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Review

Hypecoum spp.—Chemistry and Biological Activity of Alkaloids

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Abstract: Genus *Hypecoum* Tourn. ex L. belongs to the poppy family Papaveraceae and comprises about 19 species occurring in Europe, Northern Africa and Asia. *Hypecoum* species have been widely used in traditional medicine as antipyretic, analgesic and anti-inflammatory remedies. Their effects are associated with the biologically and pharmacologically active isoquinoline alkaloids in them, such as protopines, protoberberines, benzophenanthridines, aporphines, simple isoquinolines, secoberbines, spirobenzylisoquinolines and others. In this study, we aimed to review and organize information on ethnomedicinal, phytochemical, chemotaxonomical and pharmacological studies of alkaloids and extracts obtained from *Hypecoum* plants, and to suggest opportunities for further research.

Keywords: *Hypecoum* spp.; isoquinoline alkaloids; chemotaxonomical relevance; biological activity

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1. Introduction

The flowering plants of the genus *Hypecoum*, belonging to the family Papaveraceae, subfamily Fumarioideae, are widely distributed in temperate areas from Europe to Africa to Southwestern Asia. It is represented by 19 species (23 synonyms), with 2 accepted subspecies and 1 ambiguous name [1]. These plants have recognized medicinal value and are used in different forms of traditional medicine in the treatment and prevention of many diseases—colds, pneumonia, pharyngitis, inflamed red eyes, hepatitis, cholecystitis and other [2–6]. Scientific investigations of the *Hypecoum* species show that many of the therapeutic effects of the plants are primarily related to the bioactive isoquinoline alkaloids found in them. The known alkaloids in the genus belong to the various classes of isoquinolines—protopines, protoberberines, benzophenanthridines, aporphines, simple isoquinolines, secoberbines, spirobenzylisoquinolines and others. Protopine is a predominant alkaloid isolated from all investigated plants of the genus [2,7–24]. Besides being biologically active compounds, isoquinoline alkaloids are characteristic secondary metabolites in the family Papaveraceae and can be used for chemotaxonomic purposes [25].

In recent years, more than 40 alkaloids have been identified in *Hypecoum* species, and new alkaloid structures, along with their pharmacological activities, are reported every year, enriching the diversity of natural compounds. Some of them have promising properties for the treatment of important diseases such as inflammation, cancer and microbial infections [18,19,22,23,26–29].

In this review, the chemical structures and biological activities of the isoquinoline alkaloids that have been reported for the genus *Hypecoum* over the past fifty years are systematically summarized. For this purpose, the relevant data were collected through the scientific databases "SCOPUS", "Google Scholar", "ISI Web of Knowledge", "ScienceDirect", "PubMed", "SciFinder Scholar" and "Wiley Online Library".

2. Botany

The plant family Papaveraceae includes two subfamilies—Fumarioideae and Papaveroidae [1]. The genus *Hypecoum* Tourn. ex L. belongs to the subfamily Fumarioideae

and consists of 19 accepted species, 2 accepted subspecies and 1 ambiguous name of flowering plants found in warm temperate areas of the Mediterranean, Europe and Southwest and Central Asia. In these geographic regions, 21 other *Hypecoum* species and 2 varieties of the genus have been reported from morphological data. According to World Flora Online, these 23 plant names have taxonomic status—synonyms of the respective species (Table 1) [1].

Table 1. *Hypecoum* species and synonyms accepted by World Flora Online.

Accepted Name Species/Subspecies/Ambiguous	**Synonym Species/Subspecies/Varieties**
H. aegypitacum (Forssk.) Asch. & Schweinf.	
H. aegyptiacum (Forssk.) Asch. & Schweinf.	*H. patens* Willd. *H. refractum* Mart. ex Fedde
H. aequilobum Viv	
H. angustilobum Å.E.Dahl	
H. dimidiatum Delile	
H. duriaei Pomel	
H. erectum L.	*H. millefolium* H.Lév. & Vaniot
H. imberbe Sibth. & Sm.	
H. imberbe Sm	*H. procumbens* subsp. *imberbe* (Sm.) Malag. *H. glaucescens* Guss. *H. grandiflorum* Benth. *H. procumbens* subsp. *grandiflorum* (Benth.) Pau
H. lactiflorum (Kar. & Kir.) Pazij	
H. leptocarpum Hook.f. & Thomson	*H. chinense* Franch. *H. alpinum* Z.X.An
H. littorale Wulfen	*H. deuteroparviflorum* Fedde *H. geslini* Coss. & Kralik *H. tetragonum* Bertol.
H. pendulum L.	*H. caucasicum* Koch ex Ledeb. *H. ferrugineomaculatum* Z.X.An *H. pendulum* var. *parviflorum* (Kar. & Kir.) Cullen *H. parviflorum* Kar. & Kir. *H. gracile* Benth Cat.
H. procumbens L.	*H. nodosum* Lam. *H. armatum* Steud. *H. ponticum* Velen
H. procumbens subsp. *atropunctatum* Å.E.Dahl	
H. procumbens subsp. *fragrantissimum* Å.E.Dahl	
H. pseudograndiflorum Petrovic	*H. imberbe* subsp. *pseudograndiflorum* (Petrovic) E.Mayer & Nikolic
H. torulosum Å.E.Dahl	
H. trilobum Trautv. [1]	*H. pendulum* var. *trilobum* Cullen
H. trullatum Å.E.Dahl	
H. zhukanum Lidén	

[1] Ambiguous name.

3. Ethnopharmacological Relevance

The plants of the genus *Hypecoum* are used extensively in various ethnic communities in China, Mongolia and India as antipyretic, analgesic and anti-inflammatory remedies [2,30,31]. A literature survey of ethnobotanical data shows that the most commonly reported species used in traditional medicine are *H. leptocarpum* and *H. erectum*.

H. leptocarpum, namely "Ba Er Wa Da", "Ba Er Ba Da", etc., is a traditional Tibetan herb with a specific use in the treatment of colds, pneumonia, hepatitis, cholecystitis and other diseases [2,3,30]. Extracts from this plant have been reported to have antipyretic and detoxifying effects, as well as antioxidant, antiviral, antibacterial, anticancer and other

activities [22,32,33]. Chinese scientists have registered patents for obtaining antiviral and antibacterial preparations based on thinfruit *Hypecoum* herb extract [34,35].

H. erectum is mainly used in China and Mongolia for traditional treatments for inflammation, fever and pain relief [2,4,5,36,37]. The whole plant and its root are used for acute pharyngitis, relief from cough and inflamed red eyes [6]. In Mongolian medicine, *H. erectum* is included in various herbal formulations such as Deva-5, which is used to treat acute infectious diseases [36]. The plant *H. erectum*, along with 20 other herbs, is used as a Tibetan medicine—Liu Gan Pills (LGP)—to treat flu, headache, cough, body aches and fever [38]. In the past few years, LGP has been widely used in the prevention and treatment of COVID-19 in the Tibetan areas of China [39,40].

4. Chemistry of *Hypecoum* Alkaloids

Alkaloids are a large group of N-containing natural compounds with diverse structures and a wide spectrum of pharmacological effects on human health. The *Hypecoum* species are recognized as important medicinal plants, biosynthesizing isoquinoline alkaloids as major active ingredients.

This section summarizes the alkaloid compounds that have been identified in the *Hypecoum* spp. since 1972 (Table 2) [2,7–24,27,40–50]. So far, a total of 86 naturally occurring alkaloids have been reported for ten plant species—*H. procumbens*, *H. procumbens* var. glaucescens, *H. imberbe*, *H. lactiflorum*, *H. pendulum*, *H. trilobum*, *H. leptocarpum*, *H. erectum*, *H. ponticum* and *H. parviflorum*. Based on their structures, the *Hypecoum* alkaloids can be divided into eight major groups: protopines (**1**–**11**), protoberberines (**12**–**17**), benzophenantridines (**18**–**28**), aporphines (**29**–**33**), simple isoquinolines (**34**–**38**), secoberbines (**39**–**66**), spirobenzilisoquinolines (**67**–**73**) and others (**74**–**86**). Two chemical structures have been detected in the literature with the name leptocarpine—protopine alkaloid **8** and alkaloid **82**. Both compounds have been identified in *H. leptocarpum* [10,22,42]. On the other hand, the structure of alkaloid **41** has been published in the literature under two different names, dihydroleptopine and coryximine, isolated from *H. leptocarpum* [22,23,43]. Similarly, the newly found in *H. erectum* 2-(1,3-dioxolo [4,5-h]isoquinolin-7-yl)-4,5-dimethoxy-N-methyl-benzenethanamine has the same structure as the alkaloid leptocarmine (**62**), isolated from *H. leptocarpum* [19,23,24].

Table 2. Alkaloid structures reported for *Hypecoum* spp.

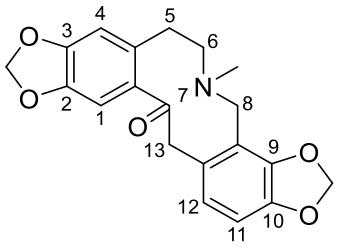
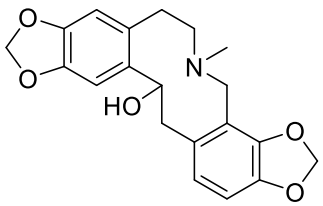
Alkaloids/Types	Structure	Species	References
Protopines			
Protopine (**1**)		*H. procumbens* *H. procumbens* var. *glaucescens* *H. imberbe* *H. lactiflorum* *H. pendulum* *H. trilobum* *H. leptocarpum* *H. erectum* *H. ponticum* *H. parviflorum*	[2,7–24]
Dihydroprotopine (**2**)		*H. procumbens* *H. imberbe* *H. leptocarpum*	[17,24]

Table 2. *Cont.*

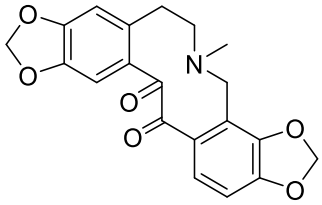
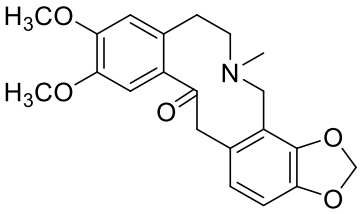
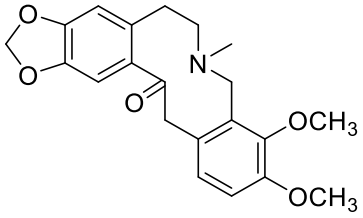
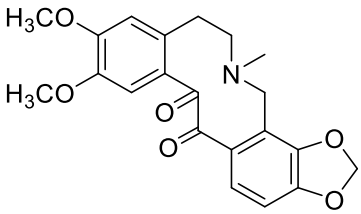
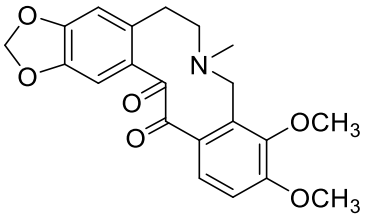
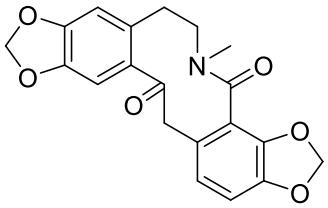
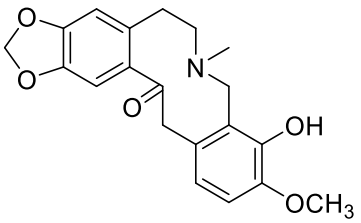
Alkaloids/Types	Structure	Species	References
13-Oxoprotopine (**3**)		*H. procumbens* *H. erectum*	[15,19]
Cryptopine (**4**)		*H. procumbens* var. *glaucescens* *H. erectum* *H. leptocarpum*	[2,11,13,19–23,40]
Allocryptopine (**5**)		*H. lactiflorum* *H. leptocarpum* *H. procumbens* *H. procumbens* var. *glaucescens* *H. erectum*	[7,8,10,11,13,14,19,21,40,41]
13-Oxocryptopine (**6**)		*H. erectum*	[19]
13-Oxoallocryptopine (**7**)		*H. erectum*	[19]
Leptocarpine (**8**) *		*H. leptocarpum*	[42]
Hunnemanine (**9**)		*H. procumbens*	[15]

Table 2. *Cont.*

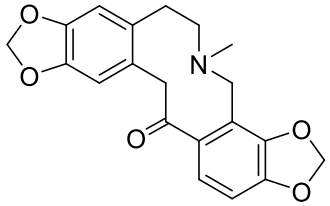
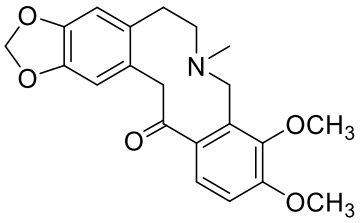
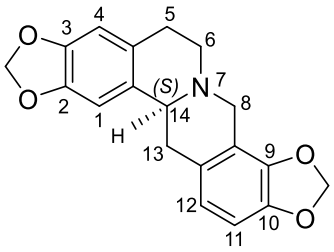
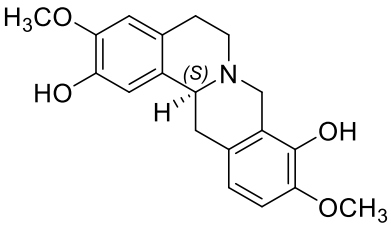
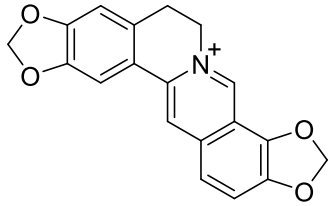
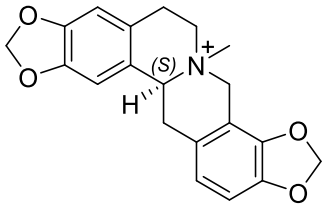
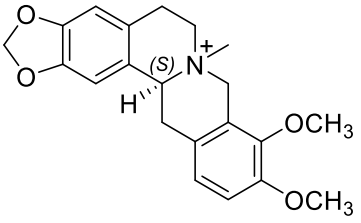
Alkaloids/Types	Structure	Species	References
Bis[1,3]benzodioxolo[4,5-c:5′,6′-g]azecin-14(4*H*)-one, 5,6,7,13-tetrahydro-5-methyl-one (**10**)		*H. erectum*	[19]
6,7,8,14-Tetrahydro-3,4-dimethoxy-6-methylbenzo [c][1,3]benzodioxolo [5,6-g]azecin-15(5*H*)-one (**11**)		*H. erectum*	[19]
Protoberberines			
(*S*)-Stylopine (**12**)		*H. procumbens*	[17]
(*S*)-Scoulerine (**13**)		*H. procumbens*	[8,15]
Coptisine (**14**)		*H. procumbens* *H. leptocarpum* *H. erectum*	[8,14,20,23,40,41]
(*S*)-*N*-Methylstylopine (**15**)		*H. lactiflorum* *H. procumbens* *H. ponticum*	[7,17,18]
(*S*)-*N*-Methylcanadine (**16**)		*H. lactiflorum* *H. erectum* *H. procumbens* *H. ponticum* *H. leptocarpum*	[7,13,17,18,21]

Table 2. *Cont.*

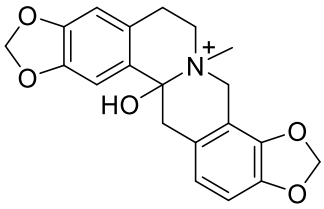
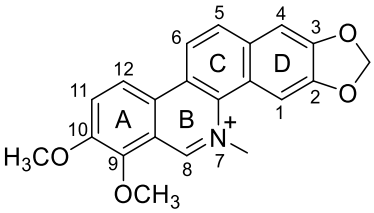
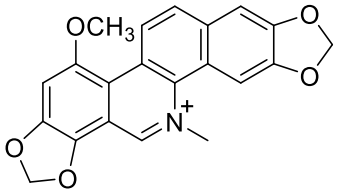
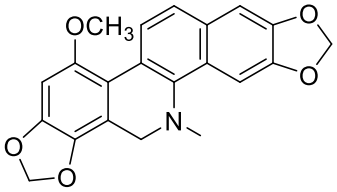
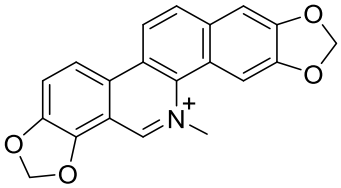
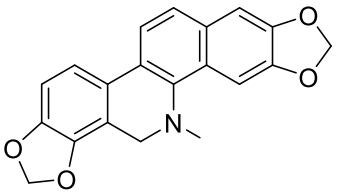
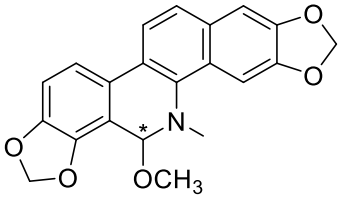
Alkaloids/Types	Structure	Species	References
Hydroprotopine (**17**)		*H. leptocarpum*	[27]
Benzophenanthridines			
Chelerythrine (**18**)		*H. procumbens* *H. leptocarpum*	[8,14,40]
Chelirubine (**19**)		*H. procumbens*	[8,14]
Dihydrochelirubine (**20**)		*H. procumbens*	[17]
Sanguinarine (**21**)		*H. procumbens* *H. leptocarpum* *H. trilobum* *H. ponticum*, *H. imberbe*	[14,17,18,21,40]
Dihydrosanguinarine (**22**)		*H. imberbe* *H. leptocarpum* *H. procumbens*	[9,10,15]
(*R*,*S*)-8-Methoxydihydrosanguinarine (**23**)		*H. procumbens* *H. leptocarpum* *H. imberbe*	[8–10]

Table 2. *Cont.*

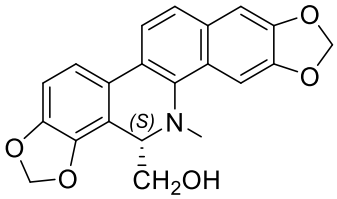
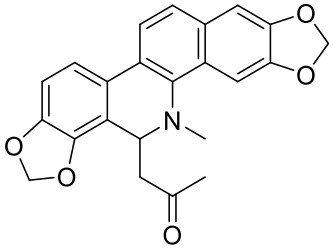
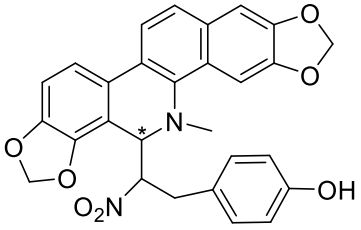
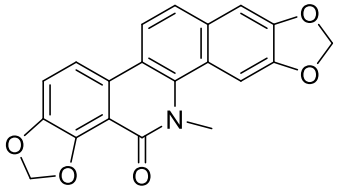
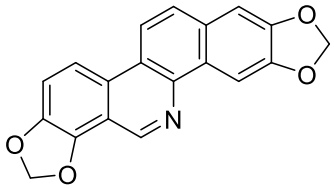
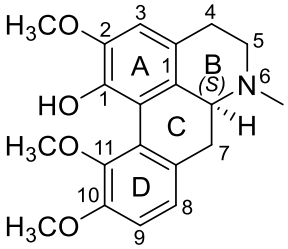
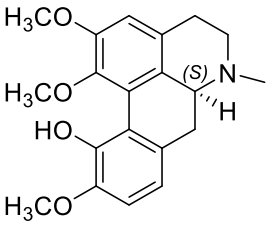
Alkaloids/Types	Structure	Species	References
(*S*)-8-Hydroxymethyldihydrosanguinarine (**24**)		*H. erectum*	[19]
8-Acetonyldihydrosanguinarine (**25**)		*H. procumbens* *H. leptocarpum*	[8,10]
(*R*,*S*)-Nitrotyrasanguinarine (**26**)		*H. imberbe* *H. pendulum* *H. procumbens*	[9]
Oxysanguinarine (**27**)		*H. procumbens*	[8,15]
Norsanguinarine (**28**)		*H. procumbens* *H. leptocarpum*	[8,15,23]
Aporphines			
(*S*)-Corydine (**29**)		*H. procumbens* *H. leptocarpum*	[40]
(*S*)-Isocorydine (**30**)		*H. procumbens* *H. procumbens* var. *glaucescens* *H. leptocarpum*	[8,11,40]

Table 2. *Cont.*

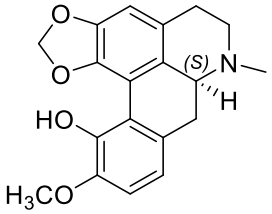
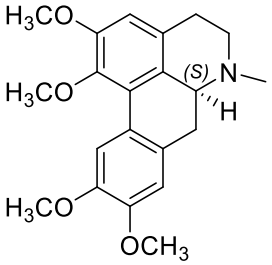
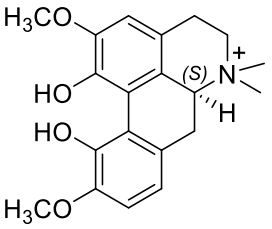
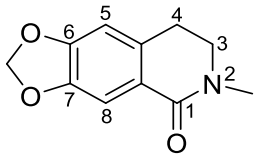
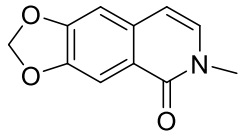
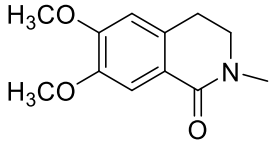
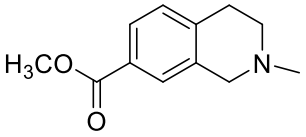
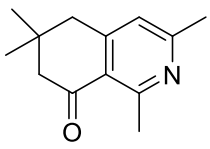
Alkaloids/Types	Structure	Species	References
(*S*)-Bulbocapnine (**31**)		*H. imberbe*	[9]
(*S*)-Glaucine (**32**)		*H. procumbens*	[8]
(*S*)-Magnoflorine (**33**)		*H. procumbens* *H. leptocarpum*	[40]
Simple isoquinolines			
Oxohydrastinine (**34**)		*H. imberbe* *H. leptocarpum* *H. erectum*	[2,9,10,12,13,19,21–24,27]
Doryanine (**35**)		*H. erectum*	[19]
N-Methylcorydaldine (**36**)		*H. erectum* *H. leptocarpum*	[13,19,23]
2-Methyl-1,2,3,4-tetrahydro isoquinoline-7-carboxylic acid methyl ester (**37**)		*H. erectum*	[19]
1,3,6,6-Tetramethyl-5,6,7,8-tetrahydroisoquiolin-8-one (**38**)		*H. erectum*	[19]

Table 2. *Cont.*

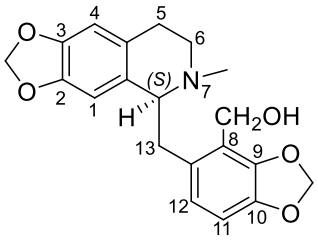
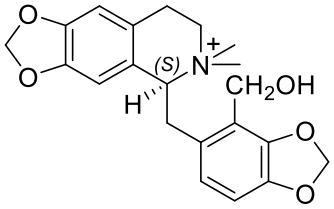
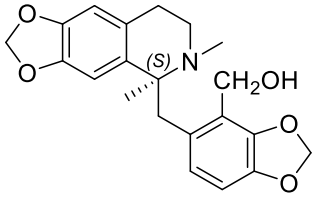
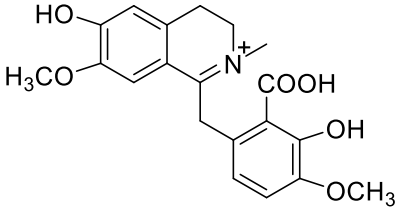
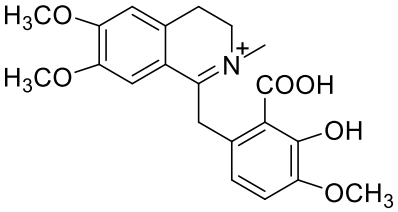
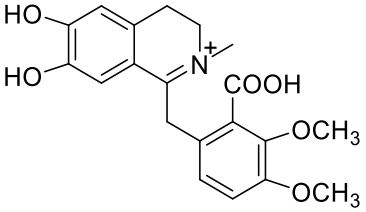
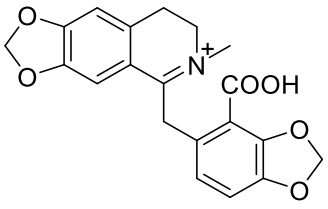
Alkaloids/Types	Structure	Species	References
Secoberbines			
(*S*)-Corydalisol (**39**)		*H. procumbens*	[8]
(*S*)-*N*-Methylcorydalisol (**40**)		*H. lactiflorum*	[7]
(*S*)-Dihydroleptopine (**41**) (Coryximine)		*H. leptocarpum*	[22,23,43]
Hypecocarpinine (**42**)		*H. leptocarpum*	[24]
Hypecocarpine (**43**)		*H. leptocarpum*	[27]
Leptopinine (**44**)		*H. leptocarpum*	[12]
Leptopine (**45**)		*H. leptocarpum*	[12,21]

Table 2. *Cont.*

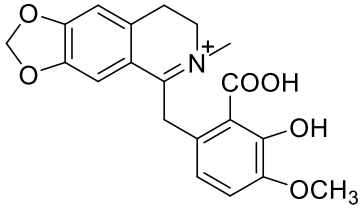
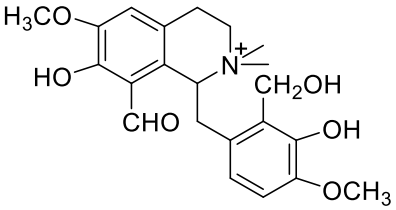
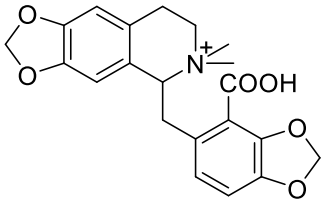
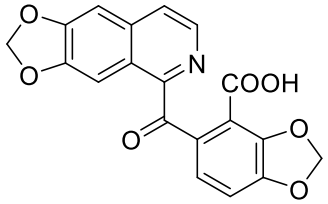
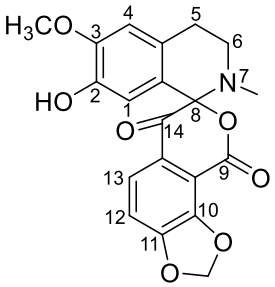
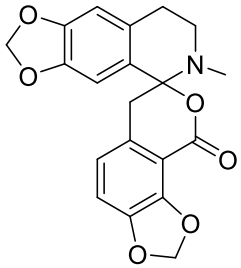
Alkaloids/Types	Structure	Species	References
Leptopidine (**46**)		*H. leptocarpum*	[12,21–24,27]
Hypepontine (**47**)		*H. ponticum*	[17,18]
N-Methylcoryximine (**48**)		*H. pendulum*	[44]
Hendersine B (**49**)		*H. leptocarpum*	[23]
Procumbine (**50**)		*H. procumbens* *H. leptocarpum*	[40,45]
Leptopidinine (**51**)		*H. leptocarpum*	[12,21,22]

Table 2. *Cont.*

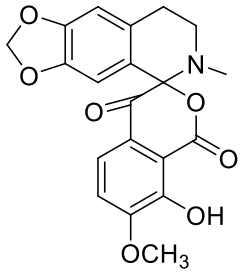
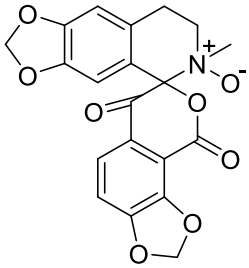
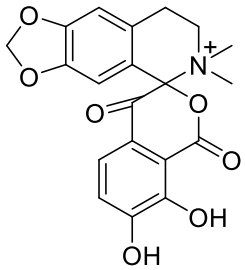
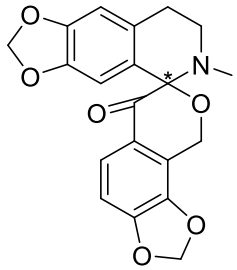
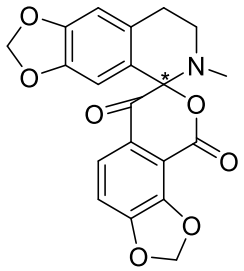
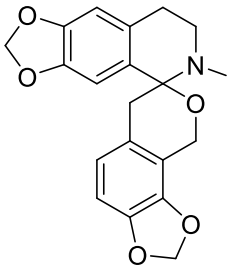
Alkaloids/Types	Structure	Species	References
Torulosine (**52**)		*H. leptocarpum*	[23,43]
8-Oxohypecorinine *N*-oxide (**53**)		*H. leptocarpum*	[43]
N-Methyldemethyltorulosine (**54**)		*H. leptocarpum*	[23,43]
(*R*,*S*)-Hypecorinine (**55**)		*H. procumbens* *H. procumbens* var. *glaucescens* *H. erectum*	[8,11,13,14,19,41,46]
(*R*,*S*)-8-Oxohypecorinine (**56**)		*H. procumbens* var. *glaucescens*	[11]
Hypecorine (**57**)		*H. erectum*	[14,41,46]

Table 2. *Cont.*

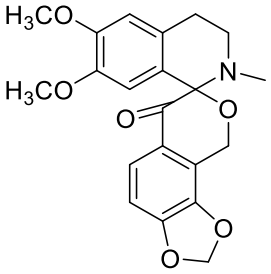
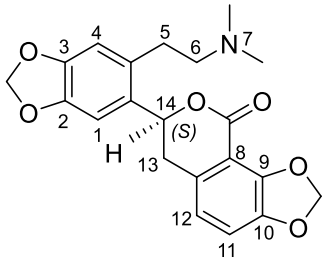
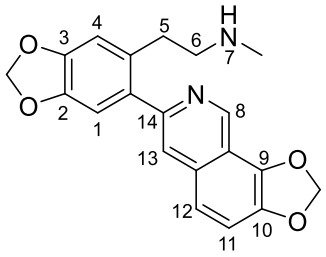
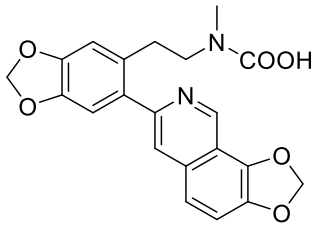
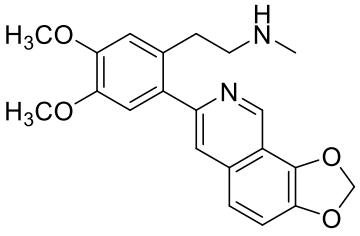
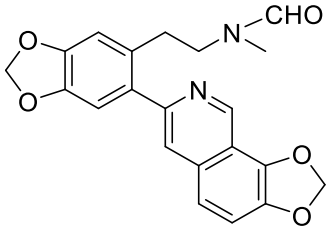
Alkaloids/Types	Structure	Species	References
2,3-Dimethoxyhypecorinine (**58**)		*H. erectum*	[19]
(*S*)-Peshawarine (**59**)		*H. parviflorum*	[8,16]
Corydamine (**60**)		*H. leptocarpum* *H. erectum*	[10,19,22–24,41]
Corydamine acid (**61**)		*H. leptocarpum*	[23]
Leptocaramine (**62**) (2-(1,3-dioxolo [4,5-*h*] isoquinolin-7-yl)-4,5-dimethoxy-*N*-methyl-benzeneethanamine)		*H. leptocarpum* *H. erectum*	[19,23,24]
N-Formylcorydamine (**63**)		*H. erectum* *H. procumbens*	[15,19]

Table 2. *Cont.*

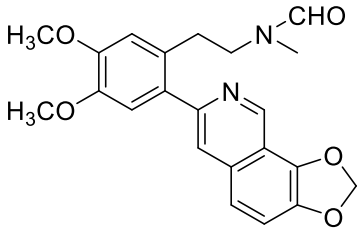
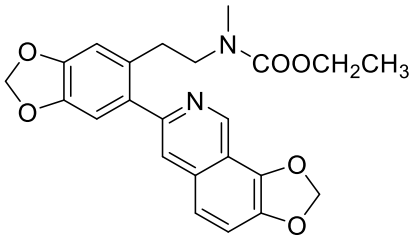
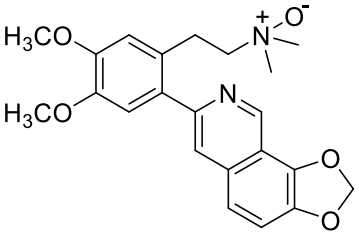
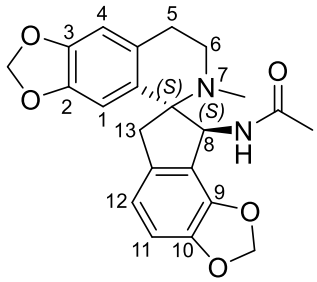
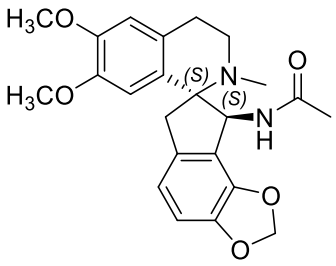
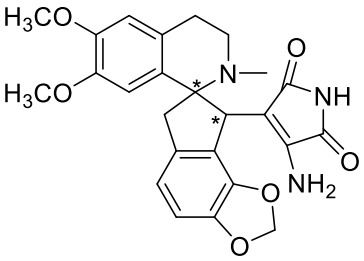
Alkaloids/Types	Structure	Species	References
2,3-Dimethoxy-*N*-formyl corydamine (**64**)		*H. erectum*	[19]
Hypecumine (**65**)		*H. procumbens*	[15]
7-*N*-Methyl-7-*N*-oxide-2,3-dimethoxycorydamine (**66**)		*H. erectum*	[19]
Spirobenzylisoquinolines			
(*S*,*S*)-Hyperectumine B (**67**)		*H. erectum*	[19]
(*S*,*S*)-2,3-Dimethoxyhyperectumine B (**68**)		*H. erectum*	[19]
(*R*,*S*) and (*S*,*R*)-2,3-Dimethoxyhyperectine (**69**)		*H. erectum*	[19]

Table 2. *Cont.*

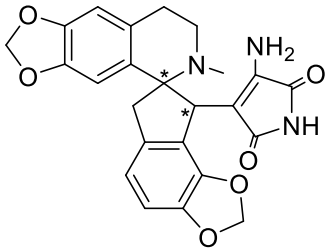
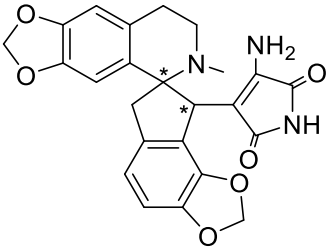
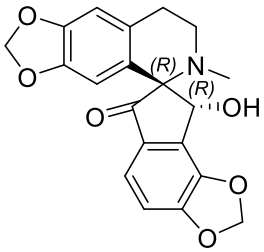
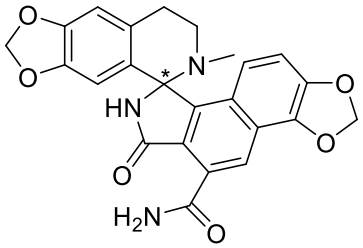
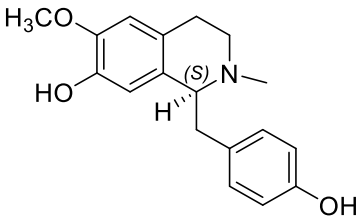
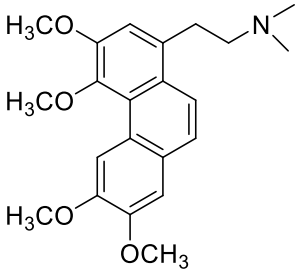
Alkaloids/Types	Structure	Species	References
(*R*,*S*) and (*S*,*R*)-Hyperectine (**70**)		*H. leptocarpum* *H. erectum*	[10,19,41,46,47]
(*S*,*S*) and (*R*,*R*)-Isohyperectine (**71**)		*H. leptocarpum* *H. erectum*	[10,12,47]
(*R*,*R*)-Sibiricine (**72**)		*H. erectum*	[19]
(*R*,*S*)-Hypecoleptopine (**73**)		*H. erectum* *H. leptocarpum*	[21,43,48]
Other alkaloids			
(*S*)-*N*-Methylcoclaurine (**74**)		*H. procumbens*	[17]
N-Methylsecoglaucine (**75**)		*H. ponticum*	[17,18]

Table 2. *Cont.*

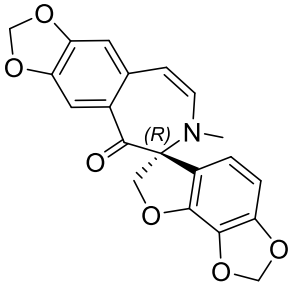
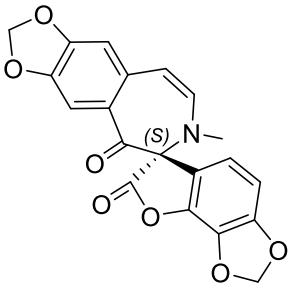
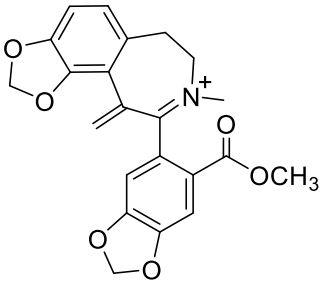
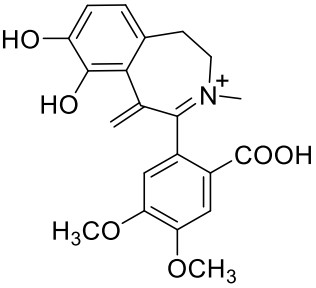
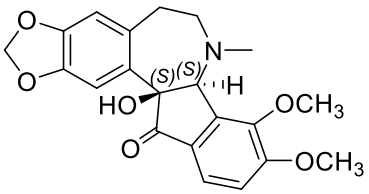
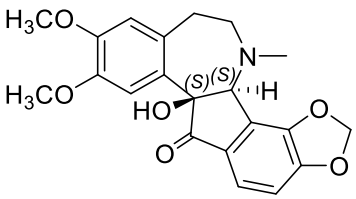
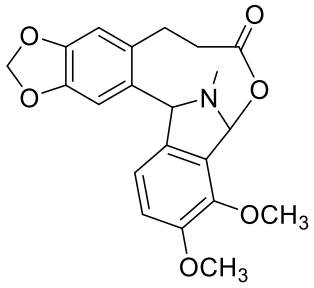
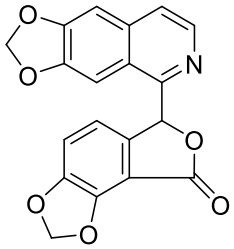
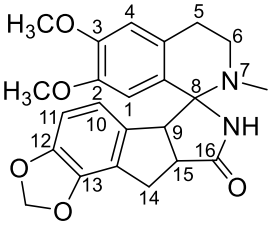
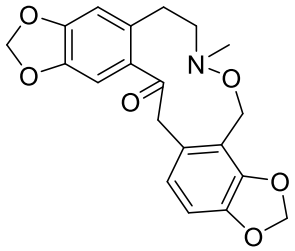
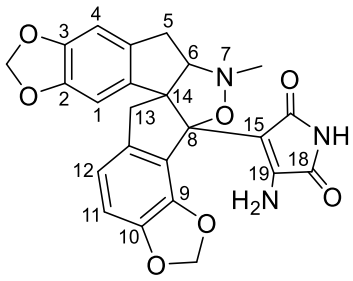
Alkaloids/Types	Structure	Species	References
(*R*)-Turkiyenine (**76**)		*H. procumbens* *H. pendulum* *H. imberbe*	[9,15,49,50]
(*S*)-Oxoturkiyenine (**77**)		*H. pendulum*	[49]
Leptocarpinine (**78**)		*H. leptocarpum*	[12]
Leptocarpinine B (**79**)		*H. leptocarpum*	[23]
(*S*,*S*)-*Trans*-benzindenoazepines (**80**)		*H. erectum*	[19]
(*S*,*S*)-*O*-Methylfumarostelline (**81**)		*H. erectum*	[19]

Table 2. *Cont.*

Alkaloids/Types	Structure	Species	References
Leptocarpine (**82**) *		*H. leptocarpum*	[10,22]
*Hypecoum*ine (**83**)		*H. procumbens*	[2]
Hyperectumine (**84**) (8*S*, 9*R*, 15*R*) (8*R*, 9*S*, 15*S*)		*H. erectum*	[25]
Dibenzooxazacycloundecine (**85**)		*H. erectum*	[19]
Hypeisoxazole A (**86**) (6*S*, 8*R*, 14*R*) (6*R*, 8*S*, 14*S*)		*H. erectum*	[48]

* Two chemical structures with the name leptocarpine (**8**, **82**).

4.1. Protopine Alkaloids

The protopine alkaloids (**1**–**11**) represent the major class of alkaloids in the *Hypecoum* species (Table 2). Their structure includes a tricyclic frame with a carbonyl group at C-14 and methoxy- or methylendioxy- groups at C-2, C-3, C-9 and C-10. Alkaloids **3**, **6** and **7** are further oxygenated at C-13. Although only eleven protopines have been identified in the genus, protopine (**1**) has been found in all studied *Hypecoum* species [2,7–24]. Alkaloid **1** together with cryptopine (**4**) and allocryptopine (**5**) are the most pharmacologically studied and biologically active protopines in the genus. It has been established that these alkaloids possess potent anti-inflammatory, analgesic and antibacterial effect [13,19].

4.2. Protoberberine Alkaloids

The protoberberine alkaloids (**12**–**17**) are a small group of *Hypecoum* isoquinolines containing only six representatives (Table 2). Most of them are of the tetrahydroprotoberberine type (**12**, **13**, **15**–**17**), and only coptisine (**14**) is a typical protoberberine with a three aromatic ring system. Alkaloid **14** has shown significant cytotoxic activity against different cancer cell lines, which is probably related to the positive *N*-ion in its molecule [23].

4.3. Benzophenantridine Alkaloids

Eleven benzophenantridine alkaloids (**18**–**28**) have been identified in six *Hypecoum* species—*H. procumbens*, *H. leptocarpum*, *H. trilobum*, *H. ponticum*, *H. imberbe* and *H. erectum* (Table 2). Their structure includes a tetracyclic skeleton with an aromatic (**18**, **19**, **21** and **28**) or nonaromatic (**20**, **22**–**27**) ring B. The alkaloids with three aromatic ring systems are usually in the form of quaternary ammonium salts (**18**, **19**, **21**), and those with non-aromatic ring B are usually C-8-substituted (**23**–**27**). Benzophenanthridine alkaloids are known to have diverse and significant biological properties, but so far, only 8-hydroxymethyldihydrosanguinarine (**24**), isolated from *H. erectum*, has been found to possess in vitro anti-inflammatory activity [19,51].

4.4. Aporphine Alkaloids

The alkaloids in this group (**29**–**33**) contain an aporphine skeleton with two aromatic rings and *N*-methyl function. Five aporphines have been isolated from four plant species—*H. procumbens*, *H. procumbens* var. *glaucescens*, *H. leptocarpum* and *H. imberbe* (Table 2). Alkaloids **29**–**32** are tertiary and only one—magnoflorine—(**33**) is a quaternary ammonium salt. Although alkaloids of this type are of great research interest due to their important biological properties such as cytotoxicity, antioxidation, immunoregulation, etc., the isolated *Hypecoum* aporphines have not been studied pharmacologically [52].

4.5. Simple Isoquinoline Alkaloids

The simple isoquinoline group includes five alkaloids (**34**–**38**) present in three *Hypecoum* species—*H. imberbe*, *H. leptocarpum* and *H. erectum* (Table 2). These alkaloids have the simplest structure, involving an isoquinoline nucleus which is C-6- and/or C-7-substituted. Compound **38** is, unusually, 1,3,6,6-tetramethylated and oxygenated at C-8. Several biological activities have been established for alkaloids **34**, **36** and **38**, including anti-inflammatory, antibacterial, anticancer and analgesic effects [13,19,27].

4.6. Secoberbine Alkaloids

The secoberbine alkaloids (**39**–**66**) are the largest group of isoquinoline alkaloids, consisting of 28 members, which have been identified in seven *Hypecoum* species—*H. procumbens*, *H. procumbens* var. *glaucescens*, *H. leptocarpum*, *H. erectum*, *H. lactiflorum*, *H. erectum*, *H. ponticum* and *H. parviflorum* (Table 2).

According to the chemical structure, the alkaloids are divided into three subgroups: 7,8-secoberbines—tricyclic (**39**–**49**) and tetracyclic (**50**–**58**); 7,8-14,7-bissecoberbine—peshawarine (**59**) and 6,7-secoberbines (**60**–**66**) [53]. All tricyclic 7,8-secoberbines in the *Hypecoum* species have substitutions at C-8 with -CH_2OH or -COOH groups. Structure–activity relationship studies on these compounds have shown that the presence of the carboxyl group in coryximine (**41**), leptopidine (**46**) and hendersine B (**49**) is the probable reason for the low cytotoxicity against different tumor cell lines [23,27]. Furthermore, the quaternary alkaloid hypepontine **47**,and -CH_2OH substituted at C-8, has demonstrated good in vitro antibacterial and antifungal activity [18]. Among the tetracyclic 7,8-secoberbines, hypecorinine (**55**) and 2,3-dimethoxyhypecorinine (**58**) have been found to possess good antimicrobial and anti-inflammatory properties, respectively [13,19]. The alkaloids **60** and **62** of the 6,7-secoberbine subgroup have moderate cytotoxicity against different cancer cell lines, probably due to possessing the most electron-donating groups in their structures [23,24].

Moreover, **60** possesses potent anticancer activity, and its acidified form can be used as a potential regulator of diabetes mellitus [28,54].

4.7. Spirobenzylisoquinoline Alkaloids

Spirobenzylisoquinolines (**67**–**73**) are a small group isoquinolines with a "spiro" structure identified in two *Hypecoum* species—*H. leptocarpum* and *H. erectum* (Table 2). In these species, most of the spirobenzylisoquinoline alkaloids are C-8 linked via a C–C bond to an amide carbonyl group (**67**, **68**) or 3-aminomaleimide group (**69**–**71**). Alkaloid **73** is spirobenzylisoquinoline with a unique 6/6/5/6/6 skeleton. Some of the isolated alkaloids, such as **68**–**70** and **72,** have shown good anti-inflammatory activity via selective inhibition of inflammatory mediators [19].

4.8. Other Alkaloids

This group summarizes the *Hypecoum* alkaloids of various structural types (**74**–**86**) such as the benzylisoquinoline—*N*-methylcoclaurine (**74**), the phenantrene—*N*-methylsecoglaucine (**75**), the indenobenzazepines (**80**, **81**), the phthalideisoquinoline—hypecoumine (**83**), the C_{19}-benzylisoquinoline—hyperectumine (**84**) and alkaloids with unusual structures that cannot be assigned to any of the established groups (**76**–**79**, **82**, **85**, **86**) (Table 2). The alkaloids **80**, **81** and **84** have shown significant anti-inflammatory properties in different in vitro models [19].

5. Biosynthesis and Chemotaxonomical Relevance of Isoquinoline Alkaloids

The isoquinoline alkaloids are characteristic secondary metabolites in the Papaveraceae family and their structural types have been used as chemotaxonomical markers to determine relationships between genera [25]. However, for a correct chemotaxonomic classification, it is important to understand the biosynthetic pathways of isoquinoline alkaloids in the plant species.

The biosynthetic pathways of the different types of isoquinoline alkaloids identified in *Hypecoum* species are presented in Figure 1.

The first step in the process is the condensation and cyclization of two tyrosine derivatives, dopamine and 4-hydroxyphenylacetaldehyde, to yield the benzylisoquinoline alkaloid (*S*)-norcoclaurine, which is the central precursor of all isoquinoline alkaloids. (Figure 1) [55]. (*S*)-Norcoclaurine is sequentially hydroxylated, *O*-methylated and *N*-methylated to give (*S*)-reticuline. It can subsequently undergo stereochemical inversion to (*R*)-reticuline, a precursor of the morphinane alkaloids. This inversion is not characteristic of *Hypecoum* plants, as this type of alkaloid has not been found in the genus [56].

As shown in Figure 1, the transformation of (*S*)-reticuline via C–C or C–O coupling enzymatic reactions is the branch point that drives the formation of protoberberine and aporphine subclasses [56].

The protoberberine alkaloid *N*-methylstylopine (**15**) is the central intermediate in branch pathways that lead to protopines and benzophenantridines, secoberbines, spirobenzylisoquinolines and the phtalideisoquinoline alkaloid hypecoumine (**86**) [56,57].

Afterward, the main scaffold of each type undergoes different enzyme reactions such as oxidations, N- and O-methylations or methylenedioxy bridge formation, yielding the structural diversity of alkaloids identified in *Hypecoum* species (Table 2). Yuan et al. presented a possible biosynthetic pathway of spirobenzylisoquinolines (**69**–**71**) C-8 linked via a C–C bond to a 3-aminomaleimide group, in which sibiricine (**72**) is further attacked by asparagine to hyperectine (**70**) (Figure 1) [19].

The protopine biosynthesis pathway is predominant in the *Hypecoum* plants, as protopine (**1**) is the main alkaloid isolated from all investigated species [2,7–24]. On the other hand, *Hypecoum* species contain great variety of secoberbine alkaloids in addition to protopines, protoberberines and benzophenatridines. Secoberbines are characteristic metabolites in the genus, and the presence of these alkaloids distinguishes *Hypecoum* plants chemotaxonomically from other genera of the subfamily Papaveroidae and is in-

dicative of a close relationship between genus *Hypecoum* and some species of subfamily Fumariaidae [25].

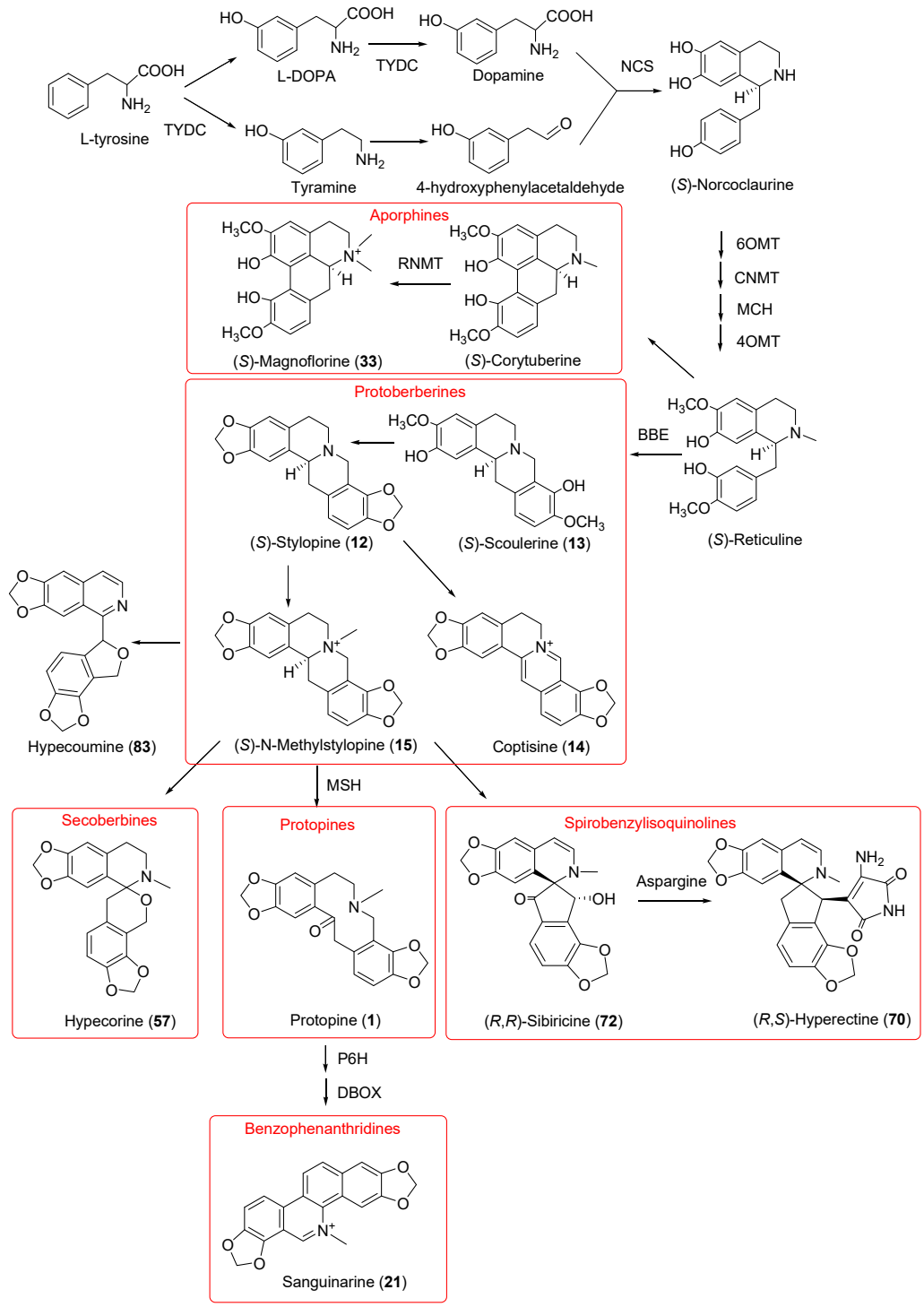


Figure 1. Possible biosynthesis pathways of isoquinoline alkaloids in *Hypecoum* species. TYDC: tyrosine/dopadecarboxylase; NCS: norcoclaurine synthase; 6OMT: norcoclaurine 6-O-methyltransferase; CNMT: coclaurine N-methyltransferase; 4′OMT: 4′-O-methyltransferase; BBE: berberine bridgeenzyme; MSH: N-methylstylopine-14-hydroxylase; P6H: protopine 6-hydroxylase; DBOX: dihydrobezophenanthridine oxidase.

Based on the chemotaxonomic significance of the isoquinoline alkaloids, attempts have been made to improve the species rank of some *Hypecoum* synonyms. Doncheva

et al. found that *H. ponticum* (synonym of *H. procumbens*) is well separated from the species -*H. procumbens* and *H. imberbe* due to the presence of a greater number of quaternary isoquinoline alkaloids [17]. However, the application of individual isoquinoline alkaloids for chemotaxonomical purpose has to be approached cautiously, as the alkaloid biosynthesis depends on many environmental factors such as geographic location, altitude, soils and others [25].

6. Biological Activities

Based on the long-standing use of *Hypecoum* species in traditional medicine, different solvent extracts and isolated alkaloids have been evaluated for their effects in the treatment of inflammation, microbial and viral infections, as well as for their analgesic, antitumor, anti-lipase and antioxidant properties.

6.1. Anti-Inflammatory Activity

H. erectum is widely used in Tibetan medicine to treat various inflammations, relieve pain and reduce fever [4,5].

In 2021, Yuan et al. [19] verified the traditional use of *H. erectum* by assessing its anti-inflammatory effect. The authors studied the in vivo anti-inflammatory activity of the methanolic (MeOH) extract, total alkaloid and non-alkaloid fractions of *H. erectum* at doses of 200, 100 and 50 mg/kg using a carrageenan-induced paw edema model. It was found that the alkaloid fraction showed significant anti-inflammatory activity at all tested doses with inhibition percentages of 60.5%, 54.3% and 47.4%, while the MeOH extract and non-alkaloid fractions showed good effects only at the dose of 200 mg/kg, with inhibition of 53.0% and 43.2%, respectively.

To determine the compounds responsible for the bioactivity of *H. erectum*, four individual isoquinoline alkaloids—protopine (**1**), cryptopine (**4**), allocryptopine (**5**) and oxohydrastinine (**34**)—at doses of 100 and 50 mg/kg were assessed for their in vivo anti-inflammatory activity using the same carrageenan-induced paw edema animal model [19]. The results indicated that compounds **4**, **5** and **34** in both doses used possessed significant anti-inflammatory activity equivalent to that of the positive control (aspirin). Therefore, the authors suggest that these isoquinoline alkaloids are the main anti-inflammatory substances in the species.

To further elucidate the possible contributions of these alkaloids to the anti-inflammatory effects of *H. erectum*, all isolated compounds were evaluated for their in vitro inhibitory effects on the production of inflammatory mediators—cyclooxygenase-2 (COX-2), interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α)—in lipopolysaccharide (LPS)-stimulated RAW 264.7 macrophages. It was found that alkaloids **1**, **24**, **34**, **36**, **38, 62**, **70**, **80** and **81,** with a treatment concentration of 5 μg/mL, showed anti-inflammatory activity via selectively inhibiting the release of inflammatory mediators—COX-2, IL-1β and TNF-α. The compounds protopine (**1**), 1,3,6,6-tetramethyl-5,6,7,8-tetrahydroisoquinolin-8-one (**38**) and trans-benzindenoazepines (**80**) showed anti-inflammatory activity against IL-1β comparable to the control, dextromethorphan (DXM) [19]. Also, the C_{19}-benzylisoquinoline alkaloid hyperectumine (**84**), isolated from *H. erectum*, exhibited moderate anti-inflammatory activity via suppressing the response in LPS-induced RAW 264.7 macrophages [26].

Other authors also found that the ethanolic extract of *H. erectum* may reduce LPS-induced inflammation [58]. Protopine (**1**) reduces nitric oxide (NO) production and inhibits the levels of prostaglandin E2 (PGE2) and COX-2 in LPS-stimulated RAW 264.7 murine cell lines in a dose-dependent manner [59]. The mechanism of action of **1** involved the suppression of phosphorylation of mitogen-activated protein kinases (MAPKs) and blocking of the activation of nuclear factor kappa-light chain-enhancer of activated B cells (NF-κB) [59].

6.2. Anticancer Activitiy

The anticancer properties of *H. leptocarpum* are well known in traditional Tibetan medicine. Therefore, Luo et al. [28], in 2022, evaluated the anticancer activity of the

isoquinoline alkaloid corydamine (**60**). It was found that the alkaloid significantly reduced hepatocellular carcinoma (HCC) growth both in vitro and in vivo. Corydamine (**60**) dose-dependently suppressed HuH7 and LM9 cell proliferation and metastasis in vitro via arresting the cell cycle in the G1/G0 phase and inducing cell apoptosis of the mitochondrial pathway. In vivo studies in LM9 xenografted nude mice showed that a 21 day therapy with **60** at a dose 50 mg/kg/day significantly inhibited tumor growth. These findings suggest that **60** may be used as a natural therapeutic agent for the treatment of HCC.

In 2015, Zang et al. [27] evaluated the cytotoxicity of hypecocarpine (**43**) and leptopidine (**46**) isolated from *H. leptocarpum* in human breast cancer cells (MDA-MB-231) with different concentrations (0, 2, 4, 6, 8, 10 g/mL) of the alkaloids for 24 and 48 h, followed by a cell viability assay. The results showed that only **46** exerted a cytotoxic effect on the growth of MDA-MB-231 cells in a dose- and time-dependent manner. In addition, this alkaloid affected intracellular fatty acid biosynthesis in breast cancer cells via downregulating fatty acid synthase expression.

An anticancer screening of the isolated alkaloids from *H. leptocarpum* was conducted using a MTT assay by Wen et al. [24] in 2022. The compounds oxohydrastinine (**34**), corydamine (**60**) and leptocaramine (**62**) had moderate cytotoxicity against human lung cancer (A549) and human gastric carcinoma (MGC-803) cell lines.

Other authors in the same year evaluated the cytotoxic activity of the 15 isolated alkaloids from *H. leptocarpum* against three tumor cell lines—human ovarian cancer cell lines (A2780), human cervical cancer cell lines (HeLa) and human hepatocellular carcinoma cell lines (HepG2) [23]. This study established that coptisine (**14**) exhibited significant cytotoxic activity against the A2780 and HeLa tumor cell lines with IC_{50} values of 31.49 and 30.72 μM, respectively, while leptocaramine (**62**) exhibited moderate cytotoxicity against HepG2 cell lines with an IC_{50} value of 22.16 μM. The cytotoxicity of **14** against A2780 and HeLa tumor cell lines is due to the presence of a positive N-ion in the alkaloid molecule. The moderate cytotoxicity of **62** against the HepG2 cancer cell line is related to the number of electron-donating groups in its structure. The presence of the carboxyl group in the alkaloids coryximine (**41**), leptopidine (**46**), hendersine B (**49**), corydamic acid (**61**) and leptocarpinine B (**79**) is the probable reason for their low cytotoxicity against the three tumor cell lines [23].

6.3. Antibacterial and Antifungal Activity

An in vitro study of the antimicrobial activity of 306 Iranian plants against *Escherichia coli*, *Klebsiella pneumoniae*, *Salmonella typhi*, *Pseudomonas aeruginosa*, *Morganella morganii* (Gram-negative bacteria), *Bacillus subtilis* and *Staphylococcus aureus* (Gram-positive bacteria) and *Candida albicans*, established that the methanolic extract of *H. pendulum* L. exhibited a significant effect against *E. coli*, *M. morganii* and *S. aureus* [60].

In 2022, a group of Turkish scientists found that the methanolic extract of *H. trullatum* Å.E.Dahl, which is an endemic species in Turkey, inhibited the in vitro growth of *Salmonella infantis*, *Listeria innocua*, *Enterococcus durans*, *Staphylococcus epidermidis* (DSMZ 20044), *E. coli* (ATCC 25922) and *Saratia marrescens* (ATCC 13048) [29].

The antimicrobial activity of tertiary and quaternary alkaloid mixtures from *H. ponticum* was screened against Gram-positive bacteria (*S. aureus* 209), Gram-negative bacteria (*E. coli* and *P. aeruginosa*) and *C. albicans* [18]. The quaternary alkaloid mixture containing N-methylstylopine (**15**), N-methylcanadine (**16**) and hypepontine (**47**) showed potent in vitro antibacterial activity against Gram-negative and Gram-positive bacteria, with MIC values of 0.036 mg/mL and 0.072 mg/mL, respectively. Furthermore, the mixture of quaternary alkaloids had remarkable antifungal activity (MIC 0.018 mg/mL), higher than the reference antibiotic, and may be a good candidate for future pharmacological tests. It was noticed that the activity of the isolated alkaloids against all tested microorganisms was lower than the activity of the quaternary alkaloid mixture. This effect is probably induced by a synergistic interaction among the quaternary alkaloids. Only alkaloid **47** demonstrated a

good inhibitory effect against Gram-negative bacteria *P. aeruginosa*, with an MIC value of 0.064 mg/mL.

Seven alkaloids isolated from *H. erectum* were evaluated for their antibacterial activity against six microorganisms—*Bacillus cereus*, *B. subtilis* and *S. aureus* (Gram-positive bacteria), and *E. coli*, *P. aeruginosa* and *Erwinia carotovora* (Gram-negative bacteria) [13]. It was established that the alkaloids protopine (**1**), cryptopine (**4**), allocryptopine (**5**), oxohydrastinine (**34**) and hypecorinine (**55**) possessed in vitro antibacterial activity, among which alkaloids **1**, **5** and **55** showed more obvious properties than others against *E. coli* and *P. aeruginosa*, with an MIC value of 125 µg/mL.

6.4. Antiviral Activity

The plant *H. erectum*, along with four other Asian plants (*Terminalia chebula*, *Polygonum bistorta*, *Momordica cochinchinensis* and *Gentiana decumbens*), is included in the herbal formulation Deva-5, used in traditional Mongolian medicine to treat acute infectious diseases [61]. The aqueous extracts of these plants were investigated for inhibitory activity against influenza A virus subtype H3N8 [3]. The in vitro study revealed that *H. erectum* extract had strong antiviral activity at concentrations of 0.5–1%, but further research is needed to identify the biologically active components with direct activity.

6.5. Analgesic Effect

The analgesic effect of three different fractions (methanolic, alkaloidal and non-alkaloidal) and four major isoquinoline alkaloids (protopine (**1**), cryptopine (**4**), allcryptopine (**5**) and oxyhydrastinin (**34**)) from *H. erectum* was evaluated using the acetic acid-induced writhing test [19]. The alkaloidal fraction exhibited significant analgesic activity at a dose of 100 mg/kg. At the same dose, only compounds **1** and **34** significantly decreased the amount of stretching or twisting in the acetic acid-induced writhing animal model. These findings support the traditional application of *H. erectum* for the treatment of inflammatory and pain disorders.

6.6. Anti-Lipase Activity

Bustanji et al. [62] studied 29 medicinal plants, including *H. dimidiatum* Delile, to evaluate their inhibitory potential against hormone sensitive lipase (HSL), which is involved in the regulation of lipid metabolism in the treatment of insulin resistance. In this study, the methanolic extract of *H. dimidiatum* showed weak antilipase activity, with an inhibitory effect of only 25.0%, compared to the plants *Malva nicaeensis* All., *Haplophyllum buxbaumii* (Poir.) G. Donand and *Anchusa italica* Retz., whose inhibitory potential was over 55% [62].

6.7. Antioxidant Activity

The antioxidant activity of *Hypecoum* species is associated with phenolic compounds [63–65]. However, there is one study in which the free radical scavenging ability of the alkaloids—protopine (**1**), cryptopine (**4**) and coptisine (**14**)—and the new nonalkaloid compound—hypecoumic acid, isolated from *H. erectum*—was examined [20]. The antioxidant activity was assessed using the DPPH-scavenging assay and the determination of IC_{50} values related to the amount of sample required to reduce 50% of free radicals. The most effective antioxidant was found to be hypecoumic acid, with an IC_{50} of 86.3 µM, followed by the alkaloids **14**, **1** and **4** with IC_{50} values 252.6, 345.2 and 430.1 µM, respectively.

6.8. Hepatoprotective Effect

The *H. erectum* aqueous extract had a marked hepatoprotective effect characterized by inhibition of the disturbances in the cholate-synthetic functions of the liver, increase of the bile secretion rate and preservation of the cholate concentration in the bile. The significant increase of the total concentration of secreted bile, as well as the amount of the main constituents in the bile—bilirubin, bile acids and cholesterol—indicated that the choleretic properties of the extract are in the dose range of 50–200 mg/kg [66,67]. Also,

the *H. erectum* extract, at an experimental dose of 50 mg/kg, limited liver degeneration in tetracycline-induced hepatitis [68].

6.9. Anti-Hyperglycemic Activity

The dipeptidyl peptidase-4 (DPP 4) is essential in the regulation of diabetes mellitus (DM), and DPP4 inhibitors can be used as potential drugs for this disease. Gong and collaborators implemented a new artificial intelligence protocol to test and validate potential inhibitors from the Traditional Chinese Medicine Database, among which was an acidified form of corydamine (**60**) from *H. leptocarpum* [54]. Combining the constructed models and algorithms, the authors reported that **60** was a potent inhibitor and that *H. leptocarpum* can be used as a potential and effective medicinal herb for the treatment of DM.

6.10. Insecticidal Activity

H. leptocarpum extracts obtained via two extraction methods (constant temperature oscillation method and Soxhlet extraction method) with different polarity solvents (ethanol, methanol, hexane and dichloromethane) were tested for insecticidal activity against *Mythimna seperata*, a pest of a number of agricultural plants [69]. The extracts were found to show a strong growth inhibitory effect on the third instar larvae of *M. seperata*, and, after 24 to 48 h of feeding, the inhibition rate was over 70%, while with the ethanol extract it was the highest—over 90%. All types of extracts had low gastric and contact toxicity. In another study, acetone extract of *H. leptocarpum* also showed clear insecticidal activity against *M. seperata* [70].

7. Conclusions and Future Perspectives

This review is a summary of the traditional Chinese, Tibetan and Mongolian medicines produced by plants of the genus *Hypecoum*. To date, the isoquinoline alkaloids are the most-studied natural compounds isolated from the *Hypecoum* spp., and a total of 86 of them have been identified and classified by structural type. The structural type of isoquinolines are used for chemotaxonomic purposes to determine the relationships between *Hypecoum* species and other genera in the Papaveraceae family. Pharmacological studies of the isolated alkaloids, as well as some *Hypecoum* extracts, show that they have anti-inflammatory, antitumor, antibacterial, antiviral, hepatoprotective and antioxidant properties, among others. The alkaloids protopine (**1**), cryptopine (**4**), allcryptopine (**5**), oxyhydrastinin (**34**) and corydamine (**60**) have shown multiple potent biological activities and could be good candidates for future pharmacological tests.

Although recent years have seen an increase in the interest of researchers in the plants of the genus, they are still relatively poorly studied. Phytochemical research has only focused on ten *Hypecoum* species, and data on the composition and biological activity of the remaining species and subspecies belonging to the genus are still lacking. Future studies on the alkaloid profile of these plants would contribute to enriching the diversity of biologically active natural compounds with the potential to improve human health. Furthermore, studies of the chemical composition should include not only the determination of the structural type of compounds but also the study of biosynthesis and metabolic processes, which are essential for the discovery of new medicinal resources. In addition, pharmacological studies of the genus are insufficient and most of the active studies remain only at the level of in vitro experiments of extracts or individual compounds, which hinders their future applications to some extent. Further assessments and in vitro and in vivo studies should be performed to confirm the bioactive compounds, as well as their toxicity, mechanisms of action and the safety of effective doses in humans. Therefore, in the next stage of research, the alkaloids of the *Hypecoum* species should be subjected to wider phytochemical and pharmacological analyses that will improve the knowledge of the genus.

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