Review

Antibacterial and Antifungal Alkaloids from Asian Angiosperms: Distribution, Mechanisms of Action, Structure-Activity, and Clinical Potentials

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Abstract: The emergence of multidrug-resistant bacteria and fungi requires the development of antibiotics and antifungal agents. This review identified natural products isolated from Asian angiosperms with antibacterial and/or antifungal activities and analyzed their distribution, molecular weights, solubility, and modes of action. All data in this review were compiled from Google Scholar, PubMed, Science Direct, Web of Science, ChemSpider, PubChem, and a library search from 1979 to 2022. One hundred and forty-one antibacterial and/or antifungal alkaloids were identified during this period, mainly from basal angiosperms. The most active alkaloids are mainly planar, amphiphilic, with a molecular mass between 200 and 400 g/mol, and a polar surface area of about 50 Å², and target DNA and/or topoisomerase as well as the cytoplasmic membrane. 8-Acetylnorchelerythrine, cryptolepine, 8-hydroxydihydrochelerythrine, 6-methoxydihydrosanguinarine, 2′-nortiliacorinine, pendulamine A and B, rhetsisine, sampangine, tiliacorine, tryptanthrin, tylophorinine, vallesamine, and viroallose-curinine yielded MIC ≤ 1 µg/mL and are candidates for the development of lead molecules.

Keywords: medicinal plants; antibacterial; antifungal; alkaloids; Asia

1. Introduction

The resistance of bacteria and fungi to antimicrobial agents necessitates the continuous development of antibiotics and antifungal agents with original chemical frameworks that may come from flowering plants. The flowering plants also termed angiosperms comprise 11 major taxa or clades grouped into three groups: (i) basal angiosperms including Protomagnoliids, Magnoliids, Monocots, Eudicots; (ii) core angiosperms including Core Eudicots, Rosids, Fabids, Malvids; and (iii) upper angiosperms including Asterids, Lamiids, and Campanulids [1]. Within each clade, plants yield both non-specific and specific secondary metabolites such as alkaloids to control the growth of phytopathogenic...
bacteria and fungi. These antimicrobial principles fall into two main groups: phytoanticipins and phytoalexins. Phytoanticipins are antimicrobial compounds in plants that are present before phytopathogenic microorganism challenge or inactive immediate precursors stored in healthy tissues that are converted into antimicrobial metabolites known as phytoalexins [2]. Phytoanticipins and phytoalexins containing primary, secondary, tertiary, or quaternary amines are called alkaloids, which belong to various chemical classes, principally amides, indoles, piperidines, quinolines, isoquinolines, pyrrolidines, imidazoles, diterpenes, sesquiterpenes, and steroidal alkaloids [3].

Phytopathogenic Gram-negative bacteria are more resistant to alkaloids than Gram-positive bacteria due, at least in part, to an outer hydrophilic and negatively charged layer of lipopolysaccharides [4]. In Gram-negative bacteria, porins allow for the entry of water and nutrients through the outer layer and hydrophilic and amphiphilic xenobiotics with a molecular mass below 600 g/mol xenobiotics without nutritional or physiological benefit or toxins are actively cleared from the cytoplasm by efflux pumps [5]. The assessment of the antibacterial and antifungal strength of isolated secondary metabolites in vitro is qualitatively appreciated by the measurement of the diameter of an inhibition zone and quantitively based on the minimum inhibiting concentration (MIC), and several thresholds of activity have been proposed [6–9]. Angiosperms produce alkaloids that inhibit the growth of both Gram-positive, Gram-negative bacteria, yeasts, and filamentous fungi and these principles are of potential therapeutic value. Among the factors that influence the antibacterial or antibacterial strength, and the targets of alkaloids are the molecular mass and water solubility [10].

Over the last 80 years, enormous research efforts have been devoted to the aim of identifying antibiotic or antifungal lead molecules in flowering plants globally, but to date, none of these have been developed as drugs. The present work attempts to provide a comprehensive review of the main findings regarding the antibacterial and antifungal alkaloids from Asian angiosperms. All data in this review were compiled from Google Scholar, PubMed, Science Direct, Web of Science, ChemSpider, PubChem, and a library search from 1979 to 2022 and were analyzed to address the following points: (i) distribution; (ii) strongest principles identified; (iii) spectrum of activity; (iv) influence of molecular mass, water solubility, and polar surface; (v) the mode of action; (vi) structure–activity; and (vii) efflux pump inhibition.

2. Distribution

Regarding the distribution of antibacterial and antifungal alkaloids from Asian angiosperms (Figure 1), the following could be observed:

- All clades yielded antibacterial and/or antifungal alkaloids, except for the Rosids.
- Most antibacterial and/or antifungal alkaloids can be found in basal angiosperms, which are isoquinolines.
- Some clades yielded a specific class of antibacterial and/or antifungal alkaloids such as the Amaryllidaceae alkaloids in the Monocots, phenanthrene alkaloid in the Magnoliids, Securinega alkaloids in Fabids, carbazole in the Malvids, and monoterpene indole alkaloids in the Lamids.
- Core angiosperms and upper angiosperms use various classes of alkaloids and phytoalexins.
- Most antibacterial and/or antifungal alkaloids have been isolated from medicinal plants (Table 1, Table S1).
- Tripathi et al. (1994) observed changes in the antibacterial alkaloid concentrations in plants over time [11].
- Core angiosperms and upper angiosperms use various classes of alkaloids and phytoalexins.
- Most antibacterial and/or antifungal alkaloids have been isolated from medicinal plants (Table 1, Table S1).
- Tripathi et al. (1994) observed changes in the antibacterial alkaloid concentrations in plants over time [11].

**Figure 1.** The phylogenetic distribution of antibacterial and/or antifungal alkaloids in angiosperms.

**Table 1.** The chemical structures of antibacterial and/or antifungal alkaloids and their botanical origin.

| CLASS             | Compound            | Chemical Structure | Genus, Species          | Family          |
|-------------------|---------------------|--------------------|-------------------------|-----------------|
| **ACRIDANONES**   |                     |                    |                         |                 |
|                   | 1-Hydroxy-3,4-dimethoxy-10-methylacridan-9-one | ![Chemical Structure](image1) | Limonia acidissima L. | Rutaceae        |
|                   | 1-Hydroxy-3-methoxy-10-methylacridan-9-one     | ![Chemical Structure](image2) | Limonia acidissima L. | Rutaceae        |
| **AMARYLLIDACEAE ALKALOIDS** |                     |                    |                         |                 |
|                   | Crinamine           | ![Chemical Structure](image3) | Crinum asiaticum L.    | Amaryllidaceae  |
|                   | Lycorididine        | ![Chemical Structure](image4) | Lycoris radiata (L'Hèr.) Herb. | Amaryllidaceae |
|                   | Lycorine            | ![Chemical Structure](image5) | Lycoris radiata (L'Hèr.) Herb. | Amaryllidaceae |
Table 1. Cont.

| CLASS        | Compound          | Chemical Structure | Genus, Species               | Family           |
|--------------|-------------------|--------------------|------------------------------|------------------|
|              | Narciclasine      | ![Narciclasine](image1) | Lycoris radiata (L’Her.) Herb. | Amaryllidaceae   |
|              | Tazettine         | ![Tazettine](image2) | Narcissus tazetta L.         | Amaryllidaceae   |
|              | **APORPHINES**    |                    |                              |                  |
|              | Anonaine          | ![Anonaine](image3) | Michelia alba DC.            | Magnoliaceae     |
|              | Artabotrine       | ![Artabotrine](image4) | Artabotrys suaveolens (Bl.) BL. | Annonaceae       |
|              | Bulbocapnine      | ![Bulbocapnine](image5) | Corydalis bulbosa DC.        | Fumariaceae      |
|              | Dicentrinone      | ![Dicentrinone](image6) | Phoebe lanceolata (Nees) Nees | Lauraceae        |
|              | Isoboldine        | ![Isoboldine](image7) | Corydalis bulbosa DC.        | Fumariaceae      |
| CLASS Compound                  | Chemical Structure | Genus, Species                     | Family          |
|--------------------------------|--------------------|-----------------------------------|-----------------|
| Lanuginosine                   | ![Lanuginosine](image) | *Eupomatia laurina* R. Br.         | Eupomatiaceae   |
| Liriodenine                    | ![Liriodenine](image) | *Cananga odorata* Hook. F. & Thomson | Annonaceae      |
| Lysicamine                     | ![Lysicamine](image) | *Phoebe grandis* (Nees) Merr.     | Lauraceae       |
| Magnoflorine                   | ![Magnoflorine](image) | *Mahonia bealei* (Fortune) Carrière | Papaveraceae    |
| Nordicentrine                  | ![Nordicentrine](image) | *Phoebe lanceolata* (Nees) Nees   | Lauraceae       |
| O-Methylmoschatoline           | ![O-Methylmoschatoline](image) | *Cananga odorata* (Lam.) Hook. F. & Thomson | Annonaceae      |
| Roemerine                      | ![Roemerine](image) | *Papaver rhoas* L.                | Papaveraceae    |
| CLASS | Compound | Chemical Structure | Genus, Species | Family   |
|-------|----------|--------------------|----------------|---------|
|       | Sampangine | ![Sampangine](image) | *Eupomatia laurina* R. Br. | Eupomatiaceae |
|       | Thailandine | ![Thailandine](image) | *Stephania venosa* (Bl.) Spreng | Menispermaceae |
|       | Xylopine | ![Xylopine](image) | *Artabotrys suaveolens* (Bl.) Bl. | Annonaceae |
|       | **BENZOPHENANTRIDINES** | | | |
|       | 8-Acetylnorchelerythrine | ![8-Acetylnorchelerythrine](image) | *Toddalia asiatica* (L.) Lam. | Rutaceae |
|       | Avicine | ![Avicine](image) | *Toddalia asiatica* (L.) Lam. | Rutaceae |
|       | Chelerythrine | ![Chelerythrine](image) | *Macleaya cordata* (Willd.) R. Br. | Papaveraceae |
|       | Corynoline | ![Corynoline](image) | *Corydalis incisa* (Thunb.) Pers. | Fumariaceae |
### Table 1. Cont.

| CLASS Compound                  | Chemical Structure | Genus, Species                  | Family       |
|---------------------------------|--------------------|---------------------------------|--------------|
| Dihydrochelerythrine            | ![Structure](image1) | *Macleaya cordata* (Willd.) R. Br. | Papaveraceae |
| Dihydrosanguinarine             | ![Structure](image2) | *Macleaya cordata* (Willd.) R. Br | Papaveraceae |
| 8-Hydroxydihydrochelerythrine   | ![Structure](image3) | *Chelidonium majus* L.          | Fumariaceae  |
| 8-Hydroxydihydrosanguinarine    | ![Structure](image4) | *Chelidonium majus* L.          | Fumariaceae  |
| 6-Methoxydihydrosanguinarine    | ![Structure](image5) | *Chelidonium japonicum* Thunb   | Fumariaceae  |
| Nitidine                        | ![Structure](image6) | *Zanthoxylum* L.                | Rutaceae     |
| Norchelerythrine                | ![Structure](image7) | *Toddalia asiatica* (L.) Lam.   | Rutaceae     |
| Norsanguinarine                 | ![Structure](image8) | *Fumaria indica* Pugsley        | Fumariaceae  |
| CLASS       | Compound                  | Chemical Structure | Genus, Species              | Family       |
|-------------|---------------------------|--------------------|-----------------------------|--------------|
|             | Rhoifoline B              | ![Rhoifoline B](image) | Toddalia asiatica (L.) Lam. | Rutaceae     |
|             | Sanguinarine              | ![Sanguinarine](image) | Fumaria officinalis L.      | Fumariaceae  |
|             | Stylopine                 | ![Stylopine](image)  | Fumaria officinalis L.      | Fumariaceae  |
| CARBAZOLE   |                           |                    |                             |              |
|             | 3,3′-[Oxybis(methylene)]bis(9-methoxy-9H-carbazole) | ![3,3′-[Oxybis(methylene)]bis(9-methoxy-9H-carbazole)](image) | Murraya koenigii (L.) Spreng. | Rutaceae     |
|             | Clausamine A              | ![Clausamine A](image) | Clausena harmandiana (Pierre) Guillaumin | Rutaceae     |
|             | Clausamine B              | ![Clausamine B](image) | Clausena harmandiana (Pierre) Guillaumin | Rutaceae     |
|             | Clausine F                | ![Clausine F](image)  | Clausena harmandiana (Pierre) Guillaumin | Rutaceae     |
|             | Clauszoline N             | ![Clauszoline N](image) | Clausena harmandiana (Pierre) Guillaumin | Rutaceae     |
Table 1. Cont.

| CLASS Compound                  | Chemical Structure | Genus, Species              | Family     |
|---------------------------------|--------------------|-----------------------------|------------|
| 3-Formylcarbazole                | ![3-Formylcarbazole](image) | Clausena mexicana Burm.f. | Rutaceae   |
| 3-Formyl-1-methoxycarbazole      | ![3-Formyl-1-methoxycarbazole](image) | Murraya koenigii (L) Spreng. | Rutaceae   |
| Girinimbine                      | ![Girinimbine](image) | Murraya koenigii (L) Spreng. | Rutaceae   |
| Glycozolidol                     | ![Glycozolidol](image) | Glycosmis pentaphylla (Retz.) DC. | Rutaceae   |
| Harmane                          | ![Harmane](image) | Murraya mexicana (L) Jack | Rutaceae   |
| Koenimbine                       | ![Koenimbine](image) | Murraya koenigii (L) Spreng. | Rutaceae   |
| Koenigine                        | ![Koenigine](image) | Murraya koenigii (L) Spreng. | Rutaceae   |
| Lansine                          | ![Lansine](image) | Micromelum pubescens Bl. | Rutaceae   |
Table 1. Cont.

| CLASS                      | Compound         | Chemical Structure | Genus, Species             | Family       |
|----------------------------|------------------|--------------------|---------------------------|--------------|
| BENZYLISOQUINOLINES        | Murrayamine J    | ![Murrayamine J](image) | *Murraya mexicana* (L.) Jack | Rutaceae     |
|                            | **BENZYLISOQUINOLINES** |                   |                           |              |
|                            | Reticuline       | ![Reticuline](image) | *Annona squamosa* L.     | Annonaceae   |
|                            | Fuyuziphine      | ![Fuyuziphine](image) | *Fumaria indica* Pugsley | Fumariaceae  |
|                            | **BISBENZYLISOQUINOLINES** |                 |                           |              |
|                            | 2′-Nortiliacorinine | ![2′-Nortiliacorinine](image) | *Tiliacora triandra* Diels | Menispermaceae |
|                            | Tetrandrine      | ![Tetrandrine](image) | *Cyclea barbata* Miets    | Menispermaceae |
|                            | Tiliacorine      | ![Tiliacorine](image) | *Tiliacora triandra* Diels | Menispermaceae |
|                            | Tiliacorinine    | ![Tiliacorinine](image) | *Tiliacora triandra* Diels | Menispermaceae |
Table 1. Cont.

| CLASS                  | Compound         | Chemical Structure | Genus, Species                   | Family       |
|------------------------|------------------|--------------------|----------------------------------|--------------|
| DITERPENE ALKALOIDS    | 8-Acetylheterophyllisine | ![Chemical Structure](image1) | Delphinium denudatum Wall. Ex Hook. F. & Thomson yields | Ranunculaceae |
|                        | Panicutine       | ![Chemical Structure](image2) | Delphinium denudatum Wall. Ex Hook. F. & Thomson yields | Ranunculaceae |
|                        | Vilmorrianone    | ![Chemical Structure](image3) | Delphinium denudatum Wall. Ex Hook. F. & Thomson yields | Ranunculaceae |
| HASUBANANS             | Glabradine       | ![Chemical Structure](image4) | Stephania glabra (Roxb.) Miers | Menispermaceae |
| IMIDAZOLES             | Allantoin        | ![Chemical Structure](image5) | Tournefortia sarmentosa Lam | Borrinaceae |
| INDOLOQUINAZOLINES     | Dehydroevodiamine| ![Chemical Structure](image6) | Euodia rutaecarpa Benth | Rutaceae     |
|                        | Evodiamine       | ![Chemical Structure](image7) | Euodia rutaecarpa Benth | Rutaceae     |
| CLASS                  | Compound          | Chemical Structure | Genus, Species                  | Family        |
|-----------------------|-------------------|--------------------|---------------------------------|---------------|
| **CLASS**             | **Compound**      | **Chemical Structure** | **Genus, Species**                  | **Family**    |
| **Tryptanthrin**      |                   | ![Tryptanthrin](image) | *Indigofera tinctoria* L.       | Fabaceae      |
| **INDOLOQUINOLINES**  | Cryptolepine      | ![Cryptolepine](image) | *Cryptolepis sanguinolenta* (Lindl.) Schltr. | Apocynaceae   |
| **MONOTERPENE INDOLE ALKALOIDS** | Alstoniascholarine A | ![Alstoniascholarine A](image) | *Alstonia scholaris* (L.) R.Br. | Apocynaceae   |
|                       | Alstoniascholarine E | ![Alstoniascholarine E](image) | *Alstonia scholaris* (L.) R.Br. | Apocynaceae   |
|                       | Alstoniascholarine J | ![Alstoniascholarine J](image) | *Alstonia scholaris* (L.) R.Br. | Apocynaceae   |
|                       | Cadambine         | ![Cadambine](image) | *Neolamarckia cadamba* (Roxb.) Bosser | Rubiaceae     |
|                       | Ibogaine          | ![Ibogaine](image) | *Ervatamia mexicana* (L.) Burkill | Apocynaceae   |
|                       | 3-Oxocoronaridine | ![3-Oxocoronaridine](image) | *Ervatamia mexicana* (L.) Burkill | Apocynaceae   |
Table 1. Cont.

| CLASS Compound       | Chemical Structure | Genus, Species               | Family       |
|----------------------|--------------------|------------------------------|--------------|
| 5-Oxocoronaridine    | ![Image](image1)   | *Ervatamia mexicana (L.) Burkill* | **Apocynaceae** |
| Strictosidine        | ![Image](image2)   | *Guettarda speciosa L.*      | **Rubiaceae** |
| Vallesamine          | ![Image](image3)   | *Ervatamia mexicana (L.) Burkill* | **Apocynaceae** |
| Voacamine            | ![Image](image4)   | *Ervatamia mexicana (L.) Burkill* | **Apocynaceae** |
| Voacangine           | ![Image](image5)   | *Ervatamia exicana (L.) Burkill* | **Apocynaceae** |
| Vobasine             | ![Image](image6)   | *Ervatamia mexicana (L.) Burkill* | **Apocynaceae** |
| Tubotaiwine          | ![Image](image7)   | *Alstonia scholaris (L.) R.Br.* | **Apocynaceae** |
| CLASS                  | Compound                                                                 | Chemical Structure | Genus, Species                  | Family         |
|-----------------------|-------------------------------------------------------------------------|--------------------|--------------------------------|----------------|
| PHENANTHRENE ALKALOIDS| Aristolochic acid                                                      | ![Aristolochic acid](image) | Aristolochia L.                 | Aristolochiaceae |
|                       | Aristolactam $N^\prime$-(6''-trans-p-coumaroyl)$\beta$-D-glucopyranoside | ![Aristolactam](image) | Aristolochia L.                 | Aristolochiaceae |
|                       | 1-N-monomethylcarbamate-arginine-3-O-$\beta$-D-glucoside                | ![1-N-monomethylcarbamate-arginine-3-O-$\beta$-D-glucoside](image) | Stephania succifera H.S. Lo & Y. Tsoong | Menispermaceae  |
| PHENANTHROINDOLIZIDINE ALKALOIDS | 7-Demethoxytylophorine                                                  | ![7-Demethoxytylophorine](image) | Cynanchum atratum Bunge         | Asclepiadaceae  |
|                       | Tylophorinine                                                           | ![Tylophorinine](image) | Tylophora indica (Burm.f.) Merr. | Asclepiadaceae  |
|                       | Tylophorinidine                                                          | ![Tylophorinidine](image) | Tylophora indica (Burm.f.) Merr | Asclepiadaceae  |
| PIPERINE ALKALOIDS    | Piperine                                                                 | ![Piperine](image) | Piper nigrum L.                 | Piperaceae      |
|                       | Piperlongumine                                                          | ![Piperlongumine](image) | Piper longum L.                 | Piperaceae      |
| CLASS                | Compound | Chemical Structure | Genus, Species | Family     |
|----------------------|----------|--------------------|----------------|------------|
| PHTHALIDES           | Adlumidine          | ![Chemical Structure](image) | *Fumaria officinalis* L. | Fumariaceae |
|                      | Bicuculline         | ![Chemical Structure](image) | *Corydalis bulbosa* DC. | Fumariaceae |
| PROTOBERBERINES      | Berberine           | ![Chemical Structure](image) | *Coptis chinensis* Franch. | Ranunculaceae |
|                      | Jatrorrhizine       | ![Chemical Structure](image) | *Coptis chinensis* Franch. |            |
|                      | Palmatine           | ![Chemical Structure](image) | *Corydalis exicana* (Thunb.) Pers. | Fumariaceae |
|                      | Sinactine           | ![Chemical Structure](image) | *Fumaria officinalis* L. | Fumariaceae |
| PYRROLIDINES         | Brachyamide B       | ![Chemical Structure](image) | *Piper nigrum* L. | Piperaceae |
|                      | Isopiperolein B     | ![Chemical Structure](image) | *Piper nigrum* L. | Piperaceae |
| CLASS | Compound                        | Chemical Structure                                                                 | Genus, Species    | Family       |
|-------|---------------------------------|------------------------------------------------------------------------------------|-------------------|--------------|
|       | **N-(3,4-Methylenedioxyphenyl)-** | **Piper nigrum L.**                                                               |                   |              |
|       | 2E,4E,8E-nonatrienoylpyrrolidine|                                                                                    |                   |              |
|       | **Pandamarilactonine A**         |                                                                                    | **Pandanus odorus** |            Pandanaceae   |
|       | **Trachyone**                    |                                                                                    | **Piper nigrum L.** |              |
|       |                                 |                                                                                    |                  |              |
| **QUINOLINONES** |                                 |                                                                                    |                   |              |
|       | **Antidesmone**                  |                                                                                    | **Waltheria indica L.** | Malvaceae   |
|       | **Evocarpine**                   |                                                                                    | **Euodia rutaecarpa** Benth | Rutaceae     |
|       | **1-Methyl-2-nonyl-4(IH)-**      |                                                                                    | **Euodia rutaecarpa** Benth | Rutaceae     |
|       | quinolone                        |                                                                                    |                   |              |
|       | **1-Methyl-2-[(Z)-5′-pentadecenyl]-** |                                                                                   | **Euodia rutaecarpa** Benth | Rutaceae     |
|       | 4(1H)-quinolone                  |                                                                                    |                   |              |
|       | **Waltherione C**                |                                                                                    | **Waltheria indica L.** | Malvaceae   |
Table 1. Cont.

| CLASS                     | Compound                      | Genus, Species       | Family         |
|---------------------------|-------------------------------|----------------------|----------------|
| QUINOLIZIDINE ALKALOIDS   |                               |                      |                |
|                           | 6,6'-Dihydroxythiobinupharidine | Nuphar japonica DC.  | Nymphaeaceae   |
|                           |                               |                      |                |
|                           | 7-Hydroxylupanine              | Sophora flavescens Aiton | Fabaceae     |
|                           |                               |                      |                |
|                           | N-Butylcytisine                | Sophora flavescens Aiton | Fabaceae     |
|                           |                               |                      |                |
| SECURINEGA ALKALOIDS      | Securinine                    | Flueggea virou (Roxb. Ex Willd.) | Phyllanthaceae |
|                           |                               |                      |                |
|                           | Viroallosecurinine            | Flueggea virou (Roxb. Ex Willd.) | Phyllanthaceae |
|                           |                               |                      |                |
| MISCELLANEOUS PIPERINE ALKALOIDS | Dihydrodioscorine            | Dioscorea bulbifera L. | Dioscoreaceae |
|                           |                               |                      |                |
|                           | Haloxylene B                  | Haloxylon salicornicum (Moq.) | Chenopodiaceae |
|                           |                               |                      |                |
|                           | Pandamarilactone-1            | Pandanus odorus Ridl. | Pandanaceae    |
| CLASS                        | Compound          | Chemical Structure | Genus, Species       | Family     |
|------------------------------|-------------------|--------------------|----------------------|------------|
| SIMPLE QUINOLINE ALKALOIDS   | Camptothecin      | ![Camptothecin](image) | Gomphandra Wall. Ex Lindl. | Icacinaceae |
|                              | Dictamine         | ![Dictamine](image)  | Dictamnus albus L.     | Rutaceae   |
|                              | γ-Fagarine        | ![γ-Fagarine](image) | Dictamnus albus L.     | Rutaceae   |
|                              | 4-Methoxy-2-phenylquinoline | ![4-Methoxy-2-phenylquinoline](image) | Lunasia amara Blanco   | Rutaceae   |
|                              | 4-Methylquinoline | ![4-Methylquinoline](image) | Citrullus colocynthis (L.) Schrad. | Cucurbitaceae |
|                              | Robustine         | ![Robustine](image)  | Dictamnus albus L.     | Rutaceae   |
| PROTOBERBERINES              | Pendulamine A     | ![Pendulamine A](image) | Polyalthia longifolia (Sonn.) | Annonaceae |
|                              | Pendulamine B     | ![Pendulamine B](image) | Polyalthia longifolia (Sonn.) | Annonaceae |
Table 1. Cont.

| CLASS            | Compound       | Chemical Structure | Genus, Species                  | Family       |
|------------------|----------------|--------------------|---------------------------------|--------------|
| PROTOPINES       | Allocryptopine | ![Structure](image) | *Macleaya cordata* (Willd.) R. Br | Papaveraceae |
|                  | Protopine      | ![Structure](image) | *Argemone mexicana* L.          |              |
| SPIROBENZYLISOQUINOLINES | (+)-Fumariline | ![Structure](image) | *Fumaria officinalis* L.        | Fumariaceae  |
|                  | Fumarophycine  | ![Structure](image) | *Fumaria officinalis* L. yields | Fumariaceae  |
|                  | (+)-Parfumine  | ![Structure](image) | *Fumaria indica* Pugsley        | Fumariaceae  |
| STEROIDAL ALKALOIDS | Conimine      | ![Structure](image) | *Holarrhena pubescens* Wall. Ex G. Don | Apocynaceae  |
|                  | N-Formylconessimine | ![Structure](image) | *Holarrhena pubescens* Wall. Ex G. Don | Apocynaceae  |
3. The Strongest Antibacterial and/or Antifungal Alkaloids Identified and Spectrum of Activity

Rios and Recio defined a crude extract with MIC greater than 1000 µg/mL as inactive and suggested interesting antibacterial activity for MICs of 100 µg/mL or lower [6]. Previously, Fabry et al. (1998) defined crude active extracts as having MIC values below 8000 µg/mL [7], while more recently, Kuete (2010) defined crude extracts with MIC values less than 100 µg/mL as active and MICs above 625 µg/mL as weakly active [9]. Here, a compound was very strongly antibacterial or antifungal for a MIC value below or equal to 1 µg/mL; strongly antibacterial (or antifungal for a MIC value above 1 and below or equal to 50 µg/mL; moderately antibacterial or antifungal for a MIC from 50 and below 100 µg/mL; weakly antibacterial (or antifungal) for a MIC from 100 and below 500 µg/mL; very weakly antibacterial or antifungal for a MIC ranging from 500 to below 2500 µg/mL; and inactive for a MIC value above 2500 µg/mL. Following this classification, 8-acetylnorchelerythrine, cryptolepine, 8-hydroxydihydrochelerythrine, 6-methoxydihydrosanguinarine, 2'-norlilacorinine, pendulamine A and B, rhetisine, sanguamine, tiliacorine, tylotanarin, tylorhinorine, vallesamine, and viroallosecurinine showed very strong activities (Table S2).

Looking at the spectrum of activity, most alkaloids showed activity against Gram-positive bacteria, followed by Gram-negative bacteria, yeasts, filamentous fungi, and mycobacteria (Table S2).

4. Influence of Molecular Mass

The molecular mass of natural products dictates their ability to fit in the catalytic pockets of enzymes and to cross biological membranes. Here, low molecular mass molecules were defined with a molecular mass below 200 g/mol; medium molecular mass molecules were defined with a molecular mass from 200 to 400 g/mol; and high molecular mass molecules were defined for a molecular mass above 400 g/mol. Following this classification, we noted that principles with very strong activity against bacteria and fungi had a molecular mass mainly from 200 to 400 g/mol whereas very strong repressors of mycobacteria mainly had a mass above 400 g/mol (Table S2).

5. Influence of Solubility and Polar Surface

Because solubility is a fundamental criterion in which to consider the efficacy of alkaloids, there is need to use mathematical values. Log P is equal to the ratio of concentrations of a compound between octanol and water. Hydrophilic compounds (hydrophilic) have low or negative values (about −3) (compounds are mainly found in the water phase). Mid-hydrophilic compounds have a Log P close to 0 (the compound is equally partitioned between the octanol and water layers). Non-hydrophilic (hydrophobic, liposoluble) compounds have a high Log P (up to about 7) (note that lipophilic alkaloids tend to remain in and destabilize the cytoplasmic membrane of bacteria and fungi). However, Log P is only relevant for non-ionizable principles and for an ionized substance, a Log D is preferable (in terms of ADME), but the pH must be fixed. In some databases, one can find a Log P of 3 for the ionic alkaloid berberine, suggesting a lipophilic substance, which is not sensible. Since compounds destined for pharmaceutical development will mainly be exposed to physiological pH and often a weak base or a weak acid, we defined, at pH 7.4, lipophilic compounds for a negative Log D value of 4, amphiphilic (mid-polar) compounds for a Log D up to about 4.5, and lipophilic for a Log D above 4.5. Note that the Log D values given here are predicted values. Following this classification, we noted that principles with very strong activity against bacteria and fungi were mainly amphiphilic, whereas very strong ant tyrnycobacterial agents were mainly lipophilic (Table S2). Most antibiotics with very strong antibacterial and/or antifungal effects have a polar surface area around 50 Å (Table S2).
6. Mechanisms of Action and Structure-Activity Relationships

Most antibacterial and/or antifungal alkaloids from Asian angiosperms either bear a quinoline or an indole framework and the main mechanisms of action involve the targeting of the DNA, topoisomerases, and cytoplasmic membrane.

6.1. Alkaloids Targeting DNA and/or Topoisomerase

Some alkaloids including aristolochic acids bind to DNA or pyrrolizidine alkaloids, which form DNA cross-linking and DNA-protein cross-linking, leading to mutations [12,13]. Planar alkaloids tend to intercalate with bacterial DNA such as sanguinarine DNA [14], canthin-6-one [15], carbazoles [16], and tryptanthrin [17]. Cryptolepine intercalates into DNA and stimulates DNA cleavage by II [18] and was bacteriolytic for *Staphylococcus aureus* (NCTC 10788) [19]. Evodiamine inhibits topoisomerase I by stabilizing the enzyme-DNA covalent complex [20].

The mode of antibacterial and antifungal action of quinoline alkaloids mainly evokes interaction with DNA. Dictamnine binds to DNA under UV light [21]. Camptothecin stabilizes the topoisomerase I–DNA complex [22]. Liriodenine blocks topoisomerase II [23]. Berberine was active against *Actinobacillus pleuropneumoniae* and *Streptococcus agalactiae* (CVCC 1886) via DNA synthesis inhibition and the blockage of synthesis [24,25]. Anonaine induces DNA damage [26] as well as magnoflorine [27]. Aporphine alkaloids are planar and intercalate DNA and inhibit topoisomerase [28] as well as Amyrillidaceae alkaloids [29]. The quaternary ammonium ion of protoberberine alkaloids and their heterocyclic planar framework account for topoisomerase I inhibition [30].

During bacterial division, topoisomerase IV catalyzes the relaxation of the DNA chain and 6,6'-dihydroxythiobinupharidine blocks this enzyme in *S. aureus* [31]. Phenanthroindolizidine alkaloids interact with DNA [32]. In Gram-positive bacteria, topoisomerase IV is a target for bactericidal quinolone antibiotics [33]. Asian angiosperms produce a vast array of quinoline, isoquinoline, piperidine, and quinolizidine alkaloids, representing a fascinating reservoir of topoisomerase IV inhibitors.

In summary, heterocyclic alkaloids with low to medium molecular mass, close to planar or planar, with the presence of a few hydroxy or ketone groups, almost always target DNA and/or RNA in bacteria and fungi. From this perspective, quinazolone alkaloids in the family Hydrangeaceae (order Saxifragales; clade Core Eudicots) could be examined for their antibacterial and or antifungal properties.

6.2. Alkaloids Targeting the Cytoplasmic Membrane

Phenanthroindolizidine alkaloids disturb the cytoplasmic membrane integrity [34]. The long alkyl chain of piperine and piperlongumine could penetrate the membrane of bacteria and fungi. In *Candida albicans*, piperine affects the membrane integrity, leading to oxidative stress followed by cell cycle arrest and apoptosis [35]. Marques et al. (2010) presented evidence that amidases were more active against *Cladosporium cladosporioides* when the non-substituted aromatic ring, single double bonds, and substitution of nitrogen with alkyl groups were present [36]. In fungi, berberine targets the mitochondrial membrane [24]. Liriodenine in *Paracoccidioides brasiliensis* evoked cytoplasmic alterations and damage to the cell wall [37] while berberine evoked cytoplasmic insults in *Streptococcus agalactiae* (CVCC 1886) [34] and targeted the mitochondrial membrane of fungi [25].

6.3. Miscellaneous Targets

Aristolochic acids inhibited the H+-ATPase-mediated proton pump in *E. coli* [12]. Securinine induces mitotic block in cancer cells by binding to tubulin and inhibits microtubule assembly [38], therefore, microtubules could be involved in the antibacterial and/or antifungal properties of cytotoxic monoterpenoid indole alkaloids.
7. Efflux Pumps Inhibitors

*P. aeruginosa* and Gram-negative bacteria can resist a broad spectrum of natural products because they have extra classes of efflux pumps such as ABC (ATP binding cassette), RND (resistance nodulation cell-division), MF (major facilitator), SMR (small multidrug resistance) and MATE (multidrug and toxic compound extrusion) pumps [39]. ABC efflux pumps located in the cytoplasmic membrane of both Gram-positive and Gram-negative bacteria that use the energy derived from ATP hydrolysis to expel xenobiotics. RND efflux pumps located in the cytoplasmic and outer membrane of the Gram-negative bacteria (specific to Gram-negative bacteria) that expel xenobiotics using the H⁺ gradient (antiporters). MF efflux pumps located in the cytoplasmic membrane of both Gram-positive and Gram-negative bacteria that expel xenobiotics using the H⁺ gradient (antiporters). SMR efflux pumps located in the cytoplasmic membrane of both Gram-positive and Gram-negative bacteria that expel xenobiotics using the H⁺ gradient (antiporters). MATE efflux pumps located in the cytoplasmic membrane and are antiporters (the exit of the xenobiotic coincides with the entry of a Na⁺).

Tryptanthrin inhibits efflux P-glycoprotein in Caco-2 cells [16] and as such may inhibit bacteria and fungal efflux pumps. Apocynaceous monoterpene indole alkaloids are often vasorelaxant [40], and therefore, with some inhibition levels of bacterial and fungal efflux pumps. For instance, the reserpine from *Rauvolfia serpentina* (L.) Benth. ex Kurz decreased the resistance of *S. aureus* (1199B, NorA hyperproducer) to ciprofloxacin and norfloxacin [10]. Reserpine is a calcium channel antagonist and an inhibitor of efflux pumps in Gram-negative bacteria and mycobacteria [41]. From *Rauvolfia serpentina* (L.) Benth. ex Kurz, ajmaline and yohimbine are neuroactive and efflux pump inhibitors in Gram-negative bacteria [42]. Verapamil is another example of a calcium channel antagonist that inhibits the efflux pump in bacteria [42]. The reason why calcium channel antagonists have the tendency to inhibit the bacterial efflux pump could be because of the correlations between the bacterial efflux pumps and bacterial calcium transport [43]. Tetrandrine, which is a calcium channel antagonist in mammalian cells, inhibited the efflux pumps in *S. aureus* and *S. typhimurium* (ATCC 23564) efflux pumps in *Mycobacterium* species [44]. Therefore, natural products known for being calcium channel inhibitors should be screened as antibiotic potentiators. 4’‐O‐Methyldopamine inhibits NorA [45], showing that N‐caffeoylphenethylamide with the strongest efflux pump inhibitor activities presented hydroxyl substitution on the aromatic rings of the caffeic acid part and methoxy substitution on the aromatic ring of the dopamine moiety, which led to an increase in activity. Dopamine is a neurotransmitter, and it could be argued that neuroactive principles are a first line candidate for the development of efflux pump inhibitors. L-dopa increased the resistance of *C. neoformans* toward amphotericin B [46]. In line, erythrinan-type alkaloids and amide alkaloids in the family Piperaceae interact with GABAergic receptors and as such may be able to inhibit bacterial efflux pumps as in pellitorine, which at 16 µg/mL increased the sensitivity of *S. aureus* (RN4220) to erythromycin at 16 µg/mL via inhibition of the efflux pumps [5]. Canthin‐6‐one has a chemical structure with some similarity with serotonin and thus might be able to inhibit bacteria and/or fungal efflux pumps. In mammalian cells, tryptanthrin inhibits the expression of P-glycoprotein efflux pumps [46] and one could investigate its effect on the expression of efflux pumps in bacteria and fungi.

8. Amide Alkaloids

8.1. Simple Amide Alkaloids

Plants in the order Piperales (clade Magnoliids) yield antibacterial amide alkaloids with strong activity against Gram-positive bacteria (Figure 1). Pellitorine inhibited the growth of *Bacillus sphaericus* (ATCC 14577), *Bacillus subtilis* (ATCC 6051), *Staphylococcus aureus* (ATCC 9144), *Escherichia coli* (ATCC 25922), *Pseudomonas syringae* (ATCC 13457), and *S. typhimurium* (ATCC 23564) with the MIC values of 25, 12.5, 20, 150, 75, and 200 µg/mL, respectively [47]. Pellitorine (50 µg/disk) inhibited the growth of *Listeria monocytogenes* with an inhibition zone diameter of 9 mm and the MIC value of 500 µg/mL [48]. Pellitorine (20 µL of a
2 \mu g/mL solution/6 mm well) inhibited the growth of Aspergillus flavus, Aspergillus fumigatus, Coniophora puteana, Fibrophoria vaillentii, Fusarium proliferatum, and Rhisopus sp. with the inhibition zone diameters of 27, 29, 26, 28, 29, and 27 mm, respectively [49]. Piperlonguminine suppressed B. sphaericus (ATCC 14577), B. subtilis (ATCC 6051), S. aureus (ATCC 9144), E. coli (ATCC 25922), P. syringae (ATCC 13457), and S. typhimurium (ATCC 23564) with the MIC values of 20, 9, 12.5, 150, 75, and 175 \mu g/mL, respectively [47]. Piperlonguminine inhibited Mycobacterium tuberculosis with a MIC value of 50 \mu g/mL [50].

8Z-N-isobutyleicosatrienamide and pellitorine had moderate potencies with S. aureus (MIC: 34 \mu M) [51]. Pellitorine restrained M. tuberculosis (H_{37}Ra) with the MIC value of 25 \mu g/mL [52]. dip-Coumaroyl-caffeoylspermidine weakly inhibited the mycelial growth of Pyrenophora avenae and Blumeria graminis [53]. In the clade Clampanulids, Spilanthes paniculata Wall. ex DC yielded N-Isobutyl-2 (E), 6 (Z), 8 (E)-decatrienamide (also known as spilanthol), which was bactericidal for Streptococcus mutans with MIC/MBC values of 125/125 \mu g/mL and weakly repressed C. albicans (ATCC 10231) [44]. The condensation of ferulic acid and dopamine yielded N-trans-feruloyl-4-methyldopamine 200 \mu g/disk that developed halos with a broad-spectrum of bacteria [54] and increased the susceptibility of multidrug-resistant S. aureus (overexpressing the multidrug efflux transporter NorA) to norfloxacin at 100 \mu g/mL [44].

8.2. Cyclopeptides

Plants in the Fabids and Malvids produce broad-spectrum antibacterial cyclic peptides such as frangulanine, which inhibited the growth of S. aureus, B. subtilis, E. faecium, E. coli, E. cloacae, S. typhimurium, and P. aeruginosa with the MIC values of 50, 50, 25, 6.2, 50, 50, 0.7, and 25 \mu g/mL, respectively [55]. Frangulanine inhibited the growth of C. albicans and Saccharomyces cerevisiae with the minimum amounts of 25 and 50 \mu M, respectively [56]. Nummularine H isolated from the roots of Ziziphus mauritiana L. (family Celastraceae; order Celastrales; clade Fabids) inhibited the growth of M. tuberculosis (H_{37}Ra) with the MIC of 4.5 \mu M [57].

9. Indole Alkaloids
9.1. Simple Indoles
9.1.1. Brassicaceous Indoles

Plants in the family Brassicaceae yield antifungal sulfurated indole alkaloids such as caulilexin A from Brassica oleracea L. and at the concentration of 5 \times 10^{-4} M, inhibited the growth of Leptosphaeria maculans, Sclerotinia sclerotiorum, and Rhizoctonia solani by 55, 100, and 100%, respectively [58]. The thiazyol-substituted indole camalexin was active against Alternaria brassicae (MIC: 80 \mu g/mL) [59].

9.1.2. \beta-Carbolines

The condensation of tryptophan and oxaloacetaldehyde yields strong broad-spectrum antibacterial and antmycobacterial \beta-carboline alkaloids in the clades Malvids and Lamiids. Canthin-6-one restrained the growth of S. aureus (1199B), S. aureus (XU212), and S. aureus (ENRSA-15) with the MIC values of 8, 8, and 32 \mu g/mL, respectively [60] as well as Mycobacterium fortuitum (ATCC 6841), Mycobacterium smegmatis (ATCC 14468), M. smegmatis (mc\textsuperscript{2}22700), Mycobacterium phlei (ATCC 111758), and Mycobacterium abscessus (ATCC 19977) with the MIC values of 16, 8, 8, 8, and 16 \mu g/mL, respectively [60]. Rhetsinine very strongly suppressed Xanthomonas oryzae pv oryzae, Xanthomonas oryzae pv oryzicola with the EC\textsubscript{50} values of 1 and 4.5 \mu g/mL, respectively [61]. The condensation of 2 \beta-carboline yielded borrerine yields in Borreria verticillata (L.) G. Mey. (clade Lamiids), which at the concentration of 50 \mu g/mL inhibited the growth of S. aureus and at 6 \mu g/mL restrained Vibrio cholerae [62].
9.1.3. Carbazoles

The condensation of anthranilic acid and malonyl-CoA yields quinolinones that after prenylation and cyclization yield carbazole alkaloid phytoalexins in the family Nitrariaceae and Rutaceae in the order Sapindales (clade Malvids) (Figure 1). One such carbazole is glycozolidol (also known as 6-hydroxy-2-methoxy-3-methylcarbazole; 200 µg/mL/well), which restrained \( S. aureus \), \( Bacillus subtilis \), \( Agrobacterium tumefaciens \), and \( Proteus vulgaris \) [63].

3-Formylcarbazole moderately inhibited the growth of \( Mycobacterium \) sp. [64]. Clausamine A (Log D = 3.9 at pH 7.4; molecular mass = 293.3 g/mol) inhibited the growth of MRSA (SK1), \( S. aureus \) (TISTR 1466), \( E. coli \) (TISTR 780), and \( S. typhimurium \) (TISTR 292) with the MIC values of 8, 32, 128, and 128 µg/mL, respectively [65]. Clausamine B very strongly inhibited the growth of MRSA (SK1) (MIC: 0.2 µg/mL) [65]. Clauszoline N inhibited the growth of MRSA (SK1) and \( S. aureus \) (TISTR 1466) with the MIC values of 16, 64, and 128 µg/mL, respectively [65]. The prenylated carbazole clausine F very strongly inhibited MRSA (SK1) and \( S. aureus \) (TISTR 1466) with the MIC values of 4 µg/mL, respectively, and was moderately active for \( E. coli \) (TISTR 780) and \( S. typhimurium \) (TISTR 292) [65]. In the Rutaceae, lansine yielded a MIC of 14.3 µg/mL against \( M. tuberculosis \) (H37Rv) [66]. Murrayamine J restrained \( S. aureus \) (ATCC 29213), \( Bacillus cereus \) (IIIM 25) with the IC\(_{50}\) values of 11.7 and 23.2 µM [67]. The prenylated carbazole girinimbine was active against \( B. cereus \) (IIIM 25) with the IC\(_{50}\) value of 3.4 µM as well as \( S. aureus \) and \( Aspergillus niger \) with the MIC values of 3.1 and µg/mL, respectively [68]. Koenimbine repressed \( S. aureus \) (ATCC 29213) and \( B. cereus \) (IIIM 25) with IC\(_{50}\) values of 17 and 22.5 µM [67] and koenigine was active against a variety of \( Candida \) sp. (MIC\(_{90}\): 12.5–100 µg/mL) [68].

3-Formyl-1-1methoxycarbazole moderately inhibited the growth of \( S. aureus \) \( C. albicans \), and \( C. albicans \) [74]. 3,3′-[Oxybis(methylene)]bis(9-methoxy-9H-carbazole) inhibited the growth of \( Proteus vulgaris \) and \( C. albicans \) with the MIC values of 6.2 and 25 µg/mL, respectively [69]. In the Nitrariaceae, harmine is very strongly active against \( Vibrio anguillarum \) (MIC: 3.1 µg/mL), [70]. In a subsequent study, harmaine weakly inhibited the growth of \( A. niger \), \( C. albicans \) (Neenah, 2010), \( Cryptococcus gattii \), and \( Cryptococcus neoformans \) [71].

9.1.4. Monoterpene Indole Alkaloids

Plants in the order Gentianales produce monoterpene indole alkaloids with moderate broad-spectrum antibacterial properties (Figure 1).

**Strictosidine-type indole alkaloid glycosides:** The condensation of tryptophan and iridoid glycoside secolaginin yields strictosidine, the precursor of 5α-carboxystrictosidine (Log D-3.1 at pH 7.4; molecular mass = 574.5 g/mol), which inhibited the growth of \( M. tuberculosis \) (H37Rv) with the MIC value of 26.3 µg/mL [72].

**Iboga indole alkaloids:** Iboga indole alkaloids are derived from strictosidine. Voacangine and ibogaine moderately inhibited the growth of \( M. tuberculosis \) and \( Mycobacterium kansasii \) [73]. 5-Oxocoronaridine and coronaridine were moderately active against repressed \( E. coli \), \( B. subtilis \), \( A. flavus \), \( A. niger \), and \( Rhizoctonia phaseoli \) [74]. The growth \( E. coli \), \( K. pneumoniae \), \( S. aureus \), \( S. pneumoniae \) [74], \( A. flavus \), \( C. albicans \), and \( R. phaseoli \) was moderately inhibited by ibogamine [74]. \( Penicillium chrysogenum \) was moderately inhibited by 5-oxocoronaridine, 3-oxocoronaridine, and tabernamontamine [74].

**Vobasine-type indole alkaloids:** The growth of \( A. niger \) and \( A. flavus \) was moderately suppressed by vobasine [74]. Voacamine repressed \( R. phaseoli \), \( P. chrysogenum \), and \( C. albicans \) [74]. The growth was moderately hampered by vobasine [74].

**Isomalindan-type indole alkaloids:** Cadambine from \( Neolamarckia cadamba \) (Roxb.) Bosser (clade Lamiids) was weakly active toward \( Staphylococcus epidermidis \), \( S. aureus \), \( B. cereus \), and \( B. subtilis \), and \( C. albicans \) [75].

**Corynanthe indole alkaloids:** Strictosidine is the precursor to corynanthe indole alkaloids such as alstoniascholarine A, which hindered \( K. pneumoniae \), \( Providencia smatii \), and \( E. coli \) with the MIC values of 12.5, 25, and 50 µg/mL, respectively [76] while alstoniascholarine E yielded the MIC values of 25, 25, and 25 µg/mL, against \( K. pneumoniae \), \( P. smatii \), and \( E. coli \) with the MIC values of 100, 50, 50, respectively. Alstoniascholarine A and E mod-
erately restrained *M. gypseum*, *E. floccosum*, and *T. mentagrophytes* [76]. Alstoniascholarine J repressed *E. floccosum* with the MIC of 31.2 μg/mL, and yielded the MICs of 3.1, 3.1, 3.1, 6.3, and 31.2 μg/mL, against *T. mentagrophytes*, *Trichophyton rubrum*, *Trichophyton tonsurans*, *Microsporum canis*, *M. gypseum*, and *E. floccosum* respectively [76]. Vallesamine and 5-hydroxy-19,20-Z-alschomine very strongly inhibited the growth of *E. faecalis* (ATCC 10541) and *P. aeruginosa* (ATCC 27853) with the MIC values of 1.5 and 0.7 μg/mL, respectively [77,78].

**Strychnos-type indole alkaloids:** Strictosidine is the precursor of Strychnos-type indole alkaloids such as tubotaiwine that moderately inhibited the growth of *M. tuberculosis* H37Rv (MIC: 100 μg/mL) [79].

9.1.5. Miscellaneous

The condensation of anthranilic acid with isatin yielded the indoloquinazoline alkaloid tryptanthrin, which very strongly inhibited MRSA (MIC: 0.5 μg/mL) and *Malassezia furfur* (MIC: 4 μg/mL) [34,80]. Tryptanthrin is a broad-spectrum antifungal alkaloid that yielded the MIC values of 3.1, 3.1, 3.1, 6.3, and 3.1 μg/mL, against *T. mentagrophytes*, *Trichophyton rubrum*, *Trichophyton tonsurans*, *Microsporum canis*, *M. gypseum*, and *E. floccosum* respectively [81,82].

Tryptanthrin was strongly fungicidal with *C. neoformans* [83]. Tryptanthrin is a broad-spectrum antifungal alkaloid that yielded the MIC values of 3.1, 3.1, 3.1, 3.1, 6.3, and 3.1 μg/mL [79].

Plants in the genus *Euodia* from cryptophan via the condensation of dihydronorharman and *N*-methylanthranilic acid yield evodiamine with weak potencies against *K. pneumoniae* (MDR, clinical strain) [84]. Dehydroevodiamine (molecular mass = 301.3 g/mol) from the fruits of *Euodia rutaecarpa* Benth very strongly restrained *X. oryzae pv oryzae* with MIC of 10 mg/mL/11 mm well) from *Phomopsis adianticola* [85].

In the family Apocynaceae (clade Lamiids), the condensation of anthranilic acid with indoxyl yielded the indoloquinoline alkaloid cryptolepine, which repressed *S. aureus* (ATCC 13313), *V. cholerae* (ATCC 11623), *S. sclerotiorum*, and *Botrytis cinerea* with the MIC values of 5, 6.2, <1.5, 5.5, and 0.05 μg/mL, respectively [76,78]. Vallesamine and 5-hydroxy-19,20-Z-alschomine very strongly inhibited *S. aureus* [87] and at the concentration of 100 μg/mL with *E. coli* [87]. Piperine is an antibiotic potentiator that inhibits mycobacterial efflux pumps [50,87]. Piperine very strongly restrained *E. coli* [47,87]. Piperine (200 μL of the 10 mg/mL/11 mm well) muzzled *S. aureus*, *P. aeruginosa*, and *C. albicans* [87]. Piperine is an antibiotic potentiator that inhibits mycobacterial efflux pumps [50,87]. Piperine very strongly constrained albicans [87] and at the concentration of 100 μg/mL suppressed *R. solani*, *Fusarium gramineum*, *Alternaria tenuissima*, *Gloeosporium theae-sinensis*, *Phytophthora capsici*, and *Phomopsis adianticola* by 63.1, 53, 66.1, 76.9, 41.8, and 29.3%, respectively [88]. Piperlongumine (200 μL of the 10 mg/mL/11 mm well) from *Piper longum* L. is active against *S. aureus* and *P. aeruginosa* increased the susceptibility of *S. aureus* to rifampicin [87] and very strongly inhibited *C. albicans* (MIC: 3.9 μg/mL) [87].

10. Piperidine Alkaloids

10.1. Piperine Alkaloids

Plants in the family Piperaceae (clade Magnoliids) convert L-lysine into piperidine, which combines with piperoyl-CoA to yield the strong broad-spectrum antibacterial piperine alkaloids (Figure 1). Piperine moderately impeded *B. sphaericus* (ATCC 14577), *B. subtilis* (ATCC 6051), *E. coli* (ATCC 25922), *P. syringae* (ATCC 13457), and *S. typhimurium* (ATCC 23564) and yielded a MIC of 3.9 μg/mL with *S. aureus* [47,87]. Piperine (200 μL of the 10 mg/mL/11 mm well) muzzled *S. aureus*, *P. aeruginosa*, and *C. albicans* [87]. Piperine is an antibiotic potentiator that inhibits mycobacterial efflux pumps [50,87]. Piperine very strongly constrained albicans [87] and at the concentration of 100 μg/mL suppressed *R. solani*, *Fusarium gramineum*, *Alternaria tenuissima*, *Gloeosporium theae-sinensis*, *Phytophthora capsici*, and *Phomopsis adianticola* by 63.1, 53, 66.1, 76.9, 41.8, and 29.3%, respectively [88]. Piperlongumine (200 μL of the 10 mg/mL/11 mm well) from *Piper longum* L. is active against *S. aureus* and *P. aeruginosa* increased the susceptibility of *S. aureus* to rifampicin [87] and very strongly inhibited *C. albicans* (MIC: 3.9 μg/mL) [87].

10.2. Quinolizidine Alkaloids

From L-lysine are produced quinolizidine alkaloids [89] in the Nymphaeaceae and Fabaceae (Figure 1). 6,6'-Dihydroxythiobinupharidine very strongly suppressed *E. faecalis* and *Enterococcus faecium* with the MIC ranging from 2 to 4 μg/mL and MRSA with a MIC of 2 μg/mL [90]. 7-Hydroxylupanine and *N*-butylcytisine from *Sophora flavescens* Aiton (clade Fabids) hindered *S. aureus* with the MIC values of 16 μg/mL [90] and *N*-butylcytisine yielded the MIC of 8 μg/mL with *E. coli* [90].
10.3. Phenanthroindolizidine Alkaloids

Plants in the family Lauraceae (clade Magnoliids), Moraceae (clade Fabids, and Asclepiadaceae (clade Lamiiids) combine cinnamic acid and ornithine to yield strong broad-spectrum antifungal phenanthroindolizidine alkaloids [91] (Figure 1). One such alkaloid is tylophorinine, which suppressed *C. albicans* (14503), *Candida krusei*, *Candida glabrata*, and *A. fumigatus* with MIC values of 0.6, 0.6, 2.5, and 5 µg/mL, respectively [92]. Tylophorinidine yielded MIC values of 2, 4, 8, and 8 µg/mL with *C. albicans* (14503), *C. krusei*, *C. glabrata*, and *A. fumigatus*, respectively [92] (Table 1). 7-Demethoxytylophorine from *Cynanchum atratum* Bunge was very strongly antifungal with *Penicillium italicum* (MIC/MFC: 1.5/6.2 µg/mL) [25] and *Penicillium digitatum* (MIC/MFC: 1.5/12.5 µg/mL) [92].

10.4. Securinega Alkaloids

Plants in the family Phyllanthaceae (clade Fabids) produce Securinega alkaloids (Figure 1) such as viroallosecurinine, which is very active against *P. aeruginosa* and *S. aureus* (MIC: 0.4 µg/mL) [93]. Securinine weakly restrained *P. aeruginosa*, *S. aureus*, and *M. smegmatis* [93]. Allosecurinine and ent-seco norsecurinine inhibited the growth of a broad-spectrum of filamentous fungi [94,95].

10.5. Miscellaneous

Dihydridioscorine (0.1% of agar) from *Dioscorea bulbifera* L. inhibited the mycelial growth and spore production of *Sclerotium rolfsii*, *C. lunata*, *F. moniliforme*, *Botryodiplodia theobromae*, and *Macrophomina phaseolina* [8]. Pandamarilactone-1 weakly restrained *E. coli*, *P. aeruginosa*, and *S. aureus* [96]. Among the Chenopodiaceae, haloxyline B moderately restrained *M. tuberculosis* H37Rv with the MIC of 50 µg/mL [97].

11. Quinoline Alkaloids

11.1. Simple Quinolines

From tryptophan via anthranilic acid with condensation with malonyl CoA plants in the clade Fabids yielded simple quinolines (Figure 1). 4-Methylquinoline hindered *S. aureus* (KCCM 11335) with the MIC/MBC values of 12.2/50 µg/mL [98]. *Lunasia amara* Blanco yielded 4-methoxy-2-phenylquinoline with MIC values of 16 µg/mL against *M. tuberculosis* H37Rv [98].

In the family Rutaceae (clade Malvids), the condensation of anthranilic acid with malonyl CoA followed by prenylation yielded antibacterial furanoquinolines such as dictamine from *Dictamus albus* L. hindered *Micrococcus luteus* (TISTR 884) and *B. cereus* (TISTR 688) with the MIC values of 26 and 64 µg/mL, respectively [99,100] and was active against *M. tuberculosis* H37Rv [101]. γ-Fagarine and robustine are moderate broad-spectrum antibacterial furanoquinolines [100,101].

Members of the genus *Gomphandra* Wall. ex Lindl. are produced from the condensation of tryptamine and secologanin yields via strictodamide camptothecin, which is a strong broad-spectrum antifungal pyrrolquinoline alkaloid [102,103].

11.2. Benzylisoquinolines

In basal angiosperms (clade Magnoliids, Eudicots), the condensation of dopamine and p-hydroxyphenylacetaldehyde yielded strong broad-spectrum antibacterial and antifungal benzylisoquinoline alkaloids (Figure 1). One such alkaloid is reticuline [104,105]. From *Fumaria indica* Pugsley, fuyuziphine at a concentration of 500 ppm hindered the germination of spores of *Alternaria brassicicola*, *A. solani*, *Alternaria melongenae*, *C. maculans*, *Erysiphe cichoracearum*, and *Helminthosporium penniseti* by more than 80% [106].

11.3. Bisbenzylisoquinolines

The radical coupling of benzylisoquinolines gives birth to antibacterial and antifungal bisbenzylisoquinoline alkaloids in plants in the clade Eudicots (Figure 1). For instance, the coupling of *N*-methyl coclaurine yields tetrandine, which is weakly bactericidal for
S. aureus (ATCC 25923) and MRSA (ATCC 33591) [107] and is a bacterial efflux pump inhibitor [90,107].

**Tiliacora triandra** Diels produces tiliacorinine, 2′-nortiliacoriline, and tiliacorine, which achieved MIC values of 6.2, 3.1, and 3.1 μg/mL, respectively, toward *M. tuberculosis* (H37Rv) and MIC values ranging from 0.7 to 6.2 μg/mL against several clinical isolates of multidrug-resistant *M. tuberculosis* [108]. Tiliacorine inhibited the germination of the conidia of *A. tenuissima* by more than 60% at 100 μg/mL [109].

### 11.4. Aporphines

The cyclization by oxidative coupling of benzylisoquinolines yields aporphines in basal angiosperms. For instance, in Figure 1, liriodenine [110] inhibited a very broad spectrum of bacteria and phytopathogenic fungi [111] as well as *Histoplasma capsulatum* (MIC: 1.9 μg/mL) [28].

Anonaine developed halos against *B. cereus* (ATCC-14.579), *E. coli* (ATCC-11.105), *S. aureus* (ATCC-6538), and *S. epidermidis* (ATCC-12.228) with diameters of 20, 8, 14, and 12 mm, respectively (1 mg/mL, 70 μL/well) [84]. In a subsequent study, anonaine weakly inhibited the growth of *S. mutans* (ATCC 25175) (Lall et al., 2017), *T. rubrum*, and *M. gypseum* [85].

Lysicamine was moderately active with *S. epidermidis* (MIC: 50 μg/mL) [112], and very strongly repressed *L. monocytogenes*, *MSSA*, *S. pneumoniae*, and *Actinobacillus sp.* with the MIC values of 2.5, 1, 4, and 2.5 μg/mL, respectively, and *K. pneumoniae* (ESBL) with the MIC of 20 μg/mL [113]. Lysicamine (10 μg/6 mm disk) developed inhibition zone diameters of 12, 13, and 15.5 mm toward *S. epidermidis*, *S. aureus*, and *B. subtilis*, respectively [113], and had meek effects with *Candida dubliniensis* (ATCC 7777) [33].

O-methylmoschatoline (200 μg/disk) inhibited the growth of *S. aureus*, *E. coli*, *P. aeruginosa*, *S. typhi*, and *K. pneumoniae* with zone diameters of 20, 12, 12, 20, and 22 mm, respectively [114]. Xylopine hindered *B. cereus*, *Micrococcus sp.*, and *S. aureus* [115] as well as *V. cholerae*, *E. coli*, and *S. dysenteriae* [116]. Artabotrine was very strongly bactericidal against *K. pneumoniae* (ESBL) (MIC/MBC: 2.5/2.5 μg/mL) [113]. The azaaoxoaporphine sampangine (Log D 2.7 at pH 7.4; molecular weight 232.2 g/mol) was very strongly active with *S. aureus* (ATCC 90028), *C. glabrata* (ATCC 90028), *C. krusei* (ATCC 6258), *A. fumigatus* (ATCC 90906), and *C. neoformans* (ATCC 90113) with MIC values of 3.1, 3.1, 6.2, 6.2, and 0.05 μg/mL, respectively [117] and at 10 μg/disk developed halos with *B. cereus*, *S. aureus*, *E. coli*, and *S. typhi* [118]. Lanuginosine (10 μg/disk) inhibited inhibition zone diameters of 12, 14, 10, 14, and 12 mm, with halos with *B. cereus*, *S. aureus*, *E. coli*, *K. pneumoniae*, and *P. aeruginosa*, respectively [118].

Nordicentrine (Log D 3.0 at pH 7.4; molecular weight = 325.3 g/mol) suppressed *M. tuberculosis* with a MIC of 12.5 μg/mL [119] as well as *Cladosporium cladosporioides* (6 μg/spot) [120]. Dicentrinone was moderately antimycobacterial [121].

The oxoaporphine thailandine restrained *S. pneumoniae*, *S. aureus*, and *E. faecalis* with MIC values of 30, 30, and 60 μg/mL, respectively, and yielded an IC₅₀ value of 6.2 μg/mL with *M. tuberculosis* (H₃7Ra) [122].

Isoboldine was moderately active with *E. coli*, *P. aeruginosa*, *P. mirabilis*, *K. pneumoniae*, *A. baumanii*, *S. aureus*, *B. subtilis* [104], and *C. albicans* [123]. Bulbocapnine restrained *K. pneumoniae* and *A. baumanii* with the MIC values of 32, 64, 32, 8, 8, 64, and 128 μg/mL respectively [104].

Roemerine is a moderate inhibitor of MRSA (135), *S. aureus* (ATCC25913) *C. albicans* (SC 5314), *C. glabrata* (8535), *C. krusei* (4996), *Candida tropicalis* (8915), *Candida parapsilosis* (90018), and *A. fumigatus* (7544), respectively [124] and yielded a MIC value of 10 μg/mL with *C. albicans* (ATCC 90028) [125].

Magnoflorine moderately repressed *C. albicans* (KCTC7965), *C. albicans* (KACC30071), *C. parapsilosis* var. *parapsilosis* (KACC45480), *T. rubrum*, and *T. mentagrophytes* [126,127].
11.5. Protopines

Benzylisoquinolines are precursors of protopine that restrained \textit{E. coli}, \textit{P. aeruginosa}, \textit{P. mirabilis}, \textit{K. pneumoniae}, \textit{A. baumannii}, \textit{S. aureus}, and \textit{B. subtilis} with the MIC values of 32, 64, 32, 8, 8, 64, and 128 \( \mu \text{g/mL} \), respectively [104] as well as \textit{Streptococcus agalactiae} [128]. Protopine inhibited the growth of \textit{C. albicans} with the MIC value of 4 \( \mu \text{g/mL} \) [104]. Allocryptopine was weakly active with \textit{S. aureus}, \textit{P. aeruginosa}, \textit{E. coli}, and \textit{S. agalactiae} [128].

11.6. Protoberberines

The cyclization of benzylisoquinolines yielded very strong antibacterial protoberberines such as in pendulamine A from \textit{Polyalthia longifolia} (Sonn.) Thwaites that yielded the MIC of 2, 0.02, 0.2, 0.02, 2, 2, 0.2, and 0.02 \( \mu \text{g/mL} \) against \textit{B. subtilis}, \textit{Corynebacterium hoffmannii}, \textit{S. aureus}, \textit{Micrococcus lysodeikicus}, \textit{K. pneumoniae}, \textit{P. aeruginosa}, \textit{S. typhi}, and \textit{S. paratyphi A}, respectively [129]. Pendulamine B restrained \textit{Corynebacterium hoffmannii}, \textit{S. aureus}, \textit{S. faecalis}, \textit{S. viridans}, \textit{M. lysodeikicus}, \textit{K. pneumoniae}, \textit{P. aeruginosa}, \textit{S. typhi}, and \textit{S. paratyphi A} with the MIC values of 0.02, 0.2, 0.02, 0.02, 2, 0.2, and 0.2 \( \mu \text{g/mL} \), respectively [129].

11.7. Spirobenzylisoquinolines

Spirobenzylisoquinolines are derived from benzylisoquinolines via protoberberine, and include (+)-parfumine, fumarophycine and (+)-fumariline (that moderately restrained \textit{E. coli}, \textit{P. aeruginosa}, \textit{P. mirabilis}, \textit{K. pneumoniae}, \textit{A. baumannii}, \textit{S. aureus}, and \textit{B. subtilis} [104].

11.8. Benzophenanthridines

Plants in the clade Eudicots use reticuline as a precursor of benzophenanthridines such as stylopine or sanguinarine L. that moderately repressed \textit{E. coli}, \textit{P. aeruginosa}, \textit{P. mirabilis}, \textit{K. pneumoniae}, \textit{A. baumannii}, \textit{S. aureus}, and \textit{B. Subtilis} [104]. Dihydrosanguinarine was a weak repressor of \textit{E. coli} [128]. Sanguinarine impeded \textit{S. mutans} (ATCC 25175) with the MIC value of 32 \( \mu \text{g/mL} \) [130] as well as \textit{S. aureus}, \textit{P. aeruginosa}, \textit{E. coli}, and \textit{S. agalactiae} with MIC values of 31.3, 250, 62.5, 15.6 \( \mu \text{g/mL} \), respectively [128]. 6-Methoxydihydrosanguinarine (10 \( \mu \text{g/disk} \)) developed an inhibition zone diameter of about 17 mm with \textit{S. aureus} and MRSA [131]. 8-Hydroxydihydrosanguinarine (molecular weight = 349.3 g/mol) inhibited the growth of clinical strains of MRSA with MIC ranging from 0.4 to 7.8 \( \mu \text{g/mL} \) and MBC ranging from 1.9 to 31.2 \( \mu \text{g/mL} \), ESBL strains of \textit{E. coli} with MIC ranging from 15.6 to 250 \( \mu \text{g/mL} \) and MBC ranging from 62.5 to 500 \( \mu \text{g/mL} \), and \textit{E. coli} with MIC of 15.6 \( \mu \text{g/mL} \) and MBC of 31.2 \( \mu \text{g/mL} \) [109]. 8-Hydroxydihydrosanguinarine was moderately active against \textit{C. parapsilosis}, \textit{C. tropicalis}, \textit{C. krusei}, \textit{C. glabrata}, and \textit{C. neoformans} [132].

6-Methoxydihydrosanguinarine is a very strong inhibitor of \textit{E. faecalis} and \textit{S. aureus} (ATCC 25925) with the MIC/MBC of 5/10, 2.5/5 \( \mu \text{g/mL} \), respectively, and evoked milder potencies with \textit{E. coli} (ATCC 25922) [133] and \textit{C. albicans} (CMCC 85021) [133]. Norsanguinarine is moderately antibacterial [104].

Allocryptopine is the precursor of dihydrochelerythrine that strongly hindered \textit{S. epidermidis} (ATCC 12228), \textit{S. aureus} (ATCC 6538), \textit{S. pyogenes} (ATCC 19615), \textit{B. subtilis} (ATCC 6633), \textit{K. pneumoniae} (ATCC 13883), and \textit{E. coli} (ATCC 25922) with MIC/MBC values of 6.2/12.5, 12.5/50, 12.5/50, 25/50, 12.5/25, 25/25 \( \mu \text{g/mL} \), respectively [134]. 8-Hydroxydihydrochelerythrine (molecular weight = 365.4 g/mol) inhibited the growth of 20 strains of MRSA clinical isolated with MIC ranging from 0.9 to 15.6 \( \mu \text{g/mL} \) and MBC ranging from 7.8 to 62.5 \( \mu \text{g/mL} \) [135] and displayed meeker effects with \textit{E. coli} and \textit{K. pneumoniae} (ESBL) [109,135]. Dihydrochelerythrine suppressed MRSA (SK1) and \textit{E. coli} (TISTR 780) with the MIC values of 8 and 16, and 128 \( \mu \text{g/mL} \) [100]. Dihydrochelerythrine is the precursor of chelerythrine, which very strongly hindered \textit{S. epidermidis} (ATCC 12228), \textit{S. aureus} (ATCC 6538), \textit{S. pyogenes} (ATCC 19615), \textit{B. subtilis} (ATCC 6633), \textit{K. pneumoniae} (ATCC 13883), and \textit{E. coli} (ATCC 25922) with MIC/MBC values of 1.5/12.5, 1.5/3.1, 1.5/6.2, 1.5/50, 1.5/50, and 1.5/25 \( \mu \text{g/mL} \), respectively [128,134]. Chelerythrine was also very strongly antifungal with \textit{C. albicans} (ATCC 10231), \textit{S. cerevisae} (ATCC 2601), and
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C. neoformans (ATCC 28952) with MIC/MBC values of 3.1/2.5, 6.2/2.5, and 3.1/6.2 μg/mL, respectively [134-136]. Corynoline and acetylcorynoline from Corydalis incisa (Thunb.) Pers. evoked inhibitory halos with Cladosporium herbarum (3 μg/spot) [137].

Norochelerythrine inhibited the growth of M. tuberculosis with the MIC value of 25 μg/mL [138]. Avicene very strongly suppressed S. epidermidis (ATCC 12228), S. aureus (ATCC 6538), B. subtilis (ATCC 6633), K. pneumoniae (ATCC 13883), and E. coli (ATCC 25922) with the MIC/MBC values of 3.1/12.5, 1.5/25, 1.5/12.5, 1.5/6.2, and 6.2/12.5 μg/mL, respectively [134]. 8-Acetylnorochelerythrine yielded the MIC values of 1 μg/mL with S. epidermidis, E. coli, E. cloacae, K. pneumoniae, and P. aeruginosa [139]. Rhoifoline B moderately inhibited the growth of S. aureus, S. epidermidis, E. coli, E. cloacae, K. pneumoniae, P. aeruginosa, and S. dysenteriae [139]. Nitidine, from a member of the genus Zanthoxylum L. (clade Malvids), weakly inhibited the growth of M. luteus, S. aureus, and M. smegmatis [140].

11.9. Protoberberines

Reticuline is a precursor of the broad-spectrum antibacterial berberine [29,128,141–144]. Of note, berberine curbed the growth of K. pneumoniae and A. baumannii with the MIC value of 8 μg/mL [104] and Neisseria gonorrhoea with the MIC of 13.5 μg/mL [145]. Berberine decreased the MICs of ampicillin and oxacillin against MRSA and evoked a synergistic effect [146] and impeded the MexAB antibiotic efflux pump in P. aeruginosa [147]. Berberine suppressed fluconazole-resistant clinical strains of C. tropicalis, C. albicans, C. parapsilosis, and C. neoformans as well as C. krusei (ATCC 6528) and C. parapsilosis (ATCC 22019) with the MIC values of 8, 8, 8, 8, 8, 16, 16, 16, 16, 4, and 16 μg/mL, respectively [148] and at a concentration of 500 ppm blocked the germination of spores of Curvularia lunata, Erysiphe cichoracearum, F. udum, and Penicillium sp. by more than 80% [106]. Berberine at the concentration of 1.9 μg/mL decreased the MIC of fluconazole from 1.9 to 0.4 μg/mL [149] and inhibited the growth of M. smegmatis (ATCC 607) with the MIC value of 25 μg/mL [150].

Berberine is a precursor of jatrorrhizine that curbed strains of P. acnes with MIC between 5 and 50 μg/mL, [143]. In a subsequent study, jatrorrhizine weakly inhibited S. aureus, B. subtilis, E. coli, and S. dysenteriae [151] as well as the clinical isolates of E. floccosum, T. rubrum, Trichophyton interdigitale, Trichophyton violaceum, T. mentagrophytes, T. equinum, M. canis, M. gypseum, C. albicans, and C. tropicalis [152]. Palmatine t is moderately antibacterial as well as a sinactine [104] and MexAB antibiotic efflux pump blocker in P. aeruginosa [147].

11.10. Phthalides

Protoberberine alkaloids are precursors of phthalides with moderate antibacterial potencies including adlumidine or bicuculline [104]. Bicuculline at 200 ppm restrained the spore germination of A. brassicae, Curvularia lunata, and F. udum [104,153].

11.11. Hasubanans

Within the family Menispermaceae, intramolecular coupling of benzylisoquinolines form hasubanan alkaloids. One such alkaloid is glabradine, isolated from the tubers of Stephania glabra (Roxb.) Miers, which suppressed S. aureus and S. mutans with the MIC value of 50 μg/mL as well as M. gypseum, M. canis, and T. rubrum with the MIC values of 25, 25, and 50 μg/mL, respectively [154].

11.12. Amaryllidaceae Alkaloids

Plants in the family Amaryllidaceae (clade Monocots) condensate protocatechuic aldehyde and tyramine to yield antibacterial Amaryllidaceae alkaloids such as crinamine [9]. Other examples are lycorine and lycoridine (1 mg/mL/8 mm disk), which developed an inhibition zone of 13 and 12 mm with E. coli, respectively [106]. Lycorine at the concentration of 100 μg/mL hindered Alternaria oleracea, C. gloeosporioides, F. graminearum, Colletotrichum ophiopogonis, and Pleospora lycopersici by 61.9, 57.2, 63.7, 63.2, and 52.6%, respectively [155]. Lycorine yielded the MIC values of 39, 32, 512, 64, and 97.3 μg/mL with C. albicans, Candida dubium, C. glabrata, Lodderomyces elongisporus, and S. cerevisiae,
respectively [156]. Narciclamine inhibited the growth of Corynebacterium fascians and C. neoformans [157] and hippeastrine moderately curbed C. albicans [156]. Tazettine from Narcissus tazetta L. weakly restrained C. dubliniensis and L. elongisporus [156].

11.13. Miscellaneous

11.13.1. Quinolinones

Plants in the clade Malvids yield antibacterial and antifungal quinolinones. Antidesmone at the concentration of 50 μg/mL restrained Botryosphaeria dothidea, Colletotrichum musae, Pestalotipis guepinii, Colletotrichum orbiculare, Phylophthora nicotianae, Pestalotipiosis longiseta, Carbendazim-sensitive strains of S. sclerotiorum, and Carbendazim-resistant strains of S. sclerotiorum by 71.9, 84.6, 86.7, 75.5, 78.8, 83.4, 56.5, and 100%, respectively [158]. Walthotherine C at the concentration of 50 μg/mL inhibited B. dothidea, Colletotrichum musae, Pestalotipis guepinii, Colletotrichum orbiculare, Phylophthora nicotianae, Pestalotipiosis longiseta, carbendazim-sensitive strains of S. sclerotiorum, and carbendazim-resistant strains of S. sclerotiorum by 60, 43, 71.4, 60.9, 41.6, 3.6, 79.8, and 81.8%, respectively [158].

Members of the genus Euodia J.R. Forst. & G. Forst. bring to being series of antibacterial (Gram-positive) long chain quinolinones born of the condensation of anthranilic acid, malonyl-CoA and fatty acyl-CoA (also produced by Gram-negative bacteria). 1-Methyl-2-nonyl-4(1H)-quinolone very strongly repressed S. aureus (ATCC 25393), S. epidermidis (ATCC 12228), and B. subtilis (ATCC 6633) with the MIC values of 4, 4, and 8 μg/mL, respectively [159]. 1-Methyl-2-[(Z)-5′-pentadecenyl]-4(1H)-quinolone isolated from the fruits hindered S. aureus (ATCC 25393), S. epidermidis (ATCC 12228), and B. subtilis (ATCC 6633) with the MIC values of 16, 4, and 16 μg/mL, respectively [159]. In a subsequent study, the lipophilic long chain quinolinone alkaloid evocarpine inhibited the growth of MRSA (ATCC 33591) and S. aureus (ATCC 25923) with the MIC values of 8 and 8 μg/mL, respectively [160] and very strongly suppressed M. fortuitum (ATCC 6841), M. smegmatis (ATCC 19429), and M. phlei (ATCC 19249) with the MIC values of 2, 2, and 2 μg/mL, respectively [161].

11.13.2. Acridanones

In the family Rutaceae (clade Malvids), the condensation of anthranilate with 3 malonyl-CoA and fatty acyl-CoA (also produced by Gram-negative bacteria). 1-Methyl-2-nonyl-4(1H)-quinolone very strongly repressed S. aureus (ATCC 25393), S. epidermidis (ATCC 12228), and B. subtilis (ATCC 6633) with the MIC values of 4, 4, and 8 μg/mL, respectively [159]. 1-Methyl-2-[(Z)-5′-pentadecenyl]-4(1H)-quinolone isolated from the fruits hindered S. aureus (ATCC 25393), S. epidermidis (ATCC 12228), and B. subtilis (ATCC 6633) with the MIC values of 16, 4, and 16 μg/mL, respectively [159]. In a subsequent study, the lipophilic long chain quinolinone alkaloid evocarpine inhibited the growth of MRSA (ATCC 33591) and S. aureus (ATCC 25923) with the MIC values of 8 and 8 μg/mL, respectively [160] and very strongly suppressed M. fortuitum (ATCC 6841), M. smegmatis (ATCC 19429), and M. phlei (ATCC 19249) with the MIC values of 2, 2, and 2 μg/mL, respectively [161].

11.13.3. Phenanthrene Alkaloids

Benzylisoquinolines are precursors of antibacterial phenanthrene in basal clades as aristolochic acid, which inhibited the growth of Monaxella catarrhalis (GTC 01544) with MIC/MBC values of 25/50 μg/mL [163] as well as B. subtilis and E. coli [164], P. aeruginosa, S. faecalis, S. aureus, and Staphylococcus epidermidis [165]. Another example is aristolactam N-(6′-trans-p-coumaroyl)-β-D-glucopyranoside, which restrained B. subtilis and S. lutea with the MIC values of 43.8 and 175 μg/mL, respectively [166]. These phenanthrene alkaloids bind covalently with DNA [167,168]. 1-N-monomethylcarbamate-argentinine-3-O-β-D-glucoside at 500 μg/disk hindered MRSA with an inhibition zone diameter of 8 mm [169].

12. Pyrrolidines and Imidazole Alkaloids

In the family Piperaceae (clade Magnoliids), the pyrrolidines brachyamide B yielded the IC₅₀ of 41.8 μg/mL against a clinical isolate of C. albicans [170] and suppressed C. neoformans (ATCC 90 113) with an IC₅₀ of 7.1 μg/mL [171]. Other instances are trachyone and isopiperolein B with S. aureus (MIC of 30 and 36 μM, respectively) [51]. The pyrrolidine alkaloid lactone pandamari lactonine A moderately inhibited the growth of E. coli, P. aeruginosa, and S. aureus [96]. The pyrrolidine amide N-[9-(3,4-Methylenedioxyphenyl)-
2E,4E,8E-nonatrienoyl] pyrrolidine was active toward *M. tuberculosis* (H37Ra MIC: 25 µg/mL) [170].

The imidazole alkaloid allantoin very strongly hindered *B. subtilis* with the MIC value of 4 µg/mL as well as *S. aureus, E. coli,* and *K. pneumoniae* with the MIC value of 8, 8, and 8 µg/mL, respectively [172] (Table 1).

13. Diterpene Alkaloids

Plants in the family Ranunculaceae (clade Eudicots) produce a unique type of moderately antifungal diterpene alkaloids. For instance, 8-acetylheterophyllisine, vilmorri-anone, and panicutine inhibited the growth of *Allescheria boydii, A. niger, E. floccosum,* and *Pleurotus ostreatus* [173] (Table 1).

14. Steroidal Alkaloids

*N*-formylconessimine and conimine suppressed MSSA and MRSA with MIC values of 32 and 128 µg/mL, respectively, and conimine increased the sensitivity of MSSA to vancomycin [174].

15. Concluding Remarks

Weinstein and Albersheim (1983) presented evidence that phytoalexins, especially flavonoids from angiosperms, act as nonspecific membrane antimicrobials that alter the structural integrity of the cytoplasmic membrane, thereby causing the membrane to be a less efficient matrix for membrane-dependent processes [175]. They also argue that phytoalexins with non-specific antimicrobial targets targeting the cytoplasm and proteins also makes it difficult for bacteria or fungi to develop resistance. Furthermore, phytoalexins are often toxic to herbivorous predators as well as repellent and therefrom exhibit low therapeutic indices. In the case of alkaloids, none have been known act on specific antibacterial or antifungal targets [176]. It is for this reason that antibiotic or antifungal alkaloids for systemic use in humans working at micromolar plasmatic concentrations have not been found yet. Research efforts, however, need to continue with the determination of the selectivity indices. Alkaloids from Asian angiosperms represent yet another mind-blowing source of original chemical frameworks that can be used for the hemisynthesis of clinical antibiotics, antimonocobacterial agents, and antifungal drugs as well as efflux pump inhibitors of clinical value. 8-Acetylnoorchelerythrine, cryptolepine, 8-hydroxydihydrochelerythrine, 6-methoxydihydrosanguinarine, pendulamine A and B, rhetsisine, sam-pangine, tiliacorine, tryptanthrin, tylophorinine, vallesamine, and viroallosecurinine with a MIC ≤ 1 µg/mL are first line candidates.

**Supplementary Materials:** The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/antibiotics11091146/s1, Table S1: Medicinal Plants of Asia and the Pacific yielding antibacterial and/or antifungal alkaloids; Table S2: Antibacterial and/or antifungal alkaloid in vitro and from Asian Angiosperms with MIC ≤ 5 µg/mL.

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