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CRINUM; AN ENDLESS SOURCE OF BIOACTIVE PRINCIPLES: A REVIEW. PART 1- *CRINUM* ALKALOIDS: LYCORINE-TYPE ALKALOIDS

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ABSTRACT

Crinum is an important Amaryllidaceous plant thanks to the valuable biological and therapeutic activities of its chemical constituents, especially alkaloids. Many *Crinum* species have been commonly used in traditional medicines worldwide. Long ago, they have been subjected to extensive chemical, cytological and pharmacological investigations. Accordingly, this work comprehensively comprises both the alkaloidal and non-alkaloidal principles of *Crinums* isolated from 1950 and up to now, together with various biological and toxicological studies conducted on both the total extracts and individual compounds. As being a major common class of *Crinum* alkaloids, the current part of this review work highlights the lycorine-type alkaloids isolated so far from this plant in addition to their distribution in different *Crinum* species.

INTRODUCTION: Amaryllidaceae is a great widely spread family all over the world and contains about 90 genera and 1310 species [1]. The genus *Crinum* represents an important sector in family Amaryllidaceae with wide geographical distribution throughout the tropics, subtropics and warm temperate regions of the world [2]. The name *Crinum* originates from the Greek "*Krinon*", which means "white lily", and they are commonly known as “Milk, river, or veld lilies”. This genus is related to a group of mostly southern African endemic genera, constituting the tribe Amaryllideae [3].

Like other members of Amaryllidaceae, *Crinums* can occupy many different habitats such as seasonally dry places, ephemeral pools, rainforests, coastal areas and rivers' banks. Worldwide, *Crinum* comprises about 130 species distributed in Africa, America, southern Asia and Australia. African lands enjoy most species and about twenty-two are endemic to Southern Africa.

However, recent regional revisions of African taxa indicated that around half this number (130 species), would be a better approximation [4]. The uncertainty about their numbers is attributed to the difficulty in naming species correctly and the high possibilities of hybridization between different species. Botanically, *Crinums* are perennial herbaceous plants with giant fleshy bulbs larger in stature than most other species of Amaryllidaceae. They can grow from 1-5 feet in height depending on the species and produce a neck or a pseudo stem made up of the sheathing old leaves. Flowers usually appear in May, June or August [5].

Worldwide, *Crinums* have a great economic value as ornamentals due to their showy flowers. In addition, huge numbers of them are traded for traditional medicines. *Crinums* attract considerable attention due to their various medicinal properties such as antitumor, immunostimulating, analgesic, antiviral, antimalarial, antibacterial and antifungal activities.

Since about 1950s, *Crinums* have been subjected to extensive chemical, cytological and pharmacological investigations due to their richness in pharmacologically active principles [6]. Phytochemical investigations have resulted in isolation of several diverse classes of compounds and have been focused predominantly on alkaloids. Phenolics prevail among the non-alkaloidal constituents identified [7].

Consequently, this work represents a comprehensive account on various classes of *Crinum* alkaloidal and non-alkaloidal constituents together with their structural and stereochemical differences. Additionally, their distribution in various *Crinum* species studied so far (**Table 1**) is also completely considered (out of around 130 species, only about 35 have been phytochemically investigated). The first part of our review work will concentrate on lycorine-type alkaloids as one of the most common *Crinum* alkaloids.

TABLE 1: A LIST OF PHYTOCHEMICALLY INVESTIGATED *CRINUM* SPECIES

No.	Species	No.	Species
1.	*C. amabile* Donn.	19.	*C. lugardiae* N.E.Br.
2.	*C. americanum* L.	20.	*C. macowanii* Baker
3.	*C. asiaticum* Linn. (syn. *C. giganteum*)	21.	*C. macrantherum* Engl.
4.	*C. asiaticum var. japonicum* Baker	22.	*C. moorei* Hook F.
5.	*C. asiaticum var. sinicum* Baker	23.	*C. natans* Linn.
6.	*C. augustum* Rox.	24.	*C. oliganthum* Urban
7.	*C. bulbispermum* Milne.	25.	*C. ornatum* (L. f. ex Aiton)
8.	*C. defixum* Ker.	26.	*C. powelli* Hort. (Hybride of *C. moorei x C. longifolium*)
9.	*C. delagoense* Verdoom	27.	*C. powelli* Hort. *var. album*
10.	*C. erubescens* Ait.	28.	*C. powelli* Hort. *var. harlemense*
11.	*C. firmifolium* Baker	29.	*C. powelli* Hort. *var. krelagei*
12.	*C. firmifolium var. hygrophilum* Baker	30.	*C. pratense* Herb. (syn. *C. longifolium*)
13.	*C. glaucum* Chevalier	31.	*C. purpurascens*
14.	*C. Jagus* Dandy	32.	*C. scabrum* Herb.
15.	*C. kirkii* Baker	33.	*C. stuhlamanii* Baker
16.	*C. kunthianum* Roem.	34.	*C. yemense* Defl.
17.	*C. latifolium* Linn.	35.	*C. zeylanicum* Linn.
18.	*C. laurentii* Durand and Dewild		

***Crinum* and Amaryllidaceae alkaloids:** Amaryllidaceae is divided into four subfamilies; the Agavoideae, Amaryllidoideae, Campynematoideae and Hypoxidoideae. Alkaloids have only been found in subfamily Amaryllidoideae [8]. It contains about nine chief different classes of alkaloids. The chemical structures of the so called "Amaryllidaceae alkaloids" are restricted to this family and have limited taxonomic distribution [9]:

1. N-Benzyl-N-(β-phenethylamine) nucleus (Belladine-type).
2. 2-Benzopyrano-(3, 4 g)-indole nucleus (Lycorenine-type).
3. Pyrrolophenanthridine nucleus (Lycorine-type).
4. Dibenzofuran nucleus (Galanthamine-type).
5. 5, 10 b-Ethanophenanthridine nucleus (Crinine-type)
6. 2- Benzopyrano- (3, 4 c)- indole nucleus (Tazettine-type).
7. 5, 11-Methanomorphanthridine nucleus (Montanine-type).
8. Benzylisoquinoline nucleus (Cherylline-type).
9. Phenanthridone nucleus (Narciclasine-type).

The genus *Crinum* is a true representative of the family as it exhibits all the main chemical traits of Amaryllidaceae. About 180 alkaloids belonging to different types of Amaryllidaceae alkaloids have been isolated and identified. Crinine-, lycorine- and tazettine-types are the most common groups among the isolated alkaloids, while montanine-type has not yet been found in *Crinum* species [10].

In addition to these common types of Amaryllidaceae alkaloids, *Crinums* yielded other types that are not common in the family e.g. Augustamine- [11-13], β-carboline- [12], Phenanthridine- [12, 14], *Sceletium*- [15], Ismine- [14, 16, 17] and Clivimine- [16] type alkaloids.

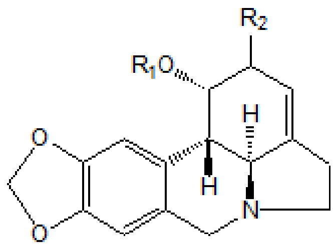
The isolated lycorine-type alkaloids from different *Crinum* species are depicted in **Table 2 and Figure 1**.

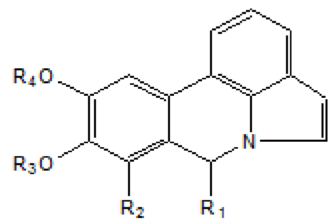
TABLE 2: A LIST OF LYCORINE-TYPE ALKALOIDS ISOLATED FROM DIFFERENT *CRINUM* SPECIES

No.	Alkaloid name	Molecular Formula	mp (˚C) / [α]$_D$	Plant source	Plant parts	References
1	Acetylcaranine.	$C_{18}H_{19}NO_4$		*C. moorei* Hook F.	---	18
2	1-O-Acetyl-lycorine.	$C_{18}H_{19}NO_5$		*C. kirkii* Baker *C. latifolium* Linn. *C. macowanii* Baker *C. moorei* Hook F. *C. powellii var. album*	Bulbs Bulbs Whole plant Seeds Whole plant Bulbs	13 19 20, 21 22 21, 23 24
3	2-O-Acetyl-lycorine.	$C_{18}H_{19}NO_5$	180–182˚/–8.72˚ ($CHCl_3$)	*C. augustum* Rox. *C. kirkii* Baker	Bulbs Bulbs	25 13
4	Anhydrolycorine-7-one.	$C_{16}H_{11}NO_3$	228 –230˚	*C. pratense*		26
5	Caranine.	$C_{16}H_{17}NO_3$		*C. laurentii* Durand & Dew. *C. powellii* Hort. *var. album* *C. powellii* Hort. *var. krelagei*	Bulbs --- ---	27 28 26
6/6'	Compound 2a/2b.	$C_{69}H_{118}NO_{12}P$		*C. asiaticum* L.	Fruits	29
7/7'	Compound 3a/3b.	$C_{69}H_{120}NO_{12}P$		*C. asiaticum* L.	Fruits	29
8	Criasbetaine.	$C_{17}H_{15}NO_3$		*C. asiaticum* L.	Fruits	29
9	Criasiaticidine A.	$C_{15}H_9NO_3$		*C. asiaticum var. japonicum*	Bulbs	30
10	4,5-Dehydro-anhydrolycorine.	$C_{16}H_{11}NO_2$		*C. latifolium* Linn.	Flower stems	31
11	9-O-Demethyl-pluviine.	$C_{16}H_{19}NO_3$	199–200˚ / –168˚ (MeOH)	*C. stuhlamanii* Baker	Bulbs	32
12	8-O-Demethyl-vasconine.	$C_{16}H_{14}NO_2$	200–202˚	*C. kirkii* Baker	Bulbs	33
13	(-)-1,2-O-Diacetyl-lycorine	$C_{20}H_{21}NO_6$	212–213˚	*C. kirkii* Baker *C. latifolium* Linn. *C. moorei* Hook F.	Bulbs Bulbs Seeds	13 19 22
14	(-)-2-Epilycorine.	$C_{16}H_{17}NO_4$	168–170˚ / –212.8˚ (MeOH)	*C. latifolium* Linn.	Flower stems	31
15	2-Epipancrassidine.	$C_{16}H_{17}NO_5$	207–210˚ / –112.5˚ (MeOH)	*C. latifolium* Linn.	Flower stems	31
16	Galanthine.	$C_{18}H_{23}NO_4$	166–167˚ / –81.6˚ (EtOH)	*C. amabile* Donn. *C. defixum* Ker. *C. laurentii* Durand and Dewild *C. moorei* Hook. F. *C. powellii* Hort. *var. harlemense*	Bulbs Bulbs --- Bulbs Bulbs	34 27 35 36 18
17	Hippacine.	$C_{15}H_9NO_3$		*C. bulbispermum* Milne.	Bulbs	37
18	Hippadine (pratorine).	$C_{16}H_9NO_3$	213–215˚ / +27.5˚ ($CHCl_3$)	*C. americanum* L. *C. asiaticum* L. *C. augustum* Rox. *C. bulbispermum* Milne. *C. kirkii Baker* *C. kunthianum* Roem. *C. latifolium* Linn. *C. powellii* Hort. *C. pratense* *C. purpurascens*	Bulbs Bulbs Bulbs Bulbs Bulbs Leaves Bulbs --- Leaves ---	38 39 40, 41 42 13 43 44 45 26 46
19	Hippamine.	$C_{17}H_{19}NO_4$		*C. bulbispermum* Milne.	Bulbs	47
20	8-Hydroxylycorine-7-one	$C_{16}H_{15}NO_6$		*C. bulbispermum* Milne.	Bulbs	47
21	Kalbretorine.	$C_{16}H_9NO_4$		*C. asiaticum* L. *C. augustum* Rox.	--- ---	10 10
22	(+)-Kirkine.	$C_{16}H_{19}NO_3$	170–172˚ / +59.6˚(MeOH)	*C. kirkii* Baker *C. stuhlamanii* Baker	Bulbs Bulbs	13, 33 32
				C. amabile Donn. *C. americanum* L. *C. asiaticum* L. *C. asiaticum var. japonicum*	Bulbs Bulbs Leaves, Bulbs Bulbs Aerial parts	34, 48, 49 7, 38 39, 50 30 51

23	(-)-Lycorine (Narcissine, Galanthidine, Amarylline, Bellamarine).	$C_{16}H_{17}NO_4$	260–262˚ / – 83.8˚ (EtOH) –71.2˚ (MeOH)	*C. augustum* Rox.	Whole plant	52
					Bulbs	25
				C. bulbispermum Milne.	Bulbs	42
					Whole plant	21
				C. defixum Ker.	Bulbs	53
				C. delagoense Verdoorn	Bulbs	54
				C. erubescens Ait.	Bulbs	55
				C. firmifolium var. hygrophilum	Whole plant	14
				C. glaucum Chevalier	Bulbs	56
				C. Jagus Dandy	Bulbs	56, 57
				C. kirkii Baker	Bulbs	13
				C. kunthianum Roem.	Leaves	43
				C. latifolium Linn.	Bulbs, Flower stems	31, 44
				C. laurentii Durand & Dew.	---	27
				C. lugardiae N.E.Br.	Bulbs, Roots	58
				C. macowanii Baker	Bulbs	59
					Whole plant	20, 21, 60
				C. macrantherum Engl.	Leaves	61
				C. moorei Hook F.	Seeds	22
					Whole plant	21, 23
				C. ornatum (L. f. ex Aiton)	Bulbs	62
				C. powellii Hort.	Bulbs	18
				C. powellii Hort. *var. album*	Bulbs	28
				C. powellii Hort. *var. harlemense*	---	63
				C. powellii Hort. *var. krelagei*	Bulbs	28
				C. pratense	---	26
				C. scabrum Herb.	Whole plant	53
				C. stuhlamanii Baker	Bulbs	32
				C. yemense Defl.	Bulbs	64
				C. zeylanicum Linn.	Bulbs	65, 66
24	Lycorine-1-O-β-D-glucoside.	$C_{22}H_{27}NO_9$	–92.4˚ (MeOH)	*C. asiaticum* L.	Roots	10, 16
				C. asiaticum var. japonicum	Roots	10, 16
				C. augustum Rox.	Roots	10
				C. latifolium Linn.	Roots	16
				C. pratense	Roots	16
25	Lycorine-1,2-O-β-D-diglucoside.	$C_{28}H_{36}NO_{14}$	–27.5˚ (H_2O)	*C. asiaticum* L.	Fruits	29
26	Lycoriside.	$C_{38}H_{57}NO_{10}$	–34.4˚ (MeOH)	*C. asiaticum* L.	Leaves, Fruits, Roots	67
27	Methylpseudolycorine.	$C_{18}H_{21}NO_4$		*C. moorei* Hook F.	---	18
				C. powellii Hort.	Bulbs	68
28	Mooreine.	$C_{17}H_{18}NO_4$		*C. moorei* Hook F.	Whole plant	23
29	Narcissidine.	$C_{18}H_{23}NO_5$	218–219˚/ –32˚(MeOH) –28˚ ($CHCl_3$)	*C. powellii* Hort.	Bulbs	68
				C. pratense	---	26
30	Neflexine.			*C. powellii* Hort.	Bulbs	69
31	Oxoassoanine.	$C_{17}H_{15}NO_3$		*C. latifolium* Linn.	Leaves	70
32	(–)-Palmilycorine.	$C_{32}H_{47}NO_5$	–58.5˚ (MeOH)	*C. asiaticum* L.	Leaves, Fruits, Roots	67
33	Pratorimine.	$C_{16}H_{11}NO_3$	263–265˚	*C. americanum* L.	Bulbs	38
				C. asiaticum L.	Bulbs	16, 39
				C. asiaticum var. japonicum	Bulbs	30
				C. augustum Rox.	Leaves, Bulbs	12, 40
				C. bulbispermum Milne.	Bulbs	12
				C. kunthianum Roem.	Leaves	43
				C. latifolium Linn.	---	44
				C. purpurascens	Leaves	46
34	Pratorinine.	$C_{16}H_{11}NO_3$	265–267˚	*C. americanum* L.	Bulbs	38
				C. asiaticum L.	Bulbs	16, 39
				C. augustum Rox.	Leaves, Bulbs	12, 40
				C. bulbispermum Milne.	Bulbs	12
				C. kunthianum Roem.	Leaves	43

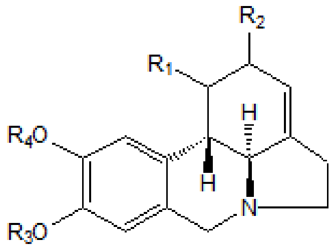
				C. pratense	---	26
35	Pratosine.	$C_{17}H_{13}NO_3$	232–233˚	*C. americanum* L. *C. asiaticum* L. *C. latifolium* Linn.	Bulbs --- ---	38 16 44
36	(-)-Pseudolycorine.	$C_{17}H_{19}NO_4$	247-249˚ / - 53˚ (EtOH)	*C. asiaticum* L.	---	16
37	Pseudolycorine-1-O-β-D-glucoside.	$C_{23}H_{29}NO_9$	– 108˚ (EtOH) – 105.5˚(MeOH)	*C. asiaticum* L. *C. latifolium* Linn.	--- ---	16 71
38	Ungeremine (lycobetaine).	$C_{16}H_{11}NO_3$	270–272˚	*C. americanum* L. *C. asiaticum* L. *C. augustum* Rox.	Bulbs Fruits Bulbs	38 29 41, 72
39	Zephyranthine.	$C_{16}H_{19}NO_4$	115–118˚ / –30.6˚ (MeOH)	*C. kirkii* Baker	Bulbs	13
40	Zephyranthine-1, 2-O-diacetyl.	$C_{20}H_{23}NO_6$		*C. kirkii* Baker	Bulbs	13



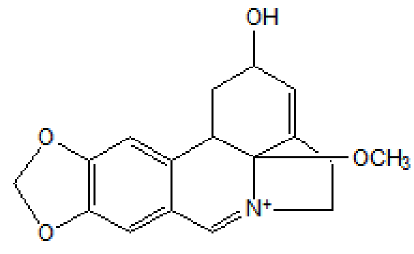


	R_1	R_2
(1)	Ac	H
(2)	Ac	βOH
(3)	H	βOAc
(5)	H	H
(13)	Ac	βOAc
(14)	H	αOH
(19)	H	βOMe
(23)	H	βOH
(24)	Glc.	βOH
(25)	Glc.	β-O-Glc.
(26)	Glc.(6′-palmitoyl)	βOH
(32)	palmitoyl	βOH

	R_1	R_2	R_3	R_4
(9)	O	H	H	H
(10)	H	H	— CH_2 —	
(17)	O	H	H	H
(18)	O	H	— CH_2 —	
(21)	O	OH	— CH_2 —	
(33)	O	H	H	Me
(34)	O	H	Me	H
(35)	O	H	Me	Me



	R_1	R_2	R_3	R_4
(11)	αOH	H	H	H
(16)	αOH	βOMe	Me	Me
(27)	αOMe	βOH	Me	Me
(36)	αOH	βOH	Me	Me
(37)	α-O-Glc	βOH	Me	Me



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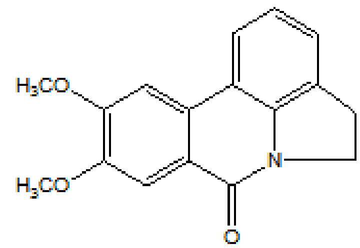

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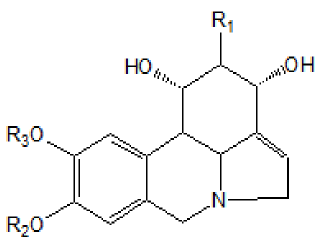
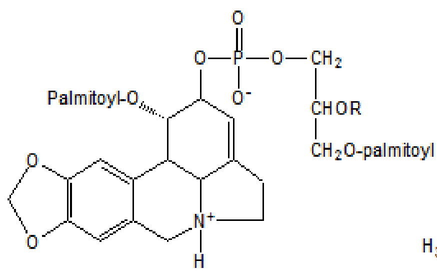
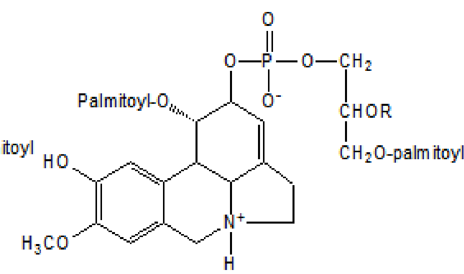


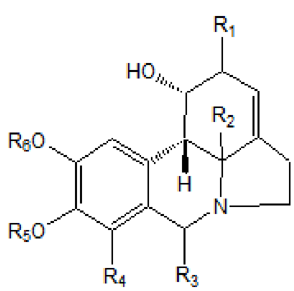
	R_1	R_2	R_3
(15)	αOH	— CH₂ —	
(29)	βOMe	Me	Me



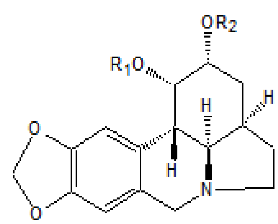
	R
(6)	stearoyl
(6′)	oleoyl



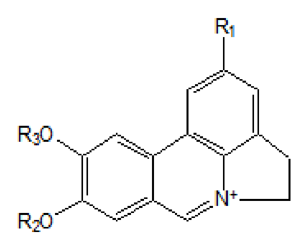
	R
(7)	stearoyl
(7′)	oleoyl



	R_1	R_2	R_3	R_4	R_5	R_6
(20)	βOH	αH	O	OH	— CH_2 —	
(22)	H	βH	H	H	OH	OMe



	R_1	R_2
(39)	H	H
(40)	Ac	Ac



	R_1	R_2	R_3
(8)	O^-	Me	Me
(12)	H	H	Me
(38)	O^-	— CH_2 —	

FIGURE 1: LYCORINE-TYPE ALKALOIDS ISOLATED FROM DIFFERENT *CRINUM* SPECIES

CONCLUSION: *Crinums* occupy an important position in plants of family Amaryllidaceae, and many of them have been used in traditional folk medicine throughout the world. The extensive survey of literature presents *Crinum* as an endless source of bioactive principles. Within the huge number and diverse classes of phytoconstituents produced by this plant, members of this genus are best known biofactories for Amaryllidaceae alkaloids. Phytochemical investigations led to isolation of several alkaloidal types and this current part of our review work summarized forty lycorine-type alkaloids isolated so far from *Crinums* as well as their structural differences and distribution in different *Crinum* species.

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