Natural Products Containing the Nitrile Functional Group and Their Biological Activities

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Abstract
The importance of nitriles as a key class of chemicals with applications across the sciences is widely appreciated. The natural world is an underappreciated source of chemically diverse nitriles. With this in mind, this review describes novel nitrile-containing molecules isolated from natural sources from 1998 to 2021, as well as a discussion of the biological activity of these compounds. This study gathers 192 molecules from varied origins across the plant, animal, and microbial worlds. Their biological activity is extremely diverse, with many potential medicinal applications.

Keywords
nitriles, natural products, bioactivity, review, origins

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Introduction
Nitriles are common organic compounds, characterized by the presence of one or more nitrile functional groups, comprising a carbon atom linked by a triple bond to a nitrogen atom, which can result in polar compounds with high dielectric constants. Although more frequently found in organic compounds, the functional group is also present in some inorganic compounds, as cyanides. Structurally related functionalities include isonitriles, cyanates, and thiocyanates. Nitriles are versatile compounds with applications across different fields of chemistry. Many nitriles are used in organic chemistry, including as solvents and synths. Acetonitrile, the smallest organic nitrile, is widely used in reverse phase chromatography applications, or as an organic solvent. Polymer chemistry has afforded several important nitrile-containing polymers, including polyacrylonitrile, poly(acrylonitrile-co-butadiene-co-styrene), poly(styrene-co-acrylonitrile), and nitrile rubber. Such polymers can be functionalized to provide new macromolecules with interesting properties. Nitrile rubber, for example, is a widely used replacement for latex in laboratory gloves. The pharmaceutical industry is a major user of nitriles. Many pharmaceuticals, including those in clinical development, contain the nitrile functional group. Seven roles have been identified for the nitrile moiety; namely as (1) a carbonyl bioisostere, (2) a hydroxyl and carboxyl surrogate, (3) an electron-withdrawing group, (4) an azomethine-water isostere (for cyanoquinolines and cyano-pyridines), (5) a carboxyl transition state analogue, (6) a halogen bioisostere, and (7) an improver of ADME-toxicology profiles. Given the diversity of the biological roles of the nitrile moiety in drugs, these compounds are encountered in prescriptions for a large variety of medicinal indications. A recent review discusses more than 30 FDA-approved nitrile-containing pharmaceuticals; citing advantageous properties associated with the functional group, including enhanced binding affinity, improved pharmacokinetic profile, and reduced drug resistance. Examples (Figure 1) include anastrozole, used to treat estrogen-dependent breast cancer, verapamil, an antiarrhythmic agent used against angina, and tofacitinib, a Janus kinase inhibitor used to treat rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis.

As stated, the nitrile group acts as a bioisostere of other functional groups, including carbonyl and halogens. Incorporation of a nitrile functionality into drug molecules can block metabolically labile sites, thus increasing their metabolic stability. The bioactivity and toxicity of nitriles highly depend on the compound considered. Exposure to toxic nitriles

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can lead to neurologic, hepatic, cardiovascular, renal, or gastrointestinal disorders. An important hazard is seen in cyanogenic compounds, capable of releasing hydrogen cyanide (HCN). Many natural nitriles exist as cyanogenic glycosides, having been reported from more than 2500 plant species, including important food sources. Such compounds have the ability to liberate HCN following ingestion and metabolism, and are therefore potentially hazardous.9

Interest in natural nitriles has been growing significantly since the discovery of the first examples, and a number of reviews about such nitriles exist in the literature. Nitrile-bearing molecules are found across Nature, with examples in plants, insects, fungi, bacteria, sponges, and other aquatic organisms. An early review from 1981 discussed compounds bearing the isomeric isonitrile functional group in natural products such as the glucosinolates, which readily convert to other cyanogenic glycosides, having the ability to liberate HCN following ingestion and metabolism, and are therefore potentially hazardous.9

Reviews about such nitriles exist in the literature. This study has the time range covered 1998 to 2021, to ensure the continuation of the scope of previous papers. Articles obtained using these criteria were sorted to retain all those that contained at least one nitrile natural product that was not already recorded in the older papers. Analysis of the listed compounds consisted of gathering their names, chemical structures, biological properties, and the organism from which they originated.

Results and Discussion

Alkyl Nitriles

A group of 19 long-chain aliphatic nitriles, 4 to 22, representing a new class of natural products featuring unbranched or methyl-branched unsaturated nitriles with an ô-7 or C-3 double bond (Figure 2), were identified in the headspace of liquid and agar cultures of Pseudomonas aeruginosa DSMZ 43816.16 Some of these nitriles showed antimicrobial activity; for example, minimum inhibitory concentration (MIC) values of 2 to 8 µg/mL were seen for 20 (3-pentadecenitrile) against various strains of Staphylococcus aureus, including multiresistant strains. Compound 13 ((E)-12-methyltridec-3-enenitrile) was active against the fungus Macrophomina phaseolina. No appreciable cytotoxic effects were seen among these nitriles when tested on human HCT-116 (colon carcinoma) cells.

Two others in the genus Mycale contain various alkyl nitriles (Figure 3). Mycale microsigmatosa (Mycalidae), collected in Venezuela, yielded 5-(19-cyano-9-endo-decen-1-enyl)pyrrole-2-carboxaldehyde 23. When tested for activity against Leishmania mexicana promastigotes, 23 had an LD50 of 12 µg/mL.17 Mycale tenuipinulata Dendy (Mycalidae) (IIC-309), collected in Indian waters, afforded (6′Z)-5′-(23′-cyano-6′-tricosenyl)pyrrole-2-carboxaldehyde 24.18 Three further mycalenitriles were isolated from Mycale acilia collected in the Gulf of California. The compounds were evaluated for their cytotoxicity using a panel of cancer cell lines, with compounds 25 to 27 having GI50 values ranging from 2.4 to 4.8 µg/mL in PANC1 (pancreatic carcinoma), LOVO (colon adenocarcinoma), and HeLa (cervix epithelial adenocarcinoma) cells.19 Bioassay-guided isolation of a lipid extract from a Mycale sp. from Palau afforded various 5-alkylpyrrole-2-carboxaldehyde metabolites, including fourteen mycalenitriles 28 to 41. Compounds were shown to inhibit hypoxia-inducible factor 1 (HIF-1) activation in T47D (breast carcinoma) cells, with the most active compounds 30

Methodology

The databases used for this review were SciFinder, PubMed, and Google Scholar. To obtain relevant references, the keywords “nitrile” and/or “cyanide” and “natural products” were used, combined with criteria regarding language and time range. Two languages were included; English and French,
and 31) having IC$_{50}$ values of 7.8 μM and 8.6 μM, respectively. It was noted that while a highly lipophilic alkyl side chain was essential for the observed HIF-1 inhibitory activity, extremely hydrophobic unsubstituted long-chain analogues were nearly inactive, highlighting the importance of the nitrile functionality in modulating activity. Compounds 30 and 31 were also shown to suppress cell respiration at the mitochondrial electron transport chain (ETC) complex I in a concentration-dependent manner (1-30 μM, with an IC$_{50} < 10$ μM).

Albanitriles A-G, 42 to 48, were isolated from a Mycale sp. SS5 sample, (Mycalidae) WAM Z35806, (Figure 4). Compounds 42 to 48 did not exhibit significant anti-bacterial or anti-fungal properties when tested against Bacillus subtilis, Escherichia coli, or Candida albicans, but did show moderate anti-protozoal activity against Giardia duodenalis, with 42 (octadeca-6,8,10-triynedinitrile) having activity at a minimum concentration of 12 μM, comparable to the positive control metronidazole (2.9 μM). Within the compounds tested, anti-protozoal activity appeared to be dependent on alkyl chain length. No cytotoxicity was noted and the compounds were not considered to be cyanogenic.

A cyanohydrin-containing phosphonate, (cyano(hydroxy)methyl)phosphonic acid, 49 (Figure 5), was isolated from Streptomyces regensis strain WC-3744. The molecule represents the first naturally occurring, cyanohydrin-containing phosphonate to be isolated and characterized. The cyanohydrin of
glyoxylic acid, 50 (Figure 5) was identified as the precursor of hydrocyanic acid in the fungus *Marasmius oradeus* (Bolton) Fr., where it acts as a wound-activated chemical defence.23 (R)-3-Hydroxybutanonitrile 51 (Figure 5), was isolated from the culture of *Aspergillus* sp. KJ-9, a fungal endophyte isolated from the stem bark of *Melia azedarach* L. (Meliaceae).24 When screened against various phytopathogenic fungi (*Gibberella saubinetii*, *Magnaporthe grisea*, *Botrytis cinerea*, *Colletotrichum gloeosporioides*, and *Alternaria solani*), 51 showed MIC ranges of 6.25 to 50 μM, compared to the positive controls carbendazim and hymexazol. When assessed for antibacterial activity against *Bacillus cereus* and *S aureus*, 51 had a MIC value of 50 μM against both organisms, compared with the positive controls streptomycin sulfate (MIC 1.57 and 12.5 μM respectively) and ampicillin (MIC 3.13 and 1.57 μM, respectively), while 51 was inactive against *E coli* and *B subtilis*. Based on comparison of the GC-MS output from a methanolic extract of *Mukia maderaspatana* (L.) M.Roem. (Cucurbitaceae), an Indian traditional medicine collected in the dry deciduous forests of Tamil Nadu, India, with the aid of spectral libraries, compound 52, a cyanoacetamide derivative (Figure 5) was reported.25

**Figure 4.** Albanitriles A-G.

**Figure 5.** Oxygenated alkyl nitriles.

Amino Nitriles

These nitriles are characterized by having an amino functionality in the alpha (or more unusually, beta) position with respect to the nitrile carbon. The phylum Porifera comprises various aquatic sponges. Renieramycins are marine alkaloids belonging to the broader saframycin family, and are classified structurally as 1,2,3,4-tetrahydroisoquinoline-quinone derivatives.26 Of the various renieramycins isolated to date, several examples stabilised with a nitrile functionality (vide infra) have been isolated from sponges in the genera *Xestospongia* and *Cribrorhachina*. Renieramycins 53 to 65 (with lettered designations) bear a nitrile (Figure 6). These compounds have interesting cytotoxic activity and their potential as anticancer drugs was recently reviewed, highlighting that several have IC50s in the nanomolar range. This includes 53 and 56, with IC50 values of 5.6 to 9.6 nM in HCT116 (colorectal carcinoma), NCI-H460 (lung carcinoma), and DLD1 (adenocarcinoma) cells; 54, with IC50 values of 28 and 40 nM in HCT116 and QG56 (lung carcinoma) cells; 57 to 58, with IC50 values of 15 to 71 nM in HCT116 and QG56 cells; 60, with an IC50 value of 4.7 nM in T47D (breast carcinoma) cells, and 53, with IC50 values of 3.1 and 6.0 nM in U373MG (brain carcinoma) and MCF-7 (breast carcinoma) cells.27,28 However, as their separation and extraction from marine organisms is complex, the attention of researchers has lately focused more on their total synthesis from commercially available materials, and on the development of semisynthetic analogues.29

Renieramycin-type alkaloids have also been obtained from the nudibranch, *Jorunna funebris* (Mollusca: Gastropoda: Opisthobranchia: Nudibranchia: Kentrodorididae). It has been suggested the nudibranch sequesters renieramycins ingested within its *Xestospongia* prey sponges.30 In addition to the renieramycin-type alkaloids, related nitriles were isolated from KCN-treated homogenates of Thai *Jorunna funebris*.31 These compounds, jorunnamycins A-C, 66 to 68, are stabilized renieramycin-type bistetrahydroisoquinolines (Figure 7). Jorunnamycins, notably 68, showed cytotoxic activity against a range of cancer cell lines, including colon (HCT116 IC50 1.5 nM), lung (QG56 IC50 2.8 nM), and prostate (DU145 IC50 0.32 nM) compared to those of ecteinascidin 770 (0.40, 1.8 and, 0.66 nM respectively).
Further nitrile-substituted isoquinoline derivatives are ecteinascidins 770 and 786 (69-70), 2 members of an interesting class of compounds derived from sea squirts, which show cytotoxic activity (Figure 7). Both compounds were isolated from KCN-treated homogenates of the Thai tunicate Ecteinascidia thurstoni Herdman 1891. The KCN pre-treatment described in the isolation of these types of compound was developed to protect the labile α-hydroxyamine functionality of the natural products. The importance of the C-21 substituent is reinforced by the suggestion that elimination of the cyano (or hydroxyl) group at this position under physiological conditions results in a reactive iminium species that is responsible for covalent bond formation with the drug target. The related compound, ecteinascidin-743, or trabectedin, which became the

Figure 6. Amino nitriles: renieramycins.
first marine drug to be licensed to treat soft tissue sarcoma, has a C-21 hydroxyl functionality. It was subsequently licensed for relapsed ovarian cancer in combination with doxorubicin. Ecteinascidins work as selective transcription inhibitors, uniquely poisoning transcription-coupled nucleotide excision repair. The structural complexity and rarity of the natural ecteinascidins have led to the development of a semisynthetic process from another nitrile, the readily available cyanosafacin B.26 The simple 1,2,3,4-tetrahydroisoquinoline 71 (Figure 7) was isolated from a low polar fraction of the crude extract of the KCN-pretreated Thai tunicate, *Ecteinascidia thurstoni*.33

Examination of a Chinese strain of *Streptomyces* sp. HS-NF-1006, led to the isolation of the anthracycline analog 72, designated 6''-cyano-6''-deoxy-TAN-1120 (Figure 7).34 Evaluation of the cytotoxicity of 72 was explored using 2 human tumor cell lines, human hepatocellular liver carcinoma (HepG2) cells and human lung tumor cells (A549). Compound 72 had IC_{50} values of 0.06 and 0.04 μM against these strains, respectively, compared to the reference compound doxorubicin, whose corresponding IC_{50} values were 1.49 and 0.40 μM.

Bezerramycin C 73, a phenoxazinone antibiotic with a beta amino (and amido) substitution pattern (Figure 7), was isolated from *Streptomyces grisius* (HKI 0545, DSM 41823) growing on the plaster of an old building in Herne, Germany. The compound showed anti-proliferative activity against human vascular endothelium cells (HUVEC), with a GI_{50} value of 14.5 μM, but was inactive against K-562 (human chronic myeloid cells) and HeLa cells.35

Auranthine 74, a benzodiazepinone with a γ-amido nitrogen (Figure 7), was isolated from the fungal pathogen *Penicillium aurantiogriseum* (CBS 112021). Although originally reported in 1986, its structure was recently refined, revealing the presence of a previously unrecognized nitrile moiety.36 Following this structural refinement, its biological activity was further assessed. Cytotoxicity was evaluated using human liver cancer cells (HepG2) and human kidney epithelial cells (IHKE), using T-2 toxin (10 μM) as positive control. Cytotoxicity was established to be low, with no statistical significance observed compared to the solvent-treated control, except at the highest concentration (100 μM) tested on IHKE cells.
Phenyl nitriles

Organisms in the phylum Arthropoda produce a number of simple nitrile-containing molecules, typically produced by the arthropods as components of viscous proteinaceous defensive secretions. Various millipedes produce HCN, alongside benzoyl nitrile 75, mandelonitrile 76, and mandelonitrile benzoate 77 (Figure 8).37 The centipedes Strigamia balticorpus and Geophilus vitatus also produce 75, with 76 additionally found in the latter species.38 The sternal gland secretions of Himantaria gabrieldi L. (Himantariidae), a geophilomorph centipede, revealed the presence of 75 to 77, and also benzyl nitrile 78. This isolation was the first report on the presence of 77 and 78 in secreted substances from centipedes.38 All 4 compounds are considered to be HCN precursors.

Benzyl nitrile 78 has also been identified as a constituent of the volatile oil of Salvador perisica L. (Salvadoraceae),39 and in the acetone extract of root bark.40 The stem oil was shown to exhibit antibacterial effects (expressed as zones of inhibition) on both sensitive and resistant strains of Pseudomonas aeruginosa (Schroeter and Migula) and S. aureus (Rosenbach). The oil also showed significant inhibition against C. albicans (C. P. Robin) and Trichosporon cutaneum (Beurm, Govegrot, and Vaucher), with comparable results to the reference drugs erythromycin, nystatin, tetracycline, and chloramphenicol.

Highly reactive α-ketonitrile compounds had not been reported in any plant-derived natural product; however, in a study of Arabidopsis thaliana genes upregulated in response to pathogens, the unprecedented cyanogenic metabolite 4-hydroxy-1H-indole-3-carbonyl cyanide (4-OH-ICN; 79) was isolated (Figure 8).41

Cruciferous vegetables, including various Brassica spp., are known for their various benefits and seem active in preventing carcinogenesis. In a review of chemopreventive activities of volatile organic compounds of common vegetables, nitriles 80 (3-phenylpropanenitrile) and 81 (2-(1H-indol-3-yl-acetonitrile) (Figure 8) isolated from broccoli (Brassica oleracea L., Italica group), were highlighted for their cardioprotective and neuroprotective applications.42

The new nitrile glycoside, 4-([6-deoxy-α-L-mannopyranosyl]oxy)-3-hydroxybenzeneacetonitrile, named as niazirinid, 82 (Figure 9), alongside the previously known niazirin, were obtained from the leaves, pods, and bark of Moringa oleifera Lam. (Moringaceae).43 Niaziridin was described as a bioenhancer for drugs and nutrients, having synergistic properties alongside antibiotics and aiding gastrointestinal absorption of drugs and nutrients.

In a study of the activity of niazirin and niaziridin against clinical isolates of multidrug-resistant E. coli, it was observed that the glycosides did not possess antibacterial activity of their own, but when used in combination, they reduced the MIC of tetracycline from 8 to 16-fold.44 Niaziridin (82) inhibited efflux pumps, downregulated expression of the efflux pump genes aerB and yqiL, and over-expressed the porin forming genes ompA and ompX. It also decreased the mutation prevention concentration of tetracycline.44

Investigation of the ethanol extract of the roots of Semiaquilegia adoxoides DC. Makino (Ranunculaceae), a plant of traditional Chinese medicine, led to the isolation of the novel glycoside 2-(β-D-glucopyranosyl)-4-hydroxybenzeneacetonitrile 83 (Figure 9), although its biological activity was not reported.45 In a later study of nitrile and nitro-containing compounds from the roots of S. adoxoides, the researchers isolated various nitriles, including 4-[β-D-apiofuranosyl-(1→6)-O-β-D-glucopyranosyl oxy]phenylacetonitrile (84) (Figure 9).46

In addition to cyanogens (vide infra), the ornamental plant Hydrangea macrophylla (Thunb.) Ser. (Saxifragaceae) yielded four non-cyanogenic cyanoglucosides; 3-(β-D-glucopyranosyl)-4-hydroxybenzeneacetonitrile 85, named hydranitriloside A1; 3-(β-D-glucopyranosyl)-4-methoxybenzeneacetonitrile 86, named hydranitriloside A2; 4-(β-D-glucopyranosyl)-3-methoxybenzeneacetonitrile 87, named hydranitriloside B1; and 4-(β-D-glucopyranosyl)benzeneacetonitrile 88, named hydrantrolsides B2 (Figure 9).47 Biological activities were not reported. Further constituents of H. macrophylla include 5-(β-D-glucopyranosyl)-2-hydroxy-4-methoxybenzeneacetonitrile 89, termed hydracyanoside E (Figure 9).48

Four esters; benzeneacetonitrile, 4-hydroxy-2-[6-O-(3,4,5-trihydroxybenzoyl]-β-D-glucopyranosyl]oxy 90; benzeneacetonitrile, 2-[3,6-bis-O-(3,4,5-trihydroxybenzoyl]-β-D-glucopyranosyl]oxy-4-hydroxy 91; benzeneacetonitrile, 4-hydroxy-2-[6-O-(4-hydroxybenzyl]-β-D-glucopyranosyl]oxy 92, and benzeneacetonitrile, 4-hydroxy-2-[6-O-(2-(4′-OH)-4-hydroxy-1-cyclohexen-1-yl[acetyl]-β-D-glucopyranosyl]oxy 93, of a nitrile-containing phenolic glucoside were isolated from the leaves of Glomis anumatum Müll. Arg. (Euphorbiaceae).49 These degalloylated analogues of 90 had been previously isolated from Ebreia philippinensis A. DC. (Boraginaceae), as ehatroside B.50 Biological data were not reported.

The Actinobacteria is mainly constituted of Gram-positive bacteria. Within this phylum, Salinispora pacifica CNS103, an obligate marine actinomycete bacterial species, produces cyanosporasides A-F (94-99).51,52 These natural products contain a chlorinated cyclopeptide[α-indene core (Figure 10). Bioactivity data were not reported for these isolates.

Figure 8. Simple phenyl nitriles.
Cyanogenic Glycosides

Cyanogenic glycosides represent the most common naturally occurring nitriles. These compounds are defined by the presence of an α-nitrile group adjacent to a glycosidic bond. These compounds are biosynthesized from a small number of amino acids, typically valine, leucine, isoleucine, phenylalanine, and tyrosine, or more rarely, 2-(2'-cyclopentenyl)-glycine or 2-(2'-hydroxy-3'-cyclopentenyl)-glycine. A typical biosynthetic sequence involves hydroxylation at the amino group, followed by elimination of carbon dioxide to afford an aldoxime and ultimately dehydration to yield the nitrile (Scheme 1). Further elaboration such as alpha-hydroxylation and β-glycosylation yields the glycosides. Hydrolysis of these compounds by glycosidases, followed by oxidation of the resultant cyanohydrin, releases the corresponding carbonyl compound (aldehyde/ketone), and hydrocyanic (prussic) acid. Many important food species (e.g., cassava, lima beans, and almonds) contain cyanogens, which can only be consumed following treatment of the source plant material to destroy the cyanide content, typically by heat treatment.

Figure 9. Phenylnitrile glycosides.
Alongside already known constituents, a new cyanogenic glycoside, \(2\beta\)-\(\beta\)-D-d-apio-D-furanosyl-(1\(\rightarrow\)2)-\(\beta\)-D-glucopyranosylmandelonitrile, \(100\), was isolated from the leaves of \textit{Sambucus nigra} L. (Adoxaceae) (Figure 11). Biological data were not reported.

Leaf and stem material of the passion fruit, \textit{Passiflora edulis} Sims (Passifloraceae) were found to contain new cyanogenic glycosides \((2\alpha\beta\)-\(\beta\)-D-allopyranosyloxy-2-phenylacetonitrile \(101\) and \((2\beta\)-\(\beta\)-D-allopyranosyloxy-2-phenylacetonitrile \(102\) (Figure 11), alongside known compounds.\(^{54}\) The galloylated cyanogen \((\alpha\alpha\)-\(\alpha\)-[6-O-(34,5-trihydroxybenzoyl)-\(\beta\)-D-glucopyranosyloxy]benzeneacetonitrile, named \(6\prime\)-O-galloylsambunigrin, \(103\) (Figure 11) was isolated from the foliage of the Australian tropical rainforest tree species \textit{Elaeocarpus sericopetalus} F. Muell. (Elaeocarpaceae). Biological activity was not reported. Exploration of the ethyl acetate fraction of the ethanolic extract of the traditional Chinese medicinal plant \textit{Dracocephalum peregrinum} L. (Lamiaceae) afforded a novel compound, \(104\) (Figure 11), \((2\beta\)-\(\beta\)-D-(6-O-acetyl)-glucosyl-2-phenylacetonitrile, named as peregrinumcin A, a \(6\prime\)-O-acetyl derivative of the known cyanogen 2R-prunasin.\(^{56}\) The compound was tested for its effects on nitric oxide (NO) and nuclear factor (NF)-kB activity on RAW 264.7 and pNF-kB-luc-293 cells, and showed 49% inhibitory activity of NO production induced by LPS at a dose of 100 \(\mu\)g/ml compared to the standard aminoguanidine (75% inhibition at 50 mM), but lacked significant effects on NF-kB activity at the same dose (18% inhibition compared to 75% inhibition by the standard LGT at 10 \(\mu\)g/mL). Reports of toxicity following ingestion of the leaves of the ornamental plant \textit{Hydrangea macrophylla} (Thunb.) Ser. (Saxifragaceae) led to the isolation of three new cyanogenic glycosides: \((\alpha\alpha\)-\(\alpha\)-[6-O-\(\beta\)-D-glucopyranosyl-\(\beta\)-D-glucopyranosyl oxy]-3-hydroxy-4-methoxybenzeneacetonitrile, named hydracyanoside A \(105\); \((\alpha\alpha\)-\(\alpha\)-[(6-O-\(\beta\)-D-glucopyranosyl-\(\beta\)-D-glucopyranosyl oxy]-3-hydroxy-4-methoxybenzeneacetonitrile, named hydracyanoside B \(106\), and \((\alpha\alpha\)-\(\alpha\)-[(3-O-\(\beta\)-D-glucopyranosyl-\(\beta\)-D-glucopyranosyl oxy]-3-hydroxy-4-methoxybenzeneacetonitrile, named hydracyanoside C \(107\) (Figure 11) from the leaves and/or stems, along with the known cyanogen, taxiphyllin.\(^{57}\)

\textit{Hedyotis scandens} Roxb. (Rubiaceae) is used in traditional Chinese medicine for the treatment of respiratory diseases. Compound \(111\), benzeneacetonitrile \(6\prime\)-O-(5-O-p-coumaroyl)-\(\beta\)-D-apiofuranosyl-\(\beta\)-D-glucopyranoside, termed hedyotoside A (Figure 12), was isolated from the ethyl acetate fraction of the ethanol extract of the whole plant.\(^{58}\) Hedyotoside A was subject to evaluation for antiviral properties using the cytopathic effect reduction assay but showed no inhibitory activity.
against RSV at its maximal nontoxic concentration, compared to the control drug ribavirin (IC\textsubscript{50} value of 1.5 μg/mL).

A new cyanogenic glucoside, benzeneacetonitrile, α-[6-O-(2-methyl-1-oxo-2-propen-1-yl)-β-D-glucopyranosyl]oxy-, (αR\textsubscript{2}), named 6'-methacrylate prunasin \textsuperscript{112} (Figure 12), was isolated from aerial parts of Centaurea microcarpa Coss. & Dur. (Asteraceae).\textsuperscript{60}

The cyanogenic glycoside 2-(β-D-glucopyranosyl)oxy)-2-(hydroxymethyl)butanenitrile, named as sachaloside V, \textsuperscript{113} (Figure 12), alongside known cyanogens rhodiocyanoside A, lotaustralin, and heterodendrin, was isolated from the methanolic extract of the roots of Rhodiola sachalensis A. Bor. (Crassulaceae).\textsuperscript{61}

The effects of the extract and its principal constituents were evaluated on D-Galactosamine-induced cytotoxicity in primary cultured mouse hepatocytes, with both the crude extract (98.8% inhibition at 100 μg/mL) and some isolated constituents showing promising activity. However, those constituents (including \textsuperscript{113}) occurring in smaller quantities (such as the 0.0007% reported for \textsuperscript{113}) were not individually assessed.

Linum grandi\textsubscript{florum} Desf. (Linaceae) has been used as a medicinal herb for various ailments, and has shown cytotoxicity against the EL4 cell line. In addition to its previously known

Figure 11. Cyanogenic glycosides.
nitrile content in the form of various cyanogenic glycosides, other research established the presence of 2-[(3'-isopropoxy-O-β-D-glucopyranosyl)oxy]-2-methylbutanenitrile 114 in the leaves of the plant (Figure 12). When evaluated for cytotoxic activity, 114 had an IC₅₀ value of 0.3 μM against the EL₄ cell line, compared to the positive control, the cytotoxin thapsigargin, which had an IC₅₀ value of 1.9 μM.

The first report of a cyanogenic glycoside in mistletoes was that of 2-methylpropionitrile-2-O-(6-O-galloyl)-β-D-pyranoglucoside, named as linamarin gallate 115 (Figure 12), isolated from the leafy twigs of the Nigerian species Loranthus micranthus L. (Loranthaceae), parasitic on Hevea brasiliensis Müll.Arg (Euphorbiaceae). The compound was evaluated for antioxidant activity and had an IC₅₀ value of 39 μM, being more active than the reference compound chlorogenic acid (IC₅₀ value of 67.9 μM) in the DPPH assay.

The aqueous acetone extract of the Chinese medicinal species, Balanophora involucrata Hook. f. & Thomson (Balanophoraceae), a parasitic plant that grows on the roots of leguminous plants, showed radical scavenging activity. Phytochemical profiling revealed a novel cyanogenic glycoside, proacapetalin 6'-O-β-D-glucopyranoside 116 (Figure 12).

Linustatins A ((2-[(O-β-D-glucopyranosyl-(1→4)-O-β-D-glucopyranosyl-(1→6)-β-D-glucopyranosyl]oxy]-2-methyl-(2R)-butanenitrile) 117, B ((2-[(O-β-D-glucopyranosyl-1→6)-O-β-D-glucopyranosyl]oxy]-2-methyl-(2R)-butanenitrile) 118, and C ((2-[(O-β-D-glucopyranosyl-1→6)-O-β-D-glucopyranosyl]oxy]-2-methylpropionitrile) 119, new cyanogenic triglycosides (Figure 12), were isolated from linseed meal (L. usitatissimum L. (Linaceae)). Compounds 117 to 119 had moderate activity.

Figure 12. Cyanogenic glycosides.
against aldose reductase (30.0%, 35.5%, and 30.0% at 1 \times 10^{-5}\text{M}, respectively, compared to 99.4% for the positive control, epalrestat) and weak activities against \(\alpha\)-glucosidase, DPP-IV, and FBPase.

**Nitrilosides**

A smaller group of cyanoglycosides are characterized by the position of the cyano group not next to the glycosidic bond of the molecule, so their hydrolysis does not result in the release of cyanide, thus decreasing their toxicity. One such compound is \((2Z)-8-(\beta-D\text{-glucopyranosyloxy})-6,7\text{-dihydroxycyclohex-4-en-3-ylidene})\text{-ethane-nitrile}\), named as riachin 120 (Figure 13), obtained from the root bark of *Bauhinia pentandra* (Bong.) Vog. Ex Steud (Fabaceae).\(^67\) Riachin was tested for antimicrobial activity against various bacterial strains (*E\ coli* ATCC 25922, *S\ aureus* ATCC 25923, and *P\ aeruginosa* ATCC 25853), using gentamicin, amikacin, and clindamycin as control antibiotics. The MIC in all cases was \(\geq 1024\ \mu\text{g/mL}\), with the exception of the sample against *E\ coli* 25922, which had a MIC value of 128 \(\mu\text{g/mL}\), thus showing the compound had no antimicrobial activity against the tested organisms.\(^68\) However, it did show synergism when combined with amikacin against *P\ aeruginosa* and combined with clindamycin against *S\ aureus*, an effect suggested to be due to altered pharmacokinetics.

\[(2Z)-[\{2\delta,3\delta,4\delta,6\delta\}-(\text{Benzoyloxy})-6-(\beta-D\text{-glucopyranosyloxy})-2,4\text{-dihydroxycyclohexylidene})\text{acetonitrile}\], named as lancelolin C 121 (Figure 13), is another nitrile glucoside, isolated from the stem heartwood of *Lophira alata* Banks ex C.F.Gaertn. (Ochnaceae).\(^69\) It was subsequently isolated from the related *L. lanceolata* Van Tiegh. Ex Keay, and its antitubercular activity were evaluated against *M. tuberculosis* AC45 and AC83 strains; however, the compound was not considered active, with a MIC value of 62.5 \(\mu\text{g/mL}\) against AC45 and a CMI \(>250\ \mu\text{g/mL}\) against strain AC83, compared to the control drug isoniazid (MIC 3.9 \(\mu\text{g/mL}\)).\(^70\) In the aforementioned study of nitrile and nitro-containing compounds from the roots of *Semiaquilegia adoxoides*,\(^46\) another novel nitrile isolated was the cyclohexenylidene derivative 122, \((1E,4\alpha,5\beta,6\alpha)-45,6\text{-trihydroxy-2-cyclohexen-1-ylidene})\text{acetonitrile}\) (Figure 13).

The leaves of *Bauhinia holophylla* (Bong.) Steud. (Fabaceae), a plant used in Brazilian traditional medicine to treat diabetes,\(^71\) afforded the new compound \((-)-(1E,4R,5S,6R)-6-(\beta-D\text{-glucopyranosyloxy})-4,5\text{-dihydroxy-2-cyclohexen-1-ylidene})\text{acetonitrile}\) 123 (Figure 13), a stereoisomer of the known compound \((-)-(1E,4\alpha,5\beta,6\alpha)-45,6\text{-trihydroxy-2-cyclohexen-1-ylidene})\text{acetonitrile}\), itself also isolated, along with its steric isomer aglycone at C-1, \((\pm)-(1E,4R,5S,6S)-45,6\text{-trihydroxy-2-cyclohexen-1-ylidene})\text{acetonitrile}\).

In addition to known nitriles, four new cyclohexenylideneacetonitrile derivatives; acetonitrile, \(2-(4R,6\delta)-6-(\beta-D\text{-glucopyranosyloxy})-\)
The 6-glycoside of the nitrile-containing metabolite (Z)-5α,6β-dihydroxy-4β-methoxy-2-cyclohexene-Δ(1,6)-acetonitrile 134 (Figure 14), was isolated from an ethanol extract of the crushed canes of Bauhinia aurita H.Lév. (Fabaceae). Biological activities were not reported.

Another cyanoside, (Z)-2-cyano-4-(β-D-glucopyranosyl)-2-buten-1-yl 4-hydroxy-3,5-dimethoxybenzoate 135, named as rhoubucycanone A (Figure 14), was first isolated from the ethanol extract of the stems of Rhodolia bupleuroides. The compound was re-isolated later from R. walllicheniana and its antitumor effects evaluated. The related compound rhoubucycanone B, 136 was later isolated from R. bupleuroides and its effects on inhibition of α-glucosidase evaluated. 136 had an IC₅₀ value of 278.28 ± 0.55 µM while the IC₅₀ for the positive control, acarbose was 210.40 ± 0.32 µM.

(3α,4a,5R,6α)-5-Ethenyl-6-(β-D-glucofuranosyl)-4,4,5,6-tetrahydro-1-oxo-1H,3H-pyra[3,4]-pyran-3-carbonitrile 137, named as hydracyanone F (Figure 14), was isolated among the constituents of H. macrophylla. Allarinones, or (Z)-4-(β-D-glucopyranosyl)but-2-enenitrile 138 (Figure 14), is a cyanoallyl glycoside isolated from Allaria petiolata (M.Bieb.) Cavara & Grande (Brassicaceae), or garlic mustard, an invasive plant of North America. The compound is known as an allelochemical, acting as a feeding inhibitor against carabid larvae of Pieris napi okanea.

**Methylbutenonitriles**

Five new γ-hydroxynitrile glucosides, [(6-acetate)-β-D-glucopyranosyl]-3-methyl-2Z-butenenitrile 139, 4-[4-(2E)-2-butenoate]-β-D-glucopyranosylxylo-3-methyl-2Z-butenenitrile 140, 4-[6-(2E)-2-butenoate]-β-D-glucopyranosylxylo-3-methyl-2Z-butenenitrile 141, 4-[6-(2E)-2-butenoate]-β-D-glucopyranosylxylo-3-hydroxymethyl-2Z-butenenitrile 142, and 4-[6-(3-ethoxyl)-butyrate]-β-D-glucopyranosylxylo-3-methyl-2Z-butenenitrile 143, named prinspicyanones A–E, (Figure 15) were isolated from the seeds of the Chinese medicinal plant Prinsepia utilis Royle (Rosaceae). Among these, prinspicyanone B 140 was the first reported γ-hydroxynitrile glucoside in which the hydroxyl group on C-4 of glucose was derivatized. When screened for antimicrobial activity, 139 inhibited Salmonella galinarum with a MIC value of 30.1 µg/mL, compared to the standard drug ciprofloxacin with a MIC value of 0.41 µg/mL.

Subsequently, 4 additional glucosides, prinspicyanosides F-I, 144 to 147 (Figure 15) were obtained from the seed oil residue, with 146 exhibiting weak α-glucosidase inhibitory activity (15% inhibition at 50 µM) compared to 61.2% and 63.2% inhibition using the standard drugs quercetin (at 10 µM) and acarbose (at 500 µM), respectively.

Riber species (Grossulariaceae), such as R. rubrum and R. nigrum, are usually cultivated for their edible berries, but their seeds contain interesting metabolites. 2-(4-hydroxybenzoxoyloxy)methyl]-4-β-D-glucopyranosylxylo-2(E)-butenenitrile 148 and 2-(4-hydroxy-3-methoxybenzoyloxy)methyl]-4-β-D-glucopyranosylxylo-2(E)-butenenitrile 149 were isolated from R. rubrum.
Figure 14. Nitrilosides.

Figure 15. Methylbutenenitriles.
seeds, while 2-trans-p-coumaroyloxymethyl-4-β-D-glucopyranosyloxy-2(E)-butenenitrile 150, known as nigrumin-5-p-coumarate and 2-trans-feruloyloxymethyl-4-β-D-glucopyranosyloxy-2(2E)-butenenitrile 151, known as nigrumin-5-ferulate were obtained from R. nigrum seeds (Figure 16). These structures are related to the previously isolated sutherlandin-5-trans-p-coumarate 152 found in Sorbaria sorbifolia (L.) A. Br. var. stellipila MAX. (Rosaceae). Astringency of nitriles 148 and 149 was evaluated, and showed that these compounds were not primarily responsible for the astringency of the plant, having threshold concentrations similar to those of most of the naturally occurring flavon-3-ol glycosides. 

The γ-hydroxynitrile glycoside (E)-2-(hydroxymethyl)-4-[(2R,3R,4S,5S,6R)-34,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxybut-2-enenitrile 153, known as sarmentosin (Figure 16), previously known from Sedum sarmentosum Bunge (Crassulaceae), and also known to be sequestered by lepidopteran species in the genus Parnassius (Papilionidae), was detected for the first time from the genus Bryophyllum/Kalanchoe, being isolated from both B. pinnatum L. Pers. (Crassulaceae) and Kalanchoe laciniata.89

In a study of the chemical constituents of a traditional Tibetan medicine, Rhodiola kirilowii (Regel) Maxim, used as an adaptogen in China, an ethanol extract of the roots was evaluated. In addition to known compounds, a new nitrile, 4-(β-D-glucopyranosyloxy)-3-hydroxy-2-(hydroxymethyl)-butanenitrile 154 (Figure 16), was isolated.

Glucosides with an unusual (2S,3R)-2-ethyl-2,3-dihydroxybutyric acid as the acyl moiety at the 6-position of glucose were extracted from the branches of Microtropis japonica Hallier
(Celastraceae), a tree present in Kanto and Kyushu, Japan, the Okinawa Islands, and Taiwan. These were (2R,3S)-3-hydroxy-2-methylbutanenitrile-β-D-glucopyranoside 6-O-(2"′,3"′,R)-2"′-ethyl-2\',3\'-dihydroxybutyrate, named as microtropin A, (2R,3R)-3-hydroxy-2-methylbutanenitrile-β-D-glucopyranoside 6-O-(2"′,3"′,R)-2"′-ethyl-2\',3\'-dihydroxybutyrate, named as microtropin B, (2S,3S)-3-hydroxy-2-methylbutanenitrile-β-D-glucopyranoside 6-O-(2"′,3"′,R)-2"′-ethyl-2\',3\'-dihydroxybutyrate, named as microtropin C, and (E)-4-hydroxy-2-(hydroxymethyl)but-2-enenitrile-β-D-glucopyranoside 6-O-(2"′,3"′,R)-2"′-ethyl-2\',3\'-dihydroxybutyrate, named as microtropin D (Figure 16). The nitrile component was either alkane or α,β-unsaturated (158) in nature. The biological activity of these compounds was not studied. Further work on the plant led to the isolation of the Z-isomer of 158, named microtropin Q (159).

### Cyanolipids

The cyanolipids (CLs) represent a further category of natural nitriles, and are derived through amino acid (leucine) metabolism. They occur alongside acylglycerols and triacylglycerides in seed oils of members of the Boraginaceae, the Hippocastanaceae, and the Sapindaceae. Four types of CL structures (160-163) may be defined (Figure 17) with fatty acids esterified to a mono or a dihydroxynitrile moiety. CLs of types I and IV are cyanogenic, releasing cyanoethyls which spontaneously decompose forming HCN, while CLs of types II and III are not cyanogenic.

Within the 4 CL classes, the primary variation lies in the fatty acid chains. An overview of CL-containing plants in the Sapindaceae profiled from 1998 to 2021 is shown in Table 1.

Among the metabolites of Axingssia isabela (Halichondriidae), a marine sponge, was isolated the nitrile axinynitrile-A, 164. The presence of a nitrile in this compound represents a departure from the nitrogen-containing terpenoids so far described from sponges of the order Halichondriida, which usually contain isocyanato, isothiocyanate, or formamide groups, and less frequently thiocyanate or isocyanate functionalities. When tested in cytotoxicity assays against the human cancer cell lines MDA-MB-231 (breast adenocarcinoma), A-549 (lung adenocarcinoma), and HT-29 (colon adenocarcinoma), 164 (Figure 18) was inactive at the highest concentration tested (10 μg/mL), compared to the positive control doxorubicin (GI50 = 0.1, 0.1, and 0.1 μM against MDA-MB-231, A-549, and HT-29, respectively.

Hemi-phorboxazole A, 165 (Figure 18), an oxazole-containing macrolide with a terminal nitrile, was isolated from Phorbas sp. 165 Although 165 displayed no activity when tested against C. albicans and two human cancer cell lines, a semisynthetic analogue featuring B and C-ring modifications exhibited significant tumor cell growth inhibitory activity in the nanomolar range against HCT-116 (colon) and SK-BR-3 (breast) cells, while another derivative featuring solely C-ring modification displayed promising antifungal activity against C. albicans.

The phylum Cyanobacteria is composed of Gram-negative metabolites. Among these can be found ambiguines, hapalin-doles, fischambiguines and 12-epi-hapalin-doles. 166 Although more typically characterized by an isonitrile or isothiocyanate functionality, some nitrile-containing metabolites are known to occur in this species, such as ambiguine G nitrile 166, first isolated from the blue-green alga Hapalosiphon delicatissimus (UH isolate IC-13-1) (Stigonemataceae), and the novel deschloro analogue, ambiguine Q nitrile, 167 (Figure 18). Ambiguine G nitrile inhibited the growth of S. aureus and M. tuberculosis, with MIC values of 6.6 and 53.7 μM, respectively, compared to the appropriate controls gentamicin (0.65 μM) and rifampin (0.10 μM), but had no effect on the growth of E. coli.

Four nitrile-containing fischerdin-dole derivatives, namely 12-epi-fischerdin-dole I nitrile 168, deschloro 12-epi-fischerdin-dole I nitrile 169, 12-epi-fischerdin-dole W nitrile 170, and deschloro-12-epi-fischerdin-dole W nitrile 171 were separately isolated from Fischerella sp. (SAG strain number 46.79) (Figure 18), and evaluated for antitumor properties against HT-29 (colon), NCI-H460 (large lung), MCF-7 (breast), and SF268 (glioblastoma) lines, although the structure originally attributed to 171 was later revised. Compound 169 had an IC50 value of 23 μM against HT-29 cells, and was completely inactive against the other cell lines tested, while 170 and 171 were unstable under assay conditions. None of the compounds showed inhibition of 208 proteasome activity.

The borrelidins are a group of 18-membered polyketide macrolides produced by several species of Streptomyces, with the parent compound, borrelidin, known since 1949. Recent work on a saltern-derived halophilic Nocardiopsis species (strain HYJ128) from Korea led to the isolation of three new borrelidins, C-E,

![Figure 17. Cyanolipid classes.](image-url)
Acids with a nitrile group, borrelidins J and K, derived fungus *Sapindus obovatus* from 1986 to 2021. and cytotoxic activities, 8.2 nM and 1 nM. In a comparison of enzyme inhibitory and cytotoxic activities, 8.7 (Figure 18). The compounds exhibited interesting antibacterial activity, particularly with eleven of these bearing a nitrile functional group. From other sponges, now 18 such structures are known, in 1986, with related structures subsequently isolated. First isolated from the marine sponge *D. calyx*. More recently, a truncated form of calyculin A, named hemi-calyculin A 177 was isolated from *D. calyx*. When evaluated for its ability to inhibit protein phosphatase, a known target of the calyculins, the IC50 values of 16 nM and 11 to 18:1 (30%), 11 to 20:1 (39%) against PP1 and PP2A, respectively, compared to the standard drug etoposide (IC50 values of 0.31 μM, respectively), compared to the standard oxacin (0.31 μM). Moderate cytotoxicity was demonstrated at concentrations (0.06-0.60 mM), but did not induce the germination of seeds of *Orobanche cumana* seed germination at 0.170 ng/mL). The absence of key basic functional groups on 177 was proposed to account for its reduced membrane permeability.

*Heracleum* is an umbelliferous plant genus widely distributed in Asia. Of the 10 species known in Iran, some are used for food and medicinal purposes. In a study of 2 *Heracleum* species, the essential oils obtained from the aerial parts of the plants were evaluated for antimicrobial activity. Geranyl nitrile 178 comprised 3.89% of *H. transcaucasium* essential oil, while the oil of the related species *H. anissiatis* indicated the presence of 5-cyano-22,3-trimethyl-2H-pyrrole 1-oxide 179 (4.83%) (Figure 18). The oils were screened against a panel of microorganisms (E. coli ATCC (8739), P. aeruginosa ATCC (9027), *Staphylococcus epidermidis* ATCC (12228), and *S. aureus* ATCC (6538)); however, the essential oils of both species were inactive against the tested microbial strains when compared with the standard, amikacin.

### Aromatic Nitriles

The unusual natural product, pyridine-3-carbonitrile 180 (Figure 19) was identified as a chemotaxonomic marker in *Murraya annua* L. (Euphorbiaceae), allowing differentiation from the closely related *M. perennis.*

Ryecarbonitrile A and B (181-182) (Figure 19) were isolated from rye (*Secale cereale* L. (Poaceae)) root exudate. The compounds were assayed for their potential allelopathic effect on seed germination and radicle growth. Ryecarbonitrile A, 181 significantly induced *Orobanche cumana* seed germination at the concentration range tested (0.06-0.60 mM), but did not induce the germination of seeds of *O. crenata* or *O. minor*.

Two new benzonitrile glucosides, 4-hydroxymethylphenyl 6-(4-cyanophenyl)-β-D-gluco-pyranoside 183, termed brugmansioside A and 4-(hydroxyprop-2-en-3-yl)-phenyl 6-(4-cyanophenyl)-β-D-gluco-pyranoside 184, named brugmansioside B, were isolated from the flowers of *Brugmansia arborea* L. (Solanaceae), collected in Korea (Figure 19). When tested for cytotoxicity using human gastric adenocarcinoma cells (AGS) and human hepatocyte carcinoma cells (HepG2), the compounds exhibited moderate activity; at concentrations higher than 25 μg/mL (183) and 100 μg/mL (184) against AGS, and higher than 12.5 μg/mL (183) and 25 μg/mL (184) against HepG2.

Co-culture of *Streptomyces rochei* MB037 with the gorgonian-derived fungus *Rhinolophidae similis* 35 afforded two new fatty acids with a nitrile group, borrelidins J and K, 175 to 176 (Figure 18). The compounds exhibited interesting antibacterial activity against methicillin-resistant *S. aureus*, with MIC values of 0.20 and 1.56 μg/mL, respectively, compared to the reference drug ciprofloxacin (0.31 μg/mL).

The calycins are a diverse group of cytotoxic polyketides. First isolated from the marine sponge *Discodorina calyx* in 1986, with related structures subsequently isolated from other sponges, now 18 such structures are known, with eleven of these bearing a nitrile functional group. More recently, a truncated form of calyculin A, named hemicalyculin A 177 (Figure 18), was isolated from *D. calyx*. When evaluated for its ability to inhibit protein phosphatase, a known target of the calycins, the IC50 values of 177 were 14 nM and 1 nM against PP1γ and PP2A, respectively, compared with the parent structure calyculin A (IC50 values of 8.2 nM and 1 nM). In a comparison of enzyme inhibitory and cytotoxic activities, 177 proved much less active than calyculin A against P388 cells (IC50 values of 450 ng/mL vs 0.170 ng/mL). The absence of key basic functional groups on 177 was proposed to account for its reduced membrane permeability.

### Table 1. Cyanolipids (CL) Isolated From Plant Seed Oils Profiled from 1998 to 2021.

| Source          | CL class | Dominant fatty acids                        | Reference |
|-----------------|----------|---------------------------------------------|-----------|
| *Allophylus*    | Type I, III | cis-13-eicosenoic (paullinic) acid          | 98        |
| *Allophylus*    | Type I, III | cis-11-eicosenoic acid                      | 94        |
| *Koelneriteria* | Type III  | Eicosanoic acid                             | 95        |
| *Lepisanthes*   | Type I    | Oleic acid                                  | 97        |
| *Neobresia*     | Type III  | Arachidic acid, cis-11-eicosenoic (paullinic) acid | 97        |
| *Paulinia*      | Type I    | 11 to 18:1 (30%), 11 to 20:1 (39%)          | 98        |
| *Paulinia*      | Type I    |                                             | 98        |
| *Sapindus*      | Type III  | cis-11-eicosenoic acid                      | 99        |
| *Sapindus*      |           | cis-11-octadeenoic acid                     | 100       |
| *Sapindus*      |           | Eicosanoic acid                             | 100       |

**α,β-unsaturated nitriles.**
When tested for cytotoxicity using the human promyelocytic leukemic (HL-60) cell line, the mean IC$_{50}$ value for 186 was over 100 μM.

3-Indolecarbonitrile (187) was isolated from *Salvadora persica* L. (Salvadoraceae) (Figure 19), which is widely used for oral hygiene.\textsuperscript{119}

*Euphorbia dracunculoides* Lam. (Euphorbiaceae), an annual herb of southwest Asia, North Africa, and South Europe was collected in Pakistan and various extracts were evaluated for antioxidant and anti-inflammatory activity. Due to the potent effects of the n-hexane extract on the aerial parts of the plant and the ability to reduce carrageenan-induced paw edema, the n-hexane extract was subject to GC-MS analysis. Among 30 constituents identified by comparison with mass spectral libraries, 0.4% of the nitrile dicyanoazulene 188 (Figure 19) was reported.\textsuperscript{120}

**Miscellaneous Nitriles**

Another member of the tetracyclic ambiguine subclass of alkaloids, named 12-epi-ambiguine B nitrile, 189 (Figure 20), was isolated from *Fischerella 52-1* from Lake Tennessee, USA, with the species determined as either *F. ambigua* or *F. muscicola*.\textsuperscript{121}

Researchers were interested in whether the toxicity of cyanobacteria, particularly in relation to freshwater harmful algal blooms and eutrophication, could in part be related to teratogenic effects. Using the zebrafish embryo model to probe the potential teratogenicity of 189, it was observed that the compound had relatively limited effects on development, only at the highest concentrations tested (≥10 μg/mL), with a slight curvature of the body axis noted in 3 days postfertilization. Although there appeared to be an ability to recover from the teratogenic effects, the teratogenic effects of such compounds clearly limit...
their development as potential lead compounds. Notably, teratogenicity was observed at concentrations previously demonstrated to be required for antimicrobial activity within this class of compounds.

The new nitrile derivative, 3α,4β-dihydroxy-6-oxo-1-cyclohexene-1-acetonitrile 190 (Figure 20), was isolated from the whole plant of Aquilegia ecalcarata Maxim (Ranunculaceae).122 The compound did not show any cytotoxic activity when tested against different classes of cancer cell lines, including GLC-82 (human pulmonary adenoma) and HCT (human large intestine carcinoma).

Extraction of the methanol extract of the white flowers of Impatiens balsamina L. (Balsaminaceae) yielded two new phenolic compounds 3-benzofuranacetonitrile, 2,3-dihydro-3-hydroxy-2-oxo-, (3S) 191 and 3-benzofuranacetonitrile, 3-(β-D-glucopyranosyloxy)-2,3-dihydro-2-oxo-, (3S) 192 (Figure 20), both containing a nitrile group.123 Compounds 191 and 192 did not show appreciable cytotoxicity using various human cancer cell lines (A549, SK-OV-3, SK-MEL-2, and HCT15), as evaluated using the sulforhodamine B assay, compared to the control drug, etoposide (IC50 values of 1.74, 1.96, 1.33, and 2.95 μM, respectively). The neuroprotective activity of the compounds was assessed by determining their effects on nerve growth factor (NGF) secretion in C6 cells, with 191 and 192 inducing NGF secretion by 155.6 and 136.7% respectively. Anti-neuroinflammatory activity by measuring NO production in lipopolysaccharide (LPS)-stimulated BV-2 cells, with compounds 191 and 192 showing IC50 values of 64.08 to 93.36 μM, with little effect on cell viability. In this regard, the compounds were 3- to 4-fold less potent than the control, L-N^G-monomethyl-l-arginine (NMMA), with an IC50 value of 20.53 μM.

**Conclusions**

In summary, this review aims to review gathered information about recently discovered natural nitrile-containing metabolites, and to classify them based on structural characteristics. Indeed, 192 molecules were identified, and are shown alongside their biological activities. It is evident that nitriles occur in diverse
organisms and are elaborated within varied molecular architectures. The many interesting biological activities recorded for these compounds indicate their potential as “hit” compounds for medicinal applications, once toxicological, metabolic, and chemical properties are more clearly understood and optimized, and issues concerning sustainable sourcing and the development of scalable, efficient synthetic methods are addressed. This is of particular relevance to many of the marine nitriles discussed, which are retrievable in vanishingly small amounts—the spectroscopic characterization of 165 was initially performed on just 16.5 μg. However, the rewards justify the effort to characterize and study these metabolites, as seen with the clinical success of the ecteinascidins. The development of tailored extraction techniques and formation of stabilized derivatives expands the potential of these compounds as drug-like entities. In addition, the commercialization of the ecteinascidins highlights the impact of the development of sustainable methodologies such as the use of more readily available precursors, an analogous strategy to that seen with other valuable natural products such as the taxanes.

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JB was responsible for conceptualization of the review. CS and JB both contributed to literature searches and to authorship of the paper. JB was responsible for editing the text.

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