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Invited mini review

Cape aloes—A review of the phytochemistry, pharmacology and commercialisation of *Aloe ferox*

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ABSTRACT

Aloe ferox Mill. (= *A. candelabrum* A. Berger), commonly known as the bitter aloe or Cape aloe, is a polymorphic species indigenous to South Africa. The plant has been used since ancient times as a generic chemopreventive and anti-tumour remedy in folk medicine and it has a well-documented history of use as a laxative. In addition to the plethora of traditional medicinal uses, *A. ferox* has recently gained popularity as an ingredient in cosmetic formulations and food supplements. Anti-oxidant, antimicrobial, anti-inflammatory, anticancer and antimalarial activities, etc. have been reported. In addition, the ability of Cape aloes to enhance the transport of poorly permeable drugs has enjoyed recent research interest. Due to its medicinal and commercial importance it has been a popular research topic for natural product scientists who have isolated several chromones and anthrones from the leaf exudate and finished product (bitters). A summary of the historical and modern day uses, commercialisation, chemical composition and biological properties of this coveted ethnomedicinally and commercially important species is presented.

Contents

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1. Introduction

Aloe ferox Mill. (= *A. candelabrum* A. Berger) (Xanthorrhoeaceae, previously Asphodelaceae, Aloaceae or Liliaceae s.l.), commonly known as the bitter aloe or Cape aloe (also *khala*, *umhlaba*, *bitteraalwyn*) is a variable species indigenous to the Cape coastal region of South Africa, occurring in Swellendam in the west and extending to the southern parts of KwaZulu-Natal in the east (Reynolds, 1950; Van Wyk and Smith, 1996; Glen and Hardy, 2000). This cherished, popular ornamental aloe is single-stemmed with erect racemes of red, orange, yellow or rarely white flowers and spreading or gracefully curved thorny leaves (Fig. 1A). The 'ferox' in the botanical name, meaning ferocious, was given due to the thorny sharp reddish spines of the leaves. Northern forms of the species, previously known as *A. candelabrum*, are morphologically, genetically and chemically within the range of variation observed for *A. ferox* (Viljoen et al., 1996; Melin, 2009).

Aloe ferox has been used since ancient times and has a well-documented history of use as medicine. This plant is one of only a few plants depicted in San rock paintings (Fig. 1B) (Reynolds, 1950; Van Wyk, 2008). The bitter latex, known as Cape aloe, is used as laxative medicine in Africa and Europe and is considered to have bitter tonic, anti-oxidant, anti-inflammatory, antimicrobial and anticancer properties. The cosmetic and food supplement uses of aloe gel is a recent development that was stimulated by the tremendous commercial success of the USA-based *Aloe vera* industry, estimated to have a world-wide turnover of around 110 billion US dollars (International Aloe Science Council, 2004). In 1996, the *A. ferox* industry was estimated to be worth R4 million annually to rural harvesters in South Africa and export has considerably increased since then to approximately R12 to 15 million (Melin, 2009). Based on annual reports from South Africa, the total export of *A. ferox* was 4549 tonnes between 1981 and 1994 with the highest amounts exported to Germany, Japan, Argentina and Italy. Industrial processing of *A. ferox* gel started in the early 1990s when an aloe factory was established in Albertinia (Newton and Vaughan, 1996). The harvesting and processing has been historically centered in the Eastern and Western Cape where *A. ferox* occurs most abundantly (Melin, 2009). Most of the raw materials are still wild-harvested (wild-crafted) but small plantations have been established in recent years, mainly for ease of harvesting (resulting in considerable savings in production costs) and to allow for irrigation during periods of drought (thus ensuring the supply). Numerous classes of compounds such as chromones, anthraquinones, anthrone-*C*-glycosides and phenolic compounds have been isolated from *A. ferox*. Although aloe preparations are considered safe, some adverse effects such as hypersensitivity have been reported. This may be caused by apoptosis-inducing anthraquinones in *A. ferox*. This review concisely reports the ethnobotany, commercial aspects, phytochemistry, biological activity as well as briefly the potential toxicity of this highly significant commercial medicinal plant.

2. Traditional and modern day uses of *Aloe ferox*

Aloe bitters is orally consumed as a purgative (laxative) medicine in humans and is used for the same indication to treat cattle in Lesotho (Watt and Breyer-Brandwijk, 1962; British Pharmacopoeia, 1993; Maliehe, 1997; Grace et al., 2008, 2009). The literature reflects numerous other ethnomedicinal applications of the leaf exudate of *A. ferox* in southern Africa, such as to relieve arthritis and sinusitis, as well as conjunctivitis, opthalmia and other eye ailments by topical application of the leaf sap as eye drops (Smith, 1888, 1895; Watt and Breyer-Brandwijk, 1962; Palmer, 1985; Van Wyk and Gericke, 2000; Crouch et al., 2006). The powdered bitter fraction is applied to open wounds as a dusting powder (Van Wyk and Gericke, 2000), and to dress traditional scarifications and venereal ulcers (Van Wyk and Gericke, 2000). Mixed with Vaseline®, powdered Cape aloes is applied topically to treat herpes and shingles (Van Wyk and Gericke, 2000). Stem and leaf decoctions are used as emetics (Pujol, 1990) and leaf decoctions are gargled as treatment for a sore throat (Bhat and Jacobs, 1995) or applied to venereal sores (Watt and Breyer-Brandwijk, 1962; Bryant, 1966). Split or crushed fresh leaves are applied directly on open wounds, sores, burns and ulcers in humans and also used to treat sores and injuries in livestock (Van Wyk and Gericke, 2000). Leaves or roots boiled in water are taken for hypertension and stress (Pujol, 1990) and unspecified parts are applied to the skin and eyes, ears or nose (Hutchings, 1989). The use of *A. ferox* as treatment against infertility in women and impotence in men has been documented (Grace et al., 2008). Previously recorded uses include the leaf sap used to treat redwater, an infectious disease caused by *Clostridium haemolyticum*, and intestinal parasites in the Eastern Cape (Bishop, 1997). The sap is mixed with meal as purgative for cattle in South Africa (Watt and Breyer-Brandwijk, 1962) and used to treat sheep scab, a contagious parasitic disease, in East Africa (Bizimana, 1994).

It has been used in small doses as a "blood purifier" in cases of acne (Van Wyk et al., 2009) and leaf preparations are used for washing hair (Watt and Breyer-Brandwijk, 1962). More recently the inner leaf parenchyma has become popular ingredient in skin care products and tonic drinks (Kleinschmidt, 2004), although it has been difficult to compete with the *A. vera* products available in the international market. Commercial preparations of the gel have been reported to heal certain chronic leg ulcers and improve some cases of eczema in addition to providing significant relief in acute sunburn (Van Wyk and Gericke, 2000). Aloe gel can be added to cosmetic products such as cleansers, moisturisers, shampoos, suntan lotions, and sunburn screens. Aloesin shows promise as a pigmentation-altering agent for cosmetic or therapeutic applications (Jones et al., 2002; Yagi and Takeo, 2003). Another modern day use of *A. ferox* is its application as an intestinal permeation-enhancing agent for poorly permeable drugs (refer to Section 5.8).

The use of the inner, non-bitter gel as a food supplement is a modern development. No documentation of its use as food is found in the literature except for the production of jam (preserve) by Cape farmers (Palmer and Pitman, 1972; Fox and Norwood Young, 1982; Palmer, 1985; Rood, 1994a; Rood, 1994b). The health benefits of beverages and fortified food products containing the leaf parenchyma of *A. ferox* have been described. The Food and Drug Administration (FDA, 2002) has permitted the use of *A. ferox* as a direct food additive for human consumption as a natural flavouring substance. Aloe is also listed by the Council of Europe as a natural source of food flavouring. This category indicates that aloes can be added to foodstuff in the traditionally accepted manner, although there is insufficient information available for an adequate assessment of potential toxicity (Barnes et al., 2007). Kleinschmidt (2004) described the health benefits of beverages and fortified food products containing the leaf parenchyma of *A. ferox*, a by-product of the Cape aloes processing industry in South Africa. A food product containing aloe has been suggested in a patent application concerning orally administered compositions

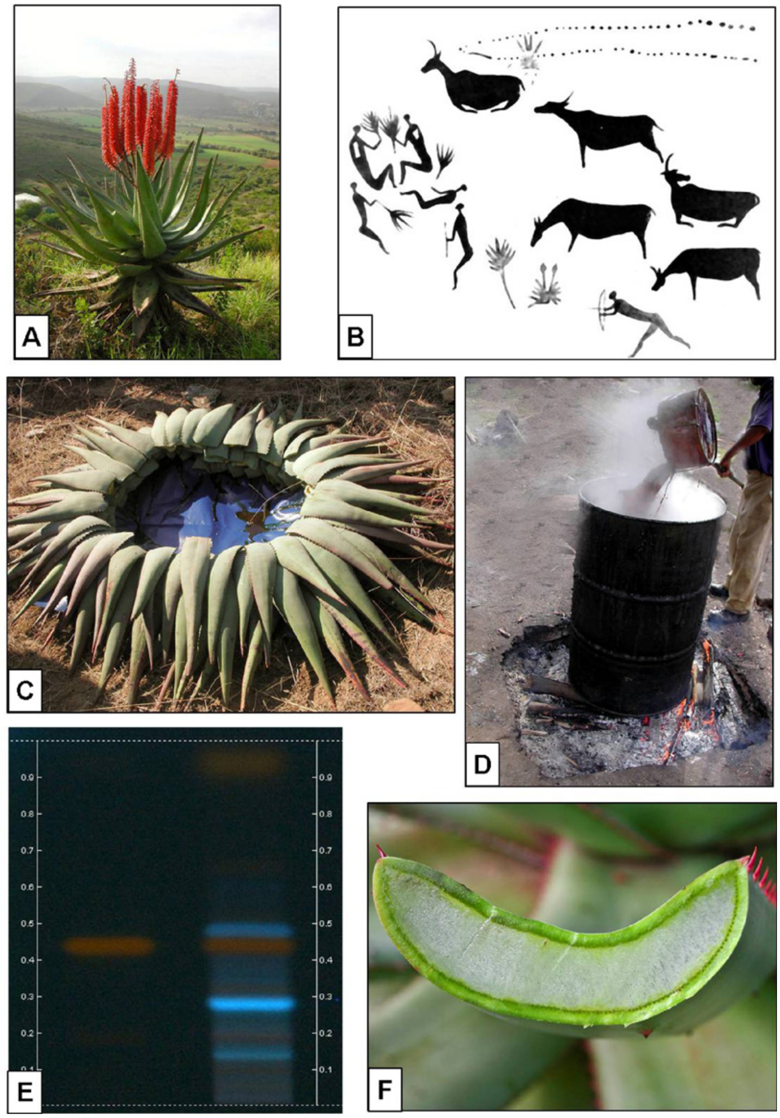

Fig. 1. (A) Photograph of *Aloe ferox* in flower; (B) San rock paintings depicting *A. ferox*; (C) tapping to collect the leaf exudate; (D) heat reduction process used to produce crystalline bitters; (E) TLC plate showing aloin (track 1) and *A. ferox* exudate (track 2); (F) cut *A. ferox* leaf showing the outer green rind, inner clear pulp and exudate-rich cells (dark green line).

meant to hydrate the skin from within as part of the consumers diet (Blumenstein-Stahl et al., 2005). Furthermore, aloe is included as a main ingredient in a patent composition for oral administration for the purpose of weight management by appetite reduction (Buchwald-Werner, 2008).

It should be noted that a large number of other *Aloe* species are used in traditional medicine in South Africa and other parts of Africa. Details can be found in Watt and Breyer-Brandwijk (1962), Neuwinger (1996, 2000), Arnold et al. (2002) and especially in the comprehensive recent reviews of Grace et al. (2008, 2009).

3. Intellectual property rights and commercialisation

The protection of intellectual property rights and benefit sharing from the commercialisation of natural products has been highlighted in recent times. Several national and international agreements have been signed governing the acquisition and application of natural resources and traditional knowledge. The Convention on Biological Diversity (CBD) formalised these agreements and it has been signed by at least 52 African countries. The CBD encompasses three main objectives: the conservation of biological diversity, the promotion of sustainable use of its components and the equitable sharing of benefits that derives from the utilisation of genetic resources (Neimark, 2009).

There is documented evidence that critical know-how about the harvesting of aloe-gum was transferred from an unidentified slave (presumably a Khoi-San person) to Johannes Petrus de Wit, a Gouritz River farmer who became the first exporter of Cape aloes in 1761 (Kruger and Beyers, 1977; Robertson, 1979). The industry is historically centered in the Gouritz River-Albertinia region but expanded long ago to include the Eastern Cape and other regions (Van Wyk et al., 1995a). Aloe tapping is an indigenous industry that involves independent rural entrepreneurs whom should be considered in terms of the equitable distribution of benefits to be derived from the aloe industry. Even though the commercialisation of the gel is a recent development and not directly related to aloe tapping, the two products are nevertheless closely linked in terms of manufacturing and processing (Standards South Africa, 2007). In 2008, the bioprospecting law was adopted in South Africa, requiring the acquisition of a research permit for anyone conducting applied research and commercial trading involving medicinal plants (Neimark, 2009). The implementation of this law will serve to protect intellectual property rights, but at the same time may slow down scientific research because it subjects researchers and developers to regulatory uncertainty and excessive bureaucracy (Crouch et al., 2008) to work on important medicinal plant species. In addition to bioprospecting laws applicable to all medicinal plants, *A. ferox* is considered a protected species under the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES). It is classified under Appendix II which stipulates species that are not currently threatened with extinction but may become so unless trade is closely regulated and controlled through the use of a permit system. Permits are granted under the understanding that export trade is restricted to levels that are not detrimental either to species survival, or to their role within ecosystems in which they occur (Article IV). Thus, internationally traded *A. ferox* must be accompanied by a valid CITES export permit (Melin, 2009; CITES, 2011).

South Africa is currently the largest exporter of wild-harvested aloe bitters and the commercial development of the aloe tapping industry is a good economic opportunity for rural communities. There has been interest from both the government as well as development agencies to expand and formalise this industry as a poverty-alleviation mechanism in rural areas. However, it is important to consider the role that sustainable harvesting plays in the lifecycle of any product derived from plants. In the case of aloe tapping, removal of the leaves used for the harvesting of bitters does not result in death of the plant thereby providing a sustainable financial resource (Melin, 2009). If the tapped leaves are then not discarded but rather used to produce aloe jelly (Botha, 1994), various other gel products or aloe fibers (Section 5.1), no part of the harvested plant goes to waste. The 250-year old traditional method of aloe tapping has changed little over the years. A shallow basin, created in the ground, is lined with a waterproof liner, and the leaves are stacked around the basin immediately after cutting (Fig. 1C). After collection of the raw bitter sap, a heat reduction process (Fig. 1D) is used to reduce the water content so that the product solidifies to form crystalline bitters known as aloe lump. Further processing may involve mechanical grinding to produce powdered bitters but in modern times high quality powdered bitters is also produced by spray-draying. The bitters is exported as such in its crystalline or powdered form. It is estimated that around 400 tonnes of bitters are produced through the harvesting of 10 million plants. Currently, value adding such as the production of cosmetics or beverages is done mainly in export destinations (Melin, 2009). Locally, the production of aloe drinks from polysaccharides released through a patented process (Botha, 1994) has become the most important and lucrative part of the local aloe manufacturing industry (C. Pattinson, Organic Aloe, pers. com. to B-EvW). More effort can be made towards adding value locally so that communities can earn more income. In addition, further patenting of the production/extraction process or novel uses should be explored (Rukangira, 2001) to ensure that the maximum benefit remains with the originators of traditional knowledge as well as the country of origin.

4. Phytochemistry of *Aloe ferox*

The aloe leaf can be divided into two major parts, the outer green rind and the inner clear pulp (Fig. 1F). Aloe bitters is found in so-called aloin cells (canals) situated adjacent to the vascular bundles in the green rind but not in the colourless parenchyma cells. The major compounds in fresh aloe bitters are aloeresin A, aloesin and aloin representing 70–97% of total dry weight, in a ratio of approximately 4:3:2, respectively (Van Wyk et al., 2009). Fig. 1E is a typical thin layer chromatography (TLC) chromatogram showing aloin in track one and an *A. ferox* exudate sample in track 2. Fig. 2 is a typical high performance liquid chromatography

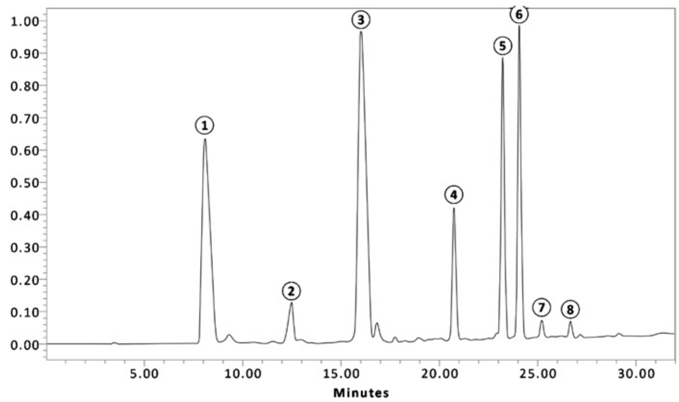

Fig. 2. An HPLC chromatogram of *A. ferox* exudate (Aloe bitters) developed with a methanol–water mobile phase. (1) Aloesin; (2) aloeresin C; (3) aloeresin A; (4) 5-hydroxyaloin; (5) aloin B; (6) aloin A; (7) aloinoside B and (8) aloinoside A.

(HPLC) chromatogram of *A. ferox* leaf exudate where the peaks of the following compounds are indicated: aloesin, aloeresin C, aloeresin A, 5-hydroxyaloin, aloin B, aloin A, aloinoside B, and aloinoside A. Using the traditional drying method (open fires), the exudate forms a dark-brown solid material responsible for the cathartic (purgative) effect (spray-drying gives an attractive, bright yellow powder). The inner pulp contains the clear slightly viscous gel generally used for its emollient and moisturising effects (Andersen, 2007). An ^{1}H NMR spectrum of *A. ferox* freeze-dried inner gel recorded at 600 MHz revealed major signals for glucose, fructose, malic acid and quinic acid (Fig. 3). Quinic acid is only a very small component of *A. vera* gel which mainly contains glucose, fructose, malic acid and aloverose.

4.1. Chromones

Most of the chromones isolated from Cape aloes are derivatives of 8-*C*-glucosyl-7-hydroxy-5-methyl-2-propyl-4-chromone. Differences arise from the degree of oxidation in the propyl side-chain, methylation of the hydroxyl group on C_7 and esterification of the glucose moiety Reynolds (2004). Furoaloesone is a derivative in which the 7-hydroxyl group is cyclised into a furan ring at C_8 of the chromone ring (Fig. 4) (Speranza et al., 1993b). A 7-hydroxy-5-methyl-chromone with a methyl group on C_2 has also been described (Fig. 4) (Speranza et al., 1993a).

Aloesin is widespread throughout the genus and could be regarded as the parent compound of the aloe chromones which was first described by Haynes et al. (1970). Speranza et al. (1988)

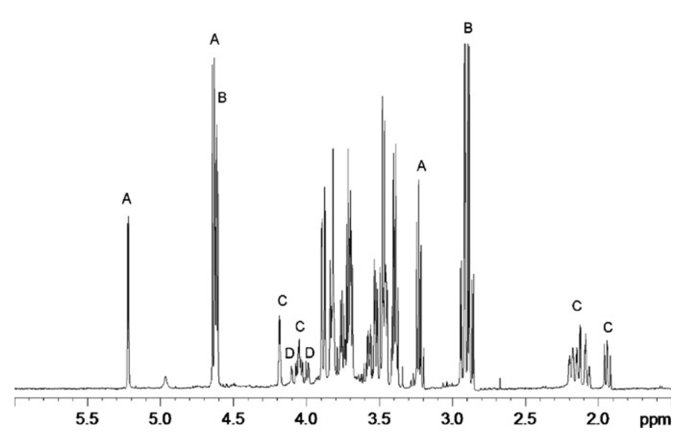

Fig. 3. ^{1}H NMR spectrum of *A. ferox* inner gel showing the characteristic signals for (A) glucose, (B) malic acid, (C) quinic acid and (D) fructose.

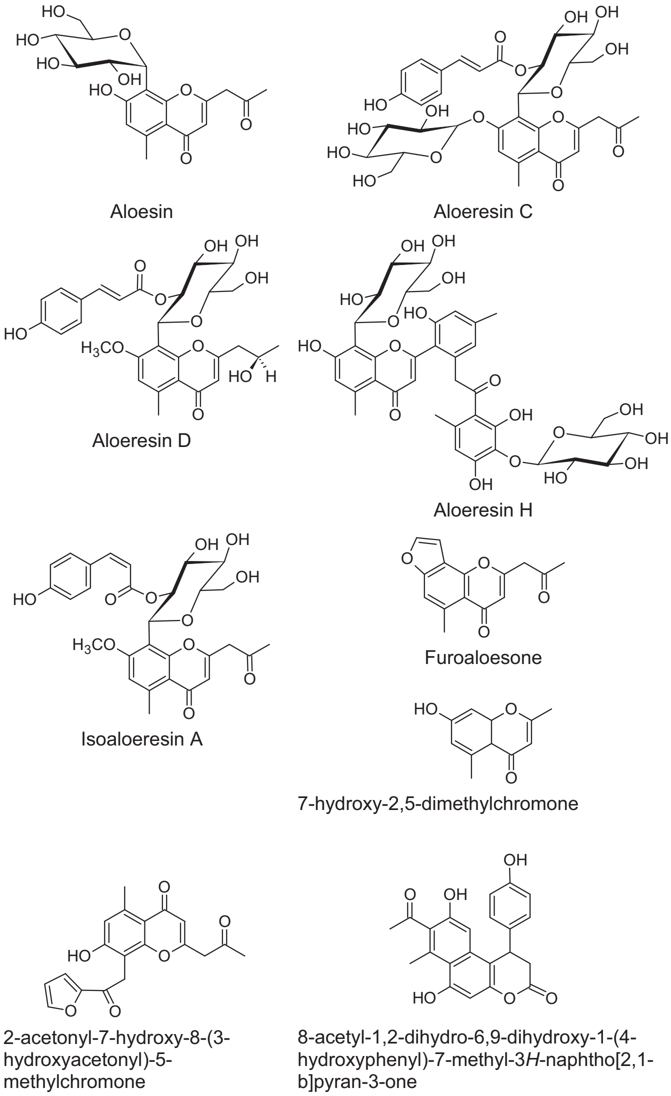

Fig. 4. Chemical structures of chromones isolated from *A. ferox*.

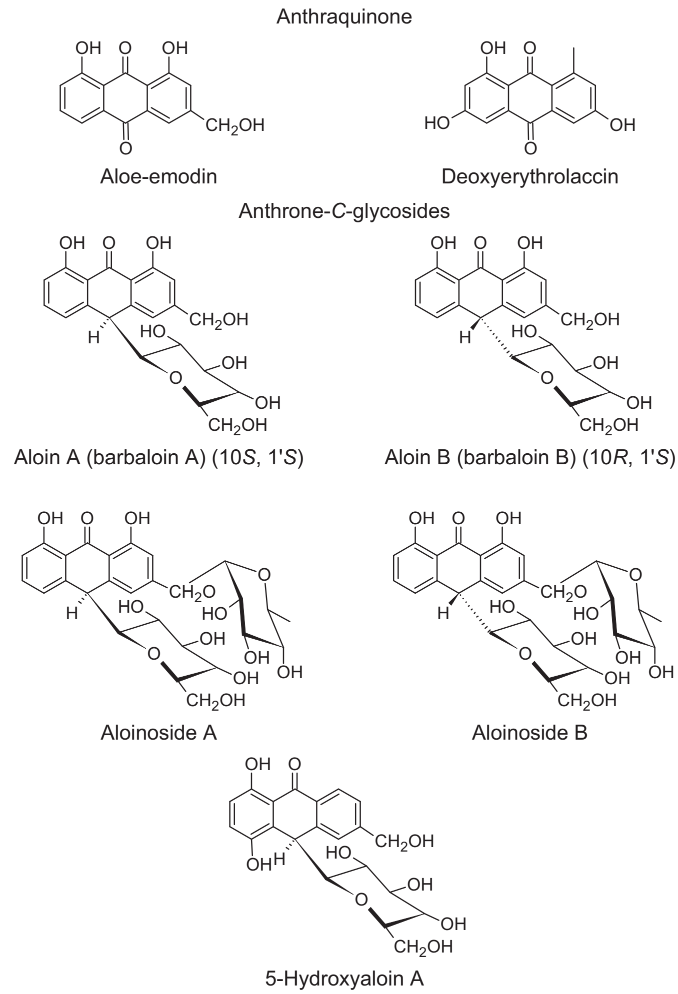

Fig. 5. Chemical structures of anthraquinone and anthrone-*C*-glycoside compounds isolated from *A. ferox*.

confirmed the structure of isoaloeresin A (Fig. 4), the 2′-*p*-coumaric acid ester of aloesin, as a minor component of Cape aloe. Speranza et al. (1985, 1986, 1996, 1997, 2005) also identified aloeresin C (2′-*p*-coumaroyl-7-glucosylaloesin), aloeresin D (7-me ether, 2″-*O*-(4-hydroxy-*E*-cinnamoyl)), 8-acetyl-1,2-dihydro-6,9-dihydroxy-1-(4-hydroxyphenyl)-7-methyl-3*H*-naphtho[2,1-b]pyran-3-one, 2-acetonyl-7-hydroxy-8-(3-hydroxyacetonyl)-5-methylchromone, 2-acetonyl-8-(2-furoylmethyl)-7-hydroxy-5-methylchromone and aloeresin I (2″-*O*-(4-hydroxy-*E*-cinnamoyl)) from Cape aloe. Manitto et al. (2003) reported a novel constituent aloeresin H from Cape aloe. Aloeresin H represents the first *C*, *C*-diglucoside discovered in commercial samples and its polyketide origin can be interpreted in terms of two-chain condensation (Fig. 4).

4.2. Anthraquinones and anthrones

Free anthraquinones and anthrones have been observed in some *Aloe* species but are not a major component of aloe bitters as they are mostly localised in the subterranean plant parts (Yagi et al., 1974; Dagne et al., 1994; Van Wyk et al., 1995b). Using paper chromatography, aloe emodin was detected and subsequently isolated from Cape aloes (Awe et al., 1958; Hörhammer et al., 1965; Koyama et al., 1994). Deoxyerythrolaccin which is a 6-hydroxy derivative of aloesaponarin II has been isolated from *A. ferox* (Fig. 5) (Koyama et al., 1994).

4.3. Anthrone-C-glycosides

Anthrone-*C*-glycosides are considered typical of aloe bitters and are represented by aloin A and B, collectively known as aloin or barbaloin (Reynolds, 1985), characterised as the *C*-glycoside of aloe-emodin anthrone (Fig. 5). These C-glycosides of the aloe-emodin anthrone are mainly responsible for the bitter and purgative properties (Dagne et al., 2000). Aloe bitters has been reported to contain up to 10% aloin/barbaloin (Groom and Reynolds, 1987), but Van Wyk et al. (1995a) reported levels ranging between 10 and 30% in natural populations, and typically around 20% in good quality commercial products.

5-Hydroxyaloin A is characteristic of Cape aloe (Fig. 5) (Rauwald and Beil, 1993). Two stereo-isomeric 15-*O*-rhamnosides of aloin have long been known from *A. ferox* as aloinosides A and B (Fig. 5) (Hörhammer et al., 1964; Rauwald, 1990). Gao et al. (2004) found that aloinoside B can be metabolised to aloin/barbaloin, isobarbaloin, and a hydroxyl metabolite by rat intestinal bacteria.

4.4. Other phenolic compounds

Aloenin is the *O*-glucoside of a phenol-pyran-2-one dimer which was first isolated from *A. arborescens* (Suga et al., 1974; Hirata and Suga, 1978). A breakdown product (‘process product’) isolated from Cape aloe was shown to be orcinol linked by a methylated methylene bridge to a phenyl residue reflecting part of the aloenin structure (Speranza et al., 1994). In 1982, Graf and Alexa isolated an even simpler compound, methyl-*p*-coumarate from Cape aloe. Feralolide isolated as a minor component of Cape aloe was shown to be a dimer with a methylene bridge of 2,4-dihydroxyacetophenone and 6,8-dihydroxyisocoumarin (Fig. 6) (Speranza et al., 1993a).

Three 1-methyltetralins (derivatives of 5,6,7,8-tetrahydroanthracene) were isolated from Cape aloe. A number of compounds based on the naphthalene and tetralin nuclei have been assigned to aloe components. Tetrahydroanthracenes could be regarded as naphthalene derivatives with a fused cyclohexane ring. The aglycone, feroxidin, was first characterised as 3,6,8-trihydroxy-1-methyltetralin (1,3,6-trihydroxy-8-methyl-5,6,7,8-tetrahydroanthracene) (Speranza et al., 1990, 1991) with a 6*S*, 8*S* configuration whereafter the 3-*O*-glucoside (feroxin A) and its *p*-coumaric acid ester (feroxin B) were described (Speranza et al., 1992). Three naphtha [2,3-C] furans bearing some structural resemblance to a reduced isoeleutherol were also characterised from Cape aloe, and named Cape aloes compound 1–3 (Koyama et al., 1994). In 2007, Kametani et al. isolated six compounds from the dichloromethane extract of *A. ferox*, including *p*-hydroxybenzaldehyde, *p*-hydroxyacetophenone, pyrocatechol, 10-oxooctadecanoic acid, 10-hydroxyoctadecanoic acid, methyl 10-hydroxyoctadecanoate. Some of them showed a significant growth-inhibiting effect on Ehrlich ascites tumour cells. Since the traditional preparation of Cape aloe requires a very harsh process involving several hours of boiling of the exudate over an open fire to evaporate the water and to solidify the extract, some of the compounds occurring in Cape aloe may be process compounds or artefacts (Dagne et al., 2000).

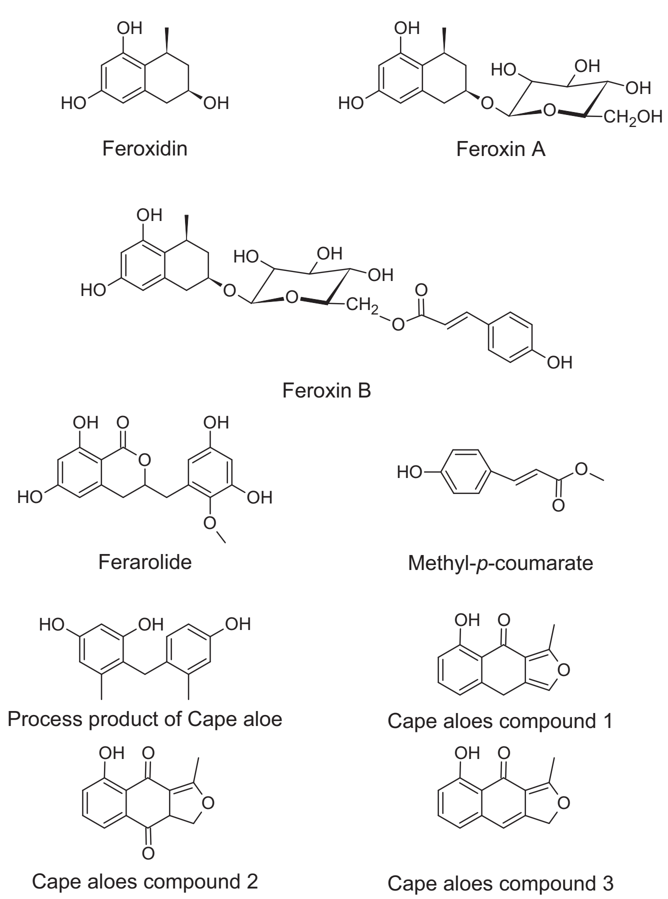

Fig. 6. Chemical structures of other phenolic compounds isolated from Cape aloes.

For this reason, spray-dried aloe bitters is nowadays preferred for some applications.

4.5. Volatile constituents

Magwa et al. (2006) reported the chemical composition of *A. ferox* volatile oil obtained by prolonged hydrodistillation and subjected to GC/MS analysis to identify the major constituents. Twenty-one compounds were identified with the major compounds including 3-cyclohexene-1-acetaldehyde, 4-dimethyl (9.5%), 2,4-decadien-1-ol, (E, E) (7.5%), 2-heptanol (7.3%) and bornylene (5.2%).

4.6. Miscellaneous compounds

Aloe ferox gel differs substantially from that of *A. vera* but the polysaccharide composition remains poorly explored (O'Brien, 2006). A report indicated that 14 distinct polysaccharide entities were distinguished from the gel of *A. ferox*, most of which were arabinogalactans or rhamnogalacturonans (Mabusela et al., 1990). Nitrogen analysis of leaf extracts revealed that the amino acid asparagine was the most abundant, followed by glutamine, alanine and histidine (Ishikawa et al., 1987). A number of enzymes were extracted and separated by starch gel electrophoresis for use as genetic markers to identify *A. arborescens* and *A. ferox* hybrids (Van der Bank and Van Wyk, 1996).

4.7. Compounds isolated from the roots

Two main types of anthraquinones (chrysophanol-type and aloesaponarin I-type) are present in the roots of *Aloe*. Anthraquinones of the chrysophanol-type are known to occur both in leaves and roots, and anthraquinones of aloesaponarin I-type are confined only to the roots. Van Wyk et al. (1995b) investigated 172 root samples of aloe species. It was determined that the compounds isolated from the roots were completely different compared to compounds isolated from the leaves and the anthraquinones and pre-anthraquinones present in the root has chemotaxonomic significance in the genus *Aloe*. These compounds appeared to have been derived through two parallel routes of the polyketide pathway leading to 1,8-dihydroxy and 1-methyl-8-hydroxy-anthraquinones (Fig. 7) (Dagne et al., 1994). The phytochemistry of the roots is important to mention due to its chemotaxonomic

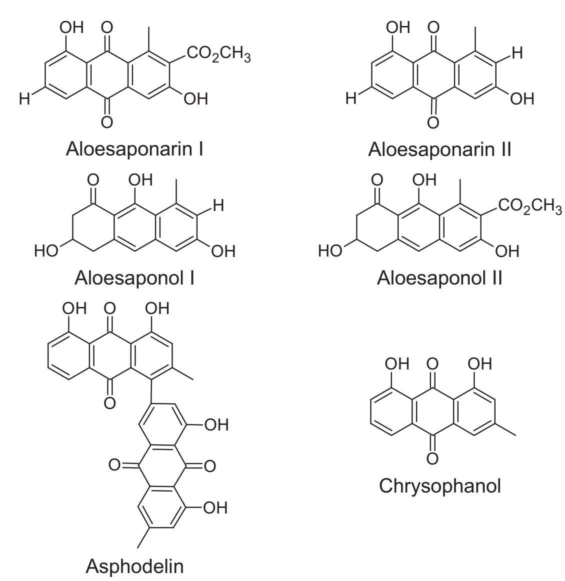

Fig. 7. Chemical structures of compounds isolated from the roots of *Aloe ferox*.

value. However, the roots of *A. ferox* are not harvested and have no commercial value.

5. The biological activities of *Aloe ferox*

This multipurpose plant was named the "Plant of Immortality" by the Egyptians because it can live and even bloom without soil. Aloe has been used since time immemorial, is still used extensively worldwide (Sikarwar et al., 2010), and has become a popular household remedy exhibiting a range of beneficial health-promoting properties.

5.1. Laxative effect

Cape aloe is widely used for its potent laxative and cathartic effects which are attributed to anthraquinones and in particular to aloe emodin (Steenkamp and Stewart, 2007). The anthrone *C*-glycosides (aloin A and B) are probably stable in the stomach and the sugar moiety prevents their absorption into the upper part of the gastrointestinal tract and subsequent detoxification in the liver. This protects them from breakdown in the intestine before they reach their site of action in the colon and rectum. Once they have reached the large intestine the glycosides behave like pro-drugs, liberating (through bacterial breakdown) the aglycones that act as the laxative (Breimer and Baars, 1976; Van Os, 1976). Izzo et al. (1999) studied the role of nitric oxide (NO) on aloe-induced diarrhoea in the rat. The results suggested that inhibition of basal calcium-dependent NO synthesis activity by aloe could reduce its diarrhoeal effect. Cape aloes is traditionally a component of Lewensessens (a bitter digestive tonic with a long history in South Africa) and more recently of 'Swedish bitters', originating in Sweden but also popular in Germany and elsewhere. This tincture is administered dropwise for indigestion and as laxative (Bisset and Wichtl, 2001). Wintola et al. (2010) evaluated the toxicological property of the aqueous extract of *A. ferox* in loperamide-induced constipated rats. The results suggested that *A. ferox* may be safe as an oral remedy to relieve constipation. A patent, filed in 2004, describes an aloe suppository, containing aloe bitters, to be used as a laxative. It is also indicated that it may be used for the treatment of hemorrhoids and bacterial infections of the anus, as an anti-inflammatory agent, anti-allergic agent and as a wound-healing promoter (Zolotariov and Zolotariov, 2004).

Conversely, aloe fibers have been suggested as a regulator of lower bowel function together with bentonite and/or kaolin in a patent application to treat irritable bowel syndrome (IBS). The aloe powder is produced using the leaves already cut by aloe tappers from which the bitter sap has been drained. These leaves are collected, sliced thinly, the remaining bitter sap removed, sun-dried and finally milled into powder (so-called whole leaf powder). The powder is incorporated into the formulation in a ratio of 30–70% with bentonite/kaolin making up the balance and formulated into granules or tablets. In addition to IBS treatment, it is suggested for use in end-stage AIDS patients with chronic diarrhoea (Taylor, 2003).

5.2. Skin and wound healing properties

Traditionally the leaves and roots of *A. ferox* are applied topically, sometimes mixed with animal fat, or taken internally to treat eczema, dermatitis and acne. It is also used to treat various other skin diseases or conditions such as skin cancer, burns and psoriasis (Hutchings et al., 1996; Maliehe, 1997; Van Wyk et al., 2009; Loots et al., 2007). Acne and other topical dermatologic lesions such as burns, varicose ulcers and seborrhoea are treated in some cases by topical application of benzoyl peroxide. In acne treatment benzoyl peroxide has a keratolytic effect, causing dryness, exfoliation and a decrease in bacterial flora. A patent formulation comprising of benzoyl peroxide and aloe gel has been filed. This patent describes the positive effects of aloe gel on the irritation normally caused by the application of benzoyl peroxide. It is hypothesised that the blend will reduce skin irritation thus enabling the use of higher concentrations of benzoyl peroxide (20%) with fewer side effects and superior clinical efficacy (Gruber, 1986).

Wound healing is a complex process involving three distinct and overlapping events: (1) inflammation (2) new tissue formation (granulation) and (3) maturation (McNees, 2006). Aloe gel (derived from *A. vera*) has been shown to improve wound healing after topical and systemic administration in several studies. Several mechanisms have been proposed for the wound healing effects of aloe, which include keeping the wound moist, increased epithelial cell migration, more rapid maturation of collagen and reduction in inflammation (Reynolds and Dweck, 1999). The mucilaginous polysaccharides contained in the clear pulp of aloe leaf have been demonstrated to be the major ingredient responsible for the healing (Eshun and He, 2004). However, new evidence from a rat study has shown that emodin is also capable of promoting the repair of excisional wounds via stimulating tissue regeneration (Tang et al., 2007). A 1963 patent describes the topical healing ability of polyuronide derived from aloe species (including *A. ferox*), especially in the treatment of open wounds and burns. It is said to detoxify the damaged surface area, and provides analgesic and anaesthetic effects while promoting new tissue formation (granulation) which fills the wound (Farkas, 1963). Barrantes and Guinea (2003) demonstrated that *A. ferox* enriched with aloins can inhibit collagenase and metalloprotease activity, which can degrade collagen connective tissue. The effect of *A. ferox* whole leaf juice on wound healing and skin repair was investigated in an animal model and the safety evaluated. The results showed that the *A. ferox* whole leaf juice preparation accelerates wound closure and selectively inhibits microbial growth. No dermal toxicity or side-effects were observed during the experimental period (Jia et al., 2008).

Skin hyperpigmentation is caused by the overproduction of epidermal melanin which is synthesised by the action of tyrosinase. Aloesin and arbutin can inhibit tyrosinase activity in a synergistic manner (Jin et al., 1999). Choi et al. (2002) reported that aloesin can inhibit hyperpigmentation in human skin after UV radiation in a dose-dependent manner and co-treatment with aloesin and arbutin showed an additive effect. Aloesin, may be included in a patent cosmetic formulation as pure aloesin, or an aloe extract containing at least 40% aloesin to be applied as a sunscreen to the skin or hair. Aloesin is known to absorb light, particularly in the ultraviolet B (UVB) region, with an absorption peak at 296 nm and may therefore be used to protect against solar radiation (Grollier et al., 1987) and consequent hyperpigmentation. In a sunscreen/anti-hyperpigmentation formulation a higher aloesin content could therefore be considered beneficial. Steenkamp et al. (2008) filed a patent describing the hydrolytic conversion of aloeresin A to aloesin, thereby increasing the amount of aloesin available for extraction from the sap. The commercial value of the sap or aloe bitters is therefore increased (Steenkamp et al., 2008).

5.3. Anti-oxidant effect

An anti-oxidant is a substance that significantly delays or inhibits oxidation of the oxidisable substrate at low concentrations (Halliwell and Gutteridge, 1999). Loots et al. (2007) confirmed the anti-oxidant capacity of *A. ferox* using oxygen radical absorbance capacity (ORAC) and ferric reducing anti-oxidant power (FRAP) analyses. The majority of the phenolic acids/polyphenols, indoles and alkaloids identified in *A. ferox* are known to possess anti-oxidant activity and may contribute to the ORAC and FRAP values of these extracts. Due to its phytochemical composition, *A. ferox* may show promise in alleviating symptoms associated with/or in the prevention of cardiovascular disease, cancer, neurodegeneration, and diabetes (Loots et al., 2007). Jones et al. (2002) demonstrated that aloeresins in *A. ferox* inhibited tyrosine at cellular level without deterring cell viability. Furthermore, it exhibited superior anti-oxidant activity compared to green tea and grape seed extracts. Frum and Viljoen (2006) reported that the methanol extract of the leaves of *A. ferox* displayed strong 2,2-diphenyl-1-picrylhydrazyl (DPPH) anti-oxidant activity with an IC_{50} value of 19.11 ± 0.10 ppm. A patent application by Jia and Farrow (2003) describes the identification and purification of 7-hydroxychromones, such as aloesin from an aloe extract prepared by whole-leaf processing. These 7-hydroxychromones suppresses free radical generation and the production of reactive oxygen species (ROS) thereby preventing and treating ROS-mediated conditions and conditions associated with other oxidative processes.

5.4. Anti-inflammatory activity

Aloe ferox has long been used to treat inflammation associated with injuries (Smith, 1888; Rodin, 1985), as well as ailments such as conjunctivitis and sinusitis (Van Wyk and Gericke, 2000; Crouch et al., 2006). Lindsey et al. (2002) investigated 53 methanolic extracts of aloe species for anti-inflammatory activity using the cyclooxygenase-1assay, and *A. ferox* exhibited inhibition. Aloeresin I (1 μmol/cm^2) isolated from Cape aloe reduces the *in vivo* oedematous response (39%) induced by croton oil in the mouse ear with the same potency as aloesin, and to a higher extent than aloeresin H and indomethacin (0.3 μmol/cm^2) (Speranza et al., 2005). Mwale and Masika (2010) evaluated the anti-inflammatory activity of *A. ferox* whole leaf aqueous extract. In high doses (400 mg/kg), *A. ferox* exhibited anti-inflammatory and analgesic activities. Rat-paw oedema induced by carrageenan and formaldehyde was inhibited by 78.2% and 89.3%, respectively. The analgesic activity was 57.1 and 67.3% in phase 1 and 2 of the formalin test and 88.2% in acetic acid test. Various species of aloe, including *A. ferox* and the compounds extracted from it, are listed in a medicinal formulation patent intended to treat various ailments such as arthritis, minor wounds and sport injuries due to topical analgesic and counter-irritant effects (Squires, 2010).

5.5. Antimicrobial activity

Aloe ferox is used to treat numerous infections, particularly sexually transmitted infections and internal parasites. In the Eastern Cape Province of South Africa it is widely used for the treatment of various diseases including gonorrhoeae and syphilis (Grace et al., 2008). The antibacterial activity of aloe emodin, chrysophanol and aloin A isolated from *A. ferox* was investigated using the microplate dilution method. Aloe emodin and aloin A showed inhibitory activity against all the test organisms (*Bacillus cereus*, *B. subtilis*, *Staphylococcus aureus*, *S. epidermidis*, *Escherichia coli*, *Shigella sonnei*), while chrysophanol only inhibited *B. subtilis*, *S. epidermidis* and *E. coli* (Kambizi et al., 2004). Coopoosamy and Magwa (2006) demonstrated that aloe emodin and aloin A had antibacterial activity with a minimum inhibitory concentration (MIC) ranging from 62.5 μg/ml against *B. subtilis* and *E. coli* to 250 μg/ml against *S. epidermidis* and *S. sonnei*. Some studies reported unspecified antifungal activity of *A. ferox* 'juice' against *Trichophyton* spp. causing athlete's foot and thrush (Soeda et al., 1966). A methanol extract and aloin exhibited activity of 0.5 and 0.1 mg/ml, respectively, against *Neisseria gonorrhoeae*. Low activity (MIC = 20 mg/ml) was recorded for the methanol extract against *Candida albicans*, while aloin exhibited activity of 5 mg/ml (Kambizi and Afolayan, 2008). The acetone extract of *A. ferox* was found to be fungicidal (10 mg/ml) against five fungi using the agar dilution method (Afolayan et al., 2002). In South Africa Cape aloe is topically applied to sores caused by viral infections such as warts, herpes and shingles (Van Wyk and Gericke, 2000). Kambizi et al. (2007) demonstrated the antiviral effects of *A. ferox* on herpes simplex virus type 1 *in vitro*. Aqueous extracts of *A. ferox* showed detectable activity at a concentration of 1 mg/ml and no cytotoxic effects were observed.

The topical antibacterial as well as anti-inflammatory properties of aloe are embodied in a laxative suppository preparation patent application used for the treatment of hemorrhoids and bacterial infections of the anus (Zolotariov and Zolotariov, 2004). Moreover, aloe extracts and compounds extracted from aloe is included as part of a multi-component preparation used to treat oral mucositis where it is suggested that it will have an antibacterial action against common wound-infecting bacteria in addition to anti-inflammatory action on mouth ulcers (Sekharam and Sekharam, 2007).

5.6. Anti-cancer activity

Aloe ferox is used as an anti-cancer agent (Soeda, 1969; Van Wyk et al., 2009; Capasso et al., 1998; Pecere et al., 2000). Aloe emodin has been reported to have selective activity against neuroectodermal tumours, with practically no effect on normal cells (Pecere et al., 2000). Aloe emodin promotes cell death through specific drug uptake by neuroectodermal tumours (Pecere et al., 2003). Koyama et al. (2001) also demonstrated the inhibitory effect of aloe emodin on the activation of Epstein–Barr virus (which plays a role in the emergence of cancer) with a log IC_{50} value of 2.656. The combined effect of aloe emodin and the chemotherapeutic agent cisplatinol (doxorubicin, 5-fluorouracil) on the proliferation of an adhering variant cell line of Merkel cell carcinoma has also been demonstrated (Fenig et al., 2004). Kametani et al. (2007a) isolated ten compounds from the dichloromethane extract of Cape aloe, including aloe emodin, *p*-hydroxybenzaldehyde, *p*-hydroxyacetophenone, pyrocatechol, 10-oxooctadecanoic acid, 10-hydroxyoctadecanoic acid, methyl 10-hydroxyoctadecanoate, 7-hydroxy-2,5-dimethyl-chromone, furoaloesone and 2-acetonyl-8-(2-furoylmethyl)-7-hydroxy-5-methylchromone. Their growth-inhibiting effect on Ehrlich ascites tumour cells (EATC) was investigated using the trypan blue method. The results suggested that the strong growth-inhibiting effect was dependent on the synergistic effect from the combination of aloe emodin and chromone compounds such as 7-hydroxy-2,5-dimethylcromone. The mechanism of action was associated with decreased retinoblastoma protein phosphorylation (Kametani et al., 2007b). Due to a "hypercoagulable state" often associated with cancer, medications having anti-thrombotic/anti-coagulant activity in addition to anti-cancer activity would be ideal. The aqueous extract of *A. ferox* was found to exhibit anticoagulant activity with an IC_{50} value of 7.74 mg/ml in the thrombin-induced clotting time assay (Kee et al., 2008).

5.7. Antimalarial activity

Traditionally, aloes are not known to possess antimalarial properties, but several scientific studies indicated that some *Aloe* species can be used treat malaria-related symptoms. Van Zyl and Viljoen (2002) tested 34 *Aloe* species and their main constituents for anti-plasmodial activity using the titrated [^{3}H]-hypoxanthine incorporation assay. It was found that several methanol extracts inhibited *Plasmodium falciparum* growth by 50% in concentrations of 32–77 μg/ml. Clarkson et al. (2004) tested 134 plant species *in* *vitro* against *P. falciparum* strain D_{10} using the parasite lactate dehydrogenase (pLDH) assay. The organic extract (DCM/MeOH 1:1) of *A. ferox* showed promising anti-plasmodial activity (IC_{50} 8 μg/ml), while the aqueous extracts did not show any activity (Clarkson et al., 2004).

5.8. Permeation-enhancing effect

The effect of aloe emodin anthrone on water-soluble and poorly permeable compounds, e.g. 5(6)-carboxyfluorescein (CF), was investigated in rat colonic mucosa using an Ussing-type chamber (Kai et al., 2002). Aloin A and B can be transformed into aloe emodin anthrone under anaerobic conditions and aloe emodin under aerobic conditions through an enzymatic redox reaction involving rat intestinal microflora. Aloe emodin anthrone significantly increased the permeation of CF in a dose-dependent manner. The enhanced permeability was significantly suppressed by a histamine H_1 receptor antagonist, pyrilamine, a mast cell stabiliser, ketotifen, and an inhibitor of protein kinase, but not by the histamine H_2 receptor antagonist, cimetidine. Aloe emodin anthrone decreased the electrical resistance of the membrane to 30%, but lactate dehydrogenase activity was not significantly different compared to the control. The proposed permeation-enhancing mechanism was that aloe emodin anthrone stimulated mast cells within the colonic mucosa to release histamine, which probably bind to the H_1 receptor. The intracellular protein kinase C route activated by H_1 receptor activation enhanced the permeability of water-soluble and poorly permeable drugs via opening of tight junctions in rat colonic membrane (Kai et al., 2002). The penetration-enhancing properties of aloe compositions are incorporated into several patent applications. One patent describes the transdermal delivery of an opioid analgesic (Meyer et al., 2007) and another, the topical application of a local anaesthetic (Fischer et al., 2003). In both cases 'aloe composition' refers to the use of any of several species including *A. ferox*, to be included in the formulation as a transdermal permeation-enhancing agent.

5.9. Anthelmintic activity

The crude aqueous extract of *A. ferox* was investigated for its *in vitro* anthelmintic activity on the egg and larvae of the nematode parasite *Haemonchus contortus*. *Aloe ferox* extracts exhibited 100% egg hatch inhibition at 20 mg/ml and larval development inhibition at 2.5 mg/ml and higher (Maphosa et al., 2010).

5.10. Adverse effects/toxicity

There is insufficient data available to properly evaluate the safety of aloe products (FDA, 2002). Reports of allergic conditions and hypersensitivity to aloe preparations have been noted and several single-case reports are available (Morrow et al., 1980; Ernst, 2000). Wang et al. (2002) reported that 8-*C*-D-glucopyranosyl-7-hydroxy-5-methylchromone-2-carboxylic acid and a 2-*O*′-*p*-coumaroyl derivative structurally related to aloesin and aloeresin A, were identified in a herbal tea that caused severe vomiting in a South African patient who had taken the traditional remedy to clean his stomach. These compounds may be formed by oxidative degradation during preparation of the herbal tea from an *Aloe* species or during its storage. A 47-year-old man from Soweto, South Africa, developed acute oliguric renal failure and liver dysfunction after ingestion of an herbal remedy containing Cape aloe (Luyckx et al., 2002). A case of multi-organ toxicity was reported after a 28-year-old Turkish man ingested a mixture of herbs containing *Pimpinella anisum*, *Rosmarinus officinalis*, *Aloe ferox*, *Matricaria chamomilla* and Swedish syrup. The patient presented with dyspnoea, sore throat, nausea, vomiting, fatigue and leg muscle cramps within 30 min after ingestion. Clinical tests revealed acute renal failure due to rhabdomyolysis, acute hepatitis-like hepatotoxicity and cardiotoxicity accompanied by angio-oedema (Berrin et al., 2006). Recently, Mello et al. (2008) investigated another phytotherapeutic formulation consisting of *Gentiana lutea* (genciana), *Rheum palmatum* (ruibarbo), *Aloe ferox* (aloe), *Cynara scolymus* (alcachofra), *Atropa belladona* (belladonna), *Paumus boldus* (boldo) and *Baccharis trimera* (carqueja) (Gotas Preciosas®) for potential toxicological effects when orally administered to New Zealand rabbits. The results showed that this combination product can be considered relatively innocuous. According to a report by Andersen (2007), *A. ferox* leaf extract exhibited no acute dermal and ocular toxicity in New Zealand white rabbits.

Some studies investigated the mechanism of aloe-induced toxicity. The primary compounds found to be responsible for toxic effects are apoptosis-inducing anthraquinones such as aloe emodin and aloin. These compounds are found in the sap and outer leaf and not in the inner gel of the aloe plant (Eshun and He, 2004). Aloe emodin induced apoptosis through a P_{53}-dependent pathway that altered the cell cycle, involved reactive oxygen species and affected mitochondria (Shieh et al., 2004; Chen et al., 2004; Lee et al., 2006; Su et al., 2005). Aloin has also been shown to alter the cell cycle at M phase (Esmat et al., 2005), to induce apoptosis through inhibition of the cell cycle via down-regulation of cyclin B1 (Esmat et al., 2006) and to induce dose-dependent apoptosis involving the mitochondria in Jurkat cells (Buenz, 2008).

6. Conclusions

The use of *A. ferox* as a multi-purpose traditional medicine has translated into several commercial applications and it is a highly valued plant in the pharmaceutical, natural health, food and cosmetic industries. *Aloe ferox* is considered South Africa's main wild harvested commercially traded species. The finished product obtained from aloe tapping, aloe bitters, has remained a key South African export product since 1761 when it was first exported to Europe. The aloe tapping industry is the livelihood of many rural communities, and formalisation of the industry in the form of establishment of co-operatives and trade agreements for example may have an extensive poverty alleviation effect (Melin, 2009).

Aloe ferox has many traditional, documented medicinal uses. It is most popularly used for its laxative effect (aloe bitters) and as a topical application to the skin, eyes and mucous membranes. Scientific studies conducted have verified many of the traditional uses. More recently, the cosmetic industry has shown interest in *A. ferox* gel. The gel is freely available for purchase and one internet site proclaims "a skin care routine without Super Aloe Gel is incomplete". According to this site, the gel is to be applied all over the face and body for repairing the skin from cuts, insect bites, burns, healing wounds and to enhance complexion. It also mentions that the gel contains at least 130 medicinal agents with anti-inflammatory, analgesic, calming, antiseptic, germicidal, antiviral, anti-parasitic, anti-tumour and anti-cancer effects encompassing all of the traditional uses of and scientific studies done on *A. ferox* and its constituents. The phytochemistry of *A. ferox* has been extensively investigated revealing that it contains chromones, anthraquinones, antrhrones, anthrone-*C*-glycosides and other phenolic compounds.

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