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Reviewing Colchicaceae Alkaloids – Perspectives of Evolution on Medicinal Chemistry

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Abstract: The subject of chemosystematics has provided insight to both botanical classification and drug development. However, degrees of subjectivity in botanical classifications and limited understanding of the evolution of chemical characters and their biosynthetic pathways has often hampered such studies. In this review an approach of taking phylogenetic classification into account in evaluating colchicine and related phenethylisoquinoline alkaloids from the family Colchicaceae will be applied. Following on the trends of utilizing evolutionary reasoning in inferring mechanisms in eg. drug resistance in cancer and infections, this will exemplify how thinking about evolution can influence selection of plant material in drug lead discovery, and how knowledge about phylogenetic relationships may be used to evaluate predicted biosynthetic pathways.

Keywords: Alkaloids, biosynthetic pathways, colchicaceae, colchicine, evolution, phylogenetic prediction.

INTRODUCTION

Using chemical information to define groups of plants is probably as old as botanical classification itself, a practice often referred to as chemosystematics or chemotaxonomy. In the modern sense it was largely introduced during the 1960s and 1970s, for example with the works of Bate-Smith [1,2], Swain [3] and Harborne [4], and by the founding of the journal now known as *Biochemical Systematics and Ecology* in 1973. In 1980 Dahlgren published the first systematic classification for flowering plants emphasizing chemical characters in defining relationships between families and higher taxa [5], visualizing the distribution of characters in the earlier introduced form of dahlgrenograms [6]. With the advent of molecular systematics based on comparison of nucleotide sequences, several of the groups which were previously to some extent defined by chemical characters, received even further support: the close relationships of the families containing betalain pigments instead of anthocyanins in Caryophyllales [7]; the occurrence of benzylisoquinoline alkaloids in the families of Dahlgren's Magnoliflorae [8]; the "mustard oil bomb" of the order Brassicales [9]; and the iridoids in the asterids [10]. The collective literature has thus confirmed the statement of Helen Abbott in 1887 that "the evolution of chemical constituents follows parallel lines with the evolutionary course of plant forms, the one being intimately connected with the other…" [11].

Natural products have been hitherto a very successful source of new drugs, with slightly more than a third of "small compounds" launched as "new chemical entities" for the past 30 years belonging to this group [12]. At the same time it has been shown that natural products occupy a different and larger chemical space than synthetic drugs [13, 14, 15], and that they have a higher probability to pass through the pharmaceutical industry drug developmental pipeline [16]. This is today usually discussed within the concept of natural products being *prevalidated* for activity [14, 15, 17, 18, 19, 20, 21]. As these compounds per definition are derived within a biological setting they are today presumed to have some sort of function or *raison d'être*, and even if this function is unknown, unstudied or only based on available bioassays, it is clear that this inherent property is influenced by evolution [22, 23]. Following on the trends of utilizing evolutionary reasoning in inferring mechanisms in eg. drug resistance in cancer and infections, this contribution will exemplify how thinking about evolution can influence selection of plant material for drug lead discovery, and how knowledge about phylogenetic relationships may be used to evaluate predicted biosynthetic pathways. As a case in point, an approach of taking phylogenetic classification into account in evaluating the medicinally important and historically fascinating alkaloid colchicine and related phenethylisoquinoline alkaloids from the family Colchicaceae is applied.

DISCOVERY AND MEDICINAL USE OF COLCHICINE

Colchicine, present in and named after the autumn crocus (*Colchicum autumnale* L., Colchicaceae), is today a well-known compound recognized for its antimitotic activity and as a treatment for acute gout and familial Mediterranean fever, a hereditary inflammatory disorder [24, 25, 26]. But the history of colchicine is full of misunderstandings and ill-advised inferences. This drug has truly ancient origins, being present in the writings of several classical Greek physicians from Nicander of Colophon, over Dioscorides, Pliny the Elder and Galen, to Alexander of Tralles [27]. Its use as a medication was however heavily discouraged by its toxicity,

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and often it was described rather as a poison than a remedy. The true identification was also heavily debated and views on whether terms such as *colchicon, ephemeron, hermodactylum* and *surugen* were equivalent differed between scholars at various times in history. Autumn crocus corm was present in the *London Pharmacopoeia* between 1618 and 1639, after which it was not mentioned until the 1788 edition [28]. The modern introduction of colchicine-based medicines for gout is usually attributed to von Störck in 1763 [29], but see Hartung [27] for counter-arguments. Colchicine-based medicines have been continuously employed as a remedy for this condition since the very early 19th century. The use of colchicine has been based on clinical experience, and it was only in 2009 the U. S. Food and Drug Administration approved it based on clinical trials defining dosage and efficacy [30].

Colchicine was identified as a "mitotic poison" in the early 1930s and its use in production of polyploid plants was described in 1937 [31]. It was used in the determination of the chromosome number for the human species [32], and has since the explanation of its tubulin-interaction been an important tool in biochemistry and development of cancer drugs [26, 33, 34]. Colchicine itself is too toxic to be used as a treatment for cancer, but other alkaloids and derivatives have been investigated. One of the first examples is the use of the alkaloid demecolcine, a deacetylated and methylated derivative against myeloid leukemia [35], and recently the allocolchinoid phosphate-derivative ZD6126 has been studied [34].

Just as the medicinal use has a complicated history, this is equally true for the alkaloid itself. The first colchicine isolation is usually considered to be by Pelletier and Caventou in 1820 [36]. However, they considered the isolated compound to be the alkaloid veratrine, a steroid-derived alkaloid from plants in the death camas family Melanthiaceae, and Geiger was the first to coin the name colchicine after crystallization of the pure compound in 1833 [37]. The structure of the alkaloid proved to be very elusive, and it was not elucidated until the x-ray crystallography investigation of King and co-workers in 1952 [38], confirming the supposition of Dewar that the compound contain two 7-membered rings of which one is a tropolone [39]. A review of synthetic approaches to colchicine was published in 2004 [40].

BIOLOGICAL ORIGIN

Colchicine is considered to have a restricted distribution within the plant kingdom [41, 42], and is isolated commercially from the related ornamental species autumn crocus (*Colchicum autumnale* L.) and flame lily (*Gloriosa superba* L.). The medicinal importance of colchicine prompted early screenings of the plant kingdom to find suitable sources for the compound. From these early reviews a much wider distribution for colchicine was inferred [43]. However, refined chemical detection methods have discarded many reports as false positives [41, 44]. The more restricted distribution originally proposed coincided largely with the, at that time, recently introduced lilioid subfamily Wurmbaeoideae [45], today more familiar as the family Colchicaceae [46].

With the advent of molecular systematics based on comparison of DNA sequences it was shown that a few genera (such as *Disporum* Salisb., *Uvularia* L., *Kuntheria* Conran & Clifford, *Schelhammera* R.Br., and *Tripladenia* D.Don) previously placed in other families should be included in an expanded Colchicaceae family and a new classification has been adopted, (see Table **1**) [47, 48]. Investigation of crude alkaloid extracts with mass spectrometry has also confirmed that colchicine is present in, and restricted to, the genera of Colchicaceae in this wider circumscription [49].

Table 1. Classification of the Family Colchicaceae [47], Including Selected Generic Synonyms Present in the Chemical Literature.

Tribe	Genus	Synonyms
Burchardieae	*Burchardia* R.Br.	
Uvularieae	*Disporum* Salisb.	
	Uvularia L.	
Tripladenieae	*Kuntheria* Conran & Clifford	
	Schelhammera R.Br.	
	Tripladenia D.Don	
Iphigenieae	*Camptorrhiza* E.Phillips	*Iphigeniopsis* Buxb.
	Iphigenia Kunth	
Anguillarieae	*Baeometra* Salisb. ex Endl.	
	Wurmbea Thunb.	*Anguillaria* R.Br. *Dipidax* Lawson ex Salisb. *Neodregea* C.H.Wright *Onixotis* Raf.
Colchiceae	*Colchicum* L.	*Androcymbium* Willd. *Bulbocodium* L. *Merendera* Ramond
	Gloriosa L.	*Littonia* Hook.
	Hexacyrtis Dinter	
	Ornithoglossum Salisb.	
	Sandersonia Hook.	

An Australian species described under the name *Kreysigia multiflora* Rchb. has been shown to contain colchicine and other alkaloids [50]. However the exact identity of this species is confounded by the application of this name to plants belonging to *Schelhammera* as well as *Tripladenia*.

Just as genera have been included in the family based on phylogenetic analysis of nucleotide data, analysis of such data has also resulted in a notable exclusion. The genus *Disporum* was considered to be present in both Asia and North America, but results from genetic studies have shown that the North American representatives should be treated as a distinct genus, *Prosartes* D.Don, and be moved to the family Liliaceae [51]. The family Colchicaceae as currently circum-

scribed thus constitutes 15 genera and about 280 species, of which more than half belong to *Colchicum* [48].

ALKALOID DIVERSITY

A number of reviews on phenethylisoquinoline alkaloids can be found in the literature [eg. 52]. However, they usually only treat a particular group of a specific structural type and will be exemplified under the respective alkaloid type below. The present contribution provides a review of Colchicaceae alkaloids of all types as well as perspectives of their origin, evolution and hypothetical biosynthetic pathways.

In the Combined Chemical Dictionary [53] there are about 150 entries with structurally elucidated alkaloids reported from Colchicaceae genera. They are biosynthetically derived from condensation of phenylalanine and tyrosine to a phenethylisoquinoline precursor, which has been shown by several feeding experiments in elucidation of colchicine biosynthesis [54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65].

Based on proposed biosynthesis, feeding experiments and analogies of pathways elucidated for benzylisoquinoline alkaloids, as presented in Fig. (**1**), we discern eight distinct structural types of alkaloids in the family Colchicaceae: phenethylisoquinolines, homoproaporphines, homoaporphines, androcymbines (homomorphinans), colchicines, allocolchicines, lumicolchicines and homoerythrinans. Phenethylisoquinolines and homoerythrinans have also been isolated from *Dysoxylum* in the mahogany family Meliaceae, which also contain a dibenzo[*d*,*f*]azecine alkaloid [53, 66, 67, 68, 69]. The homoerythrinan alkaloids also have additional disjunct occurrences in the monogeneric New Caledonian family Phellinaceae [53, 70] and the gymnosperm families Taxodiaceae, Podocarpaceae and Cephalotaxaceae [53, 71, 72]. Another group of alkaloids derived from phenethylisoquinoline precursors are the cephalotaxines unique for the family Cephalotaxaceae, which has recently been reviewed [73]. Thus, in total there are ten structural types of alkaloids with a possible common precursor. The hypothetical network of their interrelations as presented in Fig. (**1**), builds on possible transformations known to occur in biochemical reactions and transforming one structural type into another. The included diaryl-3-azahexanoid precursors could constitute alternative biosynthetic pathways to homoerythrinan alkaloids explaining their disjunct distribution.

Phenethylisoquinolines (Type A)

Six phenethylisoquinoline alkaloids have been described from Colchicaceae, see Fig. (**2**), of which autumnaline is

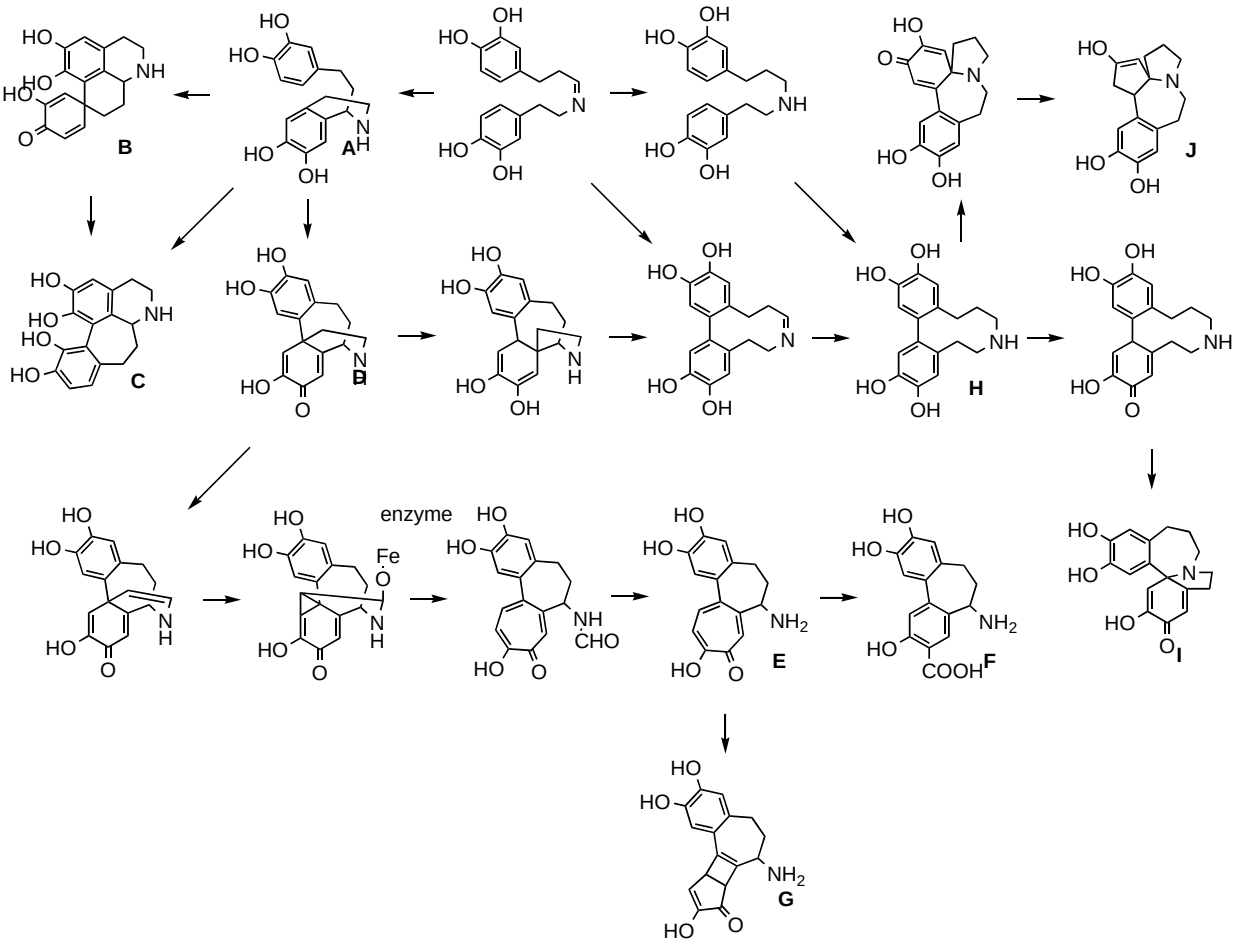
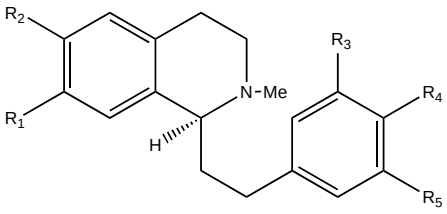
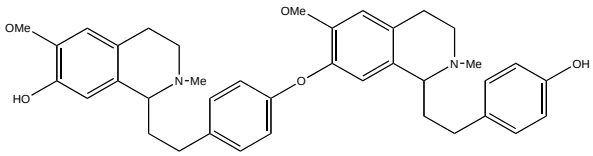


Fig. (1). Hypothetical network of phenethylisoquinoline derived alkaloids based on proposed biosynthesis, feeding experiments and analogies of pathways elucidated for benzylisoquinoline alkaloids. A: phenethylisoquinolines; B: homoproaporphines; C: homoaporphines; D: androcymbines; E: colchicines; F: allocolchicines; G: lumicolchicines; H: dibenzo[*d*,*f*]azecines; I: homoerythrinans; and J: cephalotaxines.

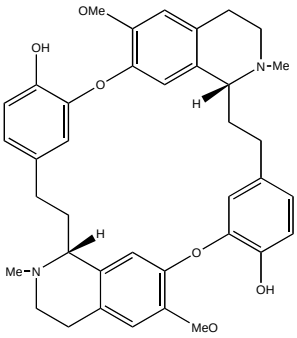
proposed as a key intermediate. There are only few reports of isolation of these alkaloids [74, 75, 76, 77, 78], perhaps due to their proposed functions as precursors and thus efficient transformation into other structural types. They do not seem to have been tested for biological activity, but phenethylisoquinolines from *Dysoxylum* have shown effects on isolated rat cardiac muscle [79].



	R1	R2	R3	R4	R5	H
autumnaline	OH	OMe	OH	OMe	OMe	β
isoautumnaline	OMe	OH	OH	OMe	OMe	β
colchiethanamine	OMe	OH	H	OH	H	α
colchiethine	OMe	OH	H	OMe	H	α



jolantinine



melanthioidine

Fig. (2). Structural diversity of the phenethylisoquinoline alkaloids in Colchicaceae.

Homoproaporphines (Type B)

These minor alkaloids, see Fig. (**3**), have been isolated primarily from the Eurasian species of *Colchicum* [80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96], but are also present in African [97] and Australian taxa [98]. Several homoproaporphines have been investigated for cholinergic activity [99, 100], showing moderate anticholinesterase activities.

Homoaporphines (Type C)

These alkaloids were last reviewed in 1989, see Fig. (**4**), [101], and very few have been investigated for biological activity [100].

Androcymbines (Type D)

This group, see Fig. (**5**), is sometimes called homomorphinandienones. The isolation and structure elucidation of androcymbine and *O*-methylandrocymbine proved to be essential for understanding the biosynthetic origin of colchicine, finally linking this "alkaloid *sui generis*" to the phenethylisoquinoline precursors [74, 102].

Colchicines (Type E)

This is the largest group of alkaloids within Colchicaceae as of today, see Fig. (**6**). A statement that is true even if, as done here, the allo- and lumicolchicine derivatives are excluded. They commonly interact with tubulin and are considered to be a main toxic principle of Colchicaceae plants. They have also been evaluated for anticholinesterase activity [103]. This is the first isolated group of alkaloids containing a tropolone ring in their structure, a fact that has been used to distinguish them from other alkaloids in simple TLC screenings due to a positive Oberlin-Zeisel reaction when sprayed with $FeCl_3$ after treatment with HCl vapor [41], and are thus sometimes known as tropolonic alkaloids. This name would however also include the unrelated tropoloisoquinoline alkaloids described from *Abuta* in the moonseed family Menispermaceae [104, 105, 106]. Colchicines were reviewed by Boyé and Brossi in 1992 [107], and have not been updated since. A further ten colchicine-type alkaloids have been described as minor components from *Colchicum* and *Gloriosa* species since that review [78, 108, 109, 110, 111]. Even though colchicine itself is deemed to be too toxic as an anticancer drug, investigation of compounds binding to the same site and interacting with tubulin is an active field of research [112]. There is also a continued interest in modification of the colchicine-type core to modify toxicity and activity of these compounds [113, 114, 115, 116].

Allocolchicines (Type F)

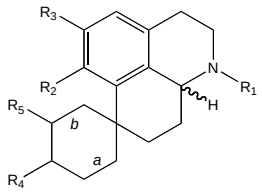
These alkaloids are also called dibenzocycloheptylamines, see Fig. (**7**), and have been suggested to be catabolic metabolites of colchicines [117, 118]. They usually retain the colchicine-type alkaloids ability to bind to tubulin but are less toxic, which has yielded some interest as potential antitumor drugs [34, 119].

Lumicolchicines (Type G)

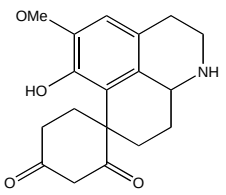
There is a debate whether these alkaloids, see Fig. (**8**), are produced in the plant or simply artifacts from the isolation since they can also be formed as photoisomers from colchicine-type alkaloids under influence by light. In contrast to allocolchicines the lumicolchicine-derivatives lack specific binding to tubulin.

Homoerythrinans (Type I)

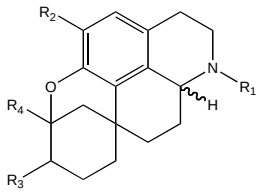
This group of alkaloids has a very narrow distribution within Colchicaceae and has only been found in the Australian genera *Schelhammera* and *Kuntheria* [120, 121, 122, 123, 124], of which the latter is a relatively recent taxonomic split from the former [125]. However, among the phenethylisoquinoline alkaloids this is a very widespread group present in *Dysoxylum* of Meliaceae [66], *Phelline* of Phellinaceae



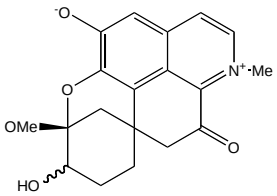
	R1	R2	R3	R4	R5	H	*a*	*b*
bulbocodine	Me	OH	OMe	=O	H	β	double	single
jolantamine	Me	OH	OMe	=O	H	β	double	single
jolantine	Me_2 (+)	OH	OMe	=O	H	β	double	single
crociflorinone	Me	OMe	OMe	=O	H	β	double	single
kreysiginone	Me	OH	OMe	=O	OMe	α	double	double
dihydrokreysiginone	Me	OH	OMe	=O	OMe	α	single	double
luteidine	Me	OH	OMe	=O	OMe	α	single	double
luteidine N_α-oxide	Me, O	OH	OMe	=O	OMe	α	single	double
luteidine N_β-oxide	Me, O	OH	OMe	=O	OMe	α	single	double
trigamine	Me	OH	OMe	OH	H	β	single	single
trigamine *N*-oxide	Me, O	OH	OMe	OH	H	β	single	single



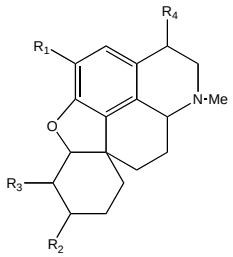
jolantimine



	R1	R2	R3	R4	H
kesselridine	Me	OH	OH (α)	OH (β)	β
regelamine	Me	OMe	OH (α)	OH (β)	β
jolantidine	H	OMe	OH (α)	OH (β)	β
kesselringine	Me	OH	OH (α)	OMe (β)	β
regeline	Me	OMe	OH (α)	OMe (β)	β
luteine	Me	OH	OH (β)	OMe (β)	β
regelinine	Me	OMe	OH (β)	OMe (β)	β
regecoline	Me (+)	O (–)	OH (α)	OMe (β)	*N*-double
isoregecoline	Me (+)	O (–)	OH (β)	OMe (β)	*N*-double
robustamine	Me	OMe	OH (β)	OMe (β)	α
robustamine N_α-oxide	Me, O	OMe	OH (β)	OMe (β)	α



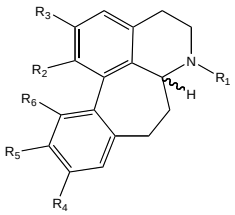
regelinone (α-form)



isoregelinone (β-form)

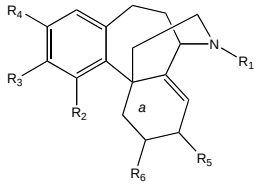
	R1	R2	R3	R4
colchilutine	OMe	H	H	=O
luteicine	OMe	OH	OMe	H

Fig. (3). Structural diversity of the homoproaporphine alkaloids in Colchicaceae.

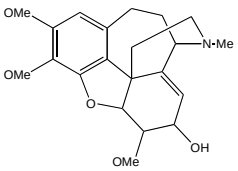


	R1	R2	R3	R4	R5	R6	H
alkaloid CC24	Me	OH	OMe	OMe	OMe	OH	β
multifloramine, (–)-form	Me	OH	OMe	OMe	OH	OMe	β
floramultine	Me	OH	OMe	OH	OMe	OMe	β
kreysigine, (–)-form	Me	OH	OMe	OMe	OMe	OMe	β
baytopine	Me	OMe	OMe	OH	OMe	OH	α
merobustinine	Me	OMe	OH	OMe	OH	OMe	α
androbine	Me	OMe	OH	OH	OMe	OMe	α
norandrobine	H	OMe	OH	OH	OMe	OMe	α
merobustine	Me	OH	OMe	OMe	OMe	OH	α
multifloramine, (+)-form	Me	OH	OMe	OMe	OH	OMe	α
merenderine	Me	OH	OMe	OH	OMe	OMe	α
merenderine *N*-oxide	Me, O	OH	OMe	OH	OMe	OMe	α
szovitsamine	Me	OMe	OMe	OMe	OMe	OH	α
szovitsamine N_{β}-oxide	Me, O	OMe	OMe	OMe	OMe	OH	α
androcimine	Me	OMe	OMe	OH	OMe	OMe	α
androcine	Me	OMe	OH	OMe	OMe	OMe	α
kreysigine, (+)-form	Me	OH	OMe	OMe	OMe	OMe	α
kreysigine N_{β}-oxide	Me, O	OH	OMe	OMe	OMe	OMe	α
O-methylkreysigine	Me	OMe	OMe	OMe	OMe	OMe	α
O-methylkreysigine *N*-oxide	Me, O	OMe	OMe	OMe	OMe	OMe	α
nor-*O*-methylkreysigine	H	OMe	OMe	OMe	OMe	OMe	α
szovitsinine	Me	OMe	OH	OMe	OMe	OH	ξ
N-methylmerenderine	Me_2(+)	OH	OMe	OH	OMe	OMe	ξ

Fig. (4). Structural diversity of the homoaporphine alkaloids in Colchicaceae.

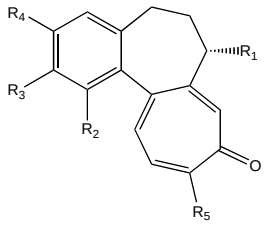


	R1	R2	R3	R4	R5	R6	*a*	ethano-bridge
alkaloid CC-2	Me	OMe	–OCH_2O–		OH (β)	OMe (β)	single	β
alkaloid CC-20	Me	OMe	–OCH_2O–		=O	OMe	double	β
alkaloid CC-3b	Me	OMe	OMe	OH	OH (β)	OMe (β)	single	β
androcymbine	Me	OMe	OH	OMe	=O	OMe	double	α
O-methyl-androcymbine	Me	OMe	OMe	OMe	=O	OMe	double	α
isoandrocymbine	Me	OMe	OMe	OH	=O	OMe	double	α
collutine	Me	OH	OMe	OMe	=O	OMe	double	α
collutine *N*-oxide	Me, O	OH	OMe	OMe	=O	OMe	double	α
alkaloid CC-10	Me	OMe	OMe	OH	=O	OMe	double	β
szovitsidine	Me	OMe	OMe	OMe	OH (ξ)	OMe	double	ξ
colchiritchine	H	OMe	–OCH_2O–		=O	OMe	double	β



(±)-kreysiginine

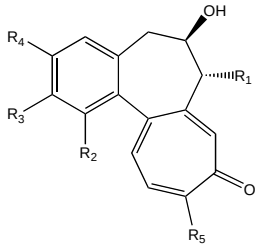
Fig. (5). Structural diversity of the androcymbine (homomorphinan) alkaloids in Colchicaceae.



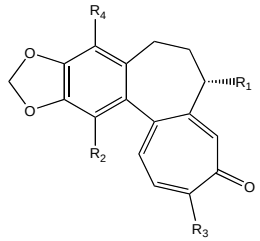
	R1	R2	R3	R4	R5
colchicine	NHAc	OMe	OMe	OMe	OMe
colchifoline	NH(AcOH)	OMe	OMe	OMe	OMe
2-demethyl-colchifoline	NH(AcOH)	OMe	OH	OMe	OMe
N-deacetyl-colchicine	NH_2	OMe	OMe	OMe	OMe
gloriosine [a]	NHCHO	OMe	OMe	OMe	OMe
N-deacetyl-*N*-(3-oxobutyryl)-colchicine	NH(AcAc)	OMe	OMe	OMe	OMe
demecolcine [b]	NHMe	OMe	OMe	OMe	OMe
N-formyldemecolcine	NMeCHO	OMe	OMe	OMe	OMe
N-ethoxycarbonyl-colchicine	NH(COOEt)	OMe	OMe	OMe	OMe
N-methyldemecolcine	NMe_2	OMe	OMe	OMe	OMe
2-demethylgloriosine	NHCHO	OMe	OH	OMe	OMe
2-demethylcolchicine	NHAc	OMe	OH	OMe	OMe
2-demethyldemecolcine	NHMe	OMe	OH	OMe	OMe
N-deacetyl-3-demethylcolchicine [c]	NH_2	OMe	OMe	OH	OMe
1'-epicolchicoside	NHAc	OMe	OMe	O-α-D-glc	OMe
colchicoside	NHAc	OMe	OMe	O-β-D-glc	OMe
3-demethylgloriosine	NHCHO	OMe	OMe	OH	OMe
3-demethylcolchicine	NHAc	OMe	OMe	OH	OMe
3-demethyldemecolcine	NHMe	OMe	OMe	OH	OMe
3-demethyl-*N*-methyldemecolcine	NMe_2	OMe	OMe	OH	OMe
deacetylcolchiceine	NH_2	OMe	OMe	OMe	OH
glorioseine [d]	NHCHO	OMe	OMe	OMe	OH
colchiceine	NHAc	OMe	OMe	OMe	OH
demecolceine [e]	NHMe	OMe	OMe	OMe	OH
1,2-didemethylcolchicine	NHAc	OH	OH	OMe	OMe
N-deacetyl-2,3-didemethylcolchicine	NH_2	OMe	OH	OH	OMe
2,3-didemethylcolchicine	NHAc	OMe	OH	OH	OMe
2,3-didemethyldemecolcine	NHMe	OMe	OH	OH	OMe
2-demethylcolchiceine	NHAc	OMe	OH	OMe	OH
3-demethylcolchiceine	NHAc	OMe	OMe	OH	OH
speciosine	NMe(2-OH-benzyl)	OMe	OMe	OMe	OMe
O-methylspeciosine	NMe(2-OMe-benzyl)	OMe	OMe	OMe	OMe
speciocolchine	NMe(2-OH-benzyl)	OMe	OH	OMe	OMe
specioritchine	NMe(2-OH-benzyl)	OMe	OMe	OH	OMe
specioseine	NMe(2-OH-benzyl)	OMe	OMe	OMe	OH
speciosamine	NMe(benzyl)	OMe	OMe	OMe	OMe

a) *N*-deacetyl-*N*-formylcolchicine; b) colchamine; c) substance U; d) *N*-deacetyl-*N*-formylcolchiceine; e) colchameine

(Fig. 6) contd….

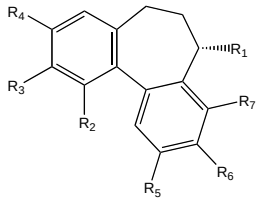


	R1	R2	R3	R4	R5
colchiciline	NHAc	OMe	OMe	OMe	OMe
alkaloid CC12 (isomeric)	NHAc	OMe	OMe	OMe	OMe
2-demethylcolchiciline	NHAc	OMe	OH	OMe	OMe
gloriosamine C	NH(AcOH)	OMe	OMe	OMe	OMe
gloriosamine D	NHCHO	OMe	OMe	OMe	OMe



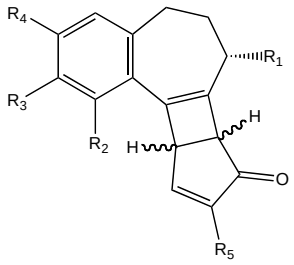
	R1	R2	R3	R4
cornigerine	NHAc	OMe	OMe	H
N-deacetyl-*N*,*N*-dimethyl-cornigerine	NMe_2	OMe	OMe	H
gloriosamine A	NHAc	OMe	OMe	OMe
gloriosamine B	NH(AcOH)	OMe	OMe	OMe

Fig. (6). Structural diversity of the colchicine-type alkaloids in Colchicaceae.



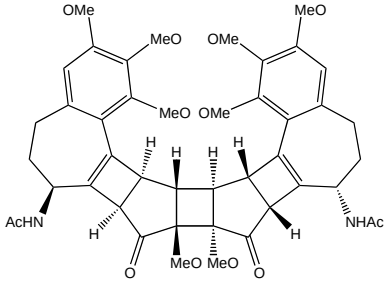
	R1	R2	R3	R4	R5	R6	R7
2-demethyl-allocolchicine	NHAc	OMe	OMe	OH	H	COOMe	H
allocolchicine [a)]	NHAc	OMe	OMe	OMe	H	COOMe	H
colchibiphenyline	NHAc	OMe	OMe	OH	H	OMe	OH
androbiphenyline	NHAc	OMe	OMe	OMe	H	OMe	OH
jerusalemine	NHMe	OMe	OH	OMe	OH	OMe	H
salimine	NHAc	OMe	OMe	OMe	COOMe	OH	H

Fig. (7). Structural diversity of the allocolchicine alkaloids in Colchicaceae. a) suhailamine may be an isomer of allocolchicine and not a synonym of that compound.

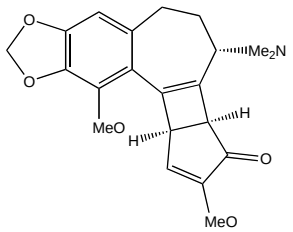


	R1	R2	R3	R4	R5	H
β-lumicolchicine	NHAc	OMe	OMe	OMe	OMe	β, β
β-lumigloriosine [a)]	NHCHO	OMe	OMe	OMe	OMe	β, β
N-deacetyl-*N*,*N*-dimethyl-β-lumicolchicine	NMe_2	OMe	OMe	OMe	OMe	β, β
β-lumispeciosine	NMe(2-OH-benzyl)	OMe	OMe	OMe	OMe	β, β
N-methyl-β-lumicolchicine	NMeAc	OMe	OMe	OMe	OMe	β, β
2-*O*-demethyl-β-lumicolchicine	NHAc	OMe	OH	OMe	OMe	β, β
3-*O*-demethyl-β-lumicolchicine	NHAc	OMe	OMe	OH	OMe	β, β
2-*O*-demethyl-β-lumigloriosine	NHCHO	OMe	OH	OMe	OMe	β, β
γ-lumicolchicine	NHAc	OMe	OMe	OMe	OMe	α, α
γ-lumigloriosine [b)]	NHCHO	OMe	OMe	OMe	OMe	α, α
2-*O*-demethyl-γ-lumicolchicine	NHAc	OMe	OH	OMe	OMe	α, α
3-*O*-demethyl-γ-lumicolchicine	NHAc	OMe	OMe	OH	OMe	α, α
Colchicum autumnale alkaloid M	NMeAc	OMe	O-β-D-glc	OMe	OMe	α, α

a) *N*-deacetyl-*N*-formyl-β-lumicolchicine; b) *N*-deacetyl-*N*-formyl-γ-lumicolchicine



α-lumicolchicine



alkaloid AM3

Fig. (8). Structural diversity of the lumicolchicine alkaloids in Colchicaceae.

[70], *Athrotaxis* of Taxodiaceae [71], *Manoao* of Podocarpaceae [72], and *Cephalotaxus* of Cephalotaxaceae [73]. Some homoerythrinan alkaloids can even be found in several of these families, eg. taxodine and 3-epischelhammericine. The ten homoerythrinan-type alkaloids found in Colchicaceae, see Fig. (**9**), have not been studied for biological activity in any great detail. The alkaloid 3-epischelhammericine as well as other alkaloids from *Dysoxylum* have shown molluscicidal activity and cardiac effects [67, 79], and dyshomoerythrine from *Manoao* is reported to have insecticidal activity [126].

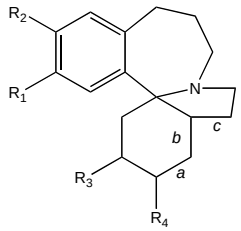
Miscellaneous Alkaloids

Five alkaloids, see Fig. (**10**), reported from Colchicaceae have structures not completely consistent with any of the previous groups. They are all isolated from different species of *Colchicum* [110, 127, 128, 129].

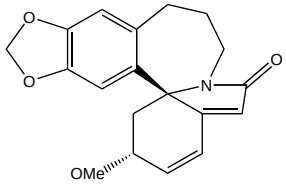
Phylogeny of Colchicaceae and Alkaloid Distribution

A phylogenetic hypothesis of plant relationships is dependent on sampling size, which is a function of the number of investigated plant species and the number of characters in the matrix. In molecular systematic studies based on nuclear sequences the characters will equal the number of nucleotides in the sequence used for analysis. For Colchicaceae a family wide investigation based on chloroplast gene sequences, representing fourteen out of fifteen genera (the single species of *Kuntheria* was not sampled) has been published [47]. A genus-level tree based on those results, with *Kuntheria* placed together with *Schelhammera* and *Tripladenia*, is shown in Fig. (**11**).

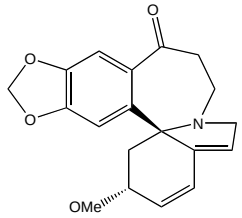
Chemosystematic prediction is likewise dependent on sampling size, here as a function of the number of investigated plant species and the limits of detection for the



	R1	R2	R3	R4	*a*	*b*	*c*
taxodine	OH	OMe	OMe (α)	H	single	double	single
3-epicomosine	–OCH_2O–		OMe (β)	H	double	singles, H (β)	
schelhammerine	–OCH_2O–		OMe (β)	OH (α)	single	double	single
schelhammericine	–OCH_2O–		OMe (β)	H	single	double	single
3-epischelhammerine	–OCH_2O–		OMe (α)	OH (α)	single	double	single
3-epischelhammericine	–OCH_2O–		OMe (α)	H	single	double	single
schelhammeridine	–OCH_2O–		OMe (β)	H	double	single	double
3-epischelhammeridine	–OCH_2O–		OMe (α)	H	double	single	double

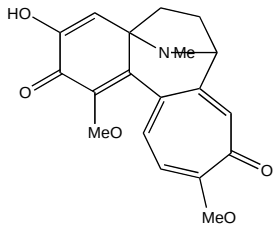


8-oxoschelhammeridine

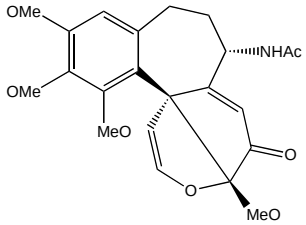


11a-oxoschelhammeridine

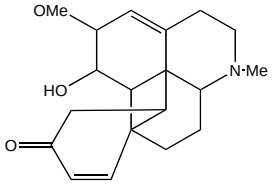
Fig. (9). Structural diversity of the homoerythrinan alkaloids in Colchicaceae.



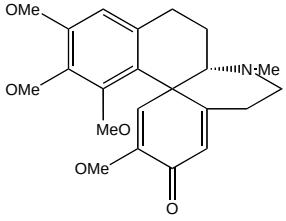
demecolcinone



10,11-oxy-10,12*a*-cyclo-10,11-secocolchicine



luteinine



crociflorinine, with crociflorine being its *N*-oxide

Fig. (10). Structural diversity of miscellaneous phenethylisoquinoline alkaloids in Colchicaceae.

compounds of interest using a specific method. As the Colchicaceae alkaloids span from alkaline compounds, over aprotic or quaternary nitrogen compounds insensitive to pH-changes, to phenolic alkaloids even within the different structural types the isolation method may bias the detection of compounds [130]. Another bias in reviewing Colchicaceae alkaloids may be the strong focus on detection of colchicine itself in the literature. This alkaloid is by far the most commonly reported compound, and it has been shown to be present in all investigated genera of the family by nanospray-MS (again with the single species of *Kuntheria* unsampled) [49].

However, the similarities between the systematic and chemical sampling on genus level makes Colchicaceae a good case study in evolution of chemical characters. The genera *Uvularia* and *Disporum* have been treated as part of the now defunct family Uvulariaceae, which by some authors also have included *Schelhammera* (including the later segregated *Kuntheria*) and *Tripladenia*, though these latter genera have also been placed in the former Convallariaceae [46, 131]. *Burchardia* has been reported to be devoid of tropolonic alkaloids [132], and its relationship to the rest of Colchicaceae have been questioned and sometimes it is instead treated in a monogeneric family Burchardiaceae [133]. The alkaloid chemistry of the early diverging lineages, Burchardieae and Uvularieae, has not been investigated in any detail according to standard literature searches, but the three genera are confirmed to contain colchicine [49].

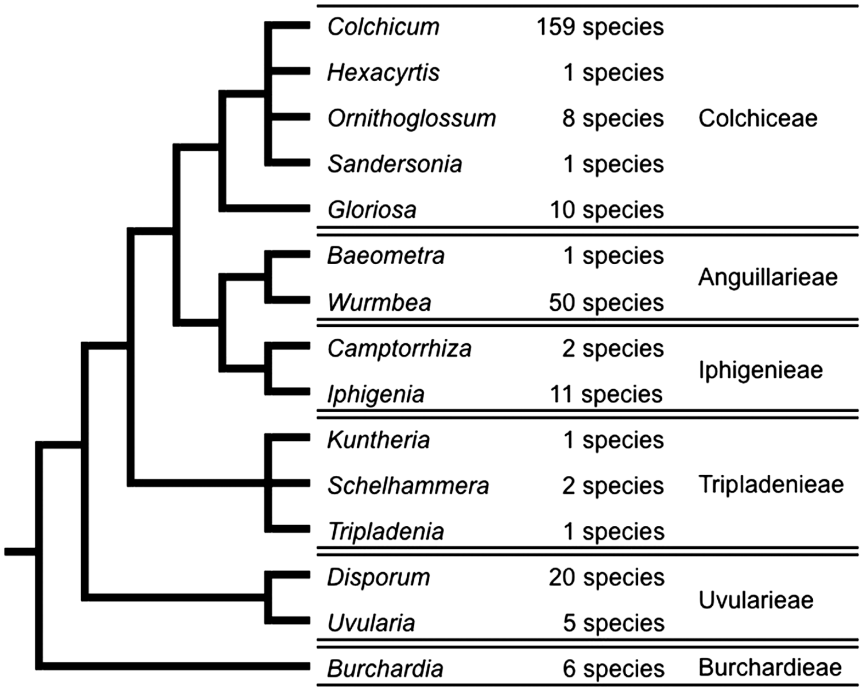


Fig. (11). The phylogenetic hypothesis and classification for Colchicaceae modified from Vinnersten and co-workers [46, 47]. The dendrogram clearly shows that the groups not traditionally associated with phenethylisoquinoline alkaloids constitute the basal clades of the family. As further discussed in the text this highlights them as potential new sources of Colchicaceae alkaloids, or even new structural types of phenethylisoquinoline alkaloids.

The chemistry of the tribe Tripladenieae, which is restricted to eastern Australia extending to New Guinea, have in comparison been fairly extensively investigated. The genera *Schelhammera* and *Kuntheria* are unique in Colchicaceae by producing homoerythrinan instead of colchicine-type alkaloids as major components [120, 121, 122, 123, 124]. Further investigations are needed to see if this is the case for *Tripladenia* as well. However, as stated above a plant under the name of *Kreysigia multiflora* has been shown to contain appreciable amount of homoaporphine, homoproaporphine and colchicine-type alkaloids [50, 134, 135], and this plant is either *Tripladenia* or a species of *Schelhammera*. The collection data for the material used by Badger and Bradbury [134] indicate that their original isolation is done on *Tripladenia cunninghamii*. Our nanospray mass spectrometry screening has confirmed the presence of colchicine in both *Schelhammera* and *Tripladenia* [49].

The three remaining tribes constitute the classical subfamily Wurmbaeoideae [45] or Colchicaceae in its strict sense [46] and several reviews of their alkaloid contents have been published [41, 44, 52, 107, 136]. Besides colchicine- and lumicolchicine-type alkaloids Iphigenieae also contain homoaporphine and homomorphine alkaloids [101, 137, 138, 139], while only colchicine- and lumicolchicine-type alkaloids have been reported from the few species investigated from the tribe Anguillarieae [44, 132]. The most species-rich tribe is Colchiceae, which also contains *Colchicum* and *Gloriosa* the two most studied genera, and it is reported to contain all structural types present in Colchicaceae except for homoerythrinan alkaloids [97, 101, 108, 109, 111, 117, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156].

Presence of Pathways

Combining this distribution data with the hypothetical biosynthetic network in Fig. (**1**) indicates that the pathway to colchicine-type alkaloid is present in all genera of Colchicaceae. Since this pathway contains the androcymbine-type alkaloids as an intermediate, these are also expected to have a family-wide distribution. The homoaporphine and homoproaporphine alkaloids are both present in the tribe Colchiceae, while only homoaporphines are present in the tribe Iphigenieae. This could indicate that the two types are biosynthesized by independent pathways, and that homoproaporphines are not precursors for homoaporphines as would be suggested by analogy with benzylisoquinoline alkaloids. There is some experimental evidence that this is the case [57].

The homoerythrinan alkaloids are often discussed together with their erythrinan counterparts [157, 158, 159], and their biosynthesis is considered to be analogous to these. The two possible pathways to homoerythrinan alkaloids in Fig. (**1**) could explain the disjunct distributions of these alkaloids without co-occurrence of androcymbine- or colchicine-type alkaloids outside Colchicaceae. A pathway analogous to that proposed for erythrinan alkaloids [159, 160] would include androcymbine-type intermediates, while a pathway from diaryl-3-azahexenoid-type precursors would by-pass these and directly produce dibenzo[*d*,*f*]azecines.

CONCLUSION AND FURTHER STUDIES

The *raison d'être* for alkaloids is still something of an enigma, and hypotheses have included views such as metabolic waste or end products, as a source of stored nitrogen,

and as defense compounds or ecological adaptors [161, 162]. Regardless of the validity of any of these hypotheses, the large structural variation and the high proportion and wide range of biological activities associated with alkaloids make them a highly interesting compound-type for medicinal chemists. However, the research focus is often limited to a very small number of compounds with extraordinary activity, such as colchicine in the present example. This might be due to presence of low concentrations of minor components, bias in selection of screening assays for biological activity, or skewed sampling of plant material. We argue that by accepting the notion that natural products are prevalidated for biological activity and taking evolutionary aspects into account, these potential problems can be attenuated and open new avenues of interesting research.

Of the phenethylisoquinoline alkaloids of Colchicaceae only colchicine-type alkaloids have been, and is still, extensively investigated and the activity under scrutiny has almost exclusively been that of cytotoxicity. This leaves seven structural groups of alkaloids within the family for which we today have very little information on possible biological activities and roles. Especially interesting from this perspective are the homoerythrinan alkaloids, seemingly absent in most of the family and replacing colchicine-type alkaloids in Tripladenieae. With the presence of these alkaloids in several distantly related plant groups it is imperative to predict that they have biological activities of potential for human use, and the reported molluscicidal and insecticidal activities can be considered as a starting point and need further investigations.

From an evolutionary standpoint it is also obvious that the sampling of Colchicaceae has been very skewed. Almost 70% of investigated species are from the genus *Colchicum*, and several genera lack in depth studies of their alkaloid content. This is notable for the early lineages as well as the second most species rich genus *Wurmbea*. Compared to the structural diversity of known benzylisoquinoline and Amaryllidaceae alkaloid types, which have at least analogous biosynthesis patterns, the phenethylisoquinoline alkaloids of Colchicaceae is a small group. This could be the result of undersampling of different phylogenetic lineages within the family.

It has been argued that we only take advantage of a very small fraction of the plant biodiversity around us. As an example De Luca and co-workers propose in depth collaborative investigations of plant metabolomes, using new technologies to elucidate and modify biosynthetic pathways to create larger yields or new chemically diverse biological active compounds [163]. Another option for finding new compounds or activities, as argued here, is taking advantage of evolutionary evidence in selection of the plants or compounds to be studied. The phylogenetic distribution of specific compounds predicts at least one of either presence of biosynthetic pathways or advantageous biological activity, thus identifying less known or unstudied chemistry. Based on the known phylogenetic hypothesis in Fig. (**1**) a number of hypotheses for further study can be identified, such as: the need to re-investigate *Burchardia*, including identification of the reported non-tropolonic alkaloid; perform studies on the presence or absence of alkaloids in the tribe Uvularieae, which at present is practically uninvestigated; an in depth study of the homoerythrinan alkaloids of the tribe Tripladenieae and their biological activities; and instigate molecular and biochemical comparison between species from Tripladenieae and Colchicaceae *sensu stricto* to investigate biosynthetic pathways.

In conclusion we have shown how thinking about evolution can influence selection of plant material in drug lead discovery, and how knowledge about phylogenetic relationships may be used to evaluate predicted biosynthetic pathways and identify priority species for further study.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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REFERENCES

[1] Bate-Smith, E. C. The phenolic constituents of plants and their taxonomic significance, I. Dicotyledons. *J. Linn. Soc. (Botany)*, **1962**, *58*, 95-173.

[2] Bate-Smith, E. C. The phenolic constituents of plants and their taxonomic significance, II. Monocotyledons. *J. Linn. Soc. (Botany)*, **1968**, *60*, 325-356.

[3] Swain, T. *Chemical plant taxonomy*; Academic Press: London, **1963**.

[4] Harborne, J. Chemosystematics and coevolution. *Pure App. Chem.*, **1977**, *49*, 1403-1421.

[5] Dahlgren, R. M. T. A revised system of classification of the angiosperms. *Botan. J. Linn. Soc.*, **1980**, *80*, 91-124.

[6] Dahlgren, R. M. T. The distribution of characters within an angiosperm system. I. Some embryological characters. *Botan. Notiser*, **1975**, *128*, 181-197.

[7] Brockington, S. F., Walker, R. H., Glover, B. J., Soltis, P. S., Soltis, D. E. Complex pigment evolution in the Caryophyllales. *New Phytol.*, **2011**, *190*, 854-864.

[8] Liscombe, D. K.; MacLeod, B. P.; Loukanina, N.; Nandi, O. I.; Facchini, P. J. Evidence for the monophyletic evolution of benzylisoquinoline alkaloid biosynthesis in angiosperms. *Phytochemistry*, **2005**, *66*, 1374-1393. Corrected version: *Phytochemistry*, **2005**, *66*, 2500-2520.

[9] Rodman, J. E.; Soltis, P. S.; Sotis, D. E.; Sytsma, K. J.; Karol, K. G. Parallel evolution of glucosinolate biosynthesis inferred from congruent nuclear and plastid gene phylogenies. *Am. J. Bot.*, **1998**, *85*, 997-1006.

[10] Albach, D. C.; Soltis, P. S.; Soltis, D. E. Patterns of embryological and biochemical evolution in the asterids. *Sys. Bot.*, **2001**, *26*, 242-262.

[11] Abbott, H. C. D. S. The chemical basis of plant forms. *Franklin Institute Lecture*, **1887**. Reprinted in: *Studies in Plant and Organic Chemistry, and Literary Papers*; Abbott Michael, H.; The Riverside Press: Cambridge, MA, **1907**.

[12] Newman, D. J.; Cragg, G. M. Natural products as sources of new drugs over the 30 years from 1981 to 2010. *J. Nat. Prod.*, **2012**, *75*, 311-335.

[13] Larsson, J.; Gottfries, J.; Bohlin, L.; Backlund, A. Expanding the ChemGPS chemical space with natural products. *J. Nat. Prod.*, **2005**, *68*, 985-991.

[14] Larsson, J.; Gottfries, J.; Muresan, S.; Backlund, A. ChemGPS-NP: tuned for navigation in biologically relevant chemical space. *J. Nat. Prod.*, **2007**, *70*, 789-794.

[15] Rosén, J.; Gottfries, J.; Muresan, S.; Backlund, A.; Oprea, T. I. Novel chemical space exploration via natural products. *Journal of Medicinal Chemistry*, **2009**, *52*, 1953-1962.

[16] Kong, D-X.; Ren, W.; Lü, W.; Zhang, H-Y. Do biologically relevant compounds have more chance to be drugs? *J.Chem. Inf. Mod.*, **2009**, *49*, 2376-2381.

[17] Arve, L.; Voigt, T.; Waldmann, H. Charting biological and chemical space: PSSC and SCONP as guiding principles for the development of compound collections based on natural product scaffolds. *QSAR Comb. Sci.*, **2006**, *25*, 449-456.

[18] Wetzel, S.; Schuffenhauer, A.; Roggo, S.; Ertl, P.; Waldmann, H. Cheminformatic analysis of natural products and their chemical space. *Chimia*, **2007**, *61*, 355-360.

[19] Newman, D. J. Natural products as leads to potential drugs: an old process or the new hope for drug discovery? *J. Med. Chem.*, **2008**, *51*, 2589-2599.

[20] Bon, R. S.; Waldmann, H. Bioactivity-guided navigation of chemical space. *Acc. Chem. Res.*, **2010**, *43*, 1103-1114.

[21] Lachance, H.; Wetzel, S.; Kumar, K.; Waldmann, H. Charting, navigating, and populating natural product chemical space for drug discovery. *J. of Med. Chem.*, **2012**, *55*, 5989-6001.

[22] Larsson, S. The "new" chemosystematics: phylogeny and phytochemistry. *Phytochemistry*, **2007**, *68*, 2903-2907.

[23] Rønsted, N.; Symonds, M. R. E.; Birkholm, T.; Brøgger Christensen, S.; Meerow, A. W.; Molander, M.; Mølgaard, P.; Petersen, G.; Rasmussen, N.; van Staden, J.; Stafford, G. I.; Jäger, A. K. Can phylogeny predict chemical diversity and potential medicinal activity of plants? A case study of Amaryllidaceae. *BMC Evo. Bio.*, **2012**, *12*, #182 (12 pp.).

[24] Le Hello, C. Chapter 5. The pharmacology and therapeutic aspects of colchicine. In: *The Alkaloids: Chemistry and Biology*, vol. 53; Cordell, G. A. (Ed.); Academic Press: London, **1999**; pp. 287-352.

[25] Cocco, G.; Chu, D. C. C.; Pandolfi, S. Colchicine in clinical medicine. A guide for internists. *Eur. J. Int. Med.*, **2010**, *21*, 503-508.

[26] Massarotti, A.; Coluccia, A.; Silvestri, R.; Sorba, G.; Brancale, A. The tubulin colchicine domain: a molecular modelling perspective. *Chem. Med. Chem.*, **2012**, *7*, 33-42.

[27] Hartung, E. F. History of the use of *Colchicum* and related medicaments in gout. *Annals of the Rheumatic Diseases*, **1954**, *13*, 190-200.

[28] Evans, W. C. *Trease and Evans Pharmacognosy*; Saunders/Elsevier: Edinburgh, **2009**.

[29] Roberts III, L. J.; Morrow, J. D. Analgesic-antipyretics and anti-inflammatory agents: drugs employed in the treatment of gout. In: *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 10th ed.; Hardman, J. G.; Limbird, L. E.; Gilman, A.G. (Eds.); McGraw-Hill: New York, **2001**; pp. 687-731.

[30] Yang, L. P. H. Oral colchicine (Colcrys®) in the treatment and prophylaxis of gout. *Drugs*, **2010**, *70*, 1603-1613.

[31] Blakeslee, A. F.; Avery, A. G. Methods of inducing doubling of chromosomes in plants: by treatment with colchicine. *J. Her.*, **1937**, *28*, 393-411.

[32] Tjio, J. H.; Levan, A. The chromosome number of man. *Hereditas*, **1956**, *42*, 1-6.

[33] Schmidts, M.; Bastians, H. Mitotic drug targets and the development of novel anti-mitotic anticancer drugs. *Drug Resi. Updates*, **2007**, *10*, 162-181.

[34] Yue, Q-X.; Liu, X.; Guo, D-A. Microtubule-binding natural products for cancer therapy. *Planta Med.*, **2010**, *76*, 1037-1043.

[35] Leonard, B. J.; Wilkinson, J. F. Desacetylmethylcolchicine in treatment of myeloid leukaemia. *Br. Med. J.*, **1955**, *1*, 874-877.

[36] Pelletier, P. J.; Caventou, J. Examen chimique de plusieurs végétaux de la famille des colchicées, et du principe actif qu'ils renferment. *Ann. de Chim. et de Phy.*, **1820**, *14*, 69-83.

[37] Geiger, P. L. Ueber einige neue giftige organische Alkalien. *Ann. Pharm.*, **1833**, *7*, 269-280.

[38] King, M. V.; de Vries, J. L.; Pepinsky, R. An x-ray diffraction determination of the chemical structure of colchicine. *Acta Cryst.*, **1952**, *5*, 437-440.

[39] Dewar, M. J. S. Structure of colchicine. *Nature*, **1945**, *155*, 141–142.

[40] Graening, T.; Schmalz, H-G. Total syntheses of colchicine in comparison: a journey through 50 years of synthetic organic chemistry. *Ang. Chem. Inter. E.*, **2004**, *43*, 3230-3256.

[41] Šantavý, F. Substanzen der Herbstzeitlose und ihre derivate. XLV. Verbreitung der Colchicinalkaloide im Pflanzenreich. *Österr. Bot. Zeit.*, **1956**, *103*, 300-311.

[42] Hegnauer, R. *Chemotaxonomie der Pflanzen*, vol. 2; Birkhäuser Verlag: Basel, **1963**.

[43] Klein, G.; Pollauf, G. Der mikrochemische Nachweis der Alkaloide in der Pflanze. XII. Der Nachweis des Colchicins. *Österr. Bot. Zeit.*, **1929**, *78*, 251-256.

[44] Yusupov, M. K.; Sadykov, A. S. Tropolone alkaloids. *Chem. Nat. Comp.*, **1978**, *14*, 1-19.

[45] Buxbaum, F. Die Entwicklungslinien der Lilioideae. I. Die Wurmbeoideae. *Bot. Archive*, **1936**, *38*, 213-293.

[46] Dahlgren, R. M. T., Clifford, H. T., Yeo, P. F. *The Families of the Monocotyledons*; Springer-Verlag: Berlin, **1985**.

[47] Vinnersten, A.; Reeves, G. Phylogenetic relationships within Colchicaceae. *American Journal of Botany*, **2003**, *90*, 1455-1462.

[48] Vinnersten, A.; Manning, J. A new classification of Colchicaceae. *Taxon*, **2007**, *56*, 171-178.

[49] Vinnersten, A.; Larsson, S. Colchicine is still a chemical marker for the expanded Colchicaceae. *Bioche. Sys. Eco.*, **2010**, *38*, 1193-1198.

[50] Šantavý, F. The presence of colchicine alkaloids in *Kreysigia multiflora* Reichb. *Experientia*, **1967**, *23*, 273.

[51] Shinwari, Z. K.; Terauchi, R.; Utech, F. H.; Kawano, S. Recognition of the New World *Disporum* section *Prosartes* as *Prosartes* (Liliaceae) based on the sequence data of the *rbcL* gene. *Taxon*, **1994**, *43*, 353-366.

[52] Kametani, T.; Koizumi, M. Chapter 4. Phenethylisoquinoline alkaloids. In: *The Alkaloids: Chemistry and Pharmacology*, vol. 36; Brossi, A. (Ed.); Academic Press: London, **1990**; pp. 171-223.

[53] CCD (2012) Combined Chemical Dictionary. Taylor & Francis Group. Published on the Internet; http://ccd.chemnetbase.com/ Retrieved December 10, 2012.

[54] Leete, E.; Németh, P. E. The biogenesis of the alkaloids of *Colchicum*. I. The incorporation of phenylalanine into colchicine. *J. Am. Chem. Soc.*, **1960**, *82*, 6055-6057.

[55] Leete, E. The biosynthesis of the alkaloids of *Colchicum*. III. The incorporation of phenylalanine-2-C14 into colchicine and demecolcine. *J. Am. Chem. Soc.*, **1963**, *85*, 3666-3669.

[56] Battersby, A. R.; Herbert, R. B.; McDonald, E.; Ramage, R.; Clements, J. H. Biosynthesis of colchicine from a 1-phenethylisoquinoline. *Che. Comm.*, **1966**, 603-605.

[57] Battersby, A. R.; Böhler, P.; Munro, M. H. G.; Ramage, R. Biosynthesis of homoaporphines. *Chem. Commu.*, **1969**, 1066-1067.

[58] Battersby, A. R.; Dobson, T. A.; Foulkes, D. M.; Herbert, R. B. Alkaloid biosynthesis. Part XVI. Colchicine: origin of the tropolone ring and studies with the C6-C3-C6-C1 system. *J. Chem. Soc., Perkin Transactions 1*, **1972a**, 1730-1736.

[59] Battersby, A. R.; Herbert, R. B.; McDonald, E.; Ramage, R. Alkaloid biosynthesis. Part XVIII. Biosynthesis of colchicine from the 1-phenethylisoquinoline system. *J. Chem. Soc., Perkin Transactions 1*, **1972b**, 1741-1746.

[60] Trozyan, A. A.; Yusupov, M. K.; Aslanov, K. A.; Sadykov, A. S. A study of the biosynthesis of colchicine and merenderine in *Merendera raddeana*. *Chem. Nat. Com.*, **1972**, *8*, 746-750.

[61] McDonald, E.; Ramage, R.; Woodhouse, R. N.; Underhill, E. W.; Wetter, L. R.; Battersby, A. R. Biosynthesis. Part 27. Colchicine: studies of the phenolic oxidative coupling and ring-expansion processes based on incorporation of multiply labelled 1-phenethylisoquinolines. *J. Chem. Soc. Perkin Transactions 1*, **1998**, 2979-2987.

[62] Barker, A. C.; Julian, D. R.; Ramage, R.; Woodhouse, R. N.; Hardy, G.; McDonald, E.; Battersby, A. R. Biosynthesis. Part 28. Colchicine: definition of intermediates between *O*-methylandrocymbine and colchicine and studies on speciosine. *J. Chem. Soc. Perkin Transactions 1*, **1998**, 2989-2994.

[63] Woodhouse, R. N.; McDonald, E.; Ramage, R.; Battersby, A. R. Biosynthesis. Part 29. Colchicine: studies on the ring expansion step focusing on the fate of the hydrogens at C-3 of autumnaline. *J. Chem. Soc, Per. Trans. 1*, **1998**, 2995-3001.

[64] Sheldrake, P. W.; Suckling, K. E.; Woodhouse, R. N.; Murtagh, A. J.; Herbert, R. B.; Barker, A. C.; Staunton, J.; Battersby, A. R. Biosynthesis. Part 30. Colchicine: studies on the ring expansion step focusing on the fate of the hydrogens at C-4 of autumnaline. *J. Chem. Soc. Per. Trans. 1*, **1998**, 3003-3009.

[65] Sivakumar, G.; Krishnamurthy, K. V.; Hao, J.; Paek, K. Y. Colchicine production in *Gloriosa superba* calluses by feeding precursors. *Chem. Nat. Comp.*, **2004**, *40*, 499-502.

[66] Aladesanmi, A. J.; Kelley, C. J.; Leary, J. D. The constituents of *Dysoxylum lenticellare*. I. Phenethylisoquinoline, homoerythrina, and dibenzazecine alkaloids. *J. Nat. Prod.*, **1983**, *46*, 127-131.

[67] Aladesanmi, A. J.; Adewunmi, C. O.; Kelley, C. J.; Leary, J. D.; Bischoff, T. A.; Zhang, X.; Snyder, J. K. Lenticellarine, a molluscicidal alkaloid from *Dysoxylum lenticellare*. *Phytochemistry*, **1988**, *27*, 3789-3792.

[68] Aladesanmi, A. J. The stem constituents of *Dysoxylum lenticellare*. *Tetrahedron*, **1988**, *44*, 3749-3756.

[69] Aladesanmi, A. J.; Hoffmann, J. J. Additional alkaloids from the stem of *Dysoxylum lenticellare*. *Phytochemistry*, **1994**, *35*, 1361-1362.

[70] Aladesanmi, A. J.; Snyder, J. K.; Kelley, C. J.; Hoffmann, J. J. Homoerythrina alkaloids of *Phelline comosa*. *Phytochemistry*, **1991**, *30*, 3497-3498.

[71] Panichanun, S.; Bich, I. R. C. *Athrotaxis* alkaloids. Part I. Alkaloids of *A. cupressoides*. *Tetrahedron*, **1984**, *40*, 2611-2684.

[72] Bloor, S. J.; Benner, J. P.; Irwin, D.; Boother, P. Homoerythrina alkaloids from silver pine, *Lagarostrobos colensoi*. *Phytochemistry*, **1996**, *41*, 801-802.

[73] Abdelkafi, H.; Nay, B. Natural products from *Cephalotaxus* sp.: chemical diversity and synthetic aspects. *Nat. Prod. Rep.*, **2012**, *29*, 845-869.

[74] Battersby, A.R.; Ramage, R.; Cameron, A. F.; Hannaway, C.; Šantavý, F. 1-phenethylisoquinoline alkaloids. Part II. The structures of alkaloids from *Colchicum cornigerum* (Sweinf.) Tackh. et Drar. *J. Chem. Soc. C*, **1971**, 3514-3518.

[75] Potěšilová, H.; Hruban, L.; Šantavý, F. Isolation and identification of alkaloids from seeds of *Colchicum latifolium* s.s. *Coll. Czec. Chem. Comm.*, **1976**, *41*, 3146-3156.

[76] Freyer, A. J.; Abu Zarga, M. H.; Firdous, S.; Guinaudeau, H.; Shamma, M. Five new alkaloids from *Colchicum ritchii*. *Journal of Natural Products*, **1987**, *50*, 684-689. Erratum *J. Nat. Prod.*, **1988**, *51*, 192.

[77] Tojo, E.; Önür, M. A.; Freyer, A. J.; Shamma, M. Two trioxygenated phenethylisoquinoline alkaloids from *Colchicum szovitsii*. *J. Nat. Prod.*, **1990**, *53*, 634-637.

[78] Alali, F. Q.; Gharaibeh, A.; Ghawanmeh, A.; Tawaha, K.; Oberlies, N. H. Colchicinoids from *Colchicum crocifolium* Boiss.: a case study in dereplication strategies for (–)-colchicine and related analogues using LC-MS and LC-PDA techniques. *Phytochemical An.*, **2008**, *19*, 385-394.

[79] Aladesanmi, A. J.; Ilesanmi, O. R. Phytochemical and pharmacological investigation of the cardioactive constituents of the leaf of *Dysoxylum lenticellare*. *J. Nat. Prod.*, **1987**, *50*, 1041-1044.

[80] Šantavý, F.; Sedmera, P.; Snatzke, G.; Reichstein, T. Alkaloide von *Bulbocodium vernum* L. Inhaltstoffe der Liliaceae-Wurmbaeoideae. *Helvetica Chimica Acta*, **1971**, *54*, 1084-1095.

[81] Zuparova, K. M.; Chommadov, B.; Yusupov, M. K.; Sadykov, A. S. Alkaloids of *Merendera iolantae*. *Chem. Nat. Prod.*, **1972**, *8*, 481-485.

[82] Yusupov, M.K.; Trozyan, A. A.; Aslanov, K. A. Alkaloids from *Merendera trigina*. Structure of trigamine. *Chem. Nat. Comp.*, **1975d**, *11*, 824-825.

[83] Abdullaeva, D. A.; Yusupov, M. K.; Aslanov, K. A. The structure of regeline. *Chem. Nat. Comp.*, **1976**, *12*, 702-705.

[84] Mukhamedyarova, N. L.; Yusupov, M. K.; Levkovich, M. G.; Aslanov, K. A.; Sadykov, A. S. (1976) Structure of luteidine. *Chem. Nat. Comp.*, **1976**, *12*, 308-312.

[85] Turdikulov, K.; van Dau, N.; Yusupov, M. K. Iolantine – a quarternary base from *Merendera iolantae*. *Chem. Nat. Comp.*, **1976**, *12*, 501-502.

[86] Yusupov, M. K.; Sadykov, A. S. The structure of kesselringine. *Chem. Nat. Comp.*, **1976**, *12*, 305-308.

[87] Yusupov, M. K.; Mukhamedyarova, N. L.; Aslanov, K. A. The structure of luteicine. *Chem. Nat. Comp.*, **1976**, *12*, 313-315.

[88] Yusupov, M. K.; Mukhamedyarova, N. L.; Sadykov, A. S.; Dolejš, L.; Sedmera, P.; Šantavý, F. Constitution of the alkaloid kesselringine. *Coll. Czech. Chem. Comm.*, **1977**, *42*, 1581-1587.

[89] Yusupov, M. K.; Chommadov, B.; Aslanov, K. A. The structure of regelinine. *Chem. Nat. Comp.*, **1985**, *21*, 396-397

[90] Chommadov, B.; Usmanov, A. M.; Yusupov, M. K. Jolantidine – a new base from *Merendera jolantae*. *Chem. Nat. Comp.*, **1983**, *19*, 755.

[91] Chommadov, B.; Yusupov, M. K.; Aslanov, K. A. Trigamine *N*-oxide from *Merendera jolantae*. *Chem. Nat. Comp.*, **1985b**, *21*, 395-396.

[92] Chommadov, B.; Usmanov, A. M.; Yusupov, M. K. Structure of isoregecoline. *Chem. Nat. Comp.*, **1985c**, *21*, 767-769.

[93] Usmanov, A. M.; Chommadov, B.; Yusupov, M. K.; Aslanov, K. A. Structure of regecoline. *Chem. Nat. Comp.*, **1985**, *21*, 233-236.

[94] Nazarov, G. B.; Ibragimov, B. T.; Talipov, S. A.; Aripov, T. F.; Yusupov, M. K.; Mukhamedyarova, N. L.; Chommadov, B. Molecular and crystal structure of luteidine. *Chem. Nat. Comp.*, **1986**, *22*, 321-325.

[95] Yunusov, M. K.; Chommadov, B. Robustamine – a new homoproaporphine base from *Merendera robusta*. *Chem. Nat. Comp.*, **1995**, *31*, 87-90.

[96] Yusupov, M. K. Robustamine *cis*-*N*-oxide and merenderine from *Merendera robusta*. *Chem. Nat. Comp.*, **1996**, *32*, 716-719.

[97] Reichstein, T.; Snatzke, G.; Šantavý, F. Beitrag zur Konstitution des Alkaloids Bulbocodin und des Alkaldoids OGG-3. *Planta Med.*, **1968**, *16*, 357-360.

[98] Battersby, A. R.; Bradbury, R. B.; Herbert, R. B.; Munro, M. H. G.; Ramage, R. 1-phenethylisoquinoline alkaloids. Part IV. Isolation, structural elucidation, and synthesis of c-homoaporphines. *J. Chem. Soc, Perkin Transactions 1*, **1974a**, 1394-1399.

[99] Basova, N. E.; Rozengart, E. V.; Suvorov, A. A. Cholinergic activity of isoquinoline alkaloids from the showy autumn crocus (*Colchicum speciosum* Stev.). *Dok. Bioch. Biop.*, **2006**, *406*, 27-31.

[100] Rozengart, E. V.; Basova, N. E.; Suvorov, A. A. (2006) Comparative study of cholinergic activity of some tropolone and isoquinoline alkaloids. *J. Evol. Bioch. Physiol.*, **2006**, *42*, 408-416.

[101] Tojo, E. The homoaporphine alkaloids. *J. Nat. Prod.*, **1989**, *52*, 909-921.

[102] Battersby, A. R.; Herbert, R. B.; Pijewska, L.; Šantavý, F. The constitution of androcymbine. *Chem. Communi.*, **1965**, 228-230.

[103] Basova, N. E.; Rozengart, E. V. Anticholinesterase efficiency of some tropolone alkaloids and their lumiderivatives. *Dok. Bioche. Biophy.*, **2005**, *405*, 410-413.

[104] Silverton, J. V.; Kabuto, C.; Buck, K. T.; Cava, M. P. Structure of imerubrine, a novel condensed tropolone-isoquinoline alkaloid. *J. Am. Chem. Soc.*, **1977**, *99*, 6708-6712.

[105] Zhao, J. Plant troponoids: chemistry, biological activity, and biosynthesis. *Curr. Med. Chem.*, **2007**, *14*, 2597-2621.

[106] Bentley, R. A fresh look at natural tropolonoids. *Nat. Prod. Rep.*, **2008**, *25*, 118-138.

[107] Boyé, O.; Brossi, A. Chapter 3. Tropolonic *Colchicum* alkaloids and allo congeners. In: *The Alkaloids: Chemistry and Pharmacology*, vol. 41; Brossi, A.; Cordell, G. A. (Eds.); Academic Press: London, **1992**; pp. 125-176.

[108] Chaudhuri, P. K.; Thakur, R. S. (1993) 1,2-didemethylcolchicine: a new alkaloid from *Gloriosa superba*. *J. Nat. Prod.*, **1993**, *56*, 1174-1176.

[109] Suri, O. P.; Gupta, B. D.; Suri, K. A.; Sharma, A. K.; Satti, N. K. (2001) A new glycoside, 3-*O*-demethylcolchicine-3-*O*-α-D-glucopyranoside, from *Gloriosa superba* seeds. *Nat. Prod. Lett.*, **2001**, *15*, 217-219.

[110] Alali, F. Q.; El-Elimat, T.; Li, C.; Qandil, A.; Alkofahi, A.; Tawaha, K.; Burgess, J. P.; Nakanishi, Y.; Kroll, D. J.; Navarro, H. A.; Falkinham III, J. O.; Wani, M. C.; Oberlies, N. H. New colchicinoids from a native Jordanian meadow saffron, *Colchicum brachyphyllum*: isolation of the first naturally occurring dextrorotatory colchicinoid. *J. Nat. Prod.*, **2005**, *68*, 173-178.

[111] Kitajima, M.; Tanaka, A.: Kogure, N.; Takayama, H. (2008) Four new colchicinoids, gloriosamines A–D, from *Gloriosa rothschildiana*. *Tetrah. Lett.*, **2008**, *49*, 257-260.

[112] Chen, J.; Liu, T.; Dong, X.; Hu, Y. Recent development and SAR analysis of colchicine binding site inhibitors. *Min-Rev. Med. Chem.*, **2009**, *9*, 1174-1190.

[113] Chang, D.-J.; Yoon, E.-Y.; Lee, G.-B.; Kim, S.-O.; Kim, W.-J.; Kim, Y.-M.; Jung, J.-W.; An, H.; Suh, Y.-G. Design, synthesis and identification of novel colchicine-derived immunosuppressant. *Bioorg. Med. Chem. Lett.*, **2009**, *19*, 4416-4420.

[114] Yang, B.; Zhu, Z. C.; Goodson, H. V., Miller, M. J. Syntheses and biological evaluation of ring-C modified colchicine analogs. *Bioorg. Med. Chem. Lett.*, **2010**, *20*, 3831-3833.

[115] Cosentino, L.; Redondo-Horcajo, M.; Zhao, Y.; Santos, A. R.; Chowdury, K. F.; Vinader, V.; Abdallah, Q. M. A.; Abdel-Rahman, H.; Fournier-Dit-Chabert, J.; Shnyder, S. D.; Loadman, P. M.; Fang, W.; Díaz, J. F.; Barasoain, I.; Burns, P. A.; Pors, K. Synthesis and biological evaluation of colchicine B-ring analogues tethered with halogenated benzyl moieties. *J. Med. Chem.*, **2012**, *55*, 11062-11066.

[116] Al-Tel, T. H.; Abu Zarga, M. H.; Sabri, S. S.; Freyer, A. J.; Shamma, M. (1990) New natural colchicinoids: indications of two possible catabolic routes for the colchicine alkaloids. *J. Nat. Prod.*, **1990**, *53*, 623-629.

[117] Nicolaou, K. C.; Valiulin, R. A.; Pokorski, J. K.; Chang, V.; Chen, J. S. Bio-inspired synthesis and biological evaluation of a colchicine-related compound library. *Bioorg. Med. Chem. Lett.*, **2012**, *22*, 3776-3780.

[118] Abu Zarga, M. H.; Sabri, S. S.; Al-Tel, T. H.; Atta-ur-Rahman; Shah, Z.; Feroz, M. New natural dibenzocycloheptylamine alkaloids: a possible catabolic route for the colchicine alkaloids. *J. Nat. Prod.*, **1991**, *54*, 936-940.

[119] Guan, J.; Zhu, X-K.; Brossi, A.; Tachibana, Y.; Bastow, K. F.; Verdier-Pinard, P.; Hamel, E.; McPhail, A. T.; Lee, K-H. Antitumour agents. 192. Antitubulin effect and cytotoxicity of C(7)-oxygenated allocolchicinoids. *Coll. Czech. Chem. Commu.*, **1991**, *64*, 217-228.

[120] Johns, S. R.; Kowala, C.; Lamberton, J. A.; Sioumis, A. A.; Wunderlich, J. A. "Homoerythrina" alkaloids from *Schelhammera pedunculata* F.Muell. (family Liliaceae). *Chem. Commu.*, **1968**, 1102-1104.

[121] Johns, S. R.; Lamberton, J. A.; Sioumis, A. A.; Suares, H. Alkaloids of *Schelhammera pedunculata* (Liliaceae). II. Reactions of schelhammeridine. *Aus. J. Chem.*, **1969a**, *22*, 2203-2218.

[122] Johns, S. R.; Lamberton, J. A.; Sioumis, A. A. Alkaloids of *Schelhammera pedunculata* (Liliaceae). III. The structures of schelhammericine and alkaloids A, B, E, G, H, J, and K. *Aus. J. Chem.*, **1969b**, *22*, 2219-2231.

[123] Fitzgerald, J. S.; Johns, S. R.; Lamberton, A. J.; Sioumis, A. A. Alkaloids of *Schelhammera pedunculata* (Liliaceae). I. Isolation of the alkaloids and the structures of the homoerythrina alkaloids schelhammerince and schelhammeridine. *Aus. J. Chem.*, **1969**, *22*, 2187-2201.

[124] Sioumis, A. A. The isolation of Schelhammera alkaloids E and B from *Schelhammera undulata* (Liliaceae). *Aus. J. Chem.*, **1971**, *24*, 2737.

[125] Conran, J. G.; Clifford, H. T. *Kuntheria*. In: *Flora of Australia*, vol. 45, Hydatellaceae to Liliaceae; George, A. S. (Ed.); Australian Government Publishing Service: Canberra, **1987**; pp. 490-491.

[126] Hart, J. B.; Mason, J. M.; Gerard, P. J. Semi-synthesis and insecticidal activity of dyshomoerythrine derivatives. *Tetrahedron*, **2001**, *57*, 10033-10038.

[127] Brossi, A.; Rösner, M.; Silverton, J. V.; Iorio, M. A.; Hufford, C. D. Revision of the structure of 'epoxycolchicine'. *Helvet. Chimi. Acta*, **1980**, *63*, 406-412.

[128] Chommadov, B.; Yusupov, M. K. Alkaloids of *Colchicum luteum*. *Chem. Nat. Comp.*, **1985**, *21*, 770-773.

[129] Shakirov, R.; Telezhenetskaya, M. V.; Bessonova, I. A.; Aripova, S. F.; Israilov, I. A.; Sultankhodzhaev, M. N.; Vinogradova, V. I.; Akhmedzhanova, V. I.; Tulyaganov, T. S.; Salimov, B. T.; Telnov, V. A. Alkaloids. Plants, structures, properties. *Chem. Nat. Comp.*, **1996**, *32*, 737-858.

[130] Kiselev, V. V.; Yavich, P. A. Methods of isolating alkaloids of the colchicine series. *Chem. Nat. Comp.*, **1990**, *26*, 502-509.

[131] Mabberley, D. J. *Mabberley's plant-book*, 3rd ed.; Cambridge University Press: Cambridge, **2008**.

[132] Potěšilová, H.; Macfarlane, T. D.; Guénard, D.; Šimánek, V. Alkaloids and phenolics of *Wurmbea* and *Burchardia* species. *Phytochemistry*, **1987**, *26*, 1031-1032.

[133] Takhtajan, A. *Diversity and Classification of Flowering Plants*; Columbia University Press: New York, **1997**.

[134] Badger, G. M.; Bradbury, R. B. The alkaloids of *Kreysigia multiflora* Reichb. Part I. Isolation. *J. Chem. Soc.*, **1960**, 445-447.

[135] Battersby, A. R.; Bradbury, R. B.; Herbert, R. B.; Munro, M. H. G.; Ramage, R. Structure and synthesis of homoaporphines: a new group of 1-phenethylisoquioline alkaloids. *Chem. Comm.*, **1967**, 450-451.

[136] Wildman, W. C.; Pursey, B. A. Chapter 11. Colchicine and related compounds. In: *The Alkaloids: Chemistry and Physiology*, vol. 11; Manske, R. H. F. (Ed.); Academic Press: London, **1968**; pp. 407-457.

[137] Kapadia, V. H.; Dev, S.; Rao, R. S.; Ansari, M. Y. New sources of colchicine in *Iphigenia*. *Phytochemistry*, **1972**, *11*, 1193-1194.

[138] Šantavý, F.; Hruban, L. Substances from the plants of the subfamily Wurmbaeoideae and their derivatives. LXXVII. Bechuanine – an enantiomer of floramultine. *Coll. Czech. Chem. Communi.*, **1973**, *38*, 1712-1713.

[139] Potěšilová, H.; Dvořáčková, S.; Preininger, V.; Šimánek, V. Alkaloids from seeds of *Iphigenia stellata*. *Planta Med.*, **1985**, *33*, 72.

[140] Dvořáčková, S.; Sedmera, P.; Potěšilová, H.; Šantavý, F.; Šimánek, V. Alkaloids of *Gloriosa superba* L. *Coll. Czech. Chem. Comm.*, **1984**, *49*, 1536-1542.

[141] Chommadov, B. C. Alkaloid specioseine from *Colchicum speciosum*. *Chem. Nat. Com.*, **1991**, *27*, 218-222.

[142] Chommadov, B.; Yusupov, M. K.; Aslanov, K. A. 2,10-didemethylcolchicine – a new alkaloid from *Merendera robusta*. *Chem. Nat. Com.*, **1991**, *27*, 158-161.

[143] Popova, O. I.; Muraveva, D. A.; Tolkachev, O. N. Alkaloids of the corms of *Colchicum laetum*. *Chem. Nat. Com.*, **1991**, *27*, 647-648.

[144] Yusupov, M.K.; Chommadov, B. C.; Aslanov, K. A. *N*-oxides of homoaporphine alkaloids from *Merendera raddeana*. *Chem. Nat. Com.*, **1991**, *27*, 75-79.

[145] Alikulov, R. V.; Yusupov, M. K. Homoaporphine alkaloids from *Merendera robusta*. *Chem. Nat. Com.*, **1993**, *29*, 767-770.

[146] Ondra, P.; Válka, I.; Vičar, J.; Sütlüpınar, N.; Šimánek, V. (1995) Chromatographic determination of constituents of the genus *Colchicum* (Liliaceae). *J. Chroma. A*, **1995**, *704*, 351-356.

[147] Alikulov, R. V.; Levina, E. V.; Yusupov, M. K. New homoaporphine base from *Merendera robusta*. *Chem. Nat. Com.*, **2003**, *39*, 212-214.

[148] Ellington, E.; Bastida, J.; Viladomat, F.; Šimánek, V.; Codina, C. Occurrence of colchicine derivatives in plants of the genus *Androcymbium*. *Bioch. Sys. Eco.*, **2003**, *31*, 715-722.

[149] Alali, F.; El-Alali, A. LC-MS analysis of corms of *Colchicum hierosolymitanum* (Colchicaceae). *Acta Phar. Tur.*, **2005b**, *47*, 143-150.

[150] Alali, F. Q.; Tawaha, K.; El-Elimat, T.; Qasaymeh, R.; Li, C.; Burgess, J.; Nakanishi, Y.; Kroll, D. J.; Wani, M. C.; Oberlies, N. H. (2006) Phytochemical studies and cytotoxicity evaluations of *Colchicum tunicatum* Feinbr and *Colchicum hierosolymitanum* Feinbr (Colchicaceae): two native Jordanian meadow saffrons. *Nat. Pro. Res.*, **2006**, *20*, 558-566.

[151] Alali, F. Q.; Tawaha, K.; El-Elimat, T. Determination of (–)-demecolcine and (–)-colchicine content in selected Jordanian *Colchicum* species. *Pharmazie*, **2007**, *62*, 739-742.

[152] Alali, F. Q.; Tahboub, Y. R.; Al-Daraysih, I. S.; El-Elimat, T. LC-MS and LC-PDA vs. phytochemical analysis of *Colchicum brachyphyllum*. *Pharmazie*, **2008a**, *63*; 860-865.

[153] Alali, F. Q.; Gharaibeh, A. A.; Gawanmeh, A.; Tawaha, K.; Qandil, A.; Burgess, J. P.; Sy, A.; Nakanishi, Y.; Kroll, D. J.; Oberlies, N. H. Colchicinoids from *Colchicum crocifolium* Boiss. (Colchicaceae). *Nat. Prod. Res.*, **2010**, *24*, 152-159.

[154] Al-Mahmoud, M. S.; Alali, F. Q.; Tawaha, K.; Qasaymeh, R. M. Phytochemical study and cytotoxicity evaluation of *Colchicum stevenii* Kunth (Colchicaceae): a Jordanian meadow saffron. *Nat. Prod. Res.*, **2006**, *20*, 153-160.

[155] Joshi, C. S.; Priya, E. S.; Mathela, C. S. (2010) Isolation and anti-inflammatory activity of colchicinoids from *Gloriosa superba* seeds. *Pharma. Biol.*, **2010**, *48*, 206-209.

[156] Pırıldar, S.; Sütlüpınar, N.; Atasever, B.; Erdem-Kuruca, S.; Papouskova, B.; Šimánek, V. Chemical constituents of the different parts of *Colchicum baytopiorum* and their cytotoxic activities on K562 and HL60 cell lines. *Pharma. Biol.*, **2010**, *48*, 32-39.

[157] Tsuda, Y.; Sano, T. Chapter 4. *Erythrina* and related alkaloids. In: *The Alkaloids: Chemistry and Pharmacology*, vol. 48; Cordell, G. A. (Ed.); Academic Press, London, **1996**; pp. 249-337.

[158] Reimann, E. Synthesis pathways to *Erythrina* alkaloids and *Erythrina* type compounds. *Prog. Chem.Org. Nat. Prod.*, **2007**, *88*, 1-62.

[159] Parsons, A. F.; Palframan, M. J. Chapter 2. *Erythrina* and related alkaloids. In: *The Alkaloids: Chemistry and Biology*, vol. 68; Cordell, G. A. (Ed.); Academic Press, London, **2010**; pp. 39-81.

[160] Maier, U. H.; Rödl, W.; Deus-Neumann, B.; Zenk, M. H. Biosynthesis of *Erythrina* alkaloids in *Erythrina christa-galli*. *Phytochemistry*, **1999**, *52*, 373-382.

[161] Robinson, T. Metabolism and function of alkaloids in plants. *Science*, **1974**, *184*, 430-435.
[162] Mithöfer, A.; Boland, W. Plant defense against herbivores: chemical aspects. *Ann. Rev. Plant Biol.*, **2012**, *63*, 431-450.
[163] De Luca, V.; Salim, V.; Atsumi, S. M.; Yu, F. Mining the biodiversity of plants: a revolution in the making. *Science*, **2012**, *336*, 1658-1661.

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