IJPSR (2012), Vol. 3, Issue 10 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 13 June, 2012; received in revised form 14 August, 2012; accepted 27 September, 2012

CRINUM; AN ENDLESS SOURCE OF BIOACTIVE PRINCIPLES: A REVIEW. PART III; *CRINUM* ALKALOIDS: BELLADINE-, GALANTHAMINE-, LYCORENINE-, TAZETTINE-TYPE ALKALOIDS AND OTHER MINOR TYPES

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Keywords:
Alkaloids,
Amaryllidaceae,
Crinum,
Galanthamine,
Tazettine

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ABSTRACT

Crinums occupy an important position within plants of family Amaryllidaceae, and many of them have been broadly used in traditional and ethnomedicines throughout the world. Due to their richness in bioactive phytoconstituents, *Crinums* have been subjected to extensive chemical, cytological and pharmacological investigations that focused chiefly on their alkaloidal content. Continuing our appraisal about the results of phytochemical, biological and toxicological studies on *Crinums* and after considering lycorine- and crinine-alkaloids as the major classes in its two previous parts; the current part of our review work draws attention to members of the other less common alkaloidal classes as well as the new types that are not common in the family.

INTRODUCTION: The genus *Crinum* represents an important sector in family Amaryllidaceae with broad geographical distribution throughout the tropics, subtropics and warm temperate regions of the world [1]. Worldwide, *Crinum* comprises about 130 species distributed in Africa, America, southern Asia and Australia. The African lands enjoy most species and about twenty-two are endemic to Southern Africa [2]. Many species are common emetic, laxative, expectorant, diaphoretic, anti-asthmatic, analgesic, anti-inflammatory, anti-microbial and anti-tumor remedies in various folkloric medicines [3].

During the last decade, *Crinums* have extensively attracted the attention of phytochemists due to their pharmacologically active principles. Within the huge number and diverse classes of phytocompounds produced by these plants, members of this genus are best known biofactories for Amaryllidaceae alkaloids [4]. It is worth mentioned that out of approximately 180 alkaloids have been isolated and identified from *Crinums*, about 120 bases belong to crinine- and lycorine-types. As a part of our ongoing comprehensive review work on various classes of *Crinum* alkaloidal and non-alkaloidal constituents as well as their biological activities, the present part of our work highlights bases of the less common alkaloidal classes e.g. belladine-, cherylline-, galanthamine-, lycorenine-, narciclasine- and tazettine-types as well as further uncommon minor types e.g. augustamine-, β-carboline-, phenanthridine-, sceletium-, ismine- and clivimine-type alkaloids together with their structural and stereochemical differences (**Table 1 and Figure 2**). Furthermore, their distribution in various species studied so far is also totally considered.

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Biosynthesis of Amaryllidaceae alkaloids: Amaryllidaceae alkaloids are derived from the amino acids phenylalanine and tyrosine via norbelladine (**Figure 1**). The latter undergoes oxidative phenolic coupling to give rise to the different carbon skeletons of these alkaloids. Accordingly, norbelladine and its various *O*- and *N*- substituted derivatives are considered the key biosynthetic intermediates for Amaryllidaceae alkaloids. In their route of biosynthesis, the two six- membered rings are derived from the aromatic amino acids, while, the additional ring closures are produced by a mechanism of phenolate free radical coupling [5].

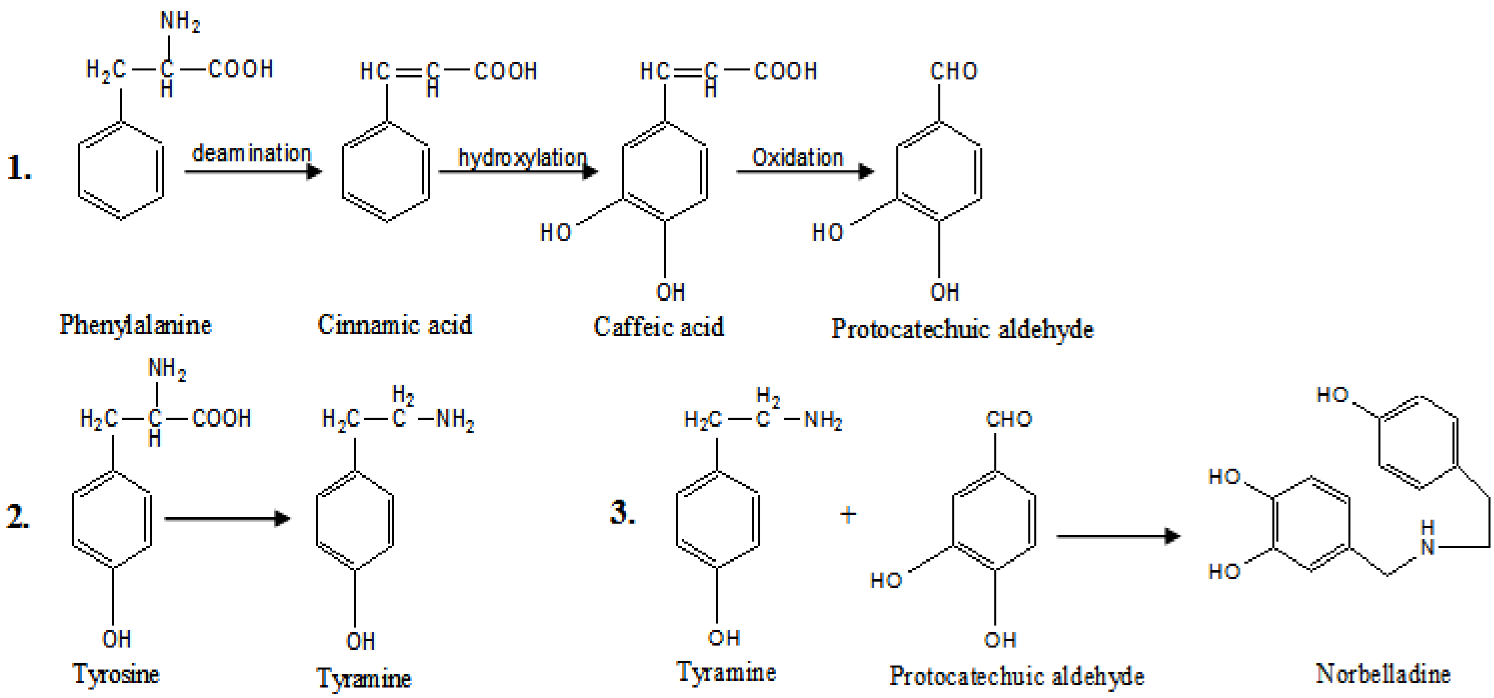


FIGURE 1: PROBABLE PATHWAY TO NORBELLADINE

TABLE 1: A LIST OF ALKALOIDS ISOLATED FROM DIFFERENT *CRINUM* SPECIES

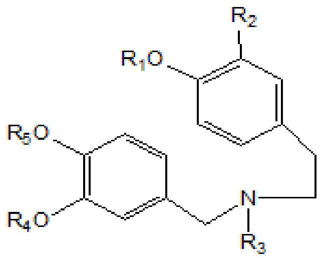
No.	Alkaloid name	Molecular Formula	mp (˚C) / $[\alpha]_D$	Plant source	Plant parts	References
			I- Belladine-type alkaloids:			
1	Belladine.	$C_{19}H_{24}NO_3$		*C. asiaticum* L. *C. latifolium* Linn. *C. powellii* Hort.	---- ---- ----	6 7 8
2	Craugsodine.	$C_{16}H_{17}NO_3$		*C. asiaticum* L. *C. augustum* Rox.	Fruits Flower stems	9 10
3	Isocraugsodine.	$C_{16}H_{17}NO_3$	220˚	*C. asiaticum* L. *C. augustum* Rox.	Fruits Fruits	9 9
4	Latisodine.	$C_{17}H_{21}NO_3$	205–207˚	*C. latifolium* Linn.	----	11
5	Latisoline.	$C_{24}H_{31}NO_8$	– 48.5˚ (MeOH)	*C. latifolium* Linn.	----	11
6	*O*-Methylnorbelladine.	$C_{16}H_{19}NO_3$	161–164˚	*C. asiaticum* L. *C. augustum* Rox. *C. kirkii* Baker *C. pratense*	---- ---- Bulbs ----	6 12 13 14
7	Ryllistine.	$C_{19}H_{25}NO_4$	77–79˚	*C. asiaticum* L. *C. augustum* Rox. *C. latifolium* Linn. *C. pratense*	---- ---- ---- ----	6 6, 15 16 15
			II- Galanthamine-type alkaloids:			
8	3-*O*-Acetyl-sanguinine.	$C_{17}H_{19}NO_4$	215 –218˚ / –13.5˚ (MeOH)	*C. kirkii* Baker	Bulbs	13
9	Epinorgalanthamine.	$C_{16}H_{19}NO_3$		*C. asiaticum* var. *japonicum*	Aerial parts	17
10	(–)-Galanthamine.	$C_{17}H_{21}NO_3$	127–129˚ / –121.4˚ (EtOH)	*C. amabile* Donn. *C. asiaticum* L.	Bulbs Bulbs	18 19

				C. defixum Ker. *C. laurentii* Durand & Dewild *C. macowanii* Baker *C. moorei* Hook F. *C. powellii* Hort. *C. powellii* Hort. *var. krelagei*	Bulbs ---- ---- Whole plant Bulbs Bulbs Bulbs	20 21 22 23 24 25 26
11	Galanthamine-*N*-demethyl [(–)-norgalanthamine].	$C_{16}H_{19}NO_3$	156–158˚	*C. asiaticum var. japonicum*	Leaves	27
12	Galanthamine-*O*, *N*- diacetyl.	$C_{20}H_{23}NO_5$	204–205˚	*C. asiaticum var. japonicum* *C. augustum* Rox.	---- ----	28 6
13	Lycoramine.	$C_{17}H_{22}NO_3$		*C. powellii* Hort.	Bulbs	29
14	Narwedine.	$C_{17}H_{19}NO_3$	188–189˚ +100˚($CHCl_3$)	*C. amabile* Donn.	Bulbs	18
15	Sanguinine.	$C_{15}H_{17}NO_3$		*C. kirkii* Baker	Bulbs	13
			III- Lycorenine-type alkaloids:			
16	(+)-9-*O*-Demethyl-homolycorine.	$C_{17}H_{19}NO_4$		*C. defixum* Ker. *C. moorei* Hook F.	Bulbs Bulbs	30 24
17	Hippeastrine.	$C_{17}H_{17}NO_5$	214–217˚ / + 160˚ ($CHCl_3$)	*C. amabile* Donn. *C. asiaticum* L. *C. defixum* Ker. *C. latifolium* Linn. *C. powellii* Hort.	Bulbs Bulbs Bulbs Bulbs, Leaves Bulbs	18 19 20 30 29
18	Homolycorine.	$C_{18}H_{21}NO_4$	173–175˚	*C. defixum* Ker.	Bulbs	30
19	5-Hydroxy-homolycorine.	$C_{18}H_{21}NO_5$		*C. defixum* Ker.	Bulbs	30
20	Neruscine (deoxylycorenine).	$C_{18}H_{23}NO_3$		*C. powellii* Hort.	Bulbs	29
			IV- Tazettine-type alkaloids:			
21	(+)-Criwelline (3-epitazettine).	$C_{18}H_{21}NO_5$		*C. delagoense* Verdoorn *C. erubescens* Ait. *C. firmifolium var. hygrophilum* *C. macrantherum* Engl. *C. powellii* Hort. *C. powellii* Hort. *var. album*	Bulbs ---- Whole plant Leaves ---- Bulbs	31 29 32 33 34 26
22	8-α-Ethoxy-precriwelline.	$C_{20}H_{25}NO_5$	+116.6˚ ($CHCl_3$)	*C. bulbispermum* Milne.	Whole plant	35
23	(+)-Macronine.	$C_{18}H_{19}NO_5$		*C. erubescens* Ait. *C. macrantherum* Engl.	Bulbs Leaves	36 33
24	*N*-desmethyl-8-α-ethoxy-pretazettine.	$C_{19}H_{23}NO_5$	+160.63˚ ($CHCl_3$)	*C. bulbispermum* Milne.	Whole plant	35
25	*N*-desmethyl-8-β-ethoxy-pretazettine.	$C_{19}H_{23}NO_5$	+34˚ ($CHCl_3$)	*C. bulbispermum* Milne.	Whole plant	35
26	(+)-*N*-demethyl-macronine.	$C_{17}H_{17}NO_5$		*C. erubescens* Ait.	Bulbs	36
27	(+)-*N*-demethylcarboethoxy-macronine.	$C_{20}H_{21}NO_7$		*C. erubescens* Ait.	Bulbs	36
28	Ornamine.	$C_{18}H_{21}NO_3$		*C. ornatum* (L.f.ex Aiton)	Bulbs	37
29	Ornazamine.	$C_{18}H_{22}NO_4$		*C. ornatum* (L.f.ex Aiton)	Bulbs	37
30	Ornazidine.	$C_{16}H_{20}NO_3$		*C. ornatum* (L.f.ex Aiton)	Bulbs	37
31	Precriwelline.	$C_{18}H_{21}NO_5$		*C. powellii* Hort.	Bulbs	36
32	(+)-Tazettine.	$C_{18}H_{21}NO_5$	202–208˚ / +160˚ ($CHCl_3$)	*C. amabile* Donn. *C. americanum* L. *C. asiaticum* L. *C. laurentii* Durand & Dewild *C. moorei* Hook F. *C. powellii* Hort. *var. harlemense* *C. powellii* Hort. *var. krelagei*	Bulbs Leaves Bulbs ---- Bulb ---- Bulb	6, 18 38 19 25 24 39 29
33	Zeylamine.	$C_{18}H_{21}NO_5$		*C. zeylanicum* Linn.	Roots	38
			V- Cherylline-type alkaloids:			
34	Boit's crinine.			*C. moorei* Hook F. *C. powellii* Hort.	---- ----	40 8, 34
35	Cherylline.	$C_{17}H_{19}NO_3$	212–213˚ / – 61.6˚ (EtOH)	*C. bulbispermum* Milne. *C. latifolium* Linn. *C. macowanii* Baker	Bulbs Bulbs Bulbs	41 41 42

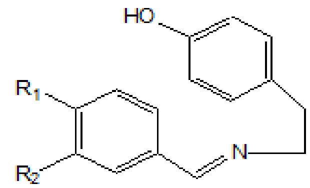
				 C. moorei Hook F. *C. powellii* Hort.	Whole plant Whole plant Bulblets Bulbs	43,44,45 23, 45 46 47
36	Latifine.	$C_{17}H_{19}NO_3$		*C. latifolium* Linn.	Leaves	48
			VI- Narciclasine-type alkaloids:			
37	Crinasiadine.	$C_{14}H_9NO_3$	276–278˚	*C. asiaticum* L.	----	49
38	Crinasiatine.	$C_{22}H_{17}NO_4$	> 270˚ (dec.)	*C. asiaticum* L.	----	49
39	Narcicrinine.	$C_{14}H_{17}NO_5$		*C. oliganthum* Urban	Leaves	38

VII- Other minor alkaloidal types:

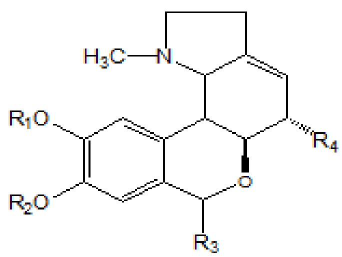
No.	Alkaloid name	Molecular Formula	Type	mp (˚C) / $[\alpha]_D$	Plant source	Plant parts	Reference
40	Augustamine.	$C_{17}H_{19}NO_4$	Augustamine	173–175˚	*C. augustum* Rox. *C. bulbispermum* Milne. *C. kirkii* Baker *C. latifolium* Linn.	Whole plant Bulbs Bulbs Leaves	50, 51, 52 53, 54 13 55
41	4a, *N*-Dedihydro-noraugustamine.	$C_{16}H_{15}NO_4$	Augustamine	127–130˚ / – 242.6˚(MeOH)	*C. kirkii* Baker	Bulbs	13
42	Noraugustamine.	$C_{16}H_{17}NO_4$	Augustamine	149–151˚ / – 50˚ (MeOH)	*C. kirkii* Baker	Bulbs	13
43	Cripowelline A.	$C_{25}H_{31}NO_{12}$	Novel type	– 43.8˚ (MeOH)	*C. powellii* Hort.	Bulbs	56
44	Cripowelline B.	$C_{25}H_{33}NO_{11}$	Novel type	– 64.1˚ (MeOH)	*C. powellii* Hort.	Bulbs	56
45	3-Hydroxy-8,9-methylene dioxy-phenanthridine.	$C_{14}H_9NO_3$	Phenanthridine	215–218˚	*C. firmifolium var. hygrophilum*	Whole plant	32
46	Trisphaeridine.	$C_{14}H_9NO_2$	Phenanthridine	139–141˚	*C. americanum* L. *C. asiaticum* L. *C. augustum* Rox. *C. bulbispermum* Milne *C. firmifolium var. hygrophilum* *C. kunthianum* Roem.	Bulbs Fruits Leaves Bulbs Whole plant Leaves	57 58 53 53 32 59
47	Ismine.	$C_{15}H_{15}NO_3$	Ismine	99–100˚	*C. firmifolium var. hygrophilum* *C. powellii* Hort. *C. powellii* Hort. *var. album* *C. pratense*	Whole plant Bulbs Bulbs ----	32 60 61 6
48	Latindine.	$C_{41}H_{31}N_3O_{10}$	Clivimine	> 300˚ (dec.)	*C. latifolium* Linn.	----	6, 15
49	Mesembrenol.	$C_{16}H_{21}NO_3$	Sceletium		*C. oliganthum* Urban	----	62
50	Perlolyrine.	$C_{16}H_{12}N_2O_2$	β-carboline	182–183˚	*C. augustum* Rox.	Leaves	53
51	Asiaticumine A.				*C. asiaticum var. sinicum*	Bulbs	63
52	Asiaticumine B.				*C. asiaticum var. sinicum*	Bulbs	63
53	Cribetamine.				*C. oliganthum* Urban	Leaves	38
54	Macranthine.				*C. macrantherum* Engl.	Leaves	33
55	Macranthine-*O*-acetyl.				*C. macrantherum* Engl.	Leaves	33
56	Macranthine-*O,O*-diacetyl				*C. macrantherum* Engl.	Leaves	33
57	Yemensine.				*C. yemense* Defl.	----	20



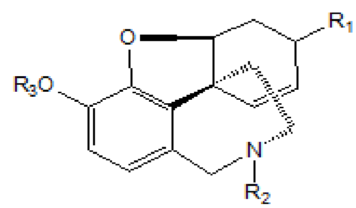
	R_1	R_2	R_3	R_4	R_5
(1)	Me	H	Me	Me	Me
(4)	H	H	H	Me	Me
(5)	Glc.	H	H	Me	Me
(6)	H	H	H	H	Me
(7)	Me	OMe	H	Me	Me



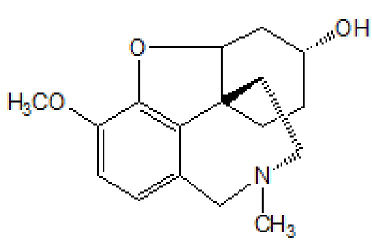
	R_1	R_2
(2)	OMe	OH
(3)	OH	OMe



	R_1	R_2	R_3	R_4
(16)	Me	H	O	H
(17)	— CH_2 —		O	OH
(18)	Me	Me	O	H
(19)	Me	Me	O	OH
(20)	Me	Me	H	H



	R_1	R_2	R_3
(8)	βOAc	Me	H
(9)	αOH	H	Me
(10)	βOH	Me	Me
(11)	βOH	H	Me
(12)	βOAc	Ac	Me
(14)	O	Me	Me
(15)	βOH	Me	H



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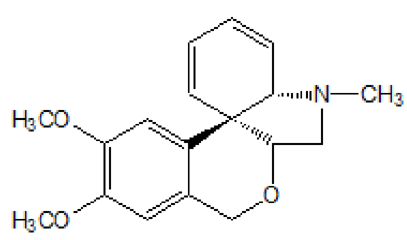

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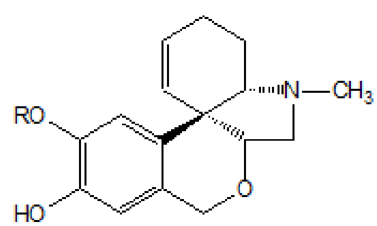
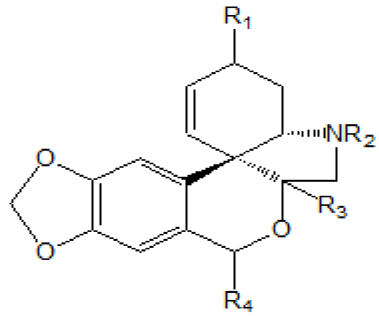
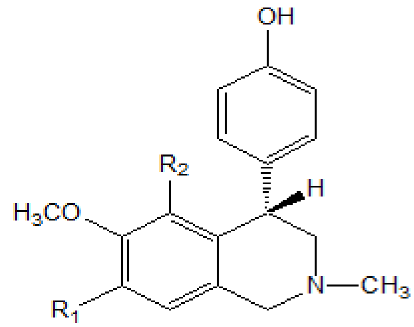


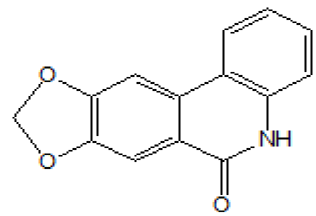
	R
(29)	Ac
(30)	H



	R_1	R_2	R_3	R_4
(21)	αOMe	Me	αOH	H
(22)	αOMe	Me	βH	αOEt
(23)	βOMe	Me	βH	O
(24)	βOMe	H	βH	αOEt
(25)	βOMe	H	βH	βOEt
(26)	βOMe	H	βH	O
(27)	βOMe	COOEt	βH	O
(31)	αOMe	Me	βH	αOH
(32)	βOMe	Me	αOH	H
(33)	βOH	Me	OMe	H



	R_1	R_2
(35)	OH	H
(36)	H	OH



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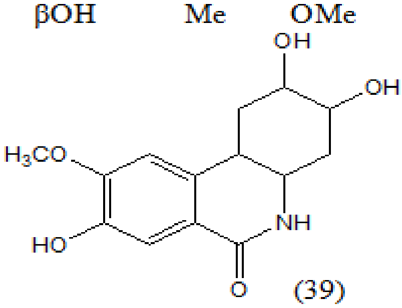

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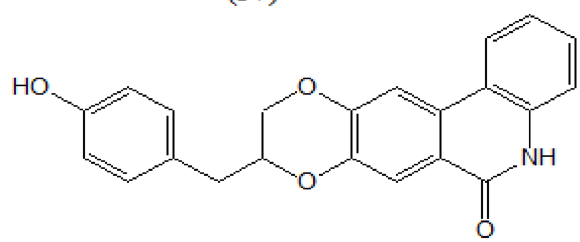

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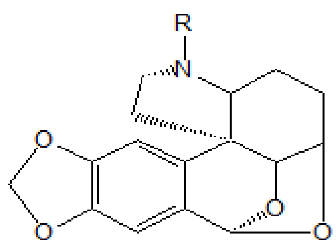
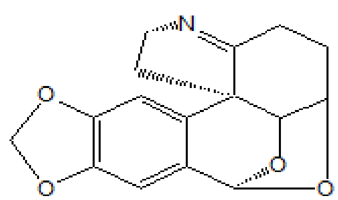


	R
(40)	CH_3
(42)	H



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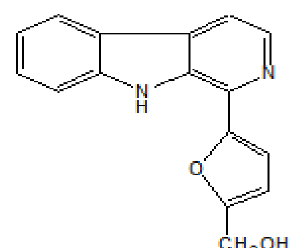

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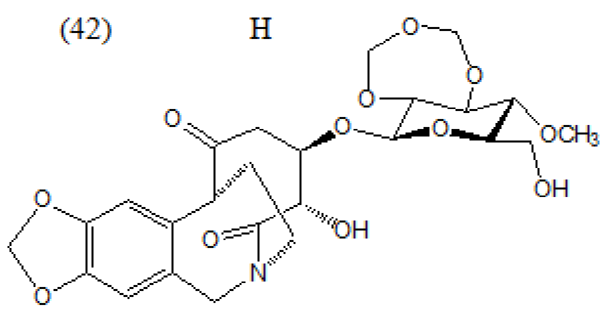

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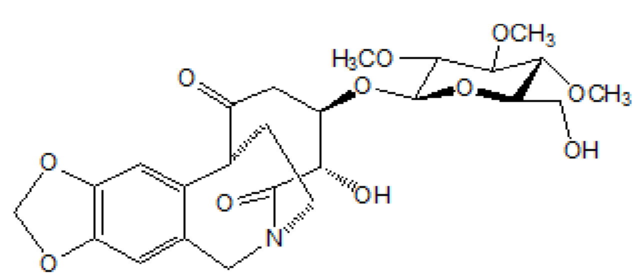

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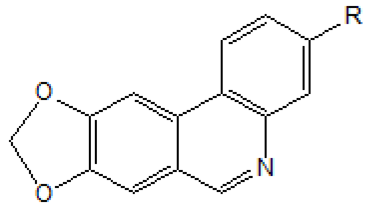
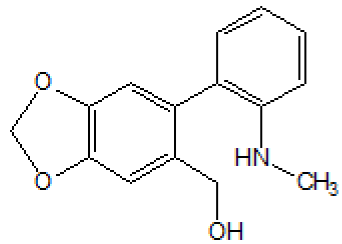


	R
(45)	OH
(46)	H



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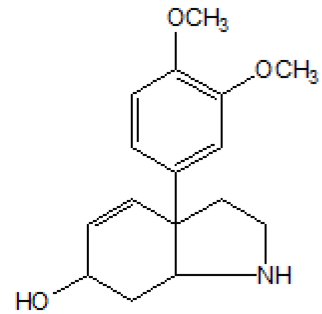

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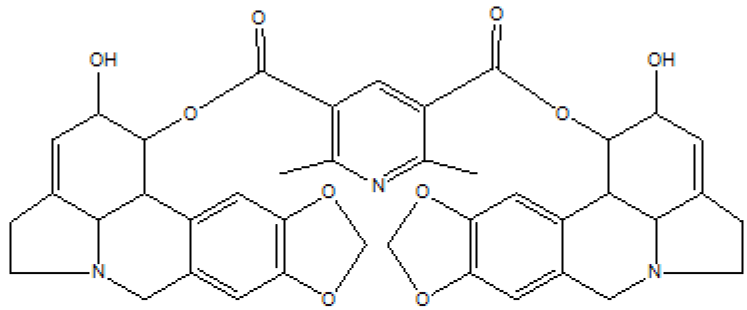

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FIGURE 2: ALKALOIDS ISOLATED FROM DIFFERENT *CRINUM* SPECIES

CONCLUSION: The genus *Crinum* can be considered a true representative of family Amaryllidaceae as it exhibits all the main chemical traits of this family. The extensive survey of literature showed that phytochemical analyses on *Crinums* have yielded a vast array of compounds, including about 180 alkaloids belonging to different types of Amaryllidaceae alkaloids. Crinine-, lycorine- and tazettine-types were found to be the most common among the isolated alkaloids, successively, while montanine-type has not yet been found in *Crinum* species.

In addition to these common classes of Amaryllidaceae alkaloids, *Crinums* yielded other types that are not common in the family e.g. augustamine-, β-carboline-, phenanthridine-, sceletium-, ismine- and clivimine-type alkaloids. Accordingly, in light of the growing global demand for natural pharmaceuticals to face the every day challenging diseases by searching for prospective active substances from natural sources, *Crinum* plants emerge as an endless source of bioactive principles, especially Amaryllidaceae alkaloids. Additionally, both the unstudied species and new hybrids open the gate towards isolation of further new phytocompounds.

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How to cite this article:
Refaat J, Kamel MS, Ramadan MA and Ali AA: Crinum; An endless source of Bioactive Principles: A Review. Part III; Crinum Alkaloids: Belladine-, Galanthamine-, Lycorenine-, Tazettine-type Alkaloids and other minor types. *Int J Pharm Sci Res*. 3(10); 3630-3638.