Chemistry of *Aloe* Species

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Abstract: The genus *Aloe (*Asphodelaceae), with nearly 420 species confined mainly to Africa, has over the years proved to be one of the most important sources of biologically active compounds. Over 130 compounds belonging to different classes including anthrones, chromones, pyrones, coumarins, alkaloids, glycoproteins, naphthalenes and flavonoids have so far been reported from the genus. Although many of the reports on *Aloe* are dominated by *A. vera* and *A. ferox*, there have also been a number of fruitful phytochemical studies on many other members of the genus. In this review an attempt is made to present all compounds isolated to date from *Aloe.* The biogenesis and chemotaxonomic significance of these compounds are also discussed.

INTRODUCTION

Aloe is a unique plant group that is predominantly found in Africa, with centres of species richness in Southern and Eastern Africa and Madagascar. The term *aloe* is derived from the Arabic word *alloeh*, which means a shining bitter substance in reference to the exudate [1]. The history of use of *Aloe* leaves dates back thousands of years [2], in particular for the treatment of constipation, burns and skin disorders [3]. The leaves of *Aloe* yield two medicinal products – mucilaginous gel and a bitter exudate. The gel is incorporated, due to its moisturising and soothing properties, in cosmetic products, shampoos, shaving and skin care creams [4]. It has been claimed that *Aloe* gel can among other things, enhance immunity, improve liver function, prevent asthma and act as anti-inflammatory, anti-ulcer, anti-diabetes and anti-hypertension agent [5, 6].

The bitter exudates also known as "bitter aloes" or "aloe drug" are used mainly as laxatives [7] and as bittering agents in certain beverages [8]. Out of a large number of *Aloe* species only few are of importance in international trade, with the most outstanding being *A. ferox* and *A. vera*. *Aloe ferox* Miller is the main species used to produce aloe drug also known in commercial circles as "Cape Aloe" [9]. This species, though heavily traded is wild-harvested in a sustainable manner and its survival is not threatened [10]. *A. vera*, having been domesticated for many centuries, with no counterpart for it in the wild, is certainly the most important species of *Aloe* used commercially for medicinal and cosmetic purposes. Its bitter dried latex is also known as "Curaçao aloe" [9] and its clear gel is an important component of many skin care and other cosmetic preparations. For industrial-scale production of the gel, *A. vera* is cultivated in large commercial farms in many countries, particularly in the USA, Mexico, Columbia, Venezuela, China and Thailand.

There is limited commercial interest in a few other species notably *A. arborescens*, sometimes known as "Japan aloe", because of it widespread introduction into Japan, *A. marlothii*, in former times traded to a limited extent as "Natal aloe" and various products of uncertain origin, such as the so-called Kenya aloe.

This review highlights the major achievements attained so far in the study of the chemistry of *Aloe* species including a discussion of the chemotaxonomic significance of *Aloe* compounds.

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A previous review on *Aloe* compounds was that of Reynolds [11].

THE GENUS *ALOE*

Taxonomic interest in *Aloe* was probably initiated due to the primal use of aloes by man since early civilization. This is confirmed by the inclusion of *Aloe vera* in Dioscorides' De Materia Medica (written in the first century) and also in a later illustrated copy known as the Codex Aniciae Juliana, written in 512 AD. This appears to be the first illustration of any species of *Aloe*, although rock paintings of *A. ferox* and *A. broomii* are known from South Africa. Although several references to *Aloe* appear since early history, the authenticity and identity of the material is often in doubt. Nowadays, aloes are sometimes confused with members of the New World genus *Agave*. In the period 1600 - 1800 various descriptions and lists of *Aloe* species were published. Initially *Gasteria* and *Haworthia* fell within the taxonomic concept of *Aloe*.

In 1908 the most comprehensive work on *Aloe* was published by Berger in Das Pflanzenreich (Liliac.-Aloin) [12]. The two monumental publications by Reynolds in 1950 and 1966 [13, 14] laid the cornerstone for the taxonomy of *Aloe*. In his 1950 book [13], Reynolds treats 132 species of *Aloe* and mostly follows Berger's system of classification, which is an utilitarian system that does not necessarily reflect natural relationships as morphological similarity is the only criterion used to group species. Since these valuable contributions by Reynolds, accounts of many new species have been published by several *Aloe* taxonomists, which, together with the recent inclusion of *Lomatophyllum* in *Aloe* [15] results in

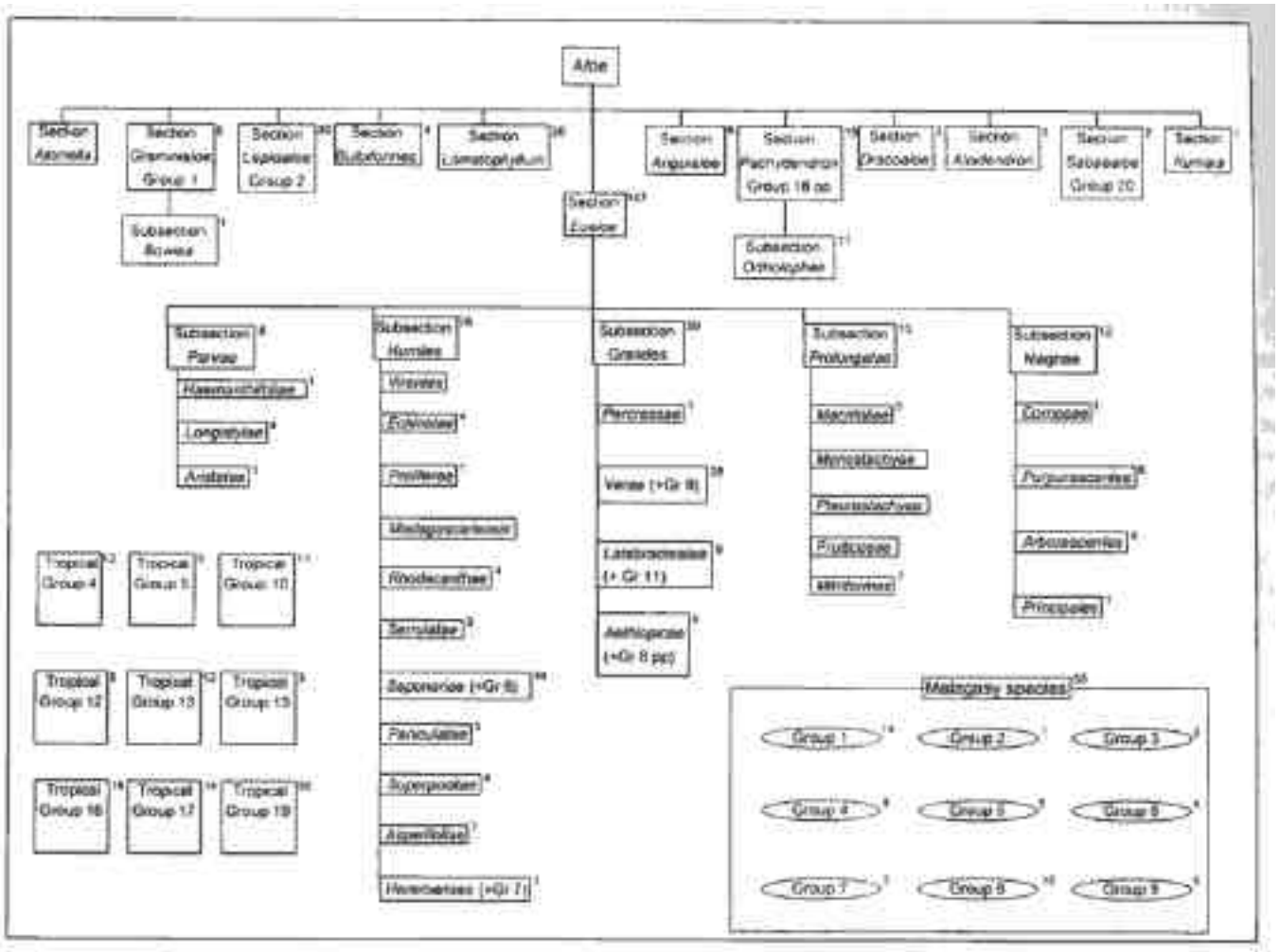


Fig. (1). Taxonomic hierarchy for *Aloe*. All 'post-Reynolds' species have been placed in groups to which authors have expressed them to be related. The number at the top right is the total number of species in each group.

a 'mega-genus' of *ca*. 420 species. The recently published book on Aloes of South Africa gives the reader further insight into the diversity of this genus [16].

THE PRESENT CLASSIFICATION SYSTEM OF *ALOE*

Dahlgren [17] divided the Monocotyledons into several superorders of which the Liliflorae is the largest. The order Asparagales houses the family Asphodelaceae which is sub-divided into two subfamilies, the Asphodeloideae and the Alooideae. The Alooideae consists of six genera of which *Aloe* is the largest. These two subfamilies were for sometime considered to be separate families, the Asphodelaceae and Aloaceae, but it is now clear that both should be included in a single family, the Asphodelaceae [18]. In a recent review of the family [18] it was argued that the subfamily Asphodeloideae is not monophyletic and the family was therefore divided into six informal but presumably monophyletic groups.

The present infrageneric classification system for *Aloe* is diagrammatically presented in Fig. (**1**). This four-hierarchical system is based on Berger's [12] and Reynolds' classification [13, 14]. In his treatment of the Aloes of Southern Africa, Reynolds [14] divided the genus into various sections, subsections and series and arranged the species in numerical groups based on an assemblage of morphological characters or on a single characteristic morphological feature [14]. The section dealing with the Malagasy species remains the biggest challenge as these species are simply arranged in groups without well-defined morphological characteristics.

ANALYTICAL METHODS

The two most important analytical methods in the study of leaves and roots of *Aloe* are TLC and HPLC. Reynolds [19] recommended for TLC of leaf components a mixture of di-isopropyl ether/n-propanol and water (7:5:1) followed by use of the lower layer of $CHCl_3$/EtOH/H_2O (7:3:1) to

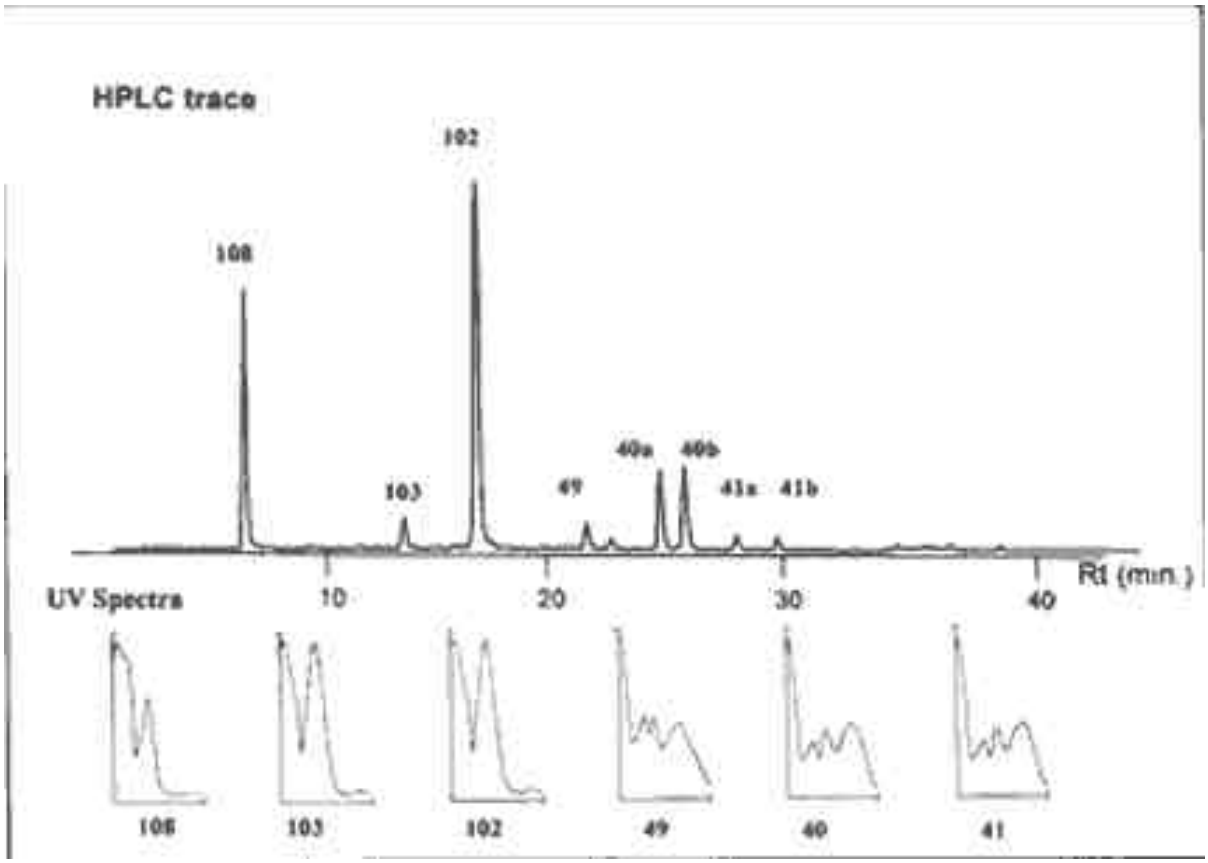


Fig. (2). Atypical HPLC/UV profile of *Aloe* leaf exudate compounds (*A. ferox*, Cape Aloe). See ref. 41 for LC conditions. Numbers on peaks correspond to compound numbers given in Table 1. Note that compounds: **102**, **103** and **108** are chromones (UVλ_{max}: **215**, **234**, **265**, **297** nm), while 40, 41 and 49 are anthrones (UVλ_{max}: 268, 296, 355 nm).

develop the spots in a direction at right angles to the first. It has been found that petrol/$CHCl_3$ (1:1) and $CHCl_3$-EtOAc (7:3) are appropriate solvent systems for analysis of root constituents [20], and EtOAc-MeOH-H_2O (77:13:10) and $CHCl_3$-MeOH (4:1) for leaf components. Developed TLC plates may be viewed under UV_{254} and UV_{366}, or sprayed with 0.5% aqueous solution of Fast Blue Salt B followed by spraying with 10% caustic soda solution [21]. 5-Hydroxyaloin gives a characteristic violet-brown colour when sprayed with 5% aqueous sodium metaperiodate [22].

Reversed phase HPLC of the methanol extract of leaf exudate has proved to be one of the best methods for establishing chemical profiles in *Aloe.* Whereas it is very difficult to distinguish between aloin A and B by TLC, these epimers can be easily separated by HPLC [19]. If the analysis is done using photodiode array detection, the UV spectrum can be used to get a rapid idea of the different classes of compounds present in the extract. A typical chromatogram with the UV spectra of some of the most important compounds present in *Aloe* is given in Fig. (**2**).

The roots of seven species of *Lomatophyllum* were analysed by TLC and HPLC for the presence of nine anthraquinones and pre-anthraquinones which are known to be characteristic constituents of roots of *Aloe* [23]. Furthermore comparative studies of roots of 46 species belonging to the genera *Bulbine*, *Bulbinella* and *Kniphofia* (family Asphodelaceae) [24] revealed the relationships as well as differences between groups of genera of the Asphodelaceae and Aloaceae, which are now accepted as belonging to a single family [18].

Due to the wide use of *A. vera* products as alternative medicine and dietary supplements, a need arose recently to develop methods to control the quality of these products, in particular to detect adulterants and undesirable additives. Authentication of genuine *A. vera* gel was achieved by use of ^1H NMR spectroscopy [25], which is used to establish presence of the typical compounds of the gel namely acemannan, glucose and malic acid.

COMPOUNDS PRESENT IN *ALOE*

Due to the medicinal properties attributed to *Aloe*, chemists took an early interest in this genus to discover the chemical compounds responsible for the healing properties. The leaves and roots of *Aloe* species are store houses of many interesting secondary metabolites belonging to different classes of compounds. These species elaborate many types of compounds, such as alkaloids, anthraquinones, pre-anthraquinones, anthrones, bianthraquinoids, chromones, flavonoids, coumarins and pyrones. Each of the major classes of *Aloe* compounds is discussed below. In Table 1, we have attempted to give, to the best of our knowledge, a complete list of all compounds isolated to date from *Aloe.*

Table 1. Checklist of *Aloe* Compounds (1970-2000). The Asterisks on Plant Names Indicate that the Compounds were Isolated from Roots; all others are from Leaves

Class/Cpd.	Structure No	Source	Reference
Alkaloids (1-4)			
γ-Coniceine	**1**	*A. gillilandii*	[26]
Coniine	**2**	*A. viguieri*	[26]
N-Methyltyramine	**3**	*Aloe* spp	[27]
O,N-Dimethyltyramine	**4**	*Aloe* spp	[27]
Anthraquinones (5-19), pre-anthraquinones (20-31) and bianthraquinoids (32-36)			
Aloe-emodin	**5**	*Aloe* spp.	[11,35]
Aloe-emodin-11-O-rhamnoside	**6**	*A. rabaiensis*	[80]
Aloesaponarin I	**7**	*A. saponaria**	[31]

(Table 1). contd.....

Class/Cpd.	Structure No	Source	Reference
Aloesaponarin II	**8**	*A. saponaria**	[31]
Chrysophanol	**9**	*A. saponaria**	[28]
Chrysophanol-8-methyl ether	**10**	*A. berhana**	[20]
Desoxyerythrolaccin	**11**	*A. saponaria**	[31]
1,5-Dihydroxy-3-hydroxymethylanthraquinone	**12**	*A. excelsa*	[59]
Helminthosporin	**13**	*A. saponaria**	[28]
7-Hydroxyaloe-emodin	**14**	*A. succotrina*	[48]
Isoxanthorin	**15**	*A. saponaria**	[28]
Laccaic acid D methyl ester	**16**	*A. saponaria**	[31]
Nataloe-emodin	**17**	*A. nyeriensis*	[32]
Nataloe-emodin-2-O-glucoside	**18**	*A. nyeriensis*	[32]
Nataloe-emodin-8-methyl ether	**19**	*A. specrosa*	[81]
Aloechrysone	**20**	*A. berhana**	[82]
Aloesaponol I	**21**	*A. saponaria**	[31]
Aloesaponol II	**22**	*A. saponaria**	[31]
Aloesaponol III	**23**	*A. saponaria**	[28,83]
Aloesaponol IV	**24**	*A. saponaria**	[28]
Aloesaponol I-6-O-glucoside	**25**	*A. saponaria**	[50]
Aloesaponol II-6-O-glucoside	**26**	*A. saponaria**	[50]
Aloesaponol III-8-O-glucoside	**27**	*A. saponaria**	[50]
Aloesaponol IV-4-O-glucoside	**28**	*A. barbadensis*	[84]
Aloesaponol IV, O-demethyl, 4-O-glucoside	**29**	*A. barbadensis*	[84]
Aloesaponol IV-8-O-glucoside	**30**	*A. saponaria*	[85]
Prechrysophanol	**31**	*A. graminicola**	[30]
Asphodelin	**32**	*A. saponaria**	[36]
Bianthracene II	**33**	*A. saponaria**	[36]
Bianthracene III	**34**	*A. saponaria**	[36]
Bianthracene IV	**35**	*A. saponaria**	[36]
Elgonicardine (Elgonica-dimers A & B)	**36**	*A. elgonica*	[35]
Anthrones (37-61)			
Aloe barbendol	**37**	*A. barbadensis**	[86]
Aloe-emodinanthrone	**38**	*Aloe* spp.	[48]

(Table 1). contd.....

Class/Cpd.	Structure No	Source	Reference
Aloe-emodin-10-C-rhamnoside	**39**	*A. rabaiensis*	[80]
Aloin A/B (barbaloin)	**40**	*Aloe* spp.	[42,44,87]
Aloinoside A/B	**41**	*Aloe* spp	[88]
Chrysophanolanthrone	**42**	*Aloe* spp	[48]
8-O-Methyl-7-hydroxylaloin A/B	**43**	*A. barbadensis*	[49]
6'-O-Cinnamoyl-8-O-methyl-7-hydroxylaloin A/B	**44**	*A. barbadensis*	[49]
7-Hydroxyaloin A/B	**45**	*A. barbadensis*	[89]
6'-O-*p*-Coumaroyl-7-hydroxylaloin A/B	**46**	*A. barbadensis*	[49]
7-Hydroxyaloin-6'-O-monoacetate A/B	**47**	*A. succotrina*	[48,90]
7-Hydroxyaloin-4',6'-O-diacetate A/B	**48**	*A. succotrina*	[48,90]
5-Hydroxyaloin A	**49**	*Aloe* spp.	[22, 66]
5-Hydroxyaloin A 6'-O-acetate	**50**	*A. marlothii*	[60]
6'-O-cinnamoyl-5-hydroxyaloin A	**51**	*A. broomii*	[91]
Microstigmin A	**52**	*A. microstigma*	[66]
10-Hydroxyaloin B	**53**	*Aloe* spp.	[43,45]
10-Hydroxyaloin B 6'-O-acetate	**54**	*A. claviflora*	[92]
Deacetyllittoraloin	**55**	*A. littoralis*	[45,47]
Littoraloin	**56**	*A. littoralis*	[45,47]
Littoraloside	**57**	*A. littoralis*	[46]
Microdontin A/B	**58**	*A. microdonta*	[65]
Homonataloin A/B	**59**	*A. jacksonii*	[93,94]
Homonataloside B	**60**	*A. lutescens*	[76]
Nataloin A/B	**61**	*A. nyeriensis*	[32]
Benzene, naphthalene and furan derivatives (62-76)			
3-Furanmethanol	**62**	*A. arborescens*	[95]
5-OH-3-Methylnaphto[2,3-c]furan-4(1*H*)-one	**63**	*A. ferox*	[96]
5-OH-3-Methylnaphto[2,3-c]furan-4(9*H*)-one	**64**	*A. ferox*	[96]
5-OH-3-Methylnaphto[2,3-c]furan-4,9-dione	**65**	*A. ferox*	[96]
CA-12 (1,1-Diphenylethane derivative, process product)	**66**	Cape aloe	[52]
Dihydrocoumarone (2,3-dihydrobenzofuran)	**67**	*A. arborescens*	[95]
Feroxidin	**68**	*A. ferox*	[54]
Feroxin A	**69**	Cape aloe	[55]
Feroxin B	**70**	Cape aloe	[55]
Isoeleutherol	**71**	*Aloe* spp.	[20]
Isoeleutherol-5-O-glucoside	**72**	*A. saponaria*	[50]

(Table 1). contd.....

Class/Cpd.	Structure No	Source	Reference
Methyl-p-coumarate	**73**	*A. ferox*	[97]
Plicataloside	**74**	*A. plicatilis*	[53]
Pluridone	**75**	*A. pluridens*	[51]
Protocatechuic acid	**76**	*A. berhana*	[29]
Chromones (77-118)			
(E)-2-acetonyl-8-(2',6'-di-O,O-coumaroyl)-β-D- glucopyranosyl-7-hydroxy-5-methylchromone	**77**	*A. speciosa*	[91]
(E)-2- acetonyl-8-(2'-O-caffeoyl)-β-D-glucopyranosyl-7-methoxy-5-methylchromone	**78**	*A. broomii*	[91]
(E)-2- acetonyl-8-(2'-O-cinnamoyl)-β-D-glucopyranosyl-7-methoxy-5-methylchromone	**79**	*A. broomii*	[91]
(E)-2-acetonyl-8- (2'-O-feruloyl)-β-D-glucopyranosyl-7-methoxy-5-methylchromone	**80**	*A. africana*	[91]
2-(Carboxyethenyl)-5,7-dihydroxychromone	**81**	*A. cremnophila*	[93]
2-acetonyl-7-hydroxy-8-(3-hydroxyacetonyl)-5-methylchromone	**82**	Cape aloe	[98]
2-acetonyl-8-(2-furoylmethyl)-7-hydroxy-5-methylchromone	**83**	Cape aloe	[98]
2'-O-Feruloylaloesin	**84**	*A. arborescence*	[99]
2'-O-Tigloylaloesin	**85**	*Aloe* spp.	[93]
2'-*p*-O-Methylcoumaroylaloesin	**86**	*A. excelsa*	[59]
6'-O-coumaroylaloesin	**87**	*A. castanea*	[75]
7''-Deoxyaloeresin D[a]	**88**	*A. barbadensis*	[95]
4'-O-glucosyl-isoaloeresin DI	**89**	*A. vera*	[100]
4'-O-glucosyl-isoaloeresin DII	**90**	*A. vera*	[100]
7-Hydroxy-2,5-dimethylchromone	**91**	Cape aloe	[67]
7-O-Methylaloeresin A	**92**	*A. marlothii*	[60]
7-O-Methylaloesin	**93**	*A. rupestris*	[60]
7-O-methylaloesinol	**94**	*A. capensis*	[101]
8-[C-β-D-[2-O-(E)-cinnamoyl]glucopyranosyl]-2-[(R)-2-hydroxypropyl]-7-methoxy-5-methylchromone	**95**	*A. barbadensis*	[102]
8-C-glucosyl-(2'-O-cinnamoyl)-7-O-methyl-aloediol A [b]	**96**	*A. vera*	[100]
8-C-glucosyl-(2'-O-cinnamoyl)-7-O-methyl-aloediol B [b]	**97**	*A. vera*	[100]
8-C-glucosyl-(S)-aloesol	**98**	*A. vera*	[103]
8-C-glucosyl-7-O-methyl-(S)-aloesol	**99**	*A. vera*	[104]
8-C-glucosyl-7-O-methylaloediol	**100**	*A. vera*	[103]

(Table 1). contd.....

Class/Cpd.	Structure No	Source	Reference
8-C-glucosyl-noreugenin	**101**	*A. vera*	[100]
Aloeresin A (2'-O-*p*-Coumaroylaloesin)	**102**	*Aloe* spp.	[56, 99]
Aloeresin C	**103**	Cape aloe	[105]
Aloeresin D	**104**	*Aloe* spp	[80,106]
Aloeresin E [c]	**105**	*A. peglerae*	[78]
Aloeresin E [d]	**106**	*A. vera*	[104]
Aloeresin F	**107**	*A. peglerae*	[78]
Aloesin (Aloeresin B)	**108**	*Aloe* spp.	[57, 107]
Aloesol	**109**	*Aloe* spp.	[58]
Aloesone	**110**	*Aloe* spp.	[58]
Deacetylaloesin	**111**	*A. vera var. chinensis*	[95]
Furoaloesone (see the reference for total synthesis)	**112**	Cape aloe	[67]
Iso-aloeresin A	**113**	Cape aloe	[108]
Isoaloeresin D	**114**	*A. vera*	[104]
Isoaloesin	**115**	A. vera var. chinensis	[95]
Isorabaichromone	**116**	*A. vera*	[103]
Neoaloesin A	**117**	*A. vera*	[109]
Rabaichromone	**118**	*A. rabaiensis*	[80]
Coumarins (119-121)			
Dihydroisocoumarin glucoside	**119**	*A. hildebrandtii*	[110]
Feralolide	**120**	Cape aloe	[111]
CA-14 (Benzo[f]chroman-3-one (process product)	**121**	Cape Aloe	[69]
Pyrans and Pyrones (122-128)			
Aloenin (Aloecarbonoside)	**122**	*Aloe nyeriensis*	[32,61]
Aloenin acetal	**123**	*A. arborescens*	[112]
Aloenin aglycone	**124**	*A. nyeriensis*	[32]
4",6"- Ethylidenealoenin (may be an artefact)	**125**	*A. arborescens*	[95]
Aloenin B	**126**	Kenya aloe	[62]
Aloenin-2"-p-O-coumaroyl ester	**127**	*A. nyeriensis*	[32]
Bisbenzopyran	**128**	*A. barbadensis*[*]	[113]

(Table 1). contd.....

Class/Cpd.	Structure No	Source	Reference
Flavonoids (129-132)			
Apigenin	**129**	*Aloe* spp.	[63]
Dihydroisorhamnetin	**130**	*Aloe* spp.	[63]
Naringenin	**131**	*Aloe* spp.	[63]
Isovitexin	**132**	*Aloe* spp.	[63]
Sterols (133-136)			
Campesterol	**133**	*A. barbadensis*	[114]
Cholesterol	**134**	*A. barbadensis*	[114]
Lupeol	**135**	*A. barbadensis*	[114]
ß-Sitosterol	**136**	*A. arborescens*	[115]
Miscellaneous			
Acemannan	**137**	*A. vera*	[116]

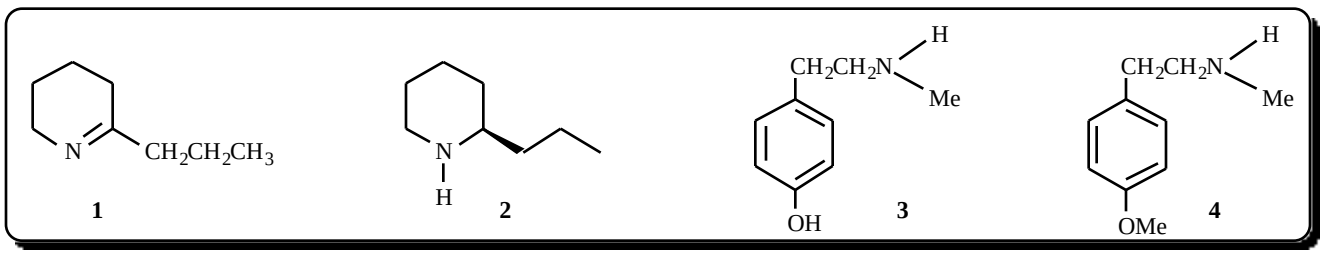
[a] (8-[C-β-D-[2-O-cinnamoyl]glucopyranosyl-]-2[(R)-2-hydroxypropyl]-7-methoxy-5-methylchromone (7"-deoxyaloeresin D). [b] Compounds **96** & **97** differ in the configurations of the 1,2-dihydroxypropyl side chain [100] [c] 2-acetonyl-8-(2-O-cinnamoyl-β-D-glucopyranosyl)- 7-β-D-glucopyranosyloxy-5-methylchromone (Aloeresin E). [d] 8-*C*-β-D-[2'-*O*-(*E*)-cinnamoyl]glucopyranosyl-2-[(*S*)-2-hydroxy]propyl-5-methylchromone (Aloeresin E).
Note that **105** & **106** are two different compounds bearing the same name Aloeresin E [78, 104]

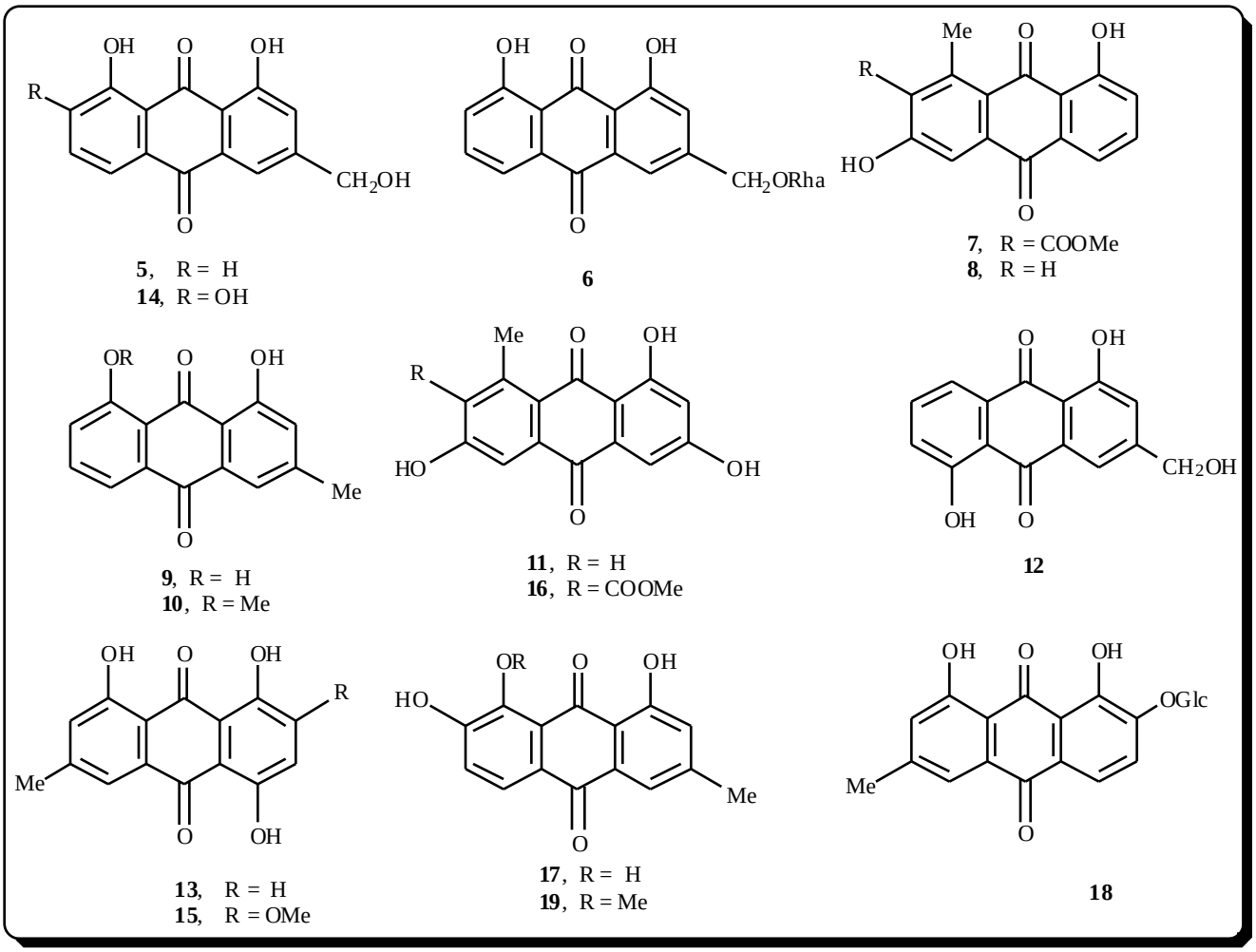
ALKALOIDS

The piperidine alkaloid, γ-coniceine (**1**) was reported to occur in six species of *Aloe* whereas coniine (**2**) was found in *A. viguieri* [26]. Screening of *Aloe* for alkaloids showed 21% to be positive, with alkaloids N-methyltyramine (**3**) and O,N-dimethyltyramine (**4**) being responsible for the positive tests in addition to the piperidine derivatives **1** and **2** [27]. In view of the potential toxicity of alkaloids, it has been pointed out that it is important to screen for alkaloids prior to recommending use of an *Aloe* species as medicine.

ANTHRAQUINONES AND PRE-ANTHRAQUINONES

Several free anthraquinones occur in roots and leaves of *Aloe* species. Aloe-emodin (**5**) is a typical leaf constituent and is widespread in the genus. The anthraquinones in leaves may be present as O-glycosides as is the case in compounds **6** and **18**. The anthraquinones, physcion and emodin or their derivatives in which the 6 position of the anthraquinone moiety is oxygenated, have so far not been reported from *Aloe.* On the other hand, chrysophanol (**9**) is a common constituent of both roots [28] and leaves [29]. Prechrysophanol (**31**), which may be a progenitor of chrysophanol, was found in the subterranean stem of *A. graminicola* [30]. Aloesaponarin I (**7**), aloesaponarin II (**8**), desoxyerythrolaccin (**11**), helminthosporin (**13**), isoxanthorin (**15**) and laccaic acid D methyl ester (**16**) were isolated first from roots of *A. saponaria* [31] but have subsequently been shown to occur in roots of many other *Aloe* species [20]. Nataloeemodin (**17**) has so far been reported only from leaves [32].





Thus two main types of anthraquinones are present in the roots of *Aloe*, these are 1,8-dihydroxyanthraquinone (e.g. chrysophanol-type) and 1-hydroxy-8-methylanthraquinone (e.g. aloesaponarin I-type). Whereas anthraquinones of the former type are known to occur both in leaves and roots, those that belong to the latter are confined only to roots. In a recent study [24] of the roots of 172 species of *Aloe*, 1,8-dihydroxyanthraquinones were detected in almost all and 1-hydroxy-8-methylanthraquinones in 129 *Aloe* species. As shown in Fig. (**3**) these two types of anthraquinones appear to be derived through two parallel biogenetic routes of the polyketide

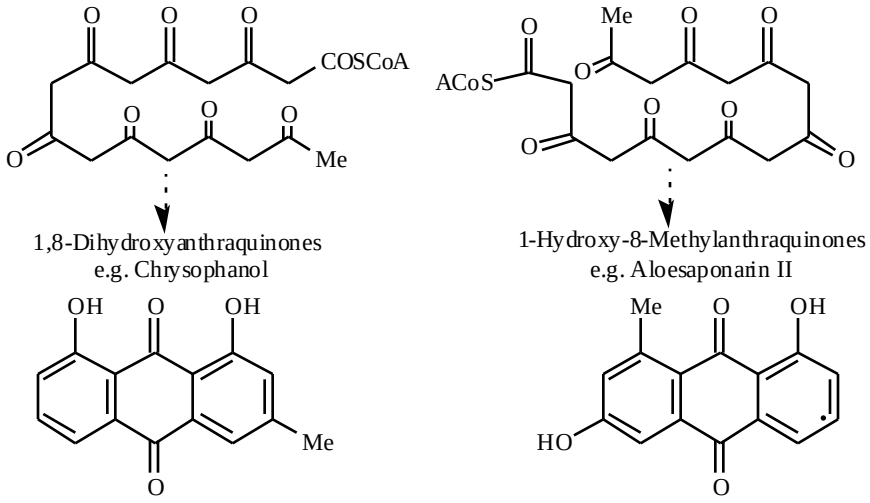
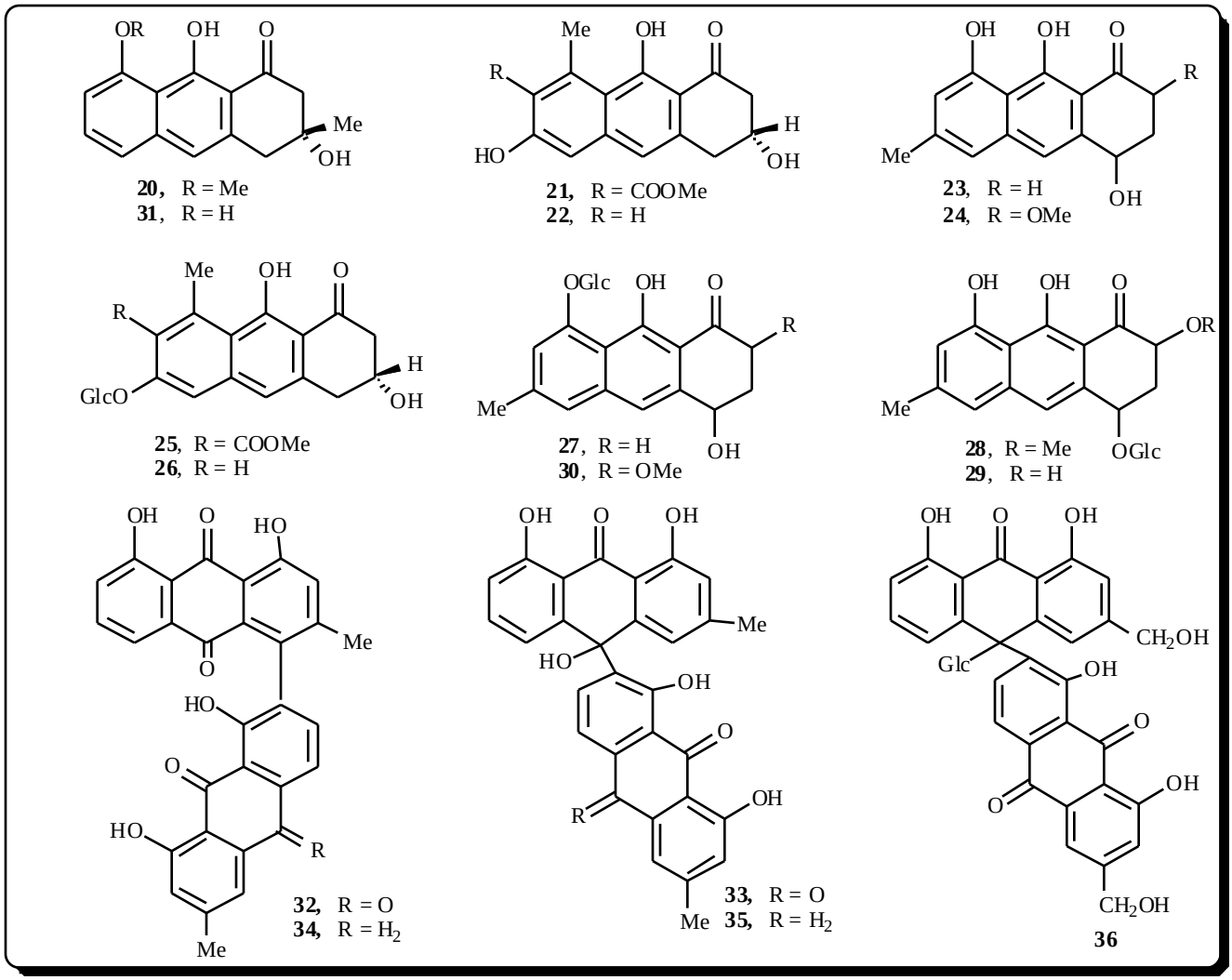


Fig. (3). Two folding types of the octaketide chain in the roots of *Aloe.*



pathway, differing by the way the octaketide chain folds [33].

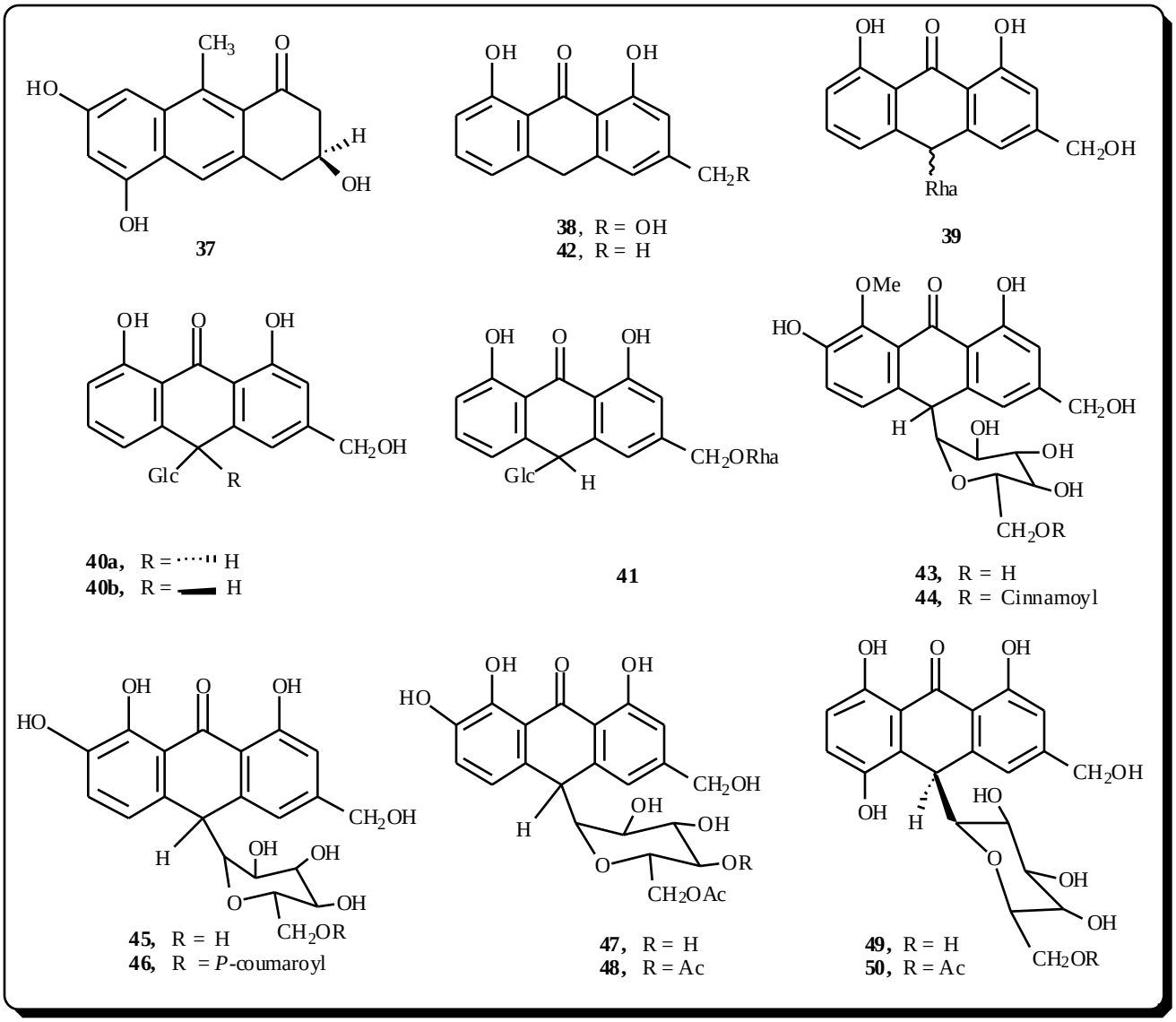
Several pre-anthraquinones which could be considered as progenitors of the above two types of anthraquinones have been isolated and characterized mainly from subterranean parts of *Aloe.* However, the pre-anthraquinone aloechrysone (**20**) was detected both in roots and leaves of four *Aloe* species from Ethiopia [29]. It is interesting to note that the related genus *Gasteria* (Asphodelaceae), elaborates *Aloe* type pre-anthraquinones both in leaves and roots [34]. The pre-anthraquinones could be readily converted to the corresponding anthraquinones by treatment with base [30].

BIANTHRAQUINOIDS

Dimers are relatively rare in *Aloe.* The glycosylated derivatives, elgonica-dimers A/B (**36**) were first reported from the leaf exudate of *A. elgonica* [35]. The other dimeric bianthraquinoids (**32**-**35**) were reported from the subterranean parts (roots and rhizomes) of *A. saponaria* [36].

ANTHRONES

Anthrones are by far the most important of all the classes of compounds present in *Aloe.* The most outstanding members of this class are aloin A and B (**40**), which are collectively known as barbaloin because they were first isolated from *A. vera*, (formerly Barbados aloe or *A. barbadensis*). Aloin A/B (barbaloin) are two diastereomeric C-glucosides that differ in the configuration at C-10 of the aloe-emodin anthrone moiety. These compounds are believed to be mainly responsible for the bitter and purgative properties of the well known commercial aloe drug, which is principally made up of the leaf exudates of *A. ferox* and *A. vera*. The leaf exudate of *A. ferox* has been



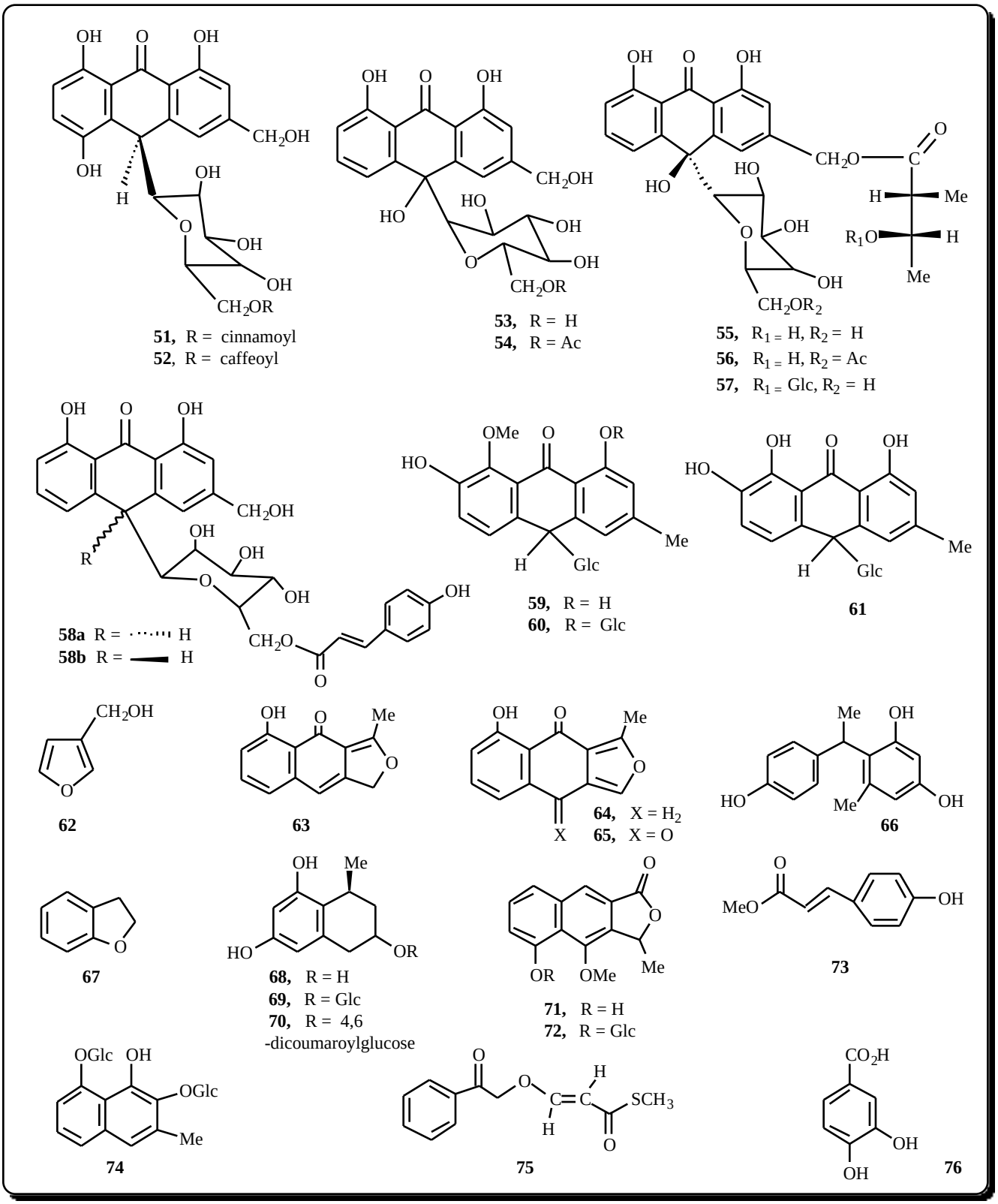
reported to contain up to 10% barbaloin [37] but variation studies [38] have shown levels of between 10-30% in natural populations, and typically around 20% in good quality product. However not all *Aloe* species are found to contain barbaloin. In a screening of 240 *Aloe* species, barbaloin was found to occur in exudates of 85 of the species examined [39] usually in 10-20% concentration. Interestingly barbaloin and homonataloin seem to be mutually exclusive, with the notable exception of *A. mutabilis* [40], *A. mendesii* and *A. retrospiciens* [41]. It should be pointed out that aloin should not be regarded to be confined only to *Aloe* species as it has also been found in the extracts of cascara bark (*Rhamnus purshiana* D.C.) [42]. Rauwald *et al.* described the chemical transformation of aloin A/B to 10-hydroxyaloin A/B (**53**) by treatment with base [43]. As described below, compound **53** was later found as the major natural substance in *Aloe littoralis*.

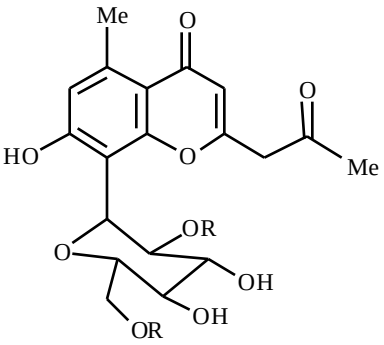
The absolute configuration of aloin B (**40**) has been established to be 10*R*,1'*S*, where the glucose moiety is attached to C-10 with the α orientation, the β orientation (i.e. 10*S*,1'*S*) follows for aloin A [44].

Although *A. littoralis* Baker is reported to be positive for the presence of aloin in the Reynolds screening [39] and aloin is reported to be present to the extent of 18.2 % by Groom and Reynolds [37], later analysis by TLC and HPLC of the exudate of *A. littoralis* did not show the presence even of a trace of aloin [45]. Instead the presence of 10-hydroxyaloin B (**53**) and its three novel nilate ester derivatives deacetyllittoraloin (**55**), littoraloin (**56**) and littoraloside (**57**) was

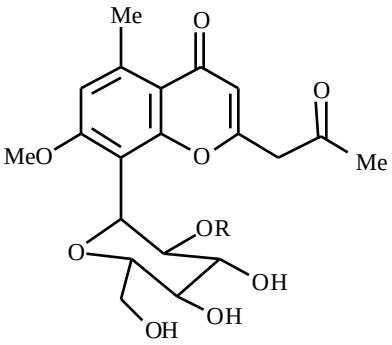
established [45, 46]. A discussion of the chemotaxonomic significance of these compounds in *Aloe* has also been recently published [47].

As indicated above, roots of *Aloe* elaborate mainly anthraquinones and pre-anthraquinones. Anthrone glycosides have not been detected in the roots of *Aloe.* It has also been shown that inflorescence of *Aloe* elaborate anthrones [48]. Besides 5- and 10-hydroxyaloin, the other hydroxyaloin present in leaves of some *Aloe*

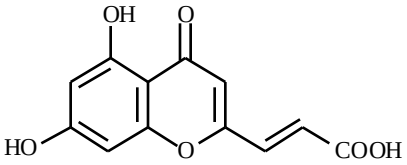




77, R = coumaroyl



78, R = caffeoyl
79, R = cinnamoyl
80, R = feruloyl



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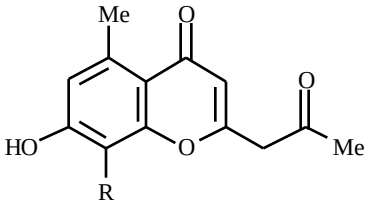
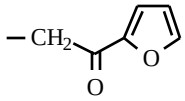
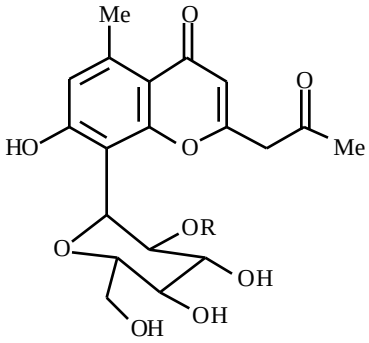


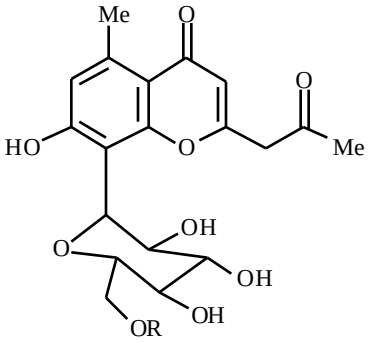
82, R = $CH_2-C(=O)-CH_2OH$



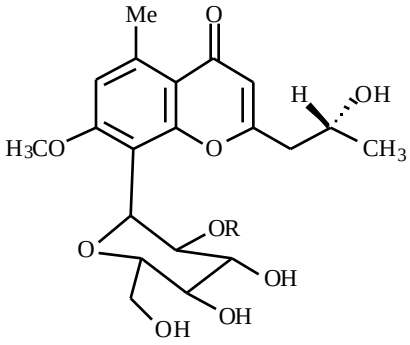
83, R =



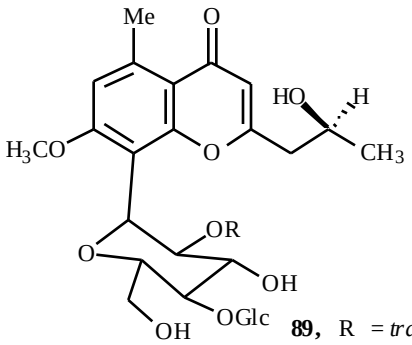
84, R = feruloyl
85, R = tigloyl
86, R = p-O-methylcoumaroyl



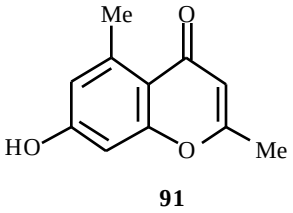
87, R = coumaroyl



88, R = *trans*-p-cinnamoyl



89, R = *trans*-p-coumaroyl
90, R = *cis*-p-coumaroyl



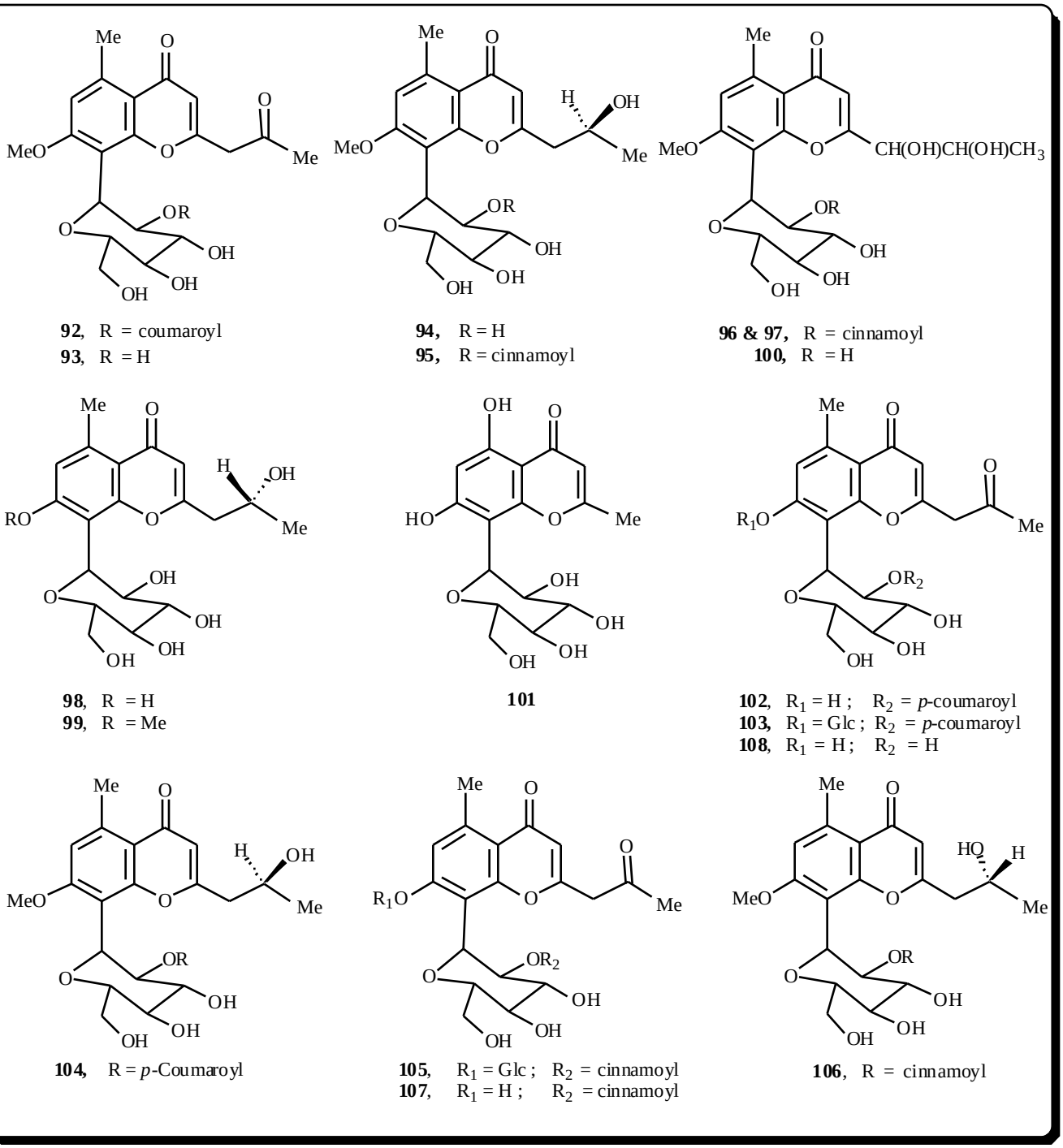
91

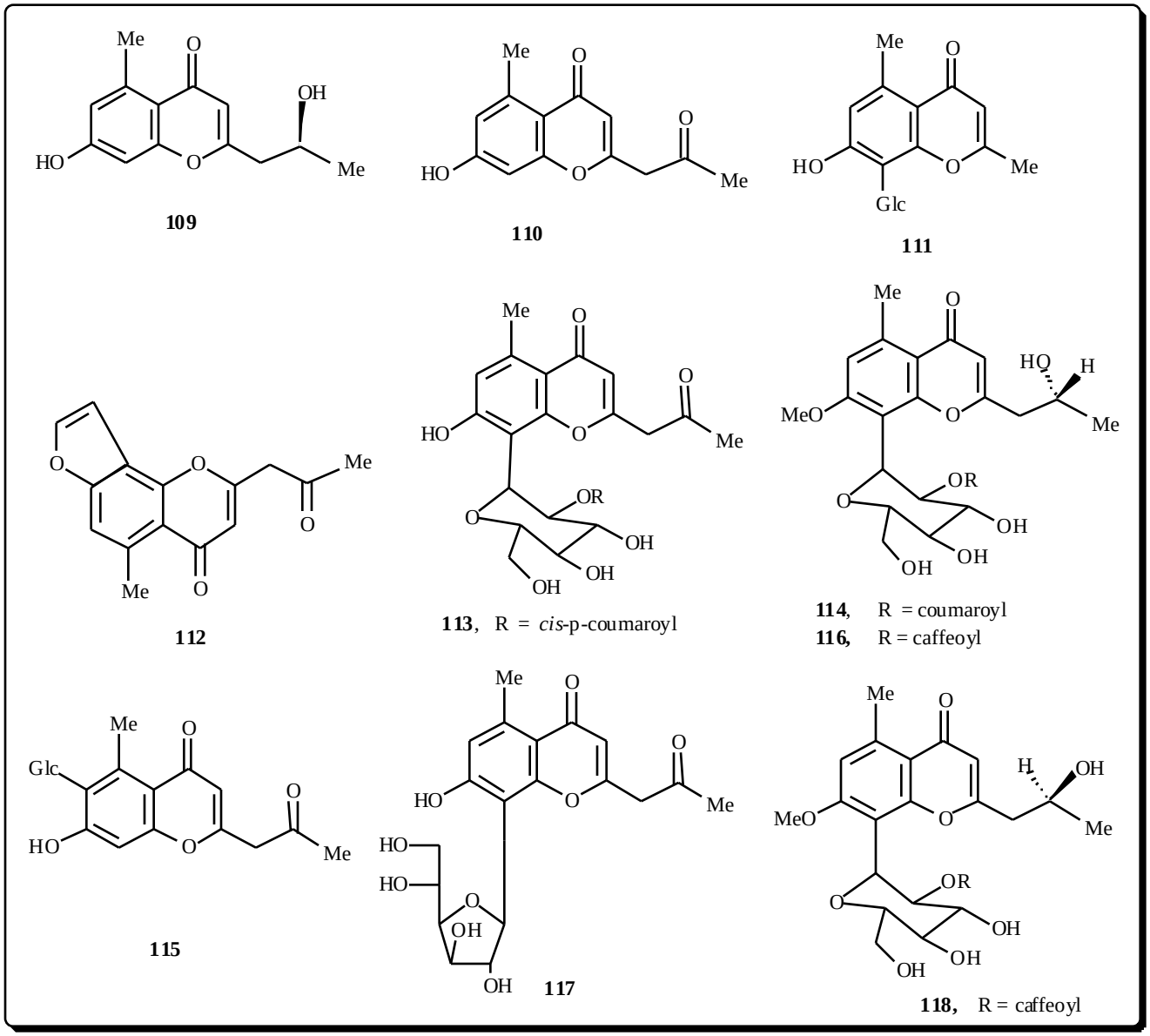
species is 7-hydroxyaloin (**45**) [29] and its natural derivative **43** [49].

BENZENE, NAPHTHALENE AND FURAN DERIVATIVES

Several naphthalene and benzene based secondary metabolites have been reported from *Aloe* species. One of the first such compounds to be reported is the naphthalene derivative, isoeleutherol-5-O-glucoside (**72**) isolated first by Yagi *et al.* [50] from the subterranean stems of *A. saponaria*. It is one of the few glycosides reported from subterranean parts of *Aloe*. The aglycone isoeleutherol (**71**) was also reported as a natural product [20] from roots of more than a dozen *Aloe* species belonging to the series Saponariae. Isoeleutherol was conspicuously absent from other series investigated, indicating its chemotaxonomic significance in delineating members of the Saponariae series from other series. The

insecticidal compound pluridone (**75**) isolated from roots of the South African *A. pluridens* is the only example of a sulphur containing compound ever isolated from *Aloe* [51]. The recently reported compound having the 1,1-diphenylethane (**66**) skeleton from Cape Aloe [52] and plicataloside (**74**) from *A. plicatilis* [53] have added more variety to benzene and naphthalene derived compounds found in *Aloe* species. Furthermore the discovery by Speranza *et al.* [54, 55] of the tetrahydronaphthalenes feroxidin (**68**), feroxin A (**69**) & B (**70**) in Cape Aloe is a further testimony of the diversity of the constituents of this *Aloe* of commerce. However, one should note that the preparation of Cape aloes requires a very harsh process involving several hours of boiling of the exudate over an open fire to evaporate off the water and to solidify the extract. Thus, as indicated in Table 1, some of the compounds reported in the literature as occurring in Cape Aloe are process compounds or artefacts.





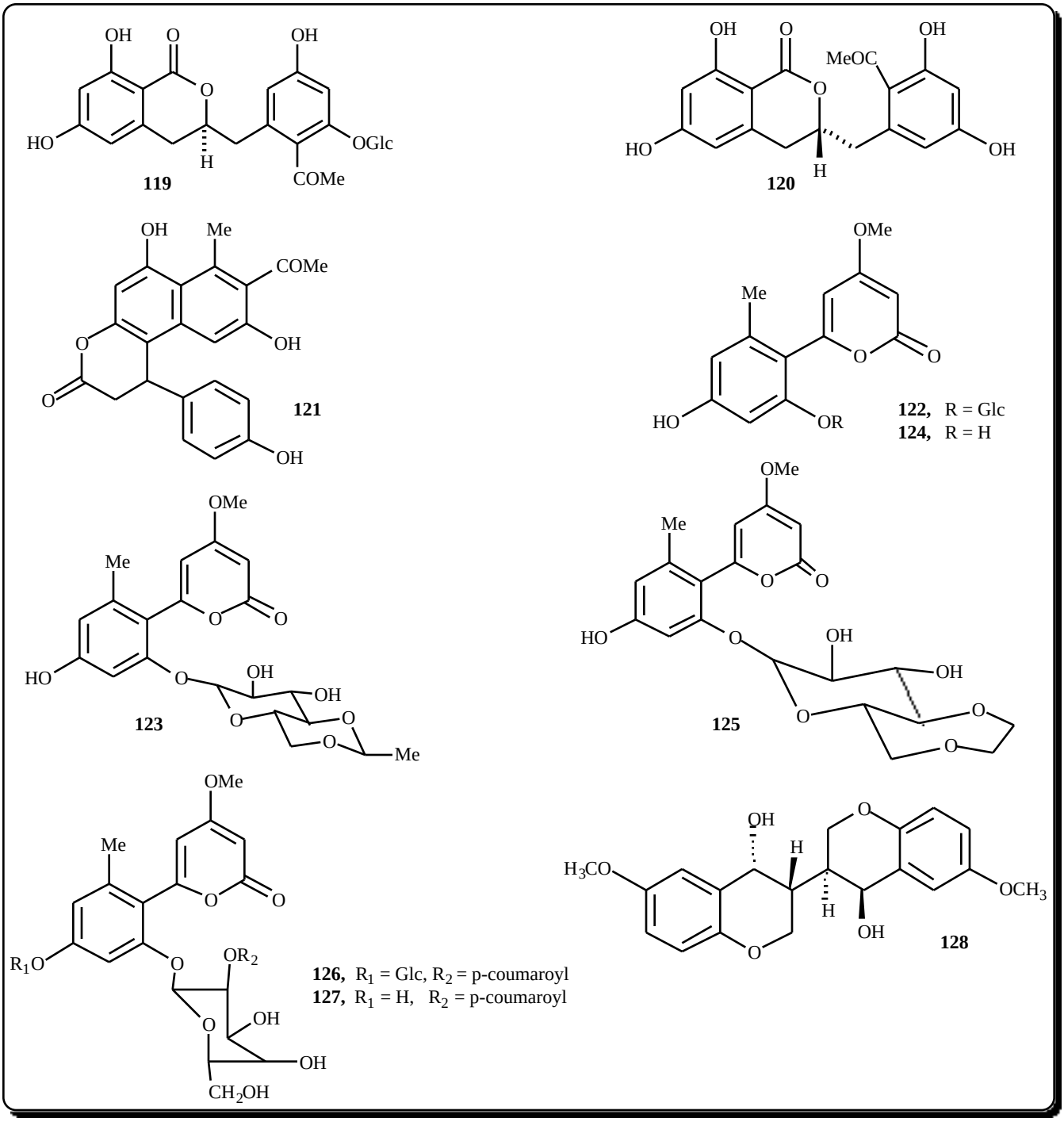
CHROMONES

Aloesin (**108**) formerly called aloeresin B [56], is one of the three most significant constituents of aloe drug, the other two being aloin (**40**) and aloeresin A (**102**). Random screening of *Aloe* species indicated presence aloesin in leaves of at least 30% of the species examined [11]. Its structure was established as **108** in 1970 by Haynes *et al.* [57] and subsequently in 1972 its aglycone, named as aloesone (**110**), was recognized as an *Aloe* leaf constituent by Holdsworth [58]. The structure of aloeresin A, first proposed incorrectly as a p-coumarate ester of aloesin esterified on C-6 of the sugar moiety, was later revised to structure **102** in which the ester was placed on C-2 of the sugar moiety [56]. The aloeresin derivative, 2'-p-O-methylcoumaroyl-aloesin (**86**) was reported from *A. excelsa* [59].

Aloe rupestris Bak. is a peculiar species that does not produce anthrones but yields various chromones, with aloesin (**108**) and 7-*O*-methyl-aloesin (**93**) [60] as the major components. The latter compound is of chemotaxonomic value since it is present in most species of *Aloe* series Asperifoliae Berger.

COUMARINS, PYRANS AND PYRONES

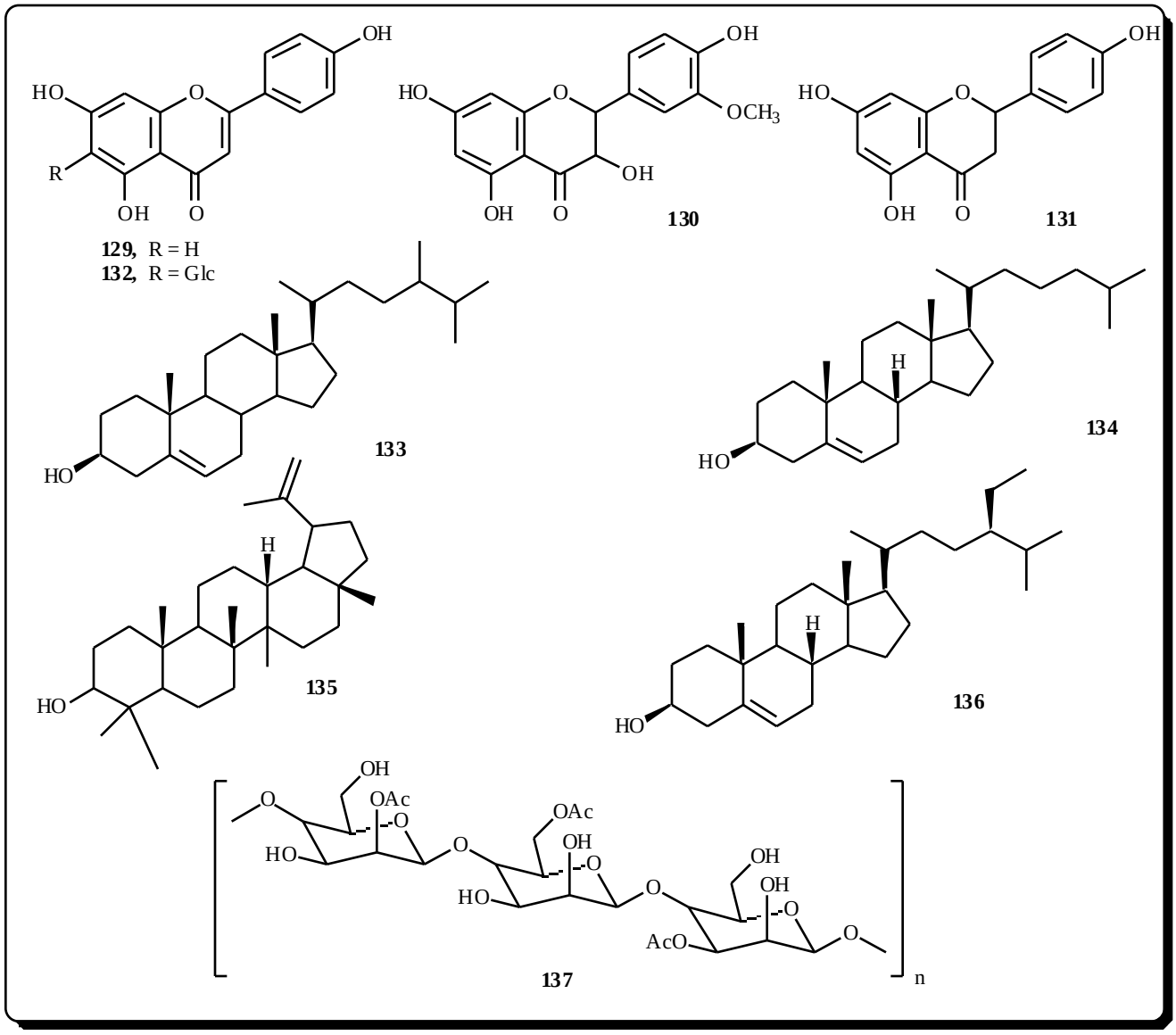
Aloenin (**122**), a phenylpyrone derivative, is a relatively infrequently encountered bitter component of *Aloe* leaf exudate, whose revised



structure was reported in 1974 [61]. Its aglycone **124** and the coumaroyl ester **127** are also well known natural products [32]. Aloenin B (**126**) is one of the major (13.5%) constituents of commercial Kenya Aloe [62].

FLAVONOIDS

It has been reported [63] that flavonoids are present in several different groups of aloes, including the sections *Graminialoe* and *Leptaloe* (the grass-like aloes), the genus *Lomatophyllum* (now included in *Aloe*) and various other species, notably *A. lineata* (Ait.) Haw. and related species from southern Africa, and some rare Malagasy endemics. Until the report cited in reference 63, there was an obvious lack of flavonoid data on *Aloe*, mainly due to the fact that most studies on the genus have concentrated on the chromone, anthrone, phenyl pyrone and to a lesser extent the alkaloids. Out of total of 380 species screened



[63], flavonoids were found in 31 species, the major compounds being: apigenin (**129**), dihydroisorhamnetin (**130**), naringenin (**131**) and isovitexin (**132**). The distribution of flavanones and flavones are mutually exclusive and provide valuable chemotaxonomic evidence in support of a basal position for some of the flavonoid-producing groups in *Aloe* [63].

STEROLS

The sterols reported from aloe are among those that are ubiquitous in the plant kingdom such as campesterol (**133**), cholesterol (**134**), lupeol (**135**) and β-sitosterol (**136**). The sterols in *Aloe* may play an important role in the anti-inflammatory activity of the gel [5].

OTHER MISCELLANEOUS COMPOUNDS

Over the years, a variety of other organic and inorganic substances have been reported to occur in *Aloe*, particularly in the gel of *A. vera*. The inorganic minerals include ions of calcium, magnesium, zinc, iron, copper etc, some of which may have role in wound healing. In addition there are at least five saccharides namely arabinose, galactose, glucose, mannose and xylose, some twenty amino acids, vitamins B_1, B_2, B_6, B_{12} and C. etc and enzymes such as amylase, lipase, folic acid etc [5]. It is believed that the biological activity of aloe comes from synergistic action of all these compounds rather than one single "magic bullet". If a single compound is sought to account for the efficacy of *A. vera* gel, certainly the polysaccharide acemannan (**137**) is the one that is currently a focus of a great deal of attention.

Acemannan is a long chain polymer consisting of randomly acetylated linear D-mannopyranosyl units.

BIOGENETIC STUDIES

The biosynthesis of aloin, the most outstanding constituent of *Aloe,* has been the subject of a study by Grün and Franz [64]. These workers have shown that aloin B is formed by attachment of glucose to aloe-emodin anthrone (**38**), a compound detected so far in flowers but not in leaves of *Aloe* [48]. They have further established that aloin B (where glucose is α at C-10) is the true natural product, which upon standing gradually epimerizes to give aloin A (glucose β at C-10). The fact that the glucose moiety has the same α orientation in 10-hydroxyaloin B (**53**) as well as in its three novel nilate ester derivatives **55**, **56** and **57** [45, 46], indicates that hydroxylation at C-10 occurs prior to epimerization of the natural aloin B. Indeed all four compounds i.e. **53**, **55**, **56** and **57** occur in *A. littoralis* without their corresponding epimers at C-10. It is interesting to note that microdontin (**58**) is found in *A. microdonta* as a 1:1 mixture of the A and B isomers [65]. On the other hand, 5-hydroxyaloin A (**49**) is known only in the A form [22] i.e. with the β orientation for the glucose moiety at C-10, an observation which is also the case for its natural derivative microstigmin A (**52**) a novel compound that was recently found in *A. microstigma* [66].

It is interesting to note that no prenylated polyketide compounds have been isolated from *Aloe* species indicating that they do not use isoprene units to build up secondary products [67].

Hirata et al. [68] showed using ^{3}H and ^{14}C labelling studies how aloenin is biosynthesized in *A. arborescens*. The pyrone system in aloenin is thus derived from a polyketide, followed by O-methylation from methionine and glucosylation. Other biosynthetic studies on aloe constituents are those of Speranza et al. [67, 69].

CHEMOTAXONOMIC SIGNIFICANCE OF *ALOE* COMPOUNDS

A comprehensive review on the distribution of *Aloe* leaf compounds was published by T. Reynolds in 1985 [11]. This article was followed by his other publications in 1986 & 1990 [40, 70], in which, TLC methods were used to determine chemical relationships between the species. In later studies Reynolds [71, 72, 73] incorporated HPLC results with TLC data. Rauwald reported in a poster abstract [74] the exudate composition of 183 species. The chemotaxonomic value of root compounds in particular of anthraquinones and pre-anthraquinones, in *Aloe* and in *Lomatophyllum* has also been discussed by other workers [20, 23,24]. Based on the similarity of the root and leaf chemistry of *Lomatophyllum* with that of *Aloe,* it has been suggested that these two genera should be amalgamated [23]. This has actually been done in 1996 [15]. Isoeleutherol (**71**) has been indicated as a chemotaxonomic marker for a group of *Aloe* that belong to the series Saponariae [20].

Viljoen [41] analysed leaf exudates of 380 species using HPLC with photo diode array detection and identified important chemotaxonomic marker compounds. Thus various *Aloe* chemotypes were defined based on the presence of a single or a combination of marker compounds. According to this study, *Aloe* species can be chemically divided into three major groups, namely the flavonoid producing species (**A**), anthrone producing species (**B**) and the plicataloside accumulating species (**C**). Each of the three major groups can be further subdivided into several chemotypes which are schematically presented in Fig (**4**)**.**

Chemotype A1 (Flavones only)

Species which only accumulate flavones (e.g. isovitexin) include the grass-like aloes. It is hypothesised that flavonoids were initially more widely distributed in the genus but were later displaced by the bitter tasting principles, anthrones and chromones, which act as possible anti-feedants to deter herbivores [63]. *Chemotype A2* (flavones, anthrones and chromones): Two distinct infrageneric groups are included in this chemotype; all members of *Aloe* series *Macrifoliae* and the berried aloes in *Aloe* sect. *Lomatophyllum* [63]. *Chemotype A3* (flavanones only): The presence of flavanones in *Aloe* is a unique occurrence. Only eight species in the survey of 380 species produce only flavanones. *Chemotype A4* (flavanones, anthrones and chromones): This

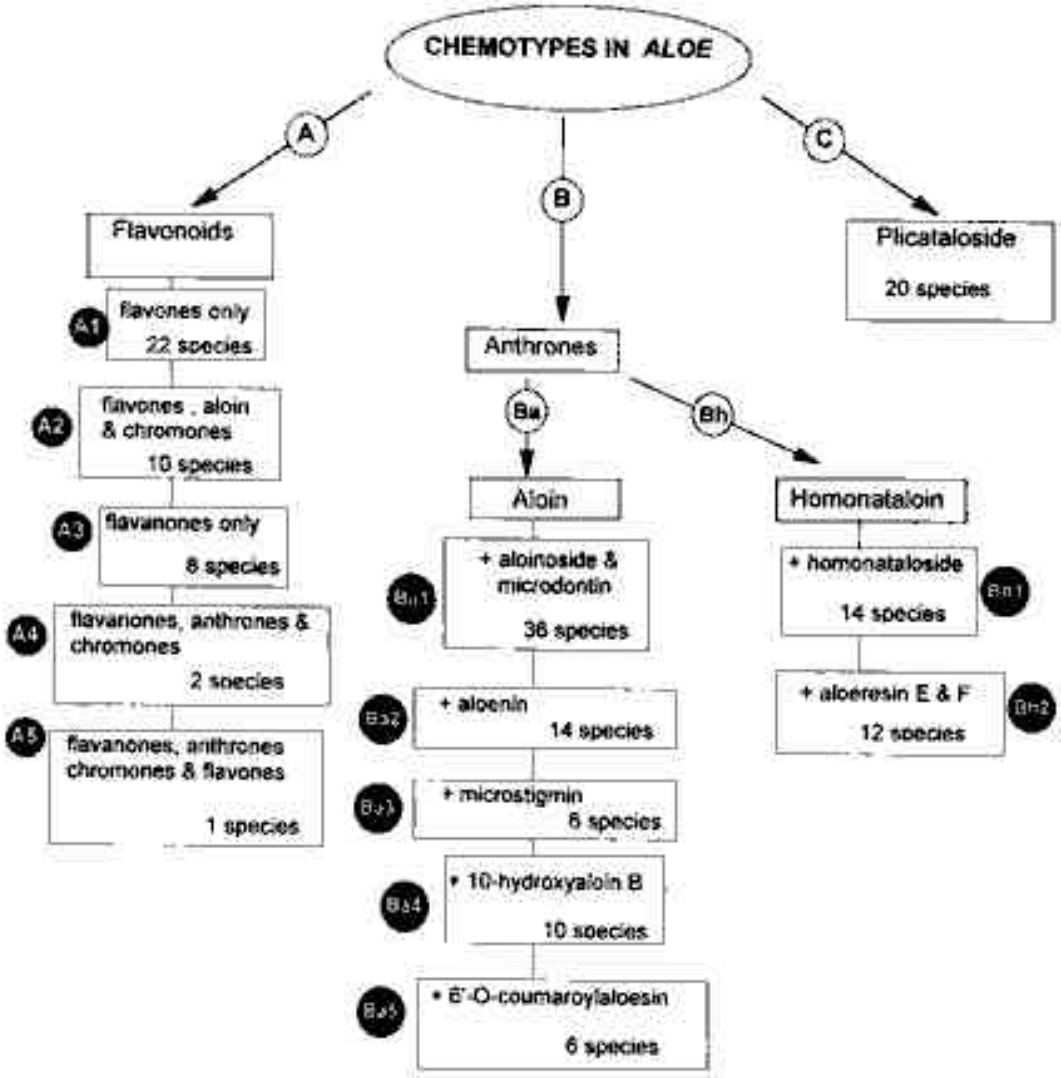


Fig. (4). Diagrammatic summary of chemotypes in *Aloe* [41].

chemotype represents a transition from chemotype *A4* to chemotype *B*. Only two species, *A. helenae* and *A. vaotsanda*, both Malagasy endemics, belong to this group. *Chemotype A5* (flavanones and flavones): Only one species, *Aloe suzannae* from Madagascar, is included in this chemotype.

Chemotype B (Aloes Containing Anthrones)

The anthrone accumulating species are divided into two sub-groups; *Ba*, the aloin (or derivatives of aloin) producing species and *Bh*, the homonataloin (**59**) producing species. With the exception of three species (*A. mutabilis*, *A. mendesii* and *A. retrospiciens*), these two anthrones are found to be mutually exclusive. Most species produce the aloin isomers, with fewer species producing homonataloin.

Chemotype Ba1 (Aloin A/B, Aloinoside A/B, Microdontin A/B)

This chemotype, comprising 36 species is the largest of all the chemotypes identified in the survey [41]. *Chemotype Ba2* (aloin A/B and aloenin; **122**). The phenyl-pyrone, aloenin is always associated with aloin, except in the case of *A. kedongensis* where nataloin is the major anthrone. *Chemotype Ba3* (microstigmin A): Microstigmin A (**52**), a derivative of aloin, is a chemotaxonomic marker for six species of which some have not previously been associated with one another. This compound was isolated from *A. microstigma* [66] and found in five other species: *A. framesii*, *A, khamiesensis*, *A. pictifolia*, *A. broomii* and *A. chlorantha* [41]. *Chemotype Ba4* (10-hydroxyaloin and derivatives thereof): As in the case of chemotype *Ba3*, this is another example where the infrageneric taxonomy is fully

congruent with the chemotaxonomic data [47]. *Chemotype Ba5* (aloin A/B and 6'-*O*-coumaroyl-aloesin; **87**): All six species in *Aloe* section *Anguialoe* including *A. castanea* produce these compounds [75]. Chemotype *Bh1* (homonataloin A/B; **59** and homonataloside B; **60**): The latter compound is the only known derivative of homonataloin [76]. *Chemotype Bh2* (homonataloin A/B and aloeresin E & F): The chemotaxonomic value of the combination of homonataloin A and B with the two cinnamoyl chromones, aloeresin E (**105**) and F (**107**) has been discussed [77, 78].

Chemotype C (Plicataloside; 74)

This naphthalene compound, first isolated from *A. plicatilis* [53] assembles all of the 20 plicataloside producing species in chemotype *C*. The chemotaxonomic importance of plicataloside has been discussed [79].

Chemical compounds in *Aloe* have become an important selection factor in evolution, and the morphology of related species is often much more conservative than the chemistry. As with most taxonomic characters, the chemical compounds are highly informative of relationships within some infrageneric groups, while they are too variable to be of taxonomic value in other groups. The subterranean and above-ground metabolisms are surprisingly different, perhaps reflecting the different environmental influences above and below the ground (anti-herbivory above, antibacterial and antifungal below). In close relatives of *Aloe* (e.g. *Gasteria* and *Haworthia*) the roots and leaves are chemically similar. It is also likely that the chemical complexity of the anthrones and chromones has evolved in response to herbivore pressure in arid environments. The absence of leaf exudate in many species of Madagascar (a region with very few herbivores) seems to support this notion.

The lack of congruence between morphological and chemical characters indicates that there must have been a relatively recent "explosion" of speciation events in *Aloe*, of which hybridization seems to have played an important role. Some compounds are clear indicators of hybridization events (e.g. nataloin, which is always present in hybrids between aloin- and homonataloin-producing species) [41].

CONCLUSION

Out of the wide range of *Aloe* species, only *A. ferox* and *A. vera* are of importance in international trade. However, it remains to be established if extracts from other species could be promoted for similar purposes as these popular species. Aside from the purgative and laxative properties, which are mainly ascribed to the bitter anthrones such as aloin and its derivatives, most of the other claimed effects of aloe are considered to be due to the polysaccharides and other components present in the gel. It is currently believed that biological activities come from synergistic actions of *Aloe* compounds rather than from a single component.

It is ironic that aloes, arguably one of the most important medicinal plants and among the best studied ones, still remain a rich source of novel chemical compounds.

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