799 and 274 μM, respectively (Sandager et al., 2005). Apart from this, Pedersen et al. (2008) employed a rat model for depression to show that Boophone disticha extracts inhibited the serotonin transporter (SERT), noradrenalin transporter (NAT) as well as the dopamine transporter (DAT), all of which are believed to be involved in the pathophysiology of depression, with IC50 of 423.8, 77.3 and 93.5 μM respectively. Furthermore, antidepressant-like effects were observed for extracts of Boophone disticha in the tail suspension test (TST) and the forced swim test (FST) in both rats and mice (Pedersen et al., 2008).

7.3.2.3. Epilepsy. Epilepsy is a neurological condition typified by repeated and unprovoked seizures often accompanied by severe convulsions (Risa et al., 2004a). Benzodiazepines are a common class of anti-convulsing agents which bind to the GABA-A–benzodiazepine receptor complex where they enhance the affinity for the inhibitory neurotransmitter γ-aminobutyric acid (GABA) (Risa et al., 2004a). A GABA stimulus on the GABA-A receptor causes an influx of chloride ions into the cell producing hyperpolarisation of the membrane, making it more difficult to generate action potential, resulting in cell arrest and consequent anti-convulsant activity (Risa et al., 2004a). Although Boophone disticha is known in the TM approach to epilepsy (Stafford et al., 2008), no pharmacological investigation has sought to clarify this usage. By contrast, the Amaryllid Brunsvigia grandiflora exhibited high binding affinities (up to 100%) for the GABA-A–benzodiazepine receptor in competition with flumazenil (Risa et al., 2004a). Furthermore, none of the components of a structurally diverse Amaryllidaceae alkaloid mini-library were responsive to GABA-A–benzodiazepine receptor binding (Elgorashi et al., 2006b).

7.3.2.4. Age-related dementia. The impact of age-related dementia on western medicine is staggering, affecting one in 20 people over 65 and one in five over the age of 80, with an estimated annual cost of over $600 billion (McNulty et al., 2010; Nair and Van Staden, 2012). By contrast, CNS disorders associated with old age such as AD, amyotrophic lateral sclerosis (ALS) and Parkinson’s disease (PD) are not a major concern for the healthcare sectors of developing nations, which has been attributed to a number of factors, including genetic, dietary, lifestyle and environmental measures entrenched in these societies (Stafford et al., 2008). Given this rising health concern for developed nations, the search and development of chemical targets into suitable therapies against this complex of neuronal diseases is at a premium (Heinrich and Teoh, 2004; Houghton et al., 2006; Nair and Van Staden, 2012). In this regard, plants provide a substantial resource base for such efforts in drug discovery, some of which have already delivered effective candidates such as rivastigmine, huperzine A and galanthamine (also referred to as galantamine) to the clinical market (Heinrich and Teoh, 2004; Houghton et al., 2006). Given the commercial success of galantamine 1 (Scheme 1), it is clear that the plant family Amaryllidaceae invokes widespread interest as a resourceful platform for discovery in this area (Lopez et al., 2002; Elgorashi et al., 2004, 2006a; McNulty et al., 2010; Monton et al., 2010; Nair et al., 2011; Nair and Van Staden, 2012). Such endeavours have highlighted the potency of other alkaloids such as sanguinine 24 (IC50 for galanthamine is 1 μM), a process thought to be significant in the pathophysiology of AD, which fits the premise that Alzheimer’s disease is associated with cholinergic insufficiency (Harvey, 1995; Greig et al., 2004; Heinrich and Teoh, 2004; Houghton et al., 2006).

Given the commercial success of galantamine 1 (Scheme 1), it is clear that the plant family Amaryllidaceae invokes widespread interest as a resourceful platform for discovery in this area (Lopez et al., 2002; Elgorashi et al., 2004, 2006a; McNulty et al., 2010; Monton et al., 2010; Nair et al., 2011; Nair and Van Staden, 2012). Such endeavours have highlighted the potency of other alkaloids such as sanguinine 24 (IC50 for galanthamine is 1 μM) and 1-O-acetyllycorine 25 (IC50 0.96 μM) (Scheme 1) as AChE inhibitors with genuine potential for clinical advancement (Lopez et al., 2002; Elgorashi et al., 2004, 2006a; McNulty et al., 2010; Monton et al., 2010; Nair et al., 2011; Nair and Van Staden, 2012). The activity of sanguinine is not unexpected given its close structural similarity to the standard AChE inhibitor galanthamine. However, its potency over galanthamine must reside with its ring-A phenolic hydroxyl group (which in the case of galanthamine is substituted by a methoxyl group). The role of the methoxyl group in galanthamine has been shown to be significant as it occupies the acyl-binding pocket, contacting both Phe-288 and Phe-290 amino acid residues within the active site, and is therefore an essential structural feature of this AChE inhibitory pharmacophore (Sussman et al., 1991; Greenblatt et al., 1999). The activity of sanguinine 24 over galanthamine 1 suggests that a small polar group in the C-9 region of the molecule, capable of hydrogen bond donor and acceptor functions (reminiscent of a phenolic hydroxyl), is better accommodated at the active site.

The potency of 1-O-acetyllycorine 25 at AChE inhibition is due chiefly to its structural proximity to galanthamine and the possibility of overlap along significant areas of their respective pharmacophores (Elgorashi et al., 2006a; Nair et al., 2011). Quantitative structure–activity relationship (QSAR) studies involving superposition of minimum energy conformations showed partial overlap for the methoxyl of galanthamine and the methylenedioxy of 1-O-acetyllycorine (Elgorashi et al., 2006a; Nair et al., 2011). Furthermore, the acetate and nitrogen atom of 1-O-acetyllycorine superimposed on the hydroxyl group and the nitrogen atom of galanthamine, respectively (Elgorashi et al., 2006a; Nair et al., 2011), making it possible for the acetyl group to participate in hydrogen bonding in a manner similar to that demonstrated for the hydroxyl of galanthamine (Greenblatt et al., 1999). In addition, the C-4/C-4a double bond in galanthamine was seen to have π–π interactions with Trp-84 (Greenblatt et al., 1999), and since the lycorine double bond is in a proximally similar position it may be able to elicit a similar response at the active site (Elgorashi et al., 2006a; Nair et al., 2011).

Boophone disticha is one of the seven different South African Amaryllidaceae plants shown to be effective in the treatment of
age-related dementia and memory loss in TM (Stafford et al., 2008). As such, verification of this property was arrived at via AChE inhibition assays by which aqueous and ethanolic bulb extracts exhibited inhibitory activities of 37% and 30%, respectively (Risa et al., 2004b). Of the 12 compounds isolated from Boophone disticha, lycorine 2, 6-hydroxycrinamine 19 and crinine 3 exhibited AChE inhibitory activities of 29.3, 445 and 461 μM respectively (Elgorashi et al., 2004; Adewusi et al., 2012; Elisha et al., 2013), which consolidate the traditional usage of the plant for these conditions (Stafford et al., 2008; Gomes et al., 2009).

In addition to AChE inhibitors, monoamine oxidase (MAO) inhibitors are also known to be effective in the treatment of AD and PD (Stafford et al., 2007). MAO enzymes are present in the brain and are responsible for the oxidative deamination of endogenous amines (Yamada and Yasuhara, 2004). The two known isoforms MAO-A and MAO-B are differentiated by substrate preference, inhibitor specificity and tissue distribution (Yamada and Yasuhara, 2004). MAO-A preferentially deaminates serotonin, adrenaline and noradrenaline and makes up around 75% of MAO in human brain tissue, while MAO-B is specific for substrates such as dopamine, p-phenylethylamine and benzylamine (Yamada and Yasuhara, 2004). In relation to this, Stafford et al. (2007) screened a collection of 20 different plant taxa known to selectively inhibit MAO-A (IC50 406 μg/mL) and selective MAO-B inhibition (IC50 344 μg/mL) (Stafford et al., 2007). This result highlights the utility of Boophone disticha as a source of selective chemo-therapeutics against motor neuron disease, given its activity in AChE inhibition.

7.4. Anticancer activity

Cancer is a leading cause of death worldwide, accounting for 7.6 million deaths (around 13% of all deaths) in 2008 (WHO, 2008). During this period 669,000 deaths as a result of cancer, including 349,000 in men and 320,000 in women, were recorded in North America (WHO, 2008). Such statistics for the African continent are more difficult to come by since a very small proportion of the total population is covered by medically certified causes of death or population-based cancer registries (WHO, 2008). However, conservative estimates have put this number around 518,000 for deaths from cancer in the African region for 2008 (WHO, 2008). Of greater concern is that global deaths from cancer are set to rise sharply with 17 million cases projected for 2030 (WHO, 2008). In North America, lung, stomach, liver, colon and breast cancers together cause the most number of deaths from cancer each year, of which lung cancer is forecast as the leading cause for both males and females in 2013 (Cancer Facts & Figures, 2013). Given these facts and their increasing burden on the healthcare sector, the search for effective new therapies is an ongoing concern for health organisations worldwide. Present therapies include chemotherapy, immunotherapy, monoclonal antibody therapy, radiation therapy and surgery. In this regard, plants provide a vast resource base for chemotherapeutic based anti-cancer drug discovery (Graham et al., 2000; Balunas and Kinghorn, 2005; Cragg and Newman, 2005; Pan et al., 2010). As such, over 60% of anti-cancer agents presently in clinical use are derived from natural sources, including plants, marine organisms and micro-organisms (Cragg and Newman, 2005; Pan et al., 2010). Examples of such commercial drugs originating in plants include vinblastine, vincristine, camptothecin, topotecan, irinotecan, etoposide and paclitaxel (Cragg and Newman, 2005; Pan et al., 2010). In the South African context, the work of Fouche et al. (2006, 2008) is most embraced of the anti-cancer properties of the country’s floral biodiversity. To this extent, 7500 randomly selected plant extracts (representing 700 species) were tested in three cell line pre-screen using MCF7, TK10 and UACC62 cells at a single dose of 100 μg/mL (Fouche et al., 2006, 2008). Out of these, a total of 950 extracts exhibited growth inhibitions of 75% or higher against two or more of the cancer cells screened (Fouche et al., 2006, 2008).

The traditional use of Amaryllidaceae plants for cancer is known from all three geographical regions of its prominence, including Andean South America, the Mediterranean and South Africa (Pettit et al., 1984; Nair et al., 1998; Botha et al., 2005; Kornienko and Evidente, 2008; Caamal-Fuentes et al., 2011). Amaryllis belladonna, Boophone disticha and Crinum delagoense are three of the local Amaryllid plants known to be used in TM for treating this disease (Botha et al., 2005; Nair et al., 1998; Pettit et al., 1984). Apart from its clinical relevance to MND, the plant family Amaryllidaceae is most widely known in pharmacology for its anti-cancer properties (Kornienko and Evidente, 2008; Evidente and Kornienko, 2009; Nair et al., 2012a). Furthermore, its alkaloid constituents are known to be responsible for these effects as shown via both in vitro and in vivo models of study (Kornienko and Evidente, 2008; Evidente and Kornienko, 2009; Nair et al., 2012a). Although cytotoxic activities are detectable across all series of alkaloids of the Amaryllidaceae, the crinine and lycorine alkaloids are the most common targets of choice in such studies due to their potency (Evidente and Kornienko, 2009; Lamoral-Thys et al., 2010; Nair et al., 2012a). As such, over 100 different crinine and lycorine structures have been evaluated for anti-tumour activity (Evidente and Kornienko, 2009; Lamoral-Thys et al., 2010; Nair et al., 2012a). Of the 12 alkaloids reported from Boophone disticha (Hauth and Stauffer, 1961; Sandager et al., 2005; Neergaard et al., 2009; Adewusi et al., 2012; Cheesman et al., 2012), all with the exception of nerbonidine 12, acetylnertbowdine 18 and buphaeetine have been subjected to cytotoxicity screening against various cancer cells (Evidente and Kornienko, 2009; Lamoral-Thys et al., 2010; Nair et al., 2012a). In this regard, studies on lycorine 2 (Scheme 1) are significant in that it was amongst the first of the Amaryllidaceae alkaloids to exhibit cytotoxic activity as shown by its inhibitory effects towards cell division and cell elongation, as well as protein synthesis in eukaryotic cells (De Leo et al., 1973; Jimenez et al., 1976). Furthermore, both in vitro and in vivo models of leukaemia (HL-60) cells support the potency of lycorine as an antiproliferative agent (Liu et al., 2004, 2007). Notably, in some cell lines these effects were manifested via the apoptotic mechanistic pathway (Liu et al., 2007; Li et al., 2007; McNulty et al., 2009a). By contrast, antiproliferative effects by lycorine 2 were also exerted in apoptosis-resistant cell lines such as OE21 oesophageal cancer and SKMEL-28 melanoma cells (Van Goetsenoven et al., 2010). In terms of potency, IC50 as low as 0.5 μM were observed for lycorine 2 against various leukaemia and lymphoma cell lines, while for carcinomas, multiple myeloma and melanoma cells IC50 were in the range 3–10 μM (Lamoral-Thys et al., 2010). In vivo, HL-60 leukaemia-bearing mice exhibited a T/C index of 134% at a lycorine treatment dosage of 10 mg/kg (Lamoral-Thys et al., 2010). Similarly, crinine alkaloids of the Amaryllidaceae have come into focus since the identification of haemantamidine 23 as a cytotoxic agent over 30 years ago (Jimenez et al., 1976). Of the crinine identified in Boophone disticha, buphanisine 15 has been most studied, having been screened against 22 different cancers with the best activity seen in Vinblastine-resistant oral epidermoid KB-V1 carcinomas, multiple myeloma and melanoma cells IC50 were in the range 3–10 μM (Lamoral-Thys et al., 2010). In vivo, HL-60 leukaemia-bearing mice exhibited a T/C index of 134% at a lycorine treatment dosage of 10 mg/kg (Lamoral-Thys et al., 2010). Similarly, crinine alkaloids of the Amaryllidaceae have come into focus since the identification of haemantamidine 23 as a cytotoxic agent over 30 years ago (Jimenez et al., 1976). Of the crinine identified in Boophone disticha, buphanisine 15 has been most studied, having been screened against 22 different cancers with the best activity seen in Vinblastine-resistant oral epidermoid KB-V1 carcinomas, multiple myeloma and melanoma cells IC50 were in the range 3–10 μM (Lamoral-Thys et al., 2010).
Activities for buphanidine 13, buphanamidine 11, crinamidine 17, crinine 3 and undulatine 14 were generally moderate to mild with crinine shown to be most effective against the multi-drug resistant human myeloid leukaemia cell line HL-60/Dox (IC₅₀ 14.04 μM) (Berkov et al., 2011; Nair et al., 2012a). Finally, out of a mini-panel of five cancer cells, distichamine 16 exhibited best activity against HeLa cervical adenocarcinoma (IC₅₀ 2.2 μM) (Nair et al., 2012a,c). Information pertaining to in vivo studies of crinane alkaloids is generally lacking in the literature; however, one study described significant reductions in the growth of sarcoma 180 ascites tumours in mice after treatment with various β-crinanes (Ghosal, 1986; Nair et al., 2012a). In relation to the mechanistic basis to these alkaloids, the apoptotic mode of death in cancers has been demonstrated for crinine 3, distichamine 16, crinine 26 and haemanthamine 23, the first two of which are significant as they are constituents of Boophone disticha (Griffin et al., 2007; McNulty et al., 2007; Van Goitsemenoven et al., 2010; Berkov et al., 2011; Nair et al., 2012c). For example, McNulty et al. (2007) showed that up to 90% of rat hepatoma (5123 tc) cells exhibited apoptotic morphology after a 48 h treatment with either crinamine or haemanthamine (ED₅₀ 12.5 and 15 μM, respectively). Interestingly, this activity was seen to be selective as normal human embryonic kidney (293t) cells remained unaffected by the treatment (Griffin et al., 2007; McNulty et al., 2007; Nair et al., 2012a). Apart from this Berkov et al. (2011) demonstrated via oligonucleosomal DNA fragmentation that the cytotoxicity of crinine 3 in HL-60/Dox cells (IC₅₀ 14.04 μM) ensues via the apoptosis pathway. In addition, caspase-mediated apoptosis induction has recently been described for distichamine 16 in lymphoblastic leukaemia (CEM) cells (IC₅₀ 4.5 μM) (Nair et al., 2012a,c). As such, flow cytometric analysis showed that treatment with distichamine 16 increased the proportion of G₂/M phase cells in a dose-dependent manner, with concomitant reductions in the proportion of G₀/G₁ and S cells (Nair et al., 2012a,c). In addition, the proportion of cells with sub-G₁ amounts of DNA (apoptotic cells) increased (up to 23.7%) following a 24 h treatment with distichamine indicating that the compound was capable of cell cycle disturbance and apoptosis induction (Nair et al., 2012a,c). Furthermore, distichamine induced a 12.5-fold increase in caspase-3/7 activity after 24 h at the highest tested concentration (20 μM) compared to untreated controls (Nair et al., 2012a,c). In addition to this, several changes in the expression of apoptosis-related proteins were detected via Western blotting in CEM cells following treatment with distichamine (Nair et al., 2012a,c). For example, after 24 h at 10 and 20 μM cleavage of PARP (89 kDa fragment) was observed which also corresponded with decreased levels of procaspase-3 (Nair et al., 2012a,c). Alongside this, expression of the tumour suppressor protein p53 was discernible in the CEM cell control, and distichamine caused its enhanced expression after 24 h, notably at 10 and 20 μM (Nair et al., 2012a,c). No change in the expression of the anti-apoptotic protein Bcl-2 was observed but at 20 μM a decreased level of the anti-apoptotic protein Mcl-1 was detected indicating the onset of apoptosis (Nair et al., 2012a,c). The traditional usage of Boophone disticha in cancer therapy can therefore be ratified through several sources of convincing pharmacological evidence.

7.5. Toxicological studies

Despite the manifold benefits associated with the usage of Boophone disticha in TM, the plant is nevertheless one of several South African Amaryllids classified as poisonous (Van Wyk et al., 2002, 2005). This is understandable given the long cultural history of Boophone disticha as an arrow poison (Watt and Breyer-Brandwijk, 1962; Bisset, 1989; De Smet, 1998; Hutchings et al., 1996).

Interestingly, forensic examination of an arrow taken from a San community in the Cape (Section 5) and known to have been treated with Boophone disticha showed that the arrow poison was capable of killing mice within 20–30 min in subcutaneous doses of 100–300 μg (De Smet, 1998; Mebs et al., 1996). Although animals and birds are known to consume various parts of the plant (Table 1, entry 16), such tendencies have not been observed in humans (Watt and Breyer-Brandwijk, 1962; Hutchings et al., 1996). However, the widespread usage of bulb concoctions, decoctions and infusions suggest that these are obviously not taken at lethal dosages (Watt and Breyer-Brandwijk, 1962; Hutchings et al., 1996).

In cases where poisoning with Boophone disticha were reported, the toxic effects produced included nausea, coma, muscular flaccidity, visual impairment, stertorous breathing, respiratory paralysis, febrile or increased pulse, dyspnoea, and hyperaemia and oedema of the lungs (Watt and Breyer-Brandwijk, 1962; Nyazema, 1986; Hutchings et al., 1996; Du Plooy et al., 2001). Acute oral toxicity studies revealed that extracts of Boophone disticha were lethal to Sprague Dawley rats at doses equal to or higher than 240 mg/kg, killing animals between 30 min and 3 h after dose administration, with an LD₅₀ determined between 120 and 240 mg/kg (Gadaga et al., 2010). Furthermore, in the same study the most prominent neurotoxicological effects linked to doses higher than 240 mg/kg were increased flaccid limb paralysis, retropulsion and hypoactivity which were evident from significant rearing, reduced mobility and gait scores (Gadaga et al., 2010). In addition, it was suggested that mydriasis, palpebral closure, tachypnoea, piloerection and spastic hind limb paralysis observed at lower doses of Boophone disticha could be due to the anticholinergic effects of its alkaloid constituent lycorine 2 (Scheme 1) (De Smet, 1996; Gadaga et al., 2010). The sub-acute toxic effects of Boophone disticha appear to be mediated via interference with the neuronal pathways especially the central dopaminergic and motor neurons (Gadaga et al., 2010). Histopathological observations suggested the liver, small and large intestines, stomach, central nervous system and peripheral nervous system as the target organs (Gadaga et al., 2010). A further investigation was carried out to ascertain whether pre-treatment of Boophone disticha poisoned BALB/c mice with a CNS acting serotonin antagonist (cyproheptadine) had a protective effect from toxicity and mortality (Muteura et al., 2013). Using the Functional Observational Battery (FOB) test to evaluate neurobehavioral and physiological changes associated with toxicity, Muteura et al. (2013) showed that cyproheptadine pre-treatment (15–20 mg/kg) led to a dose-dependent decrease in mortality from 80% in untreated animals to 30% in the pre-treated group, as well as a reduction in other toxic symptoms typically associated with Boophone disticha poisoning (Gadaga et al., 2010).

Apart from this, based on the putative effects of Boophone disticha on inflammatory response and immune function, extracts of the plant were also investigated for ATP production effects in isolated human neutrophils (Botha et al., 2005). To this extent, ethanolic bulb extracts were shown to significantly decrease ATP as well as superoxide production in the neutrophil medium (Botha et al., 2005). A decrease in intracellular ATP is known to reflect possible cell injury due to toxicity to neutrophils (Crouch et al., 1993). Conversely, it was suggested that the therapeutic benefits of Boophone disticha may reside with its ability to inhibit superoxide release from neutrophils (Botha et al., 2005). Studies on the genotoxic effects of Boophone disticha showed extracts of the plant to be genotoxic to human lymphocytic cells as determined by the micronucleus test (Taylor et al., 2003). For example, in the test against aqueous methanol bulb extracts the number of micronuclei produced per thousand binucleated cells in the lymphocytes was 8, 14 and 2 at set concentrations of 100, 500 and 2500 ppm, respectively, with a control value of 3 (Taylor et al., 2003).
these entities have been shown to be chiefly responsible for the various biological effects exhibited by the plant, of which its use in the traditional treatment of cancer is most striking. Despite this, several areas of its usage in TM still require pharmacological validation. Furthermore, stringent efforts are required to further delineate the well-documented toxicological properties of Boophone disticha. As such, these collective efforts should go some way towards maximising the potential of Boophone disticha as a beacon for the plant family Amaryllidaceae in South African traditional medicine.

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References


