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Digest

Antibacterial constituents of the plant family Amaryllidaceae

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ABSTRACT

There is a pressing need in antibiotic drug discovery for new drugs to counterbalance the effects of multidrug resistance. Plants represent a viable platform for such endeavors owing to their traditional relevance in infectious disease therapies as well as their vast chemical resources. As many as fifty different species of the Amaryllidaceae are discernible with such functions in traditional medicine, thirty-nine of which have been subjected to pharmacological evaluations. Submicromolar antibacterial activities for several of these plants have been the driving force behind studies targeting their active constituents. This review accounts for close to a hundred of such entities, mainly isoquinoline alkaloids, which have been the focus in assays of thirty different bacterial pathogens. Promising activities were detected in several instances, although disappointingly the submicromolar level could not be breached. Also considered are structure–activity relationships which have emerged within the various groups of Amaryllidaceae alkaloids.

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Some of the most devastating diseases in history such as "plague" and "Spanish flu" are a consequence of microbial pathogenesis.[1a–c] Today infectious (or communicable) diseases are amongst the leading causes of morbidity and mortality.[1d] In particular, acute lower respiratory infections such as pneumonia, diarrhoeal diseases including cholera, typhoid and dysentery, and tuberculosis are responsible for the most number of annual deaths worldwide.[1d] This despite the tremendous gains made in antibiotic therapies following the discovery of penicillin, wherein thirty different classes of antibiotics were identified and ushered into clinical trials.[1e–g] However, regulatory challenges, scientific barriers to drug discovery and diminishing returns on investment saw major drug companies drastically shift their research efforts elsewhere by the 1980s.[1e] As a consequence, nearly all antibiotics approved over the past 30 years are variations on existing drugs.[1f] Multidrug resistance and the limited lifespan of drugs have also served to make a bad situation worse.[1d] So serious are concerns in the field that global health bodies such as the World Health Organization (WHO) have raised the alarm about a "post-antibiotic" era in which common infections and minor injuries return to become lethal once again.[1d]

Several suggestions have been made on how to possibly negate such a scenario in future including, advocating alternative treatment strategies to minimize conventional antibiotic usage and broadening the basis for antibiotic discovery via the design of new chemical matter.[2a,2b] To this extent, plants have been identified as an attractive option in ongoing attempts to fulfill the tenets of these criteria.[2c,2d] The vital role plants have played in the history of man's quest for good health and well-being cannot be overstated.[2c,2d] For example, ancient Chinese, Indian and Sumerian traditional systems of medicine which exploited several thousand plant taxa can be traced back over 5000 years.[2d,2e] A significant proportion of such indigenous knowledge from around the world has to our benefit been preserved so that there is today extensive usage of plants in traditional approaches towards infectious diseases.[2f–h] For example, NAPRALERT has on record the published antimicrobial activity data of around 6000 species.[2h] More importantly, over 4000 of these have been verified for their ethnic usage against infectious diseases.[2h] Furthermore, it has been estimated that less than 20% of the global floral biodiversity has been screened for potential therapeutic benefits.[2f] In addition, plants are known for their vast chemical resources and allied structural diversities which afford an inimitable basis for antimicrobial based drug discovery.[2f]

The plant family Amaryllidaceae is renown chemically for its characteristic isoquinoline alkaloid constituents.[3a–c] Of these, galanthamine and pancratistatin have attracted the most attention owing to their interesting biological properties in the motor-neuron disease and cancer arenas, respectively.[3d,3e] Interestingly, the plants from which these molecules were

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originally identified have uses pertaining to such illnesses in traditional medicine (TM).[3d,3e] Other biological effects manifested by alkaloids of the Amaryllidaceae relate to antiviral, antifungal, antiparasitic, antioxidant, anti-inflammatory and insect antifeedant effects, as well as acetylcholinesterase (AChE), ascorbic acid biosynthesis and RNA inhibitory activities.[3a–e]

Surveys have shown that members of the family have a significant presence in ethnic medicine spanning several countries around the world.[3a–i] In particular, they are prominent in the remediation of infectious diseases where as many as fifty species have been identified with such distinct functions in TM.[3a–i] In relation to the pharmacological validation of such uses, extracts of about forty species, the majority of which are traditionally relevant, have been screened against as many as thirty different bacterial pathogens including, *Bacillus subtilis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Micrococcus luteus*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*.[3a–i] In terms of potencies, several extracts were identified having MIC values less than 1 mg/mL against various bacteria, although in most instances these were orders of magnitude less than those observed for reference standards such as ciprofloxacin and neomycin.[3a–i] Given the now established traditional background of the Amaryllidaceae in infectious diseases as well as evidence for the antibacterial activities for its extracts, this survey seeks to collate such activities for its chemical constituents.

Activities of phenanthridone alkaloids

Although several classes of natural products have been identified in the Amaryllidaceae such as; chalcones, flavonoids, lectins, lignans, peptides and terpenoids, it is the isoquinoline alkaloid constituents which are ultimately responsible for its unique chemical fingerprint.[3a–c,4a–c] Not surprisingly, it is these compounds which have formed the basis as targets in antimicrobial screening measures (Tables 1–4). The first documented study of the antimicrobial effects of the Amaryllidaceae was that of Spencer et al. (1947).[5a] However, examination of the antimicrobial properties of Amaryllidaceae constituents had to wait until 1967 when Ceriotti found that the phenanthridone representative narciclasine **1** (Scheme 1) from *Narcissus* bulbs had a bacteriostatic effect on *E. coli* cultures when applied at 8 μg/mL, noticeably with a 50% inhibition of growth observed after 24 h.[5b] Subsequently, several other studies have sought to probe the effects of phenanthridone alkaloids in various bacterial culture systems.[5c–g] Evidente et al. (1985) showed that serial dilutions of narciclasine (0.1–10 mM) were inactive against the plant pathogenic bacterium *Corynebacterium fascians*.[5c] Abou-Donia et al. (1991) isolated narciclasine-4-O-β-D-glucoside **2** from *Pancratium maritimum* L. and examined its effect on the plant pathogen *Agrobacterium tumefaciens* where it exhibited 53% growth inhibition (Table 1).[5d] The aglycone narciclasine **1** obtained from **2** via enzymatic hydrolysis was shown to be more potent, displaying a growth inhibition of 62%.[5d] Narciclasine from *Lycoris radiata* (L'Hér.) Herb. was inactive against *Helicobacter pylori* but exhibited moderate activity against *E. coli* and *S. aureus* cultures where it produced inhibition zone diameters of 13 and 11 mm (at 1 mg/mL), respectively.[5f] In the same occasion, diameters for the penicillin-treated cultures measured 25 and 28 mm, respectively, at equivalent concentrations.[5f] The other phenanthridone lycoricidine **3** also identified in *L. radiata* bulbs exhibited similar activities against *E. coli* and *S. aureus* (12 and 11 mm, respectively), but as in the case of narciclasine **1** remained inactive against *H. pylori*.[5f] Given the close structural resemblance of these two alkaloids, these are interesting observations which indicate that the C-7 phenolic hydroxy group may not be a mitigating factor in their antibacterial properties.

Furthermore, Pagning et al. (2016) recently isolated *trans*-dihydrolycoricidine **4** from the Cameroonian plant *Scadoxus pseudocaulus* (I.Bj¢rnstad & Friis) Friis & Nordal and subsequently demonstrated its activities against *E. coli*, *P. aeruginosa* and *Shigella flexneri* (MICs 4, 16 and 4 μg/mL, respectively).[5g] In view of the activities of both narciclasine **1** and *trans*-dihydrolycoricidine **4**,[5f] these results highlighted that the C-1 to C-10b double bond is also not an essential structural feature in the antibacterial action of phenanthridone alkaloids.[5g] Earlier Pettit et al. (2002) had examined three semi-synthetically derived analogs of narciclasine **5**–**7** (Scheme 1) for antigonococcal activity, showing that the responses to *Neisseria gonorrhoeae* in all cases were significant (MICs 32–64 μg/mL).[5e] Of the three species *P. maritimum*, *L. radiata* and *S. pseudocaulus* containing antibacterial phenanthridone alkaloid constituents, the latter two are vindicated by their traditional usage for infections.[3i,5d,5f,5g]

Activities of lycorane alkaloids

Of the Amaryllidaceae alkaloids evaluated for antibacterial activities, the lycorine group has received the widest coverage with nearly fifty of its members having been exposed to various pathogens (Table 2). Evidente et al. (1985) carried out the first study of any lycorine alkaloid relating to bacterial pathogenesis, showing that the parent alkaloid lycorine **8** was inactive against the Gram positive phytopathogen *Corynebacterium fascians* when tested with a standard 0.01 M solution.[5c] In the same instance, several other anhydro-analogs (**9**–**12**) (Scheme 1) of lycorine were also tested for activities, with compounds **9**, **10** and **11** at equimolar concentrations producing inhibition zone diameters of 25, 25 and

Table 1
Antibacterial activities of phenanthridone alkaloids of the Amaryllidaceae.

Alkaloid (No.)	Antibacterial activity							Reference
	A. tumefaciens	*E. coli*	*H. pylori*	*N. gonorrhoeae*	*P. aeruginosa*	*S. flexneri*	*S. aureus*	
Narciclasine **1**	62%[a]	50%[b], 13[c]	na[c]	–	–	–	11[c]	5b,d,f
Narciclasine glucoside **2**	53%[a]	–	–	–	–	–	–	5d
Lycoricidine **3**	–	12[c]	na[c]	–	–	–	11[c]	5f
trans-Dihydrolycoricidine **4**	–	4[d]	–	–	16[d]	4[d]	–	5g
Narciclasine tetraacetate **5**	–	–	–	32–64[d]	–	–	–	5e
Pancratistatin analog **6**	–	–	–	32–64[d]	–	–	–	5e
Pancratistatin analog **7**	–	–	–	32–64[d]	–	–	–	5e

Abbreviations: a (active); na (not active). Bacteria: *A. tumefaciens* (*Agrobacterium tumefaciens*); *E. coli* (*Escherichia coli*); *H. pylori* (*Helicobacter pylori*); *N. gonorrhoeae* (*Neisseria gonorrhoeae*); *P. aeruginosa* (*Pseudomonas aeruginosa*); *S. flexneri* (*Shigella flexneri*); *S. aureus* (*Staphylococcus aureus*). Activity:
[a] Inhibition percentage (at 1 mg/mL).
[b] Bacteriostatic at 8 μg/mL.
[c] Inhibition zone diameter (mm) at 1 mg/mL.
[d] MIC (μg/mL).

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