Nor-Lignans: Occurrence in Plants and Biological Activities—A Review

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Abstract: In this review article, the occurrence of nor-lignans and their biological activities are explored and described. Nor-lignans have proven to be present in several different families also belonging to chemosystematically distant orders as well as to have many different beneficial pharmacological activities. This review article represents the first one on this argument and is thought to give a first overview on these compounds with the hope that their study may continue and increase, after this.

Keywords: nor-lignans; occurrence; biological activities

1. Introduction

A large part of secondary plant phenolic natural products derives from the aromatic amino acids couple tyrosine/phenylalanine. The de-amination of these compounds gives raise, through the shikimic acid pathway, to the intermediate metabolites C(6)–C(3), i.e., propenyl-phenols and allyl-phenols, generally named as phenylpropanoids. These are the starting points of the biosynthesis of several classes of active constituents related to the stability of the cell wall and to the defense of plants against herbivorous animals and pathogens. The first line of defense in terrestrial plants is a mechanical one, related to a polymerization process which leads to the formation of lignin, the main component of wood. Lignin is a very strong and stable macromolecule. Its introduction inside the plant cell wall instead of the carbohydrate polymer cellulose, confers force and resistance, allowing the formation of giant tree’s structure and making the digestions of the adult parts of the plant from herbivorous animals very difficult. Yet, the lignin defense line has resulted to be quite insufficient in many cases and the incoming predominance of herbal species determined the shift towards another form of defense, i.e., the chemical one. Actually, the phenylpropanoids pathway has never been dismissed, but rather it has turned towards the synthesis of smaller products having more precise targets. Among these molecules, the dimerization process of C(6)–C(3) precursors gives rise to three important classes of natural secondary metabolites: lignans, neo-lignans and nor-lignans. These classes present similar features due to their common biosynthetic origin. Their general structure is characterized by the presence of two terminal phenyl groups, which are more or less functionalized with hydroxyl groups and connected by a central chain of six carbon atoms, differently arranged and oxidized. The main
difference among lignans, neo-lignans and nor-lignans is due to the different type of junction between the two C(6)C(3) (=PhC3) units. In particular, in lignans, this junction is through a β-β (8-8′) bond and in neo-lignans the junction is not a β-β type. Therefore, lignans and neo-lignans, and their several different derived subclasses, can be identified depending upon the carbon skeletons which they possess. For what concerns nor-lignans, the structure is more complicated. In fact, nor-lignans own a peculiar characteristic, with respect to lignans and neo-lignans, which is the cut of one carbon from the central chain. This loss forces this chain to be differently arranged from lignans and neo-lignans, such as in a linear sequence or in a C(3)C(2) arrangement meaning 8,9′-coupling and 7′,8-coupling or alternatively in the bis-nor-lignan and cyclo-nor-lignan skeletons (8,8′) where chirality plays a central role. From this description, it is quite easy to understand the other definition of the structure of nor-lignans: natural compounds based on diphenyl-pentanes, derived by the union of two phenylpropanoid units in the positions α, β’ or β, γ’ and characterized with the loss of the terminal carbon of the chain [1–3].

Figure 1 shows the possible different arrangements for nor-lignans.

![Figure 1. general nor-lignan basic structures.](image)

2. Occurrence of Nor-Lignans in the Plant Kingdom

From the environmental and taxonomical points of view, lignans are mainly biosynthesized in woody plants, since main occurrences are related to Gymnospermae and Angiospermae. In particular, they can be found in the trees’ members of ancient forests like the Amazonian one, but, probably because of their simple biosynthetic pathway, they can be present also in herbal plants like those of monocotyledons.

In this review article, the attention is focused on nor-lignans, their occurrence in the plant kingdom and their importance as bioactive molecules.
Table 1 reports on the nor-lignans identified in the plant kingdom differentiating them according to the species, genus and family. In addition, the organs from which these compounds have been isolated, and the techniques used for their isolation and identification were completely added.

### Table 1. of nor-lignans in the plant kingdom.

| Family       | Species                        | Studied Organs   | Compounds                                                      | Methods                                      | References |
|--------------|--------------------------------|------------------|----------------------------------------------------------------|----------------------------------------------|------------|
| Acanthaceae  | Justicia patentiflora Hemsl.   | Leaves and stems | justiflorinol                                                   | SE, CC, HPLC, [α]D, UV, IR, NMR, MS          | [4]        |
|              |                                |                  | (+)-acortatarinovin A, (+)-acortatarinovin B, (+)-acortatarinovin C, (-)-acortatarinovin A, (-)-acortatarinovin B, (-)-acortatarinovin C |                                              |            |
| Acoraceae    | Acorus tatarinowii Schott      | Rhizomes         | acorusin B                                                      | SE, CC, [α]D, UV, IR, NMR, MS                | [5]        |
|              |                                |                  | (+)-acortatarinovin A, (+)-acortatarinovin B, (+)-acortatarinovin C, (-)-acortatarinovin A, (-)-acortatarinovin B, (-)-acortatarinovin C |                                              |            |
| Annonaceae   | Duguetia confinis (Engl. and Diels) Chatrou | Bark  | pachypostaudin A, pachypostaudin B, pachyphylalin | SE, CC, TLC, UV, IR, NMR, MS                  | [6]        |
|              |                                |                  |                                                                |                                              |            |
| Aracariaceae | Araucaria angustifolia (Bertol.) Kuntze | Knot resin      | 2,3-bis-(p-hydroxyphenyl)-2-cyclopentene-1-one, nyasol, cryptoresin, nyasol, 4′-O-methyl-nyasol, 1,3-di-p-hydroxyphenyl-4-penten-1-one | SE, CC, HPLC, TLC, UV, IR, NMR, MS            | [9]        |
|              |                                |                  |                                                                |                                              |            |
| Aracariaceae | Anemarrhena asphodeloides Bunge | Roots            | nyasol, 4′-O-methyl-nyasol, 3′-methoxy-nyasol, 3′-hydroxy-4′′-methoxy-4′-dehydroxy-nyasol, nyasol | SE, CC, [α]D, UV, IR, NMR, MS                | [10,11]    |
|              |                                |                  |                                                                |                                              |            |
| Asparagaceae | Asparagus africanus Lam.        | Roots            | nyasol                                                         | CC, IC, HPLC, NMR, MS                        | [13]       |
|              |                                |                  |                                                                |                                              |            |
| Asparagaceae | Asparagus cochinensis (Lour.) Merr. | Roots         | iso-agatharesinoside, iso-agatharesinol                        | SE, CC, [α]D, UV, IR, NMR, MS                | [15]       |
|              |                                | Tubers           | nyasol                                                         | SE, CC, [α]D, IR, NMR, MS                    | [16]       |
|              |                                |                  |                                                                |                                              |            |
| Asparagaceae | Asparagus gobicus N.A.Ivanova ex Grubov | Roots   | 3′-hydroxy-4′-methoxy-4′-dehydroxy-nyasol, 3′-methoxy-nyasol, 1,3-di-p-hydroxyphenyl-4-penten-1-one, asparenydiol, 3′′-methoxy-asparenydiol, 3′′-methoxy-nyasin, iso-agatharesinol, gobicusin A | SE, CC, [α]D, UV, IR, NMR, MS                | [17]       |
|              |                                |                  |                                                                |                                              |            |
| Asparagaceae | Asparagus racemosus Wild.       | Whole plant      | iso-agatharesinol, gobicusin A                                 | SE, CC, NMR, MS                              | [19]       |
|              |                                |                  |                                                                |                                              |            |
| Drimiopsis   | Drimiopsis burkei Baker         | Bulbs            | (−)-nyasol                                                     | SE, CC, [α]D, NMR, MS                        | [20,21]    |
|              |                                |                  |                                                                |                                              |            |
| Drimiopsis   | Drimiopsis maculata Lindl. and Paxton | Bulbs        | (−)-(E)-1,3-bis(4-hydroxyphenyl)-1,4-pentadiene                | SE, CC, [α]D, NMR, MS                        | [22]       |
Table 1. Cont.

| Family               | Genus and Species                                      | Plant Part           | Chemical Constituents                                                                 | Analytical Methods               |
|----------------------|--------------------------------------------------------|----------------------|--------------------------------------------------------------------------------------|----------------------------------|
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**Berberidaceae**

- **Ledebouria ovatifolia** (Baker) Jessop
  - Whole plant
  - 5-((5Z, 7)-1-(4-hydroxyphenyl)pent-1,4-dien-3-yl)-2,3-dimethoxyphenol
  - n.r. \[21\]

- **Rhodolecanthus campanulatus H. Perrier**
  - Bulbs
  - dysoxysmanolignan A, dysoxysmanolignan B
  - SE, CC, \(\alpha\)D, IR, NMR, MS \[22\]

- **Descurainia sophia** (L.) Webb ex Prantl
  - Roots
  - descurac acid
  - SE, LC, CC, \(\alpha\)D, IR, NMR, MS \[23\]

- **Compositae**

  - **Saussurea macrota** Franch
    - Whole plant
    - egonol
    - SE, CC, TLC, \(\alpha\)D, IR, NMR, MS \[24\]

- **Cupressaceae**

  - **Chamaecyparis formosensis** Matsum.
    - Wood
    - trans-nyasol
    - SE, CC, UV, IR, NMR \[25\]

- **Libocedrus yateensis** Guillaumin
  - Heartwood
  - yateresinol, nyasol
  - SE, CC, \(\alpha\)D, UV, NMR, MS \[26\]

- **Hypericaceae**

  - **Hypericum chinense** L.
    - Leaves
    - hyperione A, hyperione B
    - SE, CC, \(\alpha\)D, IR, NMR, MS \[27\]

**Compositae**

- **Saussurea macrota** Franch
  - Whole plant
  - egonol
  - SE, CC, TLC, \(\alpha\)D, IR, NMR, MS \[28\]

- **Hypericaceae**

  - **Hypericum chinense** L.
    - Leaves
    - hyperione A, hyperione B
    - SE, CC, \(\alpha\)D, IR, NMR, MS \[29\]

**Berberidaceae**

- **Ledebouria ovatifolia** (Baker) Jessop
  - Whole plant
  - 5-((5Z, 7)-1-(4-hydroxyphenyl)pent-1,4-dien-3-yl)-2,3-dimethoxyphenol
  - n.r. \[21\]

- **Rhodolecanthus campanulatus H. Perrier**
  - Bulbs
  - dysoxysmanolignan A, dysoxysmanolignan B
  - SE, CC, \(\alpha\)D, ECD, IR, NMR, MS \[22\]

- **Descurainia sophia** (L.) Webb ex Prantl
  - Roots
  - descurac acid
  - SE, LC, CC, \(\alpha\)D, IR, NMR, MS \[23\]

- **Berberidaceae**

  - **Ledebouria ovatifolia** (Baker) Jessop
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    - 5-((5Z, 7)-1-(4-hydroxyphenyl)pent-1,4-dien-3-yl)-2,3-dimethoxyphenol
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  - SE, CC, \(\alpha\)D, ECD, IR, NMR, MS \[22\]

- **Descurainia sophia** (L.) Webb ex Prantl
  - Roots
  - descurac acid
  - SE, LC, CC, \(\alpha\)D, IR, NMR, MS \[23\]

- **Berberidaceae**

  - **Ledebouria ovatifolia** (Baker) Jessop
    - Whole plant
    - 5-((5Z, 7)-1-(4-hydroxyphenyl)pent-1,4-dien-3-yl)-2,3-dimethoxyphenol
    - n.r. \[21\]

- **Rhodolecanthus campanulatus H. Perrier**
  - Bulbs
  - dysoxysmanolignan A, dysoxysmanolignan B
  - SE, CC, \(\alpha\)D, ECD, IR, NMR, MS \[22\]

- **Descurainia sophia** (L.) Webb ex Prantl
  - Roots
  - descurac acid
  - SE, LC, CC, \(\alpha\)D, IR, NMR, MS \[23\]
| Plant Species | Location | Part | Compounds | Analytical Methods |
|---------------|----------|------|-----------|--------------------|
| Curculigo breviscapa | S.C.Chen | Rhizomes | breviscapin C, breviscaside B, curcapirol, capituloside, pilosidine, cucapitoside, crassifoside H, crassifoside F, (2S)-1-O-butyl-iso-nyasidoside, (2S)-1-O-butyl-nyasidoside, nyasicoside, curcapital, capituloside, pilosidine, cucapitoside, crassifoside H, crassifoside F | SE, CC, LC, [{α}D], IR, UV, NMR, MS |
| Curculigo capitulata (Lour.) Kuntze | Rhizomes | 3′′,4′′-dehydroxy-nyasidoside, 1-O-methyl-nyasidoside, curclignan | SE, CC, IR, UV, CD, NMR, MS |
| Curculigo crassifolia (Baker) Hook.f. | Rhizomes | crassifoside I, sinensigenin C, 1,1-bis-(3,4-dihydroxyphenyl)-1-(2-furan)-methane, crassifoside A, curcapital, crassifoside E, crassifoside F | SE, CC, LC, [{α}D], IR, UV, NMR, MS |
| Curculigo pilosa (Schumach. and Thonn.) Engl. | Rhizomes | nyasidoside, curcapirol, pilosidine | SE, CC, [{α}D], IR, UV, NMR, MS |
| Curculigo recurvata W.T.Aiton | Rhizomes | curcapirol, iso-curcapirol, 1-O-methyl-curcapirol, 1-O-methyl-iso-curcapirol, sinensigenin A, sinensigenin B, crassifoside B, crassifoside D, crassifoside A, crassifoside C, crassifoside E, curcapital, capituloside, 1-O-methyl-nyasidoside, 1-O-methyl-iso-nyasidoside, (1R)-crassifoside D, (1S)-crassifoside D, 1-O-methyl-nyasidoside | SE, CC, CE, CD, NMR, MS |
| Curculigo sinensis S.C.Chen | Rhizomes | breviscapin C, breviscaside B, curcapirol, capituloside, pilosidine, cucapitoside, crassifoside H, crassifoside F, (2S)-1-O-butyl-iso-nyasidoside, (2S)-1-O-butyl-nyasidoside, nyasicoside, curcapital, capituloside, pilosidine, cucapitoside, crassifoside H, crassifoside F | SE, CC, LC, [{α}D], IR, UV, NMR, MS |
| Hypoxis angustifolia Lam. | Rhizomes | nyasol, hypoxoside, nyasolinoside, rooperol, mononyasine A, mononyasine B, hypoxoside, nyasosidenyaside | SE, CC, [{α}D], IR, UV, NMR, MS |
| Hypoxis hemerocallidea Fisch., C.A.Mey. and Ave-Lall. | Rhizomes | dehydroxy-hypoxoside, 6′-dehydroxy-hypoxoside, rooperol, dehydroxy-rooperol, 6′-dehydroxy-rooperol | SE, HPLC, LC, UV, NMR, MS |
| Hypoxis interjecta Nel | Rhizomes | interjectin | SE, CC, [{α}D], IR, UV, NMR, MS |
| Hypoxis multiceps Buchinger ex Baker | Rhizomes | nyasicoside, mononyasine A, mononyasine B, nyasoside, hyposide, nyasoside | SE, CC, [{α}D], IR, UV, NMR, MS |
| Genus和Species | Habitat | Compounds | Analytical Methods |
|----------------|---------|-----------|--------------------|
| Hypoxis obtusa Burch. ex Ker Gawl. | Rhizomes | hypoxoside, rooperol, obtuside A, obtuside B | SE, CC, NMR, MS | [59] |
| Jungermannia exsertifolia Stephani | Whole plant | 3-carboxy-6,7-dihydroxy-1,3′,4′-dihydroxyphenoxy-naphthalene, 3-carboxy-6,7-dihydroxy-1,3′,4′-dihydroxyphenoxy-naphthalene-9,5′-O-shikimic acid ester | SE, CC, [α]D, IR, UV, NMR, MS | [60] |
| Krameria cytisoides Cav. | Roots | 3-formyl-2-(4-hydroxy-3-methoxyphenyl)-7-methoxy-5-(E)-propenylbenzofuran, 2-(2,4-dimethoxyphenyl)-5-(E)-propenylbenzofuran, rataniaphenol I, toltecol-2-(4-hydroxyphenyl)-7-methoxy-5-(E)-propenylbenzofuran, 2-(2,4-dihydroxyphenyl)-5-(E)-propenylbenzofuran, 2-(2,4-dimethoxyphenyl)-5-(E)-propenylbenzofuran, olmecol-3,3′-didemethoxy-nectandrin B, 3′-demethoxy-nectandrin B, rataniaphenol I, eupomatenoide b, 2-(2,4-dihydroxyphenyl)-5-(E)-propenylbenzofuran, (E)-2-(4-methoxyphenyl)-3-methyl-5-(prop-1-enyl)benzofuran, rataniaphenol III, 2-(2,4-dimethoxyphenyl)-5-(E)-propenylbenzofuran, 2-(4-hydroxyphenyl)-5-(E)-propenylbenzofuran, 2-(4-hydroxy-2-methoxyphenyl)-5,3′-dihydroxy-(E)-1-propen-1-yl benzofuran, 2-(2-hydroxy-4-methoxyphenyl)-5,3′-dihydroxy-(E)-1-propen-1-yl benzofuran, 2-(2,4-dihydroxy-4-methoxyphenyl)-5,3′-dihydroxy-(E)-1-propen-1-yl benzofuran, (2R,3R)-2,3-dihydro-2-(4-hydroxy-3-methoxyphenyl)-3-methyl-5-(E)-propenylbenzofuran, (+)-licarin A, 2-(2,4-dihydroxy-2-(4-hydroxy-3-methoxyphenyl)-3-methyl-5-(E)-propenylbenzofuran, 4-(5-(R)-2-hydroxypropyl)-3-methylbenzofuran-2-ylphenol | SE, CC, TLC, UV, IR, NMR, MS | [62] |
| Krameria grayi Rose and Painter | Roots | 3-formyl-2-(4-hydroxy-3-methoxyphenyl)-7-methoxy-5-(E)-propenylbenzofuran, 2-(2,4-dimethoxyphenyl)-5-(E)-propenylbenzofuran, rataniaphenol I, toltecol-2-(4-hydroxyphenyl)-7-methoxy-5-(E)-propenylbenzofuran, 2-(2,4-dihydroxyphenyl)-5-(E)-propenylbenzofuran, 2-(2,4-dimethoxyphenyl)-5-(E)-propenylbenzofuran, olmecol-3,3′-didemethoxy-nectandrin B, 3′-demethoxy-nectandrin B, rataniaphenol I, eupomatenoide b, 2-(2,4-dihydroxyphenyl)-5-(E)-propenylbenzofuran, (E)-2-(4-methoxyphenyl)-3-methyl-5-(prop-1-enyl)benzofuran, rataniaphenol III, 2-(2,4-dimethoxyphenyl)-5-(E)-propenylbenzofuran, 2-(4-hydroxyphenyl)-5-(E)-propenylbenzofuran, 2-(4-hydroxy-2-methoxyphenyl)-5,3′-dihydroxy-(E)-1-propen-1-yl benzofuran, 2-(2-hydroxy-4-methoxyphenyl)-5,3′-dihydroxy-(E)-1-propen-1-yl benzofuran, 2-(2,4-dihydroxy-4-methoxyphenyl)-5,3′-dihydroxy-(E)-1-propen-1-yl benzofuran, (2R,3R)-2,3-dihydro-2-(4-hydroxy-3-methoxyphenyl)-3-methyl-5-(E)-propenylbenzofuran, (+)-licarin A, 2-(2,4-dihydroxy-2-(4-hydroxy-3-methoxyphenyl)-3-methyl-5-(E)-propenylbenzofuran, 4-(5-(R)-2-hydroxypropyl)-3-methylbenzofuran-2-ylphenol | SE, CC, TLC, UV, IR, NMR, MS | [63] |
| Lamiaceae | | |
|---|---|---|
| **Table 1. Cont.** | | |
| | Krameria ixine L. | Roots |
| | Krameria tomentosa A. St.-Hil. | Roots |
| | Glechoma longituba (Nakai) Kuprian. | Whole plant |
| | Tectona grandis L.f. | Leaves |
| | Vitex negundo var. cannabinola (Siebold and Zucc.) Hand.-Mazz. | Fruits |
| | Vitex negundo L. | Roots |
| | **Krameria ixine L.** | **Krameria tomentosa A. St.-Hil.** | **Glechoma longituba (Nakai) Kuprian.** | **Tectona grandis L.f.** | **Vitex negundo var. cannabinola (Siebold and Zucc.) Hand.-Mazz.** | **Vitex negundo L.** |
| | roots | roots | whole plant | leaves | fruits | roots |
| | Conocarpan, rathanhiaphenol I, rathanhiaphenol II, 2-(4,6-dimethoxyphenyl-1-2-hydroxyphenyl)-5-(E)-propenylbenzofuran, 2-(4,6-dimethoxyphenyl)-5-(E)-prop-2-en-1-ylbenzofuran, 2-(2,4-dihydroxyphenyl)-5-(E)-prop-2-en-1-ylbenzofuran, 5-(E)-propenyl-2-(2,4,5-trimethoxyphenyl)benzofuran, eupomatenois15, 5-allyl-2-(4-hydroxyphenyl)-3-methylbenzofuran, hermosiisol, 4-2-(4-allyl-2-methoxyphenyl)allyl-phenol, trans-(2’S)-2′-(4-methoxyphenyl)prop-2′-yl-anethol, 3,3′-didemethoxy-nectandrin B krametosan, rathanhiaphenol II, 2-(2′-hydroxy-4′,6′-dimethoxyphenyl)-5-(E)-propenylbenzofuran, conocarpan, decurrenal (S) SE, CC, [α]D, IR, NMR, MS [64] | SE, [α]D, IR, NMR, MS [65] | SE, [α]D, IR, NMR, MS [66] | SE, CC, TLC, [α]D, CD, UV, IR, NMR, MS [67] | SE, [α]D, IR, UV, NMR, MS [68] | (+)-lyoniresinol, (+)-lyoniresinol 3a-O-β-glucopyranoside, vitrofolal E, vitrofolal F SE, CC, [α]D, IR, UV, NMR, MS [70] | (+)-lyoniresinol, (+)-lyoniresinol 3a-O-β-glucopyranoside, vitrofolal E SE, CC, [α]D, IR, UV, NMR, MS [72] |
| | **SE, CC, TLC, [α]D, CD, UV, IR, NMR, MS [64]** | **SE, CC, [α]D, IR, NMR, MS [65]** | **SE, CC, [α]D, IR, NMR, MS [66]** | **SE, CC, HPLC, IR, NMR, MS [67]** | **SE, CC, HPLC, NMR, MS [68]** | **SE, CC, TLC, IR, UV, NMR, MS [70]** | **SE, CC, [α]D, IR, UV, NMR, MS [72]** |
Table 1. Cont.

| Molecules | Seeds | Aerial parts | Vitex rotundifolia L.f. Roots | Lauraceae | Lepidoziaceae | Lepidozia incurvata Lindenb. | Lepidozia reptans (L.) Dumort. | Lophocoleaceae Chiloscyphus polyanthos (L.) Corda |
|-----------|-------|-------------|-------------------------------|-----------|----------------|--------------------------|--------------------------|-----------------------------|
| vitedoin A, 6-hydroxy-4-(4-hydroxy-3-methoxyphenyl)-3-hydroxymethyl-7-methoxy-3,4-dihydro-2-naphthaldehyde, detetrahydro-conidendrin, vitrofolal E, vitrofolal F, 2α,3β-7-O-methyl-cedrusin, vitemegheteroin E, vitemegheteroin F, vitemegheteroin G, vitemeghassise B, 6-hydroxy-4-(4-hydroxy-3-methoxyphenyl)-3-hydroxymethyl-7-methoxy-3,4-dihydro-2-naphthaldehyde, vitrofolal E, vitrofolal F | 6-hydroxy-4-(4-hydroxy-3-methoxyphenyl)-3-hydroxymethyl-7-methoxy-3,4-dihydro-2-naphthaldehyde, vitrofolal E, vitrofolal F, vitedoin A, vitedo in A, vitedoin A, vitedo in C, vitedo in D, vitedoin E | 6-hydroxy-4-(4-hydroxy-3-methoxyphenyl)-3-hydroxymethyl-7-methoxy-3,4-dihydro-2-naphthaldehyde, vitrofolal E, vitrofolal F, vitedoin A, 6-hydroxy-4-(4-hydroxy-3-methoxyphenyl)-3-hydroxymethyl-7-methoxy-3,4-dihydro-2-naphthaldehyde, vitrofolal E, vitrofolal F | SE, CC, [α]D0, NMR, MS | SE, CC, [α]D0, NMR, MS | SE, CC, LC, [α]D0, UV, IR, NMR, MS | SE, CC, LC, [α]D0, UV, IR, NMR, MS | SE, CC, LC, HPLC, [α]D0, NMR, MS | SE, CC, LC, HPLC, [α]D0, NMR, MS |
| | | | Vitex rotundifolia L.f. | Nectandra linata (Kunth) Rohwer | Bazzania trilobata (L.) Gray | | | | |
| | | | Young leaves | Whole plant | Whole plant | Whole plant | Whole plant | Whole plant |
| | | | | | | | | | |
| | | | | | | | | | |

Sources: [73], [74], [75], [76], [77], [78], [79], [80]
| Family       | Genus                  | Species                          | Parts                  | Compounds                                                                 | Method(s)                  | References |
|--------------|------------------------|----------------------------------|------------------------|---------------------------------------------------------------------------|----------------------------|------------|
| Lythraceae   | Sonneratia caseolaris  | (L.) Engl.                        | Fruits                 | nyasol, 4′-O-methyl-nyasol                                                | SE, CC, TLC, NMR, MS       | [81]       |
|              | Sonneratia ovata       | Backer                            | Fruits                 | nyasol, 4′-O-methyl-nyasol                                                | SE, CC, TLC, NMR, MS       | [81]       |
|              | Trapa natans L.        |                                  | Whole plant            | nyasol                                                                    | SE, CC, [α]D, IR, NMR, MS  | [82]       |
| Magnoliaceae | Magnolia odorata (Chun)| Figlar and Noot.                  | Twigs                  | nyasol, 4′-O-methyl-nyasol                                                | SE, CC, LC, HPLC, NMR, MS  | [83]       |
| Malvaceae    | Urena lobata L.        |                                  | Aerial parts           | ceplignan-4-O-β-D-glucoside                                               | SE, CC, [α]D, IR, UV, NMR, MS | [84]       |
| Meliaceae    | Cedrela sinensis Juss. | M. Roem.                          | Leaves                 | aglacin H                                                                 | SE, CC, TLC, NMR, MS       | [85]       |
| Oleaceae     | Syringa pinnatifolia   | Hemsl.                            | Stem barks             | noralashinol A, noralashinol B                                           | SE, CC, LC, [α]D, UV, IR, NMR, MS | [86]       |
| Pelliaceae   | Peltia ephigilla (L.)  | Corda                             | Gametophytes           | 3-carboxy-6,7-dihydroxy-1-(3′,4′dihydroxyphenyl)-naphthalene              | SE, CC, IR, NMR, MS       | [87]       |
| Phyllanthaceae| Phylanthus virgatus    | G.Forst.                          | Whole plant            | virgatyne                                                                 | SE, CC, LC, [α]D, UV, NMR, MS | [88]       |
|              | Peperomia tetraphylla  | (G.Forst.) Hook. and Arn.         | Whole plant            | methyl rel-(1R,2S,3S)-2-(7-methoxy-1,3-benzodioxol-5-yl)-3-(2,4,5-trimethoxyphenyl)-cyclobutane-carboxylate | SE, CC, LC, [α]D, UV, IR, CD, NMR, MS | [89]       |
|              | Piper obliquum Ruiz    |                                  | Leaves                 | peperotetraphin                                                           | SE, CC, LC, [α]D, UV, IR, NMR, MS | [90]       |
|              | and Pav.               |                                  |                        | justiflorin                                                               | SE, CC, [α]D, UV, IR, NMR, MS | [91]       |
|              | Imperata cylindrica (L.)| Rausch.                           | Rhizomes               | (S)+(+)imperanene                                                          | SE, CC, [α]D, UV, IR, NMR, MS | [92]       |
| Saururaceae  | Gymnoleca chinenis     | Decne.                            | Whole plant            | gymnothelignan A, gymnothelignan B                                       | SE, CC, X-ray, NMR, MS     | [93]       |
| Selaginellaceae| Selaginella moellendorffii| Hieron.                          | Whole plant            | moellenoside B                                                            | SE, CC, LC, TLC, [α]D, CD, UV, IR, NMR, MS | [94]       |
| Schisandraceae| Schisandra bicolor     | W.C.Cheng.                        | Fruits                 | marphenol C, marphenol D, marphenol E, marphenol F                       | SE, CC, LC, [α]D, UV, IR, NMR, MS | [95]       |
|              | Cestrum diurnum L.     |                                  | Leaves                 | cestrumoside, berchernol-4′-O-β-glucopyranoside, dehydrodiconiferyl        | SE, CC, [α]D, UV, CD, IR, NMR, MS | [96]       |
|              | Cestrum parqui (Lam.)  | U/H. Her.                         | Leaves                 | 3α-O-β-glucopyranoside, 3α-O-β-glucopyranoside, 9′-nor-3′,4′,4′-trihydroxy-3,5-dimethoxy-7-eno-9, 7′-lactone | SE, CC, [α]D, NMR, MS       | [97]       |
|              | Nicotiana tabacum L.   |                                  | Roots and stems        | recarphenol C, recarphenol D, sequin C, benzodioxane                      | n.r.                       | [98]       |
|              | Solanum melongena L.   |                                  | Roots                  | guaiacylglycerol 8′-vanillin ether, fusicul, polysytychol                  | SE, CC, HPLC, [α]D, NMR, MS | [99]       |
Table 1. Cont.

| Family        | Species                                      | Part             | Identified Compounds                                      | Methods                                      | References |
|---------------|----------------------------------------------|------------------|-----------------------------------------------------------|----------------------------------------------|------------|
| **Styracaceae** |                                             |                  |                                                           |                                              |            |
|               | *Styrax camporum* Pohl                        | Whole plant      | egonol, homoegonol, homoeognol, homoeognol glucoside      | SE, pTLC, CC, HPLC-UV, NMR                    | [105]      |
| Styrax ferruginosus Nees and Mart. | Leaves                                        |                  | egonol, homoegonol, homoeognol glucoside, homoeognol glucoside | SE, FCC, IR, NMR, MS                         | [106]      |
| Styrax japonica Sieb. et Zucc. | Stem bark                                     |                  | styraxlignolide A, egonol, masutakeside I                 | SE, CC, LC, [α]D, UV, NMR, MS                | [107]      |
| Styrax ohassii Sieboldi and Zucc. | Aerial parts                                  |                  | 1′′-hydroxylegonol, gentiobioside, egonol glucoside       | SE, CC, LC, NMR, MS                         | [108]      |
| Styrax officinalis L. | Fruits                                       |                  | egonol, dimethyl-egonol, homoeognol                      | SE, CC, NMR, MS                              | [109]      |
| Styrax pohlii A. DC. | Aerial parts                                 |                  | homoeognol gentiobioside, homoeognol glucoside           | SE, CC, HPLC, NMR                            | [110]      |
| Styrax ramirezii Greenm. | Fruits                                       |                  | 7-demethoxy-egonol, 4-O-demethyl-homoegonol              | SE, HPLC-DAD-MS                              | [111]      |
| Thelypteridaceae | *Abacopteris penangiana* (Hook.) Ching | Rhizomes         | penanganol A, penanganol B                               | SE, CC, [α]D, UV, IR, NMR, MS                | [112]      |
| Urticaceae     | *Pouzolzia occidentalis* (Liebm.) Wedd.  | Aerial parts     | pouzolignan A, pouzolignan B                             | SE, CC, LC, [α]D, UV, IR, NMR, MS            | [113]      |
|               | *Pouzolzia zejlanica* var. microphylla (Wedd.) Masam. | Aerial parts | pouzolignan D, pouzolignan K                             | n.a.                                         | [114]      |

Figures 2–24 below show the structures of all the identified nor-lignans.
R1 = R4 = R5 = H, R2 = OH, R3 = OMe: sequosempervirin B
R1 = R3 = OMe, R2 = OH, R4 = R5 = H: sequosempervirin C
R1 = R3 = R4 = R5 = H, R2 = OH: agatharesinol
R1 = OMe, R2 = OH, R3 = R5 = H, R4 = Me: dimethyl-agatharesinol acetonide
R1 = R3 = R4 = OMe, R2 = OH, R5 = H: metasesquirin D
R1 = R4 = R5 = H, R2 = OMe, R3 = OH, R6 = H: metasesquirin B
R1 = R3 = H, R2 = OMe: sequosempervirin D
R1 = R2 = OMe, R3 = H: sequosempervirin E
R1 = R2 = R3 = H: agatharesinol acetonide
R1 = OMe, R2 = H, R3 = Me: dimethyl-agatharesinol acetonide

**Figure 2.** The isolated nor-lignans in the plant kingdom—part 1.
R₁ = R₂ = H, R₃ = OMe, R₄ = R₅ = -O-CH₂-O-: egonol
R₁ = R₂ = H, R₃ = OMe, R₄ = R₅ = OMe: homoegonol
R₁ = R₂ = H, R₃ = OH, R₄ = R₅ = -O-CH₂-O-: demethyl-egonol
R₁ = R₂ = H, R₃ = OMe, R₄ = R₅ = -O-CH₂-O-: 7-demethoxy-egonol
R₁ = R₂ = H, R₃ = R₄ = OMe, R₅ = OH: 4-O-demethyl-homoegonol
R₁ = β-D-Glc, R₂ = H, R₃ = OMe, R₄ = R₅ = -O-CH₂-O-: egonol glucoside
R₁ = β-D-Glc, R₂ = H, R₃ = OMe, R₄ = R₅ = OMe: homoegonol glucoside
R₁ = 6-O-β-D-Glc-β-D-Glc, R₂ = H, R₃ = OMe, R₄ = R₅ = -O-CH₂-O-: egonol gentiobioside
R₁ = 6-O-β-D-Glc-β-D-Glc, R₂ = H, R₃ = OMe, R₄ = R₅ = OMe: homoegonol gentiobioside
R₁ = 6-O-β-D-Xyl-β-D-Glc, R₂ = H, R₃ = OMe, R₄ = R₅ = -O-CH₂-O-: masutakeside I
R₁ = 6-O-β-D-Xyl-β-D-Glc, R₂ = OH, R₃ = OMe, R₄ = R₅ = -O-CH₂-O-: 1"-hydroxylegonol gentiobioside

R₁ = OMe, R₂ = OH: gobicusin B
R₁ = OH, R₂ = H: 4-[5-(4-methoxyphenoxy)-3-penten-1-ynyl]phenol

R₁ = R₂ = H, R₃ = OMe: vitrofolal A
R₁ = OH, R₂ = H, R₃ = OMe: vitrofolal B

**Figure 3.** Isolated *nor*-lignans in the plant kingdom—part 2.
Figure 4. Isolated nor-lignans in the plant kingdom—part 3.
Figure 5. Isolated nor-lignans in the plant kingdom—part 4.
Figure 6. Isolated nor-lignans in the plant kingdom—part 5.
Figure 7. Isolated nor-lignans in the plant kingdom—part 6.

Figure 8. Isolated nor-lignans in the plant kingdom—part 7.
Figure 9. Isolated *nor*-lignans in the plant kingdom—part 8.
Figure 10. Isolated nor-lignans in the plant kingdom—part 9.
Figure 11. Isolated nor-lignans in the plant kingdom—part 10.
R₁ = R₂ = R₃ = R₄ = OH: hypoxoside
R₁ = H, R₂ = R₃ = OH, R₄ = O-β-D-Glc: dehydro-hypoxoside
R₁ = R₂ = H, R₃ = R₄ = O-β-D-Glc: bis-dehydro-hypoxoside
R₁ = R₂ = R₃ = OH: rooperol
R₁ = R₂ = R₃ = R₄ = OH: dehydro-rooperol
R₁ = R₂ = R₃ = OH, R₄ = O-β-D-Glc: obtuside A
R₁ = R₂ = R₃ = OH, R₄ = O-β-D-Glc: obtuside B

R₁ = R₂ = R₃ = R₄ = OH: glechomol A
R₁ = R₂ = R₃ = OH, R₄ = R₅ = OH, R₆ = Et: glechomol B

R₁ = CH2OH: noralashinol A
R = CH(OMe)₂: noralashinol C
R = O-β-D-Glc: sinenside B

Figure 12. Isolated nor-lignans in the plant kingdom—part 11.
Figure 13. Isolated nor-lignans in the plant kingdom—part 12.
Figure 14. Isolated nor-lignans in the plant kingdom—part 13.
R = CH₂OH: (+)-lyoniresinol
R = CH₂O-β-D-Glc: (+)-lyoniresinol 3α-O-β-glucopyranoside

chamaecypanone C

acorusin B
	noralashinol B

obtunorlignan A

Figure 15. Isolated nor-lignans in the plant kingdom—part 14.
Figure 16. Isolated nor-lignans in the plant kingdom—part 15.
R = H: asparenydiol
R = OMe: 3''-methoxy-asparenydiol

Figure 17. Isolated nor-lignans in the plant kingdom—part 16.
R₁ = R₂ = R₃ = H: 3-carboxy-6,7-dihydroxy-l-(3',4'-dihydroxyphenyl)-naphthalene
R₁ = Me, R₂ = O-α-L-Rha, R₃ = H: 3-carboxy-6-methoxy-1-(3',4'-dihydroxyphenyl)-naphthalene-7-O-α-L-rhamnopyranoside
R₁ = R₂ = H, R₃ = CH(COOH)CH₂COOH: 3-carboxy-6,7-dihydroxy-1-(3',4'-dihydroxy-phenyl)-naphthalene-9,2''-O-malic acid ester
R₁ = R₂ = H, R₃ = shikimic acid: 3-carboxy-6,7-dihydroxy-1-(3',4'-dihydroxyphenyl)-naphthalene-9,5''-O-shikimic acid ester

(S)-(+) imperanene

9'-nor-3',4',4'-trihydroxy-3,5-dimethoxylign-7-eno-9,7'-lactone

pouzolignan K

pouzolignan D

Figure 18. Isolated nor-lignans in the plant kingdom—part 17.
Figure 19. Isolated nor-lignans in the plant kingdom—part 18.

Figure 20. Isolated nor-lignans in the plant kingdom—part 19.
Figure 21. Isolated *nor*-lignans in the plant kingdom—part 20.
R₁ = OMe, R₂ = OH, R₃ = R₄ = R₅ = R₇ = H, R₆ = Me: rataniaphenol I
R₁ = OH, R₂ = R₃ = R₄ = R₅ = H, R₆ = R₇ = Me: rataniaphenol II
R₁ = OMe, R₂ = OH, R₃ = R₄ = R₅ = R₇ = H, R₆ = Me: rataniaphenol III
R₁ = OH, R₂ = R₃ = R₄ = R₅ = H, R₆ = R₇ = Me, R₈ = OMe: eupomatenoid 6
R₁ = OH, R₂ = R₃ = R₄ = R₅ = H, R₆ = R₇ = Me, R₈ = OMe: eupomatenoid 13
R₁ = OMe, R₂ = R₃ = R₄ = R₅ = H, R₆ = R₇ = Me: eupomatenoid 15
R₁ = R₂ = R₃ = OMe, R₄ = R₅ = R₆ = H, R₇ = Me: toltecol
R₁ = R₂ = OH, R₃ = R₄ = R₅ = R₇ = H, R₆ = Me: 5-[(E)-propenyl]-2-(2,4,5-trimethoxyphenyl)benzofuran
R₁ = R₂ = OMe, R₃ = OH, R₄ = R₅ = R₆ = H, R₇ = Me: 2-(4,6-dimethoxyphenyl-2-hydroxyphenyl)-5-[(E)-propenyl]benzofuran
R₁ = OMe, R₂ = R₃ = R₄ = R₅ = R₆ = H, R₇ = Me: (E)-2-(4-methoxyphenyl)-3-methyl-5-[(prop-1-enyl)]benzofuran
R₁ = R₂ = OH, R₃ = R₄ = R₅ = R₆ = H, R₇ = Me: 2-(2,4-dihydroxyphenyl)-5-[(E)-propenyl]benzofuran
R₁ = R₂ = OH, R₃ = R₄ = R₅ = R₆ = H, R₇ = Me: 2-(2,4-dihydroxyphenyl)-7-methoxy-5-[(E)-propenyl]benzofuran
R₁ = R₂ = OMe, R₃ = R₄ = R₅ = R₆ = H, R₇ = Me: 2-(2,4-dimethoxyphenyl)-5-[(E)-propenyl]benzofuran
R₁ = R₂ = OMe, R₃ = R₄ = R₅ = R₆ = H, R₇ = Me: 2-(4-hydroxyphenyl)-5-[(E)-propenyl]benzofuran
R₁ = OH, R₂ = R₃ = R₄ = R₅ = R₆ = H, R₇ = Me: 2-(4-hydroxyphenyl)-7-methoxy-5-[(E)-propenyl]benzofuran
R₁ = OMe, R₂ = OH, R₃ = R₄ = R₅ = R₆ = H, R₇ = CH₂OH: 2-(2'-hydroxy-4',6'-dimethoxyphenyl)-5-[(E)-propenyl]benzofuran
R₁ = OH, R₂ = OMe, R₃ = H, R₄ = R₅ = R₆ = H, R₇ = Me: 2-[(2'-hydroxy-4',6'-dimethoxyphenyl)5-[(E)-propenyl]benzofuran

Figure 22. Isolated nor-lignans in the plant kingdom—part 21.
R₁ = OMe, R₂ = H, R₃ = OH: dethetrahydro-conidendrin
R₁ = H, R₂ = R₃ = OMe: 4-(3,4-dimethoxyphenyl)-6-hydroxy-5-methoxynaphtho[2,3-c]furan-1(3H)-one
R₁ = R₃ = OMe, R₂ = H: 4-(3,4-dimethoxyphenyl)-6-hydroxy-7-methoxynaphtho[2,3-c]furan-1(3H)-one
R₁ = R₃ = OH, R₂ = H: vitexdoin G

(7S,8R)-dihydrodehydrodiconiferyl alcohol

1,2-dihydro-7-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-3-(hydroxymethyl)-6-methoxy-(1S,2R)-2-naphthalencarboxaldehyde

6-hydroxy-4-(4-hydroxy-3-methoxyphenyl)-7-methoxynaphtho[2,3-c]furan-1,3-dione

3,4-dihydro-4-(4-hydroxy-3-methoxyphenyl)-3-(hydroxymethyl)-6,7-dimethoxy-(3R,4S)-2-naphthalencarboxaldehyde

Figure 23. Isolated nor-lignans in the plant kingdom—part 22.
3. Chemotaxonomy

As Table 1 clearly shows, nor-lignans have been recognized as phytochemical constituents of several families, even chemosystematically far away from each other.

This is in accordance with the easy phytochemical pathway connected with very common PhC3 intermediate metabolites. However, the rearrangements following the junction of the two originating moieties are another matter.

Therefore, some specific compounds can be evidenced as chemotaxonomic makers at every classification level.

In particular, (+)-acortatarinowins A-C, (−)-acortatarinowins A-C (Figure 8) and acorusin B (Figure 15) may be useful chemotaxonomic markers for the species Acorus tatarinowii Schott. since they have been isolated only from that species [5,6].

Pachypostaudins A-B and pachypophyllin (Figures 16 and 17) may be chemotaxonomic markers for the entire Annonaceae family given their specific occurrence here [7,8].

Asparenydiol (Figure 17) and its derivatives are considered as some of the chemotaxonomic markers for the genus Asparagus L. [17].

Capituloside (Figure 4) and the crassifosides (Figures 10 and 11) may be used as chemotaxonomic markers for the genus Curculigo Gaertn. given their occurrence limited to only it [40,43,44,46,51,52].

For the same reason, hypoxoside and related compounds (Figure 12) are a possible chemotaxonomic marker for the genera Hypoxis L. and Curculigo Gaertner [54,56,59] whereas rataniaphenols I-II (Figure 22) may serve as chemotaxonomic markers for the genus Krameria L. [62–64].

Within the Lamiaceae family, surely negundins A–B (Figure 20) are chemotaxonomic markers for the species Vitex negundo L given their occurrence in several exemplars of this species [69–71].
Indeed, egonol, homoegonol and their derivatives (Figure 3) can serve as chemotaxonomic markers for the *Styrax* L. genus since their occurrence is quite limited to it [105–111].

### 4. Biological Activities

*Nor*-lignans show several interesting biological activities, i.e., antioxidant, antifungal, antibacterial, antiallergic, antiasthma, analgesic, anticomplement, antiatherogenic, antiparasitic, vascular, antiastress, anti-inflammatory, cytotoxic, phytotoxic, inhibitory of enzymes, proteins and platelet aggregation. In the following pages, these are characterized one by one.

#### 4.1. Antioxidant

Egonol (Figure 3) highly inhibits the production of NO and highly reduces the release of ROS in a dose dependent manner. The same is valid for homoegonol but in a minor way [111].

Indeed, curcapital, crassifogenin C (Figure 9), crassifoside E and crassifoside F (Figure 10) show strong radical scavenging activity by the 1,1-diphenyl-2-picrylhydrazyl (DPPH•) assay with IC₅₀ values equal to 7.76, 13.48, 15.54 and 17.07 µM, respectively, which are much higher than the control, L-ascorbic acid (IC₅₀ = 27.59 µM) [44].

Moreover, hypoxoside and rooperol (Figure 12) show high effects towards the inhibition of lipid peroxidation with IC₅₀ values equal to 12.6 and 2.6 µM, respectively [54].

Nyasol (Figure 7) exerts medium effects against ABTS•⁺ cation and superoxide anion radicals with IC₅₀ values equal to 45.6 and 40.5 µM, respectively [82].

Vitexdoin F, vitedoin A, 6-hydroxy-4-(4-hydroxy-3-methoxyphenyl)-3-hydroxymethyl-7-methoxy-3,4-dihydro-2-naphthaldehyde, vitexdoin A, negundin B, vitexdoin E, vitrofolal F, 1,2-dihydro-7-hydroxy-1-(4-hydroxy-3- methoxyphenyl)-3-(hydroxymethyl)-6-methoxy-(15,2R)-2-naphthalenecarboxaldehyde, vitexdoin C, vitexdoin D, vitrofolal E, vitexdoin B and detetrahydro-conidendrin (Figure 20) showed stronger effects than ascorbic acid [69,73].

#### 4.2. Antiradical

Vitrofolal E, vitrofolal F, vitedoin A, 6-hydroxy-4-(4-hydroxy-3-methoxyphenyl)-3-hydroxymethyl-7-methoxy-3,4-dihydro-2-naphthaldehyde (Figure 20), detetrahydro-conidendrin (Figure 23) and 2α,3β-7-O-methyl-cedrusin (Figure 21) exert high effects against the stable free radical, 1,1-diphenyl-2-picrylhydrazyl (DPPH•), more than L-cysteine and, in most cases, similar to α-tocopherol [73].

Vitexnegheteroin E, vitexnegheteroin F, vitexnegheteroin G, vitezcannaside B and vitexdoin A (Figure 20) also exhibit strong effects in the ABTS•⁺⁺ assay with IC₅₀ values lower than 3.20 µM [74].

Vitexdoin A, vitexdoin B, vitexdoin C, vitexdoin D, vitexdoin E, vitrofolal E and vitrofolal F (Figure 20) are potent NO production inhibitors with IC₅₀ values equal to 0.38 µM, 0.20 µM, 0.57 µM, 0.13 µM, 0.15 µM, 0.50 µM and 0.11 µM, respectively.

Instead, 6-hydroxy-4-(4-hydroxy-3-methoxyphenyl)-3-hydroxymethyl-7-methoxy-3,4-dihydro-2-naphthaldehyde (Figure 20) has a weaker effect with an IC₅₀ value equal to 3.54 µM. Anyway, they were all more powerful than the positive control L-nitroarginine (IC₅₀ = 43.6 µM) [75].

#### 4.3. Antifungal and Antibacterial

Homoegonol and egonol (Figure 3) exhibit strong effects against *Candida albicans*, *Cladosporium sphaerospermum* and *Staphylococcus aureus* with MIC values equal to 10, 5 and 10 µg/mL, respectively for the former compound, and 12, 10 and 10 µg/mL respectively for the latter compound. Indeed, egonol (Figure 3) and homoegonol (Figure 3) exhibit lower effects only against *Candida albicans* and *Staphylococcus aureus* with MIC values equal to 15 and 15 µg/mL, respectively for the former compound and 20 and 20 µg/mL, respectively for the latter compound [106].

Conversely, homoegonol (Figure 3) is totally inactive against *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Haemophilus influenzae*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* showing MIC values...
higher than 400 µg/mL. Instead, egonol (Figure 3) is weakly active only against *Streptococcus pneumoniae* showing a MIC value equal to 400 µg/mL [115].

*Iso-agatharesinol* and gobicusin A (Figure 7) are also able to exert these effects. In particular, gobicusin A is a better antibacterial compound against *Escherichia coli* and *Staphylococcus aureus* than *iso-agatharesinol* given its MIC values (0.12 and 0.05 mg/mL vs. 0.25 and 0.12 mg/mL, respectively) and its efficacy is extremely comparable to streptomycin especially against *Staphylococcus aureus* (MIC = 0.01 mg/mL) [19].

Nyasol (Figure 7) is able to inhibit the mycelial growth of *Colletotrichum orbiculare*, *Phytophthora capsici*, *Pythium ultimum*, *Rhizoctonia solani* and *Cladosporium cucumerinum* in a MIC range comprised between 1 and 50 mg/mL [13]. Moreover, it potently inhibits the growth of *Leishmania major* with an IC50 value equal to 12 µM and moderately inhibits *Plasmodium falciparum* with an IC50 value equal to 49 µM [14].

Vitrofolal C (Figure 3), vitrofolal D, vitrofolal E (Figure 20) and detetrahydro-conidendrin (Figure 23) have good activity against methicillin-resistant *Staphylococcus aureus* with a MIC value below 64 µg/mL [77].

### 4.4. Antiviral

Nicotnorlignan A, benzodioxane (Figure 19) and sequirin C (Figure 7) showed high effects against HIV-1 with IC50 values equal to 3.15, 7.62 and 9.56 µM, respectively [103].

Moreover, nicotnorlignan C, recurphenol C, recurphenol D, benzodioxane (Figure 19) and sequirin C (Figure 7) and possess moderate activity against the anti-tobacco mosaic virus with inhibition rates equal to 14.7%, 22.5%, 23.4%, 21.4% and 17.6% respectively [103]. Nicotnorlignan A (Figure 19) also shows similar effects [103].

### 4.5. Anti-Allergic

Nyasol and 4′-O-methyl-nyasol (Figure 7) exert good effects with IC50 values equal to 2.06 and 1.89 µM, respectively. These values are extremely compatible with that of DSCG (IC50 = 1.78 µM), a very common antiallergic compound used in pharmacy [10].

### 4.6. Antiasthma

Homoeogonol (Figure 3) is the only compound able to exert antiasthma effects by a complex mechanism of action composed by several paths [116]. The most important of these is that this compound is able to reduce the expression of the protease MMP-9 in the lung tissue and the presence of this protease greatly increases the asthmatic effect [117].

### 4.7. Analgesic

Hypoxoside (Figure 12) does not display any effect on the locomotor activity in mice but exerts a high analgesic effect even at low doses (5 mg/kg) probably via an anti-inflammatory mechanism [59].

### 4.8. Anticomplement

Styraxlignolide A, egonol and masutakeside I (Figure 3) show a strong effect with IC50 values equal to 123, 33 and 166 µM, respectively. This activity, in the case of egonol (Figure 3), is much higher than the control, i.e., rosmarinic acid, which shows an IC50 value equal to 182 µM [107].

### 4.9. Antitherogenic

Nyasol (Figure 7) is able to act as inhibitor against LDL-oxidation with an IC50 value equal to 5.6 µM, which is very similar to that of probucol (IC50 = 2.0 µM), the typical compound uses for these purposes. Indeed, it exerts extremely weak inhibitory effects against hACAT1, hACAT2 (cholesterol
acyltransferases) and Lp-PLA2 (lipoprotein-associated phospholipase A2) with IC₅₀ values equal to 280.6, 398.9 and 284.7 µM, respectively [82].

4.10. Antiparasitic

3′-methoxy-3,4-methylenedioxy-4′,7-epoxy-9-nor-8,5′-neolignan-9′-acetoxy (Figure 5) has a medium effect against Trypanosoma cruzi with an IC₅₀ value equal to 111 µM whereas 3′-methoxy-3,4-methylenedioxy-4′,7-epoxy-9-nor-8,5′-neolignan-7,8′-diene (Figure 5) is a good compound in this context with an IC₅₀ value equal to 60 µM [78].

4.11. Vascular

Pilosidine, nyasicoside and curculigine (Figure 4), in low doses ranging from 1 to 30 mM, are able to induce a reversible facilitating effect on adrenaline evoked contractions [47]. Moreover, they all have a dose dependent vasoconstricting effect on rabbit aorta strips [48]. Their mechanism of action involves an interaction with the peripheral adrenergic system, in particular with α₁ and β₁ adrenoceptors [48].

(2S)-1-O-butyl-nyasicoside and nyasicoside (Figure 4) possess high effects against the ouabain-induced arrhythmia in the heart preparations of guinea pig at the doses of 3 µM, especially at the left atrium level.

(2S)-1-O-butyl-nyasicoside (Figure 4) has the same effect but in minor extent [41].

Lastly, 2-(2′-hydroxy-4′,6′-dimethoxyphenyl)-5-[[(E)-propenyl]benzofuran (Figure 22) inhibits the vasodilatory effect produced by acetylcholine with an IC₅₀ value equal to 31.2 µM. This effect is concentration-dependent. Moreover, the compound inhibits basal nitric oxide production [118].

4.12. Antistress

Negundin A (Figure 20) shows a very good effect in mice by greatly decreasing the number of writhes at the dose of 25 mg/kg. Moreover, it is able to reduce the blood glucose level and serum cholesterol level but at higher doses (50 and 100 mg/kg) [119].

4.13. Anti-Inflammatory

Egonol, homoegonol, homoegonol gentiobioside, homoegonol glucoside and egonol gentiobioside (Figure 3) were found to exert weak or medium effects against COX-1 and COX-2 with percentages of inhibition ranging from 1.3 for homoegonol gentiobioside against COX-1 to 35.7 of homoegonol glucoside against COX-1 at the concentration of 30 mM [110]. Yet, egonol (Figure 7) is able to reduce the mRNA expression levels of inducible nitric oxide synthase (iNOS), COX-2, interleukin-1 β (IL-1β) and interleukin-6 (IL-6). The same effect was observed also for homoegonol (Figure 7) but in a minor extent [111].

Lastly, nyasol and 5-[(S,Z)-1-(4-hydroxyphenyl)penta-1,4-dien-3-yl)-2,3-dimethoxyphenol (Figure 7) show high effects. In particular, nyasol is able to inhibit microsomal cells by 100% as well as COX-1 while it inhibits COX-2 by 19%. Conversely, 5-[(S,Z)-1-(4-hydroxyphenyl)penta-1,4-dien-3-yl)-2,3-dimethoxyphenol (Figure 7) inhibits microsomal cells by 72% and COX-2 by 23% [21].

4.14. Cytotoxic

3′-methoxy-nyasin and nyasol (Figure 7) possess moderate effects against HO-8910 (human ovarian carcinoma) and Bel-7402 (human hepatoma) cell lines. In particular, the former compound shows IC₅₀ values equal to 84.0 and 26.2 µM, respectively whereas the latter compound shows IC₅₀ values equal to 30.6 and 29.4 µM, respectively [18]. Nyasol and 4′-O-methyl-nyasol (Figure 7) exert moderate effects against the rat glioma C-6 cell line with IC₅₀ values equal to 19.02 and 20.21 mg/mL, respectively [81]. Nyasol (Figure 7) is also able to inhibit the basic fibroblast growth factor (bFGF) and the vascular endothelial growth factor (VEGF)-induced endothelial cell proliferation [11]. The mechanism of action is related to its strong estrogen receptor binding ability [11]. In addition,
nyasol (Figure 7) has medium effects against the human HL60 cancer cell line with IC$_{50}$ value equal to 15.5 µM [27]. Moreover, nyasol, 4′-O-methyl-nyasol and 3′′-methoxy-nyasol (Figure 7) have a modest effect on the inhibition of β-hexosaminidase release in RBL-2H3 cells stimulated by DNP-BSA with IC$_{50}$ values ranging from 18.08 µM for the latter to 52.67 µM for the second compound. These values are higher than the control compound ketotifen, which owns an IC$_{50}$ value equal to 10.12 µM. Conversely, 3′′-hydroxy-4′-methoxy-4′′-dehydroxy-nyasol (Figure 7) is more efficient than the control displaying an IC$_{50}$ value equal to 2.85 µM [12].

Egonol and homoegonol (Figure 3) exhibit medium effects against B16F10 (murine melanoma), MCF-7 (human breast adenocarcinoma), HepG2 (human hepatocellular liver carcinoma), HeLa (human cervical adenocarcinoma) and MO59J (human glioblastoma) cell lines. These effects were observed to be higher with the passing of time reaching their peaks after 72 h. Anyway, they were not better than the controls doxorubicin, camptotechin and etoposide [105]. For what concerns egonol (Figure 3), the results for MCF-7 and HeLa were confirmed in another study and it was also observed that it is active against the HL-60 (human leukemia) cell line with an IC$_{50}$ value equal to 47.8 µM [108].

Agatharesinol acetonide (Figure 1) exhibits strong effects on the A549 cell line (non-small-cell lung cancer) with an IC$_{50}$ value equal to 27.1 µM, quite higher than taxol 33.72 µM [35].

Sequirin C (Figure 7) exerts good effects against the HL-60 cell line with an IC$_{50}$ value of 5.5 µM, which is comparable to that of cisplatin (2.0 µM) [33].

Cedralin A (Figure 6) has weak activities against the HL-60 and K562 (myelogenous leukemia) cell lines with IC$_{50}$ values equal to 26.2 and 22.4 mg/mL, respectively [86].

Methyl rel-(1R,2S,3S)-2-(7-methoxy-1,3-benzodioxol-5-yl)-3-(2,4,5-trimethoxyphenyl)-cyclobutane-carboxylate and methyl rel-(1R,2R,3S)-2-(7-methoxy-1,3-benzodioxol-5-yl)-3-(2,4,5-trimethoxyphenyl)-cyclobutane-carboxylate (Figure 6) exert modest effects against the HepG2, A549 and HeLa cell lines with IC$_{50}$ values equal to 38.0, 56.4 and 64.9 µM for the former in corresponding order, and 42.4, 66.3 and 77.7 µM for the latter in corresponding order [52].

Noralashinol B (Figure 15) exhibits a weak activity against the HepG2 cancer cell line with an IC$_{50}$ value equal to 31.7 µM, which is higher than the positive control, methotrexate showing an IC$_{50}$ value equal to 15.8 µM [90]. Its mechanism of action is via apoptosis [90].

Metasequirin G, metasequirin H and metasequirin I (Figure 9) possess low cytotoxic effects against the A549 cell line with IC$_{50}$ values close to 100 µM [34].

Chamaecypsanone C (Figure 15) exerts potent effects against KB (human oral epidermoid carcinoma), HONE-1 (human nasopharyngeal carcinoma) and TSGH (human gastric carcinoma) cell lines with IC$_{50}$ values equal to 0.19, 0.24 and 0.52 µM, respectively [28].

Acorusin B (Figure 15) exerts moderate effects against the CI-H1650 (non-small cell lung carcinoma), HepG2, BGC 823 (human stomach carcinoma), HCT-116 (human colon carcinoma) and MCF-7 cancer cell lines with IC$_{50}$ values equal to 6.51, 4.80, 7.23, 8.81, 3.58 and 0.52 µM, respectively [6].

Yateresinol (Figure 17) is a cytotoxic compound against the human HL60 and Hepa G2 cancer cell lines with IC$_{50}$ values higher than 20 µM [27].

Vitedoin A (Figure 20) exerts moderate effects against HCT116 cell lines with an IC$_{50}$ value equal to 10.18 µM [74].

6-hydroxy-4-(4-hydroxy-3-methoxyphenyl)-3-hydroxymethyl-7-methoxy-3,4-dihydro-2-naphthaldehyde (Figure 20) shows high effects against HepG2 cell lines with an IC$_{50}$ value equal to 8.24 µM, which is comparable to doxorubicin (IC$_{50}$ = 6.49 µM) [74].

4.15. Phytotoxic

9′-nor-3′,4,4′-trihydroxy-3,5-dimethoxylign-7-eno-9,7′-lactone (Figure 18) is a phytotoxic compound against Lactuca sativa L. (lettuce) and Lycopersicon esculentum Mill. (tomato) preventing their development [101]. Moreover, only in the case of L. esculentum, it inhibits the shoot length [101].
4.16. Inhibition on Enzymes, Proteins and Platelet Aggregation

Negundin A, negundin B, 6-hydroxy-4-(4-hydroxy-3-methoxy)-3-hydroxymethyl-7-methoxy-3,4-dihydro-2-naphthaldehyde, vitrofolal E (Figure 20) and (+)-lyoniresinol (Figure 15) showed medium effects against tyrosinase with IC$_{50}$ values equal to 10.06, 6.72, 7.81, 9.76 and 3.21 µM which are, anyway, higher than kojic acid (IC$_{50}$ = 16.67 µM) [71].

Indeed, negundin B (Figure 20) has potent effect against lipoxygenase with an IC$_{50}$ value equal to 6.25 µM [70].

Vitrofolal E (Figure 20) shows also moderate effects against butyryl-cholinesterase with an IC$_{50}$ value equal to 35.0 µM [70].

6-hydroxy-4-(4-hydroxy-3-methoxy)-3-hydroxymethyl-7-methoxy-3,4-dihydro-2-naphthaldehyde and vitrofolal E (Figure 20) have modest α-chymotrypsin (serine protease) competitive inhibitory effects with K$_i$ values equal to 31.75 and 47.11 µM, respectively [72].

Cestrumoside (Figure 14) is a strong protein kinase C inhibitor in an animal food additive [120].

Lastly, (S)-(+-)imperanene (Figure 18) strongly inhibits tyrosinase isolated from HMV-II cells with an IC$_{50}$ value equal to 1.85 mM [121]. Its mechanism of action is essentially identical to that of arbutin [121]. Moreover it shows a high effect in rabbits giving a complete inhibition at the concentration of 6 × 10$^{-4}$ M when the platelet aggregation is induced by thrombin [96].

5. Conclusions

Nor-lignans have proven to be quite present in the plant kingdom. Nevertheless, some of them can be even considered to be chemotaxonomic markers. In addition, they are endowed with a vast number of biological activities with a myriad of possible application in several medicinal and pharmacological fields. Yet, not all the nor-lignans have been studied and discovered at the present. This review article means to be a first step towards the understanding of how important nor-lignans are as well as to be an incentive to continue their research and study.

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Abbreviations

[α]D: Optical Rotation Spectroscopy; ECD: Electronic Circular Dichroism Spectroscopy; CC: Column Chromatography; CD: Circular Dichroism Spectroscopy; FCC: Flash Column Chromatography; HPLC: High Performance Liquid Chromatography; IM: Immunohistochemistry Methods; IR: Infrared Spectroscopy; LC: Liquid Chromatography; MP: Melting Point; MS: Mass Spectrometry; NMR: Nuclear Magnetic Resonance Spectroscopy; n.a.: not accessible; n.r.: not reported; pTLC: Performance Thin Layer Chromatography; SE: solvent extraction; TLC: Thin Layer Chromatography; UV: Ultra-Violet Spectroscopy.

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