Bull. Pharm. Sci., Assiut University, Vol. 47, Issue 1, 2024, pp. 151-168.

Bulletin of Pharmaceutical Sciences
Assiut University
Website: http://bpsa.journals.ekb.eg/

MACROLACTONES AND MACROLIDES FROM PLANT ENDOPHYTIC FUNGI, CHEMICAL SCAFFOLDS, BIOLOGICAL ACTIVITIES AND SPECTROSCOPY: A COMPREHENSIVE REVIEW

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Background: *The pandemic of COVID-19 has stressed the exaggerated demand for innovative treatments, prompting the search for new sources. Plant endophytic fungi produce a diverse array of biologically active compounds, including macrolides and macrolactones with varying activities.* ***Aim of the Study:*** *In this review we give an updated overview of natural macrolides and macrololactones from plant endophytes addressing original studies published up to June 2023.* ***Results:*** *Over the preceding ten years, 91 macrolides with 80 novel compounds with cytotoxic, antibacterial, antifungal, and α-glucosidase inhibitory activities. Unfortunately, the number of novel chemicals identified from marine or bacterial endophytes in the same period is substantially lower. Accordingly, further study on plant endophytes, which are critical for drug research and the development of novel medicines, including antitumors, antivirals, antibacterials, and antimalarials, should be conducted. A report of the ^{13}C NMR data of several endophytic macrolides are reported as a supplementary according to ring sizes and based on a united numbering built on literature search*

Keywords: *Macrolides, plant endophytes, biosynthesis, biological activity, ^{13}C-NMR*

INTRODUCTION

Natural products, particularly those generated by microorganisms or due to their interactions with their hosts, continually offer evidence for their critical role in medication development [1]. Natural product-driven drug development has improved, either directly from natural compounds or through semi-synthetic and synthetic derivatives inspired by natural product prototypes. Over the previous three decades, these compounds have accounted for more than half of all authorized small-molecule medications[2]. Metabolites from microorganisms, particularly fungi, and their symbiotic interaction products with other terrestrial or marine species have been recruited for natural product research. Endophytic fungi (endophytes) are a remarkable symbiotic microorganism-host interaction that has produced a plethora of new and biologically active metabolites[3,4]. These metabolites have displayed various biological capabilities, including antibacterial, antifungal, immunosuppressive, antiviral, antimalarial, anti-inflammatory, and anticancer effects[5,6].

Received : 22/7/2023 & Accepted : 16/9/2023

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Endophytic metabolites are structurally classified into alkaloids, benzopyranones, peptides, macrolides, quinones, steroids, terpenoids, tetralones, xanthones, and others [7].

Endophytic fungal macrolides are polyketides with variable-sized macrolactone ring scaffolds that have a wide range of biological actions, including antiparasitic, antifungal, and antimalarial effects[8,9]. Clinically used macrolides are effective against gram-positive and atypical bacteria. Because of their immunostimulant and anti-inflammatory properties, they have been explored as a wide adjuvant treatment for COVID-19. During the COVID-19 pandemic, repurposing of azithromycin, in particular, inhibits pro-inflammatory cytokine production (including MMPs, TNF-α, IL-6, and IL-8), increases levels of interferons and interferon-stimulated proteins, and reduces viral multiplication and release [10,11]. Since the COVID pandemic, repurposing of the existing medications to achieve new therapeutic effects has gained increased attention as a viable technique to accelerate drug development while minimizing experimental costs and time[12].

Accordingly, macrolides have acquired growing importance as a research topic for academic institutions and pharmaceutical research centers, steering efforts to identify novel molecules by chemical modification of existing natural skeletons[13].

On tracing previous macrolide articles which were published during the last decade, many reviews have been reported concerned with macrolides[14,15], for example Lenz and colleagues investigated the structures, sources, mechanism of action, and biological effects of selected macrolides with potential therapeutic uses [16]. In addition to certain papers addressing particular classes of macrolides with their biological activity, and chemical or biological synthesis[17-19]. This review provides an updated overview of new macrolides and macrolactones isolated from plant fungal endophytes, with an emphasis on new chemical structure and biological activity, or new biological activity of known unevaluated compounds in the time between 2013 and June 2023. This thorough review will be a helpful resource for natural product and medicinal chemistry researchers, as well as biologists and for drug development and/or drug repurposing.

MACROLIDES AND MACROLACTONES

Macrolactones

Macrolactones are macrocyclic lactones having at least twelve atoms in their core ring structure, they enclude a wide range of natural compounds with variable biological and helpful druglike activities [22]. The macrolactones are reported in the following text and **Fig. 2-4** based on their ring sizes.

Ten-membered macrolactones

The 10-membered macrolactones are metabolites derived from marine[21], pathogenic[22] and soil derived fungi[23]. They have been reported with various biological activities including cytotoxicity[24], antimalarial[25] and anti-inflammatory[26]. The reported 10-membered macrolactones in the last decade are described in this section and in **Fig. 1**.

Colletotriolide 1 was isolated from the leaves of the Chinese mangrove *Pandanus amaryllifolius* by the endophytic fungus *Colletotrichum* sp. It inhibited Escherichia coli with a modest IC_{50} of 500 mg/mL[27]. Four more congeners were recovered from *Phomopsis* sp., an endophyte isolated from *Pinus massoniana* in south China. They were identified according to IUPAC system as (5*S*,8*S*,9*R*,10*R*,*E*)-5,8,9-trihydroxy-10-pentyl-3,4,5,8,9,10,-hexahydro-2*H*-oxecin-2-one 2, (5*S*,8*S*,9*R*,10*R*,*E*)-5,8,9-trihydroxy-10-nonyl-3,4,5,8,9,10,hexahydro-2*H*-oxecin-2-one 3, (5*R*,8*S*,9*R*,10*S*,*E*)-5,8,9-trihydroxy-10-([*R*]-4-hydroxyoctyl)-3,4,5,8,9,10-hexahydro-2*H*-oxecin-2-one 4, and (5*S*,6*S*,9*S*,10*R*,*E*)-5,6,9-trihydroxy-10-pentyl-3,4,5,6,9,10-hexahydro-2*H*-oxecin-2-one 5 [28]. Compound 2 which acquired the name seimatopolide A was previously isolated from *Seimatosporium* sp., the endophyte from *Hypericum perforatum*[29]. Hiep and his colleagues investigated this compound as an agonist of the peroxisome proliferator-activated receptor (PPAR)- γ as a potential therapeutic option for diabetes therapy (EC_{50} of 1.15 M)[30]. The polyhydroxy congener Mangiferaelactone 6 was isolated from the Panama shrub *Pestalotiopsis manguiferae*, an endophytic fungus associated with *Hyptis dilatate*. It inhibited the growth of *Enterococcus faecalis*, *Bacillus cereus*, *Enterococcus cloacae*, *Listeria*

monocytogenes, and *Proteus mirabilis* [31]. Botero and co-researchers isolated two new modiolides D, E and A 7-9 from the endophyte *Microsphaeropsis arundinis*[32]. Modiolide A 9 was previously reported from the marine fungus *Paraphaeosphaeria* sp. These compounds revealed weak cytotoxic activities against murine breast (LM3), murine lung (LP07) and human breast (MCF-7) cell lines[33]. Pedra and his group, isolated the possible glioma therapy, Sch-642305 **10** from the unidentified endophyte MF31b11 of the Brazilian medicinal plant *Achyrocline satureioides*. It showed anti-proliferative properties against C6 and U138MG glioma cells, with IC_{50} of 1.1 and 7.6µg/mL, respectively, it promoted apoptosis, decreased cell migration, enhanced antioxidant defense system and suppressed ROS production[34]. The three (11*S*) xestodecalactones derivatives xestodecalactones D–F **11-13**, were isolated by Ebrahim and his group from *Corynespora cassiicola*, the endophyte from Chinese mangrove *Laguncularia racemosa* [33]. Zhang and his group have isolated hispidulactone B 14 from the endophyte *Chaetosphaeronema hispidulum* [4]. Two years later, Zheng and his group have isolated hispidulactone F 15 from the same fungus in 2020, both compounds 14 and 15 inhibited HepG2 cell proliferation in a dose-dependent manner with IC_{50} 61.05 and 107.69 µmol/L, respectively[35].

Twelve membered macrolctones

Numerous 12-membered macrolactones with various biological properties, including antimicrobial and anti-inflammatory activity, have been isolated from plant endophytes [28]. The 12-macrolactones, including derivatives of resorcylic acid and curvularin, are described in this section and in **Fig. 2**.

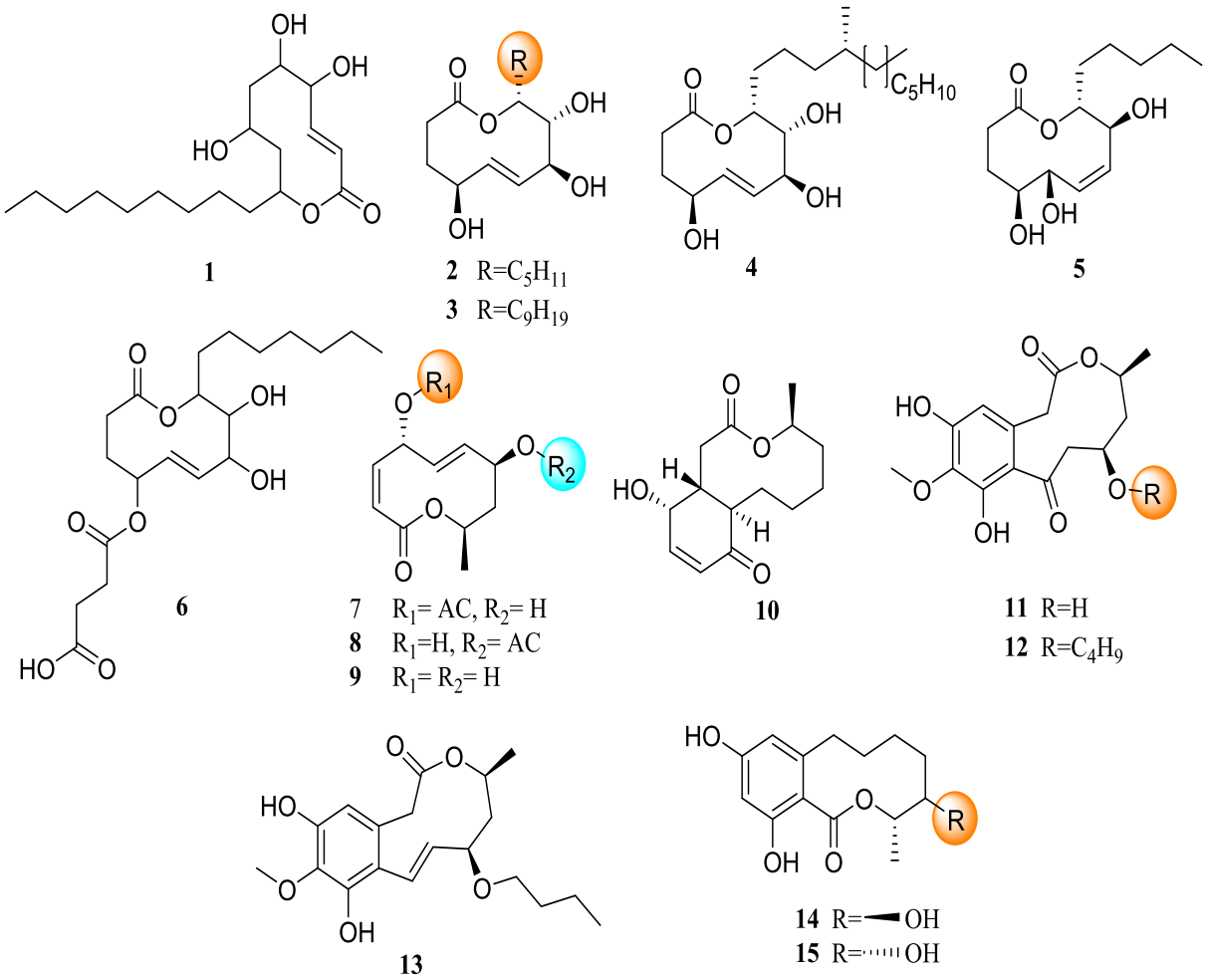

Fig. 1: Ten membered macrolctones.

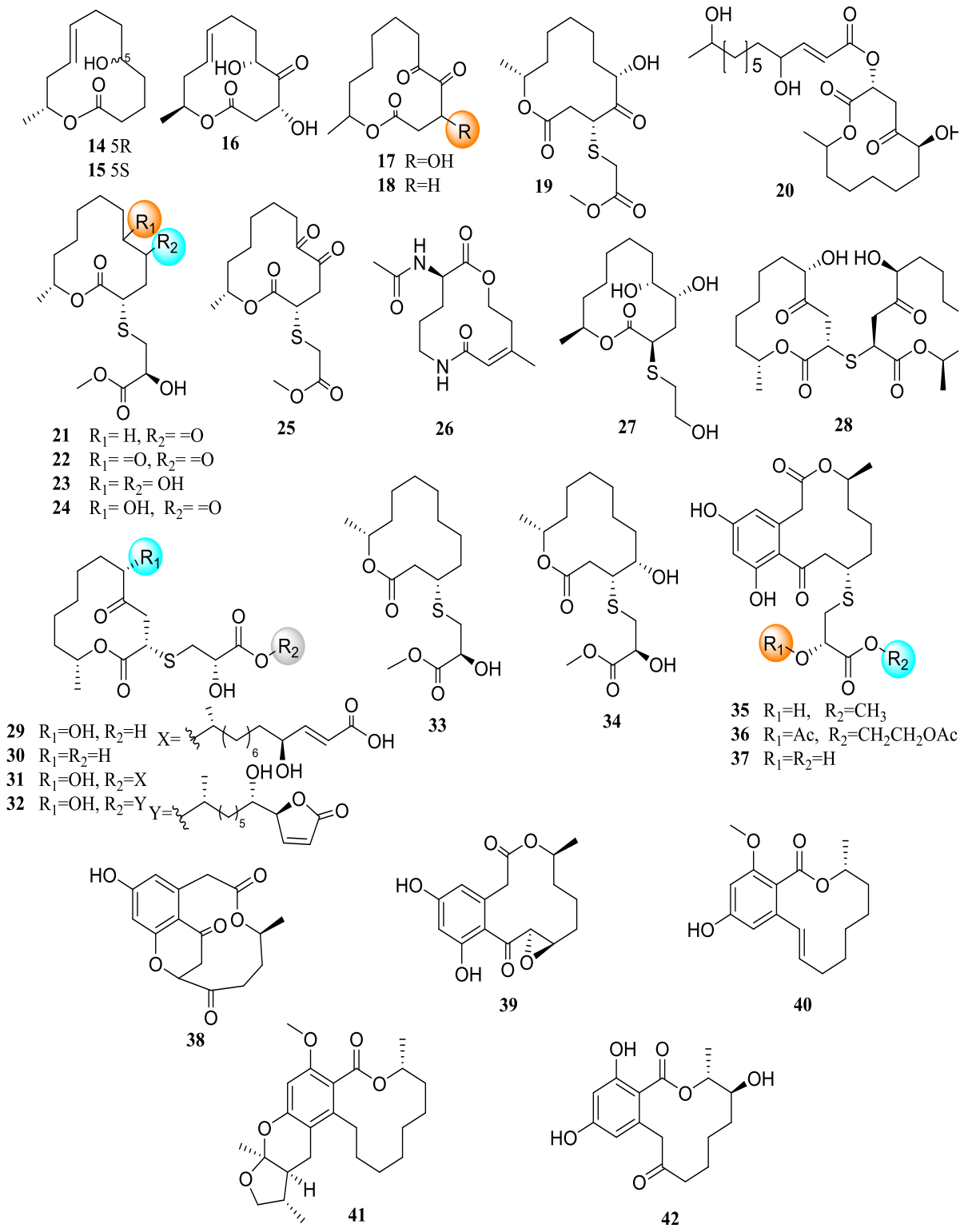

Fig. 2: Twelve membered macrolactones.

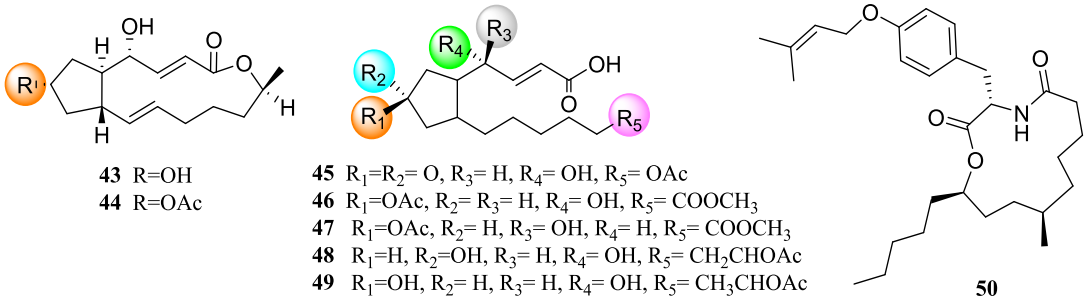

Fig. 3. Thirteen membered macrolctones.

C-12 macroloides

Investigation of the mangrove endophyte, *Cladosporium cladosporioides* MA-299, afforded 5*R*-hydroxyrecifeiolide 16 and 5*S*-hydroxyrecifeiolide 17 in addition to pandangolide 1 18[37]. Pandangolide 1 18 was previously isolated from undescribed marine fungus[38]. Liu and his group have identified 4-hydroxy-12-methyloxacyclododecane-2,5,6-trione 19 and 12-methyloxacyclo-dodecane-2,5,6-trione 20 from *Cladosprium colocasiae* A801, the endophyte from the Australian shrub *Callistemon viminalis*. A panel of biological evaluation of both compounds including antibacterial against *Staphylococcus aureus*, *Escherichia coli* and MRSA, in addition to cytotoxicity against SF-268, MCF-7, and HepG-2 cell lines, as well as *α*-glucosidase inhibitory activity, didn't show any positive results [41].

The research group of Wuringege isolated two new pandangolide derivatives from *Cladosporium* sp. IFB3lp-2, the foliar endophyte of *Rhizophora stylosa*, Hainan Island, China. Compounds were identified as methyl-2-((4*R*,6*S*,12*R*)-6-hydroxy-12-methyl-2,5-dioxooxacyclododecan-4-yl)thio)-acetate 21 and (E)-(3*R*,6*S*)-6-Hydroxy-12-methyl-2,5-dioxooxacyclododecan-3-yl4,11-dihydroxydodec-2-enoate 22[42]. The infrequent C-2 sulfur substituted metabolites, thiocladospolides A−D 23-26 were isolated from *C. cladosporioides* MA-299, from the Chinese mangrove *Bruguiera gymnorrhiza*. Compound 23 showed strong inhibition against the aquatic pathogen *Edwardsiella tarda*, while compound 26 showed strong inhibition against *E. ictarda*, both with an MIC of 1 μg/mL. The known pandangolide 3 27 was isolated and revised as well, where the sulfur side chain been located at C-2 through extensive NMR analysis and in comparison to compound 23 [43].

Investigation of *Cladosporium* sp. SCNU-F0001 afforded two new lactam macrolide cladospamide A 28, and thiocladospolide E 29 [44,45]. Thiocladospolides F–J 30–34 were isolated from *Cladosporium oxysporum* which was isolated from the roots of *Avicennia marina* [45]. Further investigation of the *Cladosporium* endophytes led to isolation of two sulfur-containing macrolides 35 and 36 from *Cladosporium cladosporioides* MA-299, both compounds were active against the aquatic pathogenic bacteria *Edwardsiella tarda* and *Vibrio anguillarum* with MIC range from 2.0 to 4.0 μg/mL [39], unfortunately these compounds were given the names thiocladospolides F and G, which is exactly the same names of compounds 30 and 31 described by wang in 2020, this nomenclature was misguiding as the same name identifies two different compound structures. Hence, we suggest that compounds 35 and 36 should be characterized as thiocladospolides K and L, instead.

Curvularins

The curvularins are substituted resorcinol fused to the *β*, *γ*-positions of a macrocyclic lactone ring. They are produced by several fungal genera as *Aspergillus*[44], *Alternaria*[45], *Curvularia*[27] and *Penicillium*[46].

The sulfur-containing curvularins, sumalarins A-C 37-39 were obtained from *Penicillium sumatrense* MA-92 the endophyte associated with the mangrove *Lumnitzera racemose* [57]. An unusual bicyclo 5/9 ring system C12-macrolide, cladocladosin A 40, was isolated from *Cladosporium cladosporioides* MA-299 from the mangrove *Bruguiera gymnorrhiza*, collected from Hainan

Island, China. It showed marked antimicrobial activity against *E. tarda*, *V. anguillarum* and *P. aeruginosa* with MIC of 1, 2 and 4 μg/mL, respectively[48].

Resorcylic acid lactones

The resorcylic acid lactones are metabolites having a *β*-resorcylic acid and a 12 or 14-membered lactone ring with a C-10 methyl substituent[49,50]. These compounds have wide range of biological activities including antiplasmodial[50], and cytotoxic[51], in addition to estrogenic and kinase inhibitory activities[49].

The *β*-resorcylic acid lactone lasiodiplodin 41, which was initially reported as plant metabolite from *Euphorbia splendens* [52] and later was purified from the endophyte *Lasiodiplodia* sp isolated from the Chinese mangrove *Acanthus ilicifolius*, in addition to (*E*)-9-etheno-lasiodiplodin 42. Both compounds showed *α*-glucosidase inhibition activity with IC_{50} 32.5 and 35.9 μM, respectively[53]. Later, lasiodiplactone A 43 was isolated from *Lasiodiplodia theobromae* ZJ-HQ1, the endophyte of the same mangrove plant. The absolute configuration was assigned as 15*R*, 18*S*, 19*S*, 21*S* by comparing experimental and calculated ECD spectra using time-dependent density-functional theory (TDDFT). Its biological evaluation showed anti-inflammatory activity through inhibition of nitric oxide production in lipopolysaccharide activated RAW264.7 cells with IC_{50} of 23.5 μM, and *α*-glucosidase inhibitory activity with IC_{50} 29.4 μM[54].

Thirteen Membered macrolactones

Several 13-membered macrolctones were isolated from several fungal species **(Fig. 4),** they were biologically evaluated as antimicrobial, anticancer, and chemopreventive agents[55,56]. According to the National Cancer Institute's *in vitro* anticancer screening, brefeldin A 43 proved to have a chemotherapeutic activity. It is an interesting C-13 macrolide with antibiotic, antiviral, cytostatic, antimitotic, and antitumor activities. It was previously isolated from several fungal genera as *Alternaria*, *Ascochyta*, *Penicillium*, *Curvularia*, *Cercospora* and *Phyllosticta* [57]. Five new brefeldin A congeners, brefeldin A 7-O-acetate 44 and the open ring derivatives brefeldin E1–E5 45-49, were isolated from *Penicillium* sp., the endophyte of *Panax notoginseng* root. These compounds displayed low cytotoxic activities[58].

The *N*-demethylmelearoride A **50** was isolated from the solid culture of the endophyte *Penicillium brefeldianum* XMK-2 isolated from the rhizome of *Pinellia ternate*. It has moderate cytotoxic activity, against HepG2 cells with IC_{50} of 36.6 μmol/L[59].

MACROLIDES

The term macrolides denotes those possessing 14-,15-, 16- and larger macrolactones rings constitute a family of natural origin with wide range of biological potency [23]. In the following text and in **Fig. 4-6,** we report the macrolides according to their ring size.

Fourteen membered macrolides

This class of macrolides have variable activities as the phytotoxic seiricurprolide from *Seiridium cupressi* [60], and zearalenone the mycotoxin with estrogenic activity from the genus *Fusarium* [61], and the cytotoxic aspergillides A−C from *Aspergillus ostianus*,[62].

Liu and his group have isolated seven new (13*S*) 14-membered macrolides, pestalotioprolides C−H 51-56 and 7-*O*-methylnigrosporolide 57 **(Fig. 4)** from *Pestalotiopsis microspore*, the endophyte of the mangrove *Drepanocarpus lunatus*[63], in addition to nigrosporide 58 which was previously isolated *Nigrospora sphaerica*[64]. all compounds were proved to have the 13*S* configuration by Single-crystal X-ray analysis, Mosher's and TDDFT-ECD experiments. Compounds 52-4 and 57 showed cytotoxic activity against L5178Y murine lymphoma cell line, while compound 53 showed potent activity against human ovarian cancer A2780 cell line with an IC_{50} of 1.2 μM[65]. Chen *et al*., have isolated a C-14 *β*-resorcylic macrolactone derivative, 3-methoxy-lasicicol 59 from *Lasiodiplodia* sp. ZJ-HQ the endophyte associated with *Acanthus ilicifolius*[53]. It is the methyl derivative of the known lasicicol 60 from *Saccharomyces cerevisiae*[21], which was also isolated in this work, X-ray diffraction analysis had confirmed the structure of 60, and the absolute configuration was determined by modified Mosher's experiment. Both compounds showed potent *α*-glucosidase inhibitory activity [53].

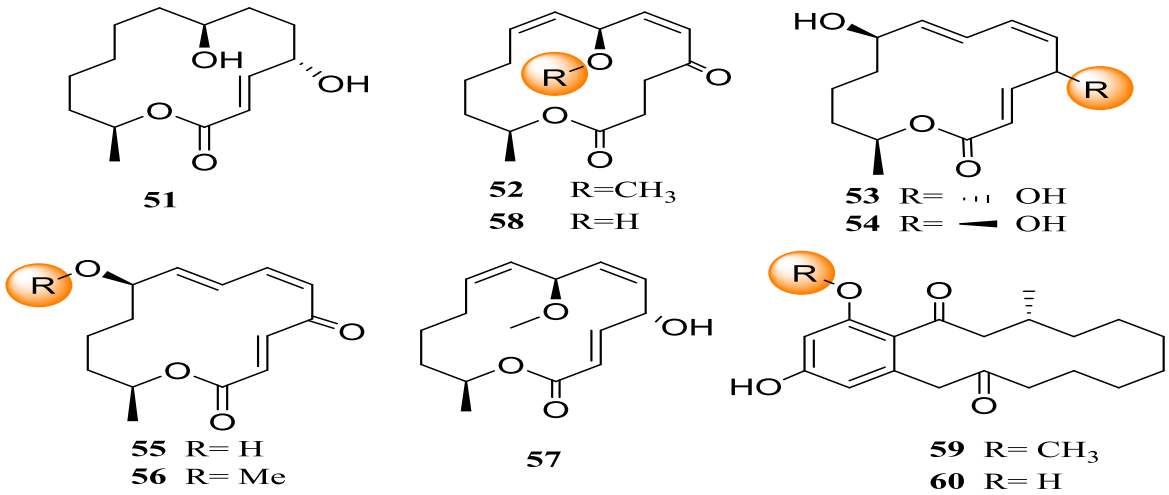

Fig. 4: Fourteen membered macrolides.

Sixteen membered macrolide

The 16-membered macrolides is a significant class of macrolides with antibiotic activity. They have been isolated from marine or terrestrial fungi, such as chalcomycin B, from the marine *Streptomycete* B7064, it exhibited antimicrobial activities against a variety of microorganisms and microalgae [66]. Later on, Juvenimicin C, was isolated from the marine *Micromonospora* sp. CNJ-878 [67]. The only natural 16-membered macrolides in clinical use today are josamycin, spiramycin and midecamycin, in addition to the semisynthetic miokamycin, rokitamycin and tildipirosin (first available in 2012). The anti-inflammatory and immunomodulatory effects have also been reported for C-16 macrolides, as well as the antimalarial activity of tylosin A and derivatives of desmycosin (tylosin B) [68]. In the following text and in Fig. 5 we report the C-16 plant endophytic macrolides isolated during the last 10 years.

Two homodimeric C-16 macrolides, pyrenophorin 61 and pyrenophorol 62 were isolated from the needle endophyte *Lopherdermium nitens* of the Canadian *Pinus strobus*[69]. Compound 61 showed significant antifungal activity against *Cronartium ribicola* at 5 μM[70]. McMullin and his group have demonstrated that 62 significantly reduced the growth of the biotrophic pathogen *Microbotryum violaceum* and *Cronartium ribicola* at 4 and 5 μM, respectively. Both 61 and 62 have been previously identified from endophytes of *Lycium intricatum*[69,71].

Tricothecene macrolides

The trichothecene macrolides is a varied class of fungal sesquiterpenoids with acyl residue(s) tethered at 4*β* and/or 15 positions[72]. They are characteristic for species of the genera *Fusarium*, *Myrothecium*, *Trichoderma*, *Trichothecium*, *Cephalosporium*, *Verticimonosporium*, and *Stachybotrys*[73]. Many trichothecenes have confirmed anticancer[74], immunomodulation[75], phytotoxicity[76], antifungal[77] and antimalarial activities[78]. According to the carbon skeleton, they are classified into C_{27} verrucarins and C_{29} roridins[72,78].

The new cytotoxic roridin-type trichothecene, roritoxin E 63 was isolated from *Myrothecium roridum* IFB-E091, showed in vitro inhibitory effect against gastric carcinoma SGC-7901 and hepatocarcinoma SMMC-7721 cell lines[79]. The myrothecines D-G 64-6769-72, 16-hydroxymytoxin B 68, and 14′-dehydrovertisporin 69 were obtained from *Myrothecium roridum*. All compounds showed antiproliferative effect against chronic myeloid leukemia K562, and colorectal carcinoma (SW1116) cell lines[72]. Meanwhile two new roridin-type trichothecenes, myrothecines H and I 70 and 71 were isolated from *Paramyrothecium roridum*,, both have been reported with high cytotoxic activity against SF-268 and HepG-2 cell lines[79]. Epiroridin acid 72, epiroridin E 73 and mytoxin B 74 were isolated from the liquid culture of *Myrothecium roridum* A553, the endophyte from the medicinal plant *Pogostemon cablin*. All compounds were evaluated for their *in vitro* cytotoxic activities against human glioma,

human breast adenocarcinoma (MCF-7), human non-small cell lung cancer (NCI-H460), and human hepatoma (HepG-2)[80]. From the endophyte *M. roridum* IFB-E012, Shen and his group have isolated dihydromyrothecine C 75 as an epimeric mixture of the (14′*S*) and (14′*R*) stereoisomers, the (14′*S*) was more stable. It showed moderate cytotoxicity with IC_{50} 44.48 μM against human nasopharyngeal carcinoma cell line (KB)[81]. The known verrucarin A 76[82] was isolated from the endophyte *Paramyrothecium roridum* associated with *Morinda officinalis* and evaluated as antiproliferative and apoptosis-inducing agent against CaP cells[80]. Nguyen *et al*., reported a nematocidal activity for this compound at a concentration of 1.88 μg/mL[83].

The 2′,3′-epoxymyrothecine A 77 and 13′,14′-hydroxymytoxin B 78, in addition to the known mytotoxin A 79 were isolated from the endophyte *Myrothecium roridum* associated with the Chinese herb *Ajuga decumbens*. It showed potent cytotoxic activity against A549, MCF-7, HepG2, and 7721 cell lines, 79 cell lines. Meanwhile, cell cycle arrest investigations showed that 77, and 79 could induce G1 arrest in HepG2 cells with nearly 20% higher than control[84].

Eighteen membered macrolides

The unique 18-membered macrolide structure with a methyl-substituted ethanoic acid functional side chain strasseriolides A−D 80-83 **(Fig. 5)**, were isolated from the endophyte *Strasseria geniculata* CF-247251. The biological evaluation showed potent antiplasmodial activity of the four compounds against *Plasmodium falciparum* 3D7 with IC_{50} 9.810, 0.013, 0.123, and 0.128 μM, respectively[85].

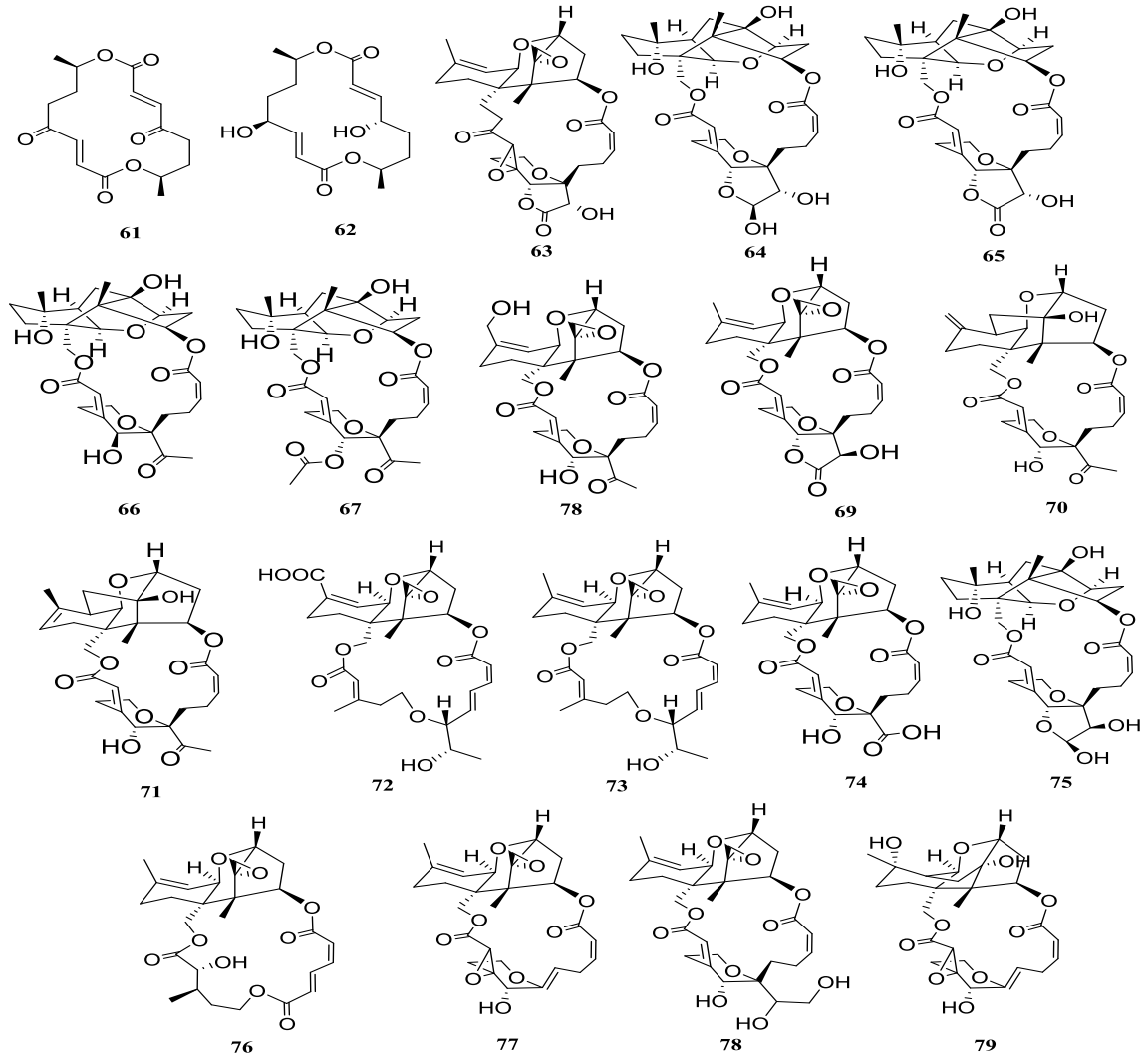

Fig. 5: Sixteen membered macrolides.

Ansa-macrolides

Ansa-macrolides or ansamycins, covered diverse and bioactive natural products that have been isolated mainly from actinomycetes. A characteristic feature of these compounds is the medium to large sized macrolide or macrolactam moiety fused to a mono- or bicyclic aromatic center[85]. The HSP90 inhibitor geldanamycin, is one of the most prominent representatives of this class[86], in addition to the antimycobacterial antibiotic rifamycin, and the antitumor agent maytansinoid[87]. Ansamacrolides from plant endophytes in the following text and in **Fig. 6**.

The first isolation of ansamacrolides from plant endophytes was the divergolides A-D 84-87 which were isolated from unspecified fungal endophyte from the mangrove *Bruguiera gymnorrhiza*. Divergolide D 87 exhibited strong inhibition of *Mycobacterium vaccae*, while divergolide C 86 was the most active against *B. subtilis* and methicillin resistant *S. aureus*, moreover, it displayed distinct cytotoxicity to lung cancer (LXFA 629L), pancreatic cancer (PANC-1), renal cancer (RXF 486L), and sarcoma (Saos-2)[88].

Isoindolone-macrolide

They are unusual macrolide skeleton with L-glutamate fragment, an isoindolone unit, and a sesquiterpene moiety. During the last 12 years the only isoindolone macrolides from plant endophytes were the emericellolides A−C 88-90 **(Fig. 6)**, which were isolated from the endophytic fungus *Emericella nidulans* HDN12-249[89].

Isolation and Detection of macrolactone and macrolides

The Mass spectrometry (MS), serving as a universal detection technique, has replaced ultraviolet (UV), fluorometric, and electrochemical detection for multi-macrolide analysis. The chromatographic separation mainly relies on the use of reversed-phase columns. In most studies, a conventional LC with a C_{18}-modified silica stationary phase was used. The mobile-phase composition, concentration, and pH are critical for the optimal ionization and chromatographic separation of macrolides. Acetonitrile and methanol are the mostly used organic solvents in LC or UPLC mobile phases. Either formic acid (0.1%) or ammonium acetate (10–20 mM) are often employed as a mobile-phase modifier[90]. The separation and /or final purification of macrolide molecules usually employ HPLC process, the separation performed on C_{18} reversed phase. The mobile phases A and B are either water and acetonitrile or water and methanol, containing 0.1% formic acid, in a gradient elution (5–100% B for 0–15 min with a linear gradient, followed by 5 min of 100% B)[91,92].

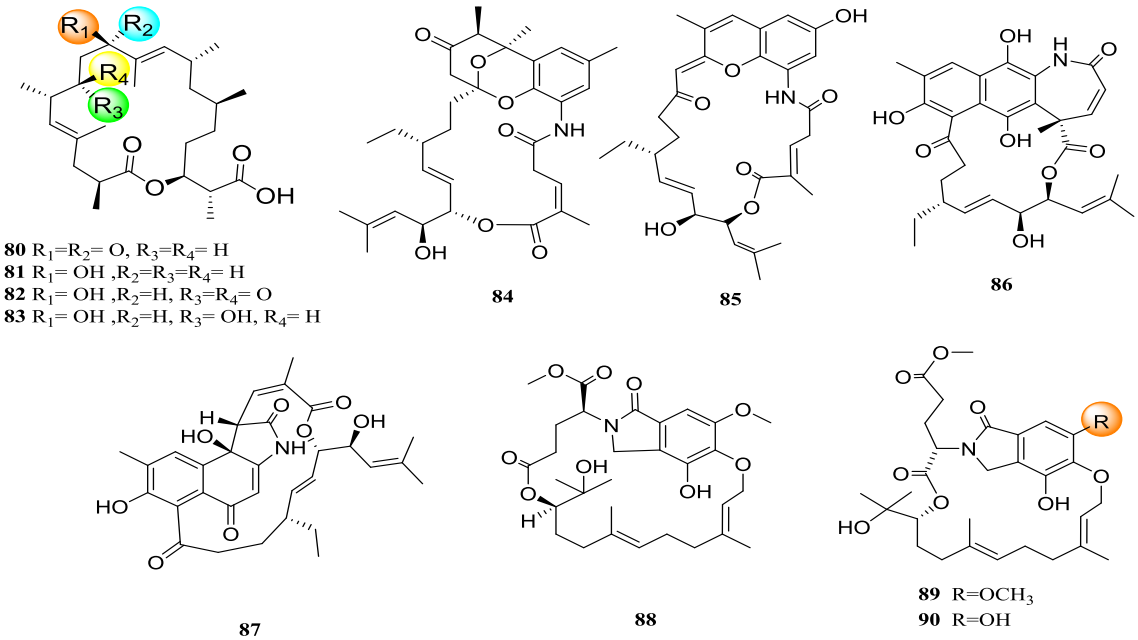

Fig. 6: Ansa- and Isoindolone-macrolides.

Structure elucidation of macrolides

Mass spectrometry

In order to identify and isolate new macrolides from microbial sources, the tandem mass-based dereplication is a common technique for screening of known bioactive compounds. Many databases' platforms are used to reach new macrolides as the Global Natural Products Social Molecular Networking (GNPS), which is an open-access data-driven tandem mass spectral platform, which particularly well-suited and widely used for this purpose. Applying the GNPS Jang *et al* discovered two new geldanamycin and streptimidone derivatives during their study of *Streptomyces* species [92].

Infrared spectroscopy

The IR spectrum showed absorption for the hydroxy group at 3418 cm^{-1} and carbonyl carbon at 1732 cm^{-1}, the peaks at 3325 and 1716 cm^{-1} indicated the presence of hydroxy groups and a carbonyl group. The IR absorption band at 1800 cm^{-1} identify both α-hydroxy-γ-lactone moieties[72,78].

Ultraviolet absorption

Due to complicated and variable structure of macrolides, there is no characteristic absorption band or bands to cover the whole class of macrolides, otherwise the absorption varied according to number of chromophores and extent of conjugation in each class of macrolide. Small to medium sized macrolactones (C10-C14), with isolated chromophores have absorption bands at 208-210 nm[92]. *β*-resorcylic acid derivatives absorption bands are at 211, 262, and 298 nm; 211, 262, 298 nm; 220, 260, 310 or 220, 258, 308[91]. Brefeldin A showed absorption band at 230 nm[24,92]. UV analysis showed a band at 266 nm for Pyrenophorol and two bands at 199, 213 (sh) for tetrahydropyrenophorol. Additionally, Myrothecene analysis revealed the presence of UV absorption bands at 219-220 nm[71], meanwhile the absorption bands for Ansamacrolides were at 233, 243 (sh), 254, 282-290 nm[78,93].

^{13}C NMR spectroscopy

The ^{13}C NMR and DEPT spectra have offered a very helpful tool for the major structural features of macrolide with respect to ring size, oxygenated methines, additional carbonyls and sulphur substitution as well as the presence of epoxide moiety[54,92].

Generally, the ^{13}C NMR when combined with HSQC-DEPT data is indicative tool. Surveying the published ^{13}C NMR spectral data we could conclude that the resonances ester and/or amide carbonyls at δ_C 170-166, and at δ_C 156.2-153.5, 140-137, 119-115, 110-108, and around 98 for aromatic carbons, in addition to resonances at δ_C 49-34 indicates and identifies the number of methines, at δ_C 32- 21 for methylenes, at δ_C 55.5-56.5 for methoxy groups, and the methyl groups at δ_C 16-23 ppm[65]. The ketone carbonyls at δ_C 209-206. While the methines resonance at δ_C 136.3, 133.4 and 128.0, olefinic methines at δ_C 108-106 and oxygenated methines at δ_C 77.3, 75.4, and 68.5, methylenes at δ_C 48.5, 38.1, 37.5, 28.8, and 27.9, and the methyl groups at δ_C 19-12[80]. Meanwhile the carbon resonance at δ_C 61.9 and 63.8 together with the proton at δ_H 4.42 (m) and 4.85 (m) ppm were diagnostic for a 1,2-disubstituted epoxide, while δ_C 41.7 - 43.4 ppm referred to sulphur bearing methine[26,44].

Conclusion

Since the inspiring isolation of numerous promising plant metabolites as camptothecin and taxol from plant endophytic fungi, they have gained increasing importance as a potential source of biologically active metabolites. Plant endophytes might be the answer to the problem of inadequate medicinal resources and slow growth rates of medicinal plants. According to the current study, research for novel natural products from plant endophytes in the past 10 years had afforded 90 macrolides, including 80 new molecules. The majority of the macrolides described in this study had 12 and 16-membered ring structures, with a few having 10, 13, 14, and 18-membered rings **(Fig. 7)**. They showed cytotoxic, antibacterial, antifungal, and α-glucosidase inhibitory properties **(Fig. 8)**.

The described compounds were reported in 30 fungal strains of 12 genera. Most of the investigated species belonging to the *Cladosporium* and *Penicilium* genera. **(Fig.9)**. It is notable that the number of novel compounds from plant endophytes is much fewer than those reported from marine endophytes during the same time period.

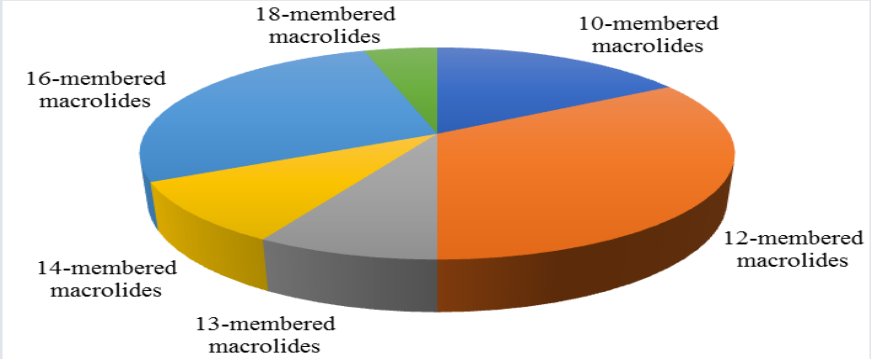

Fig. 7: Ring sizes of the new macrolides isolated during 2013 to 2023.

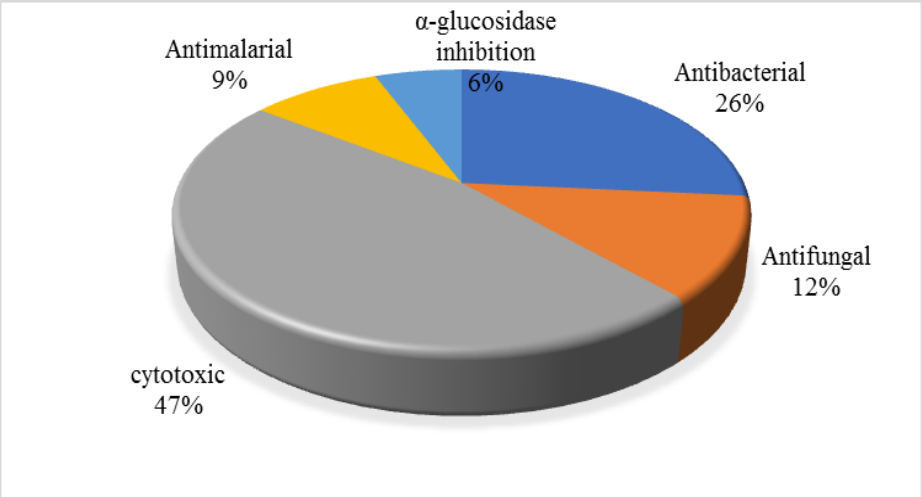

Fig. 8: Major biological activities of the macrolides isolated during 2013 to 2023.

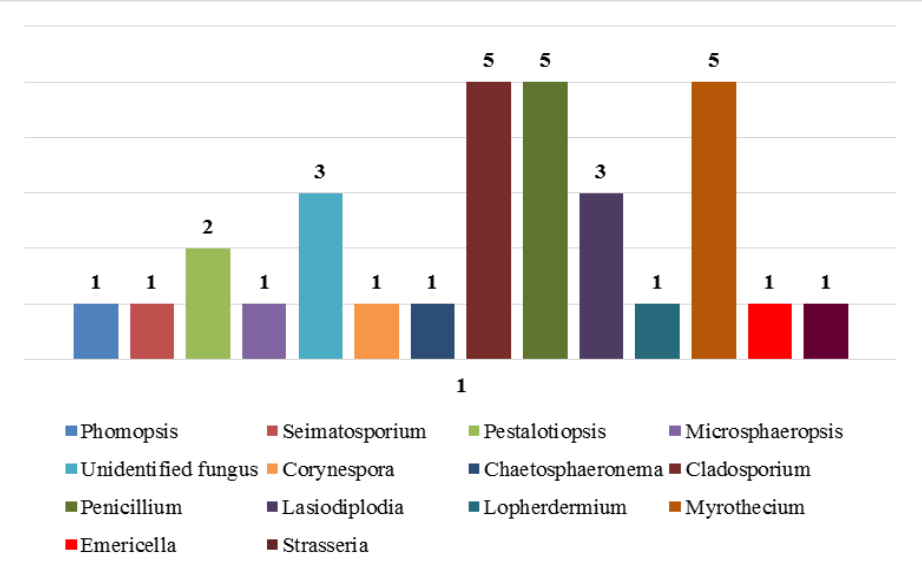

Fig. 9: Main genera of plant endophytic fungi examined between 2013 to 2023.

We addressed the standard isolation processes of macrolactones and macrolides, as well as a synopsis of the reported compounds' ^{13}C-NMR spectroscopic data, as an assistance in structural elucidation of this class. During the preparation of this review, we observed that the name thiocladospolide F identifies two different structures, as well as the name

thiocladospolide G also identifies two different structures, accordingly, we propose that compounds 30 and 31 to be recognized as thiocladospolides F and G, while compounds 35 and 36 should be recognozed as thiocladospolides K and L.

Acknowledgement

This work was supported by National Institutes of Health grant R01 GM115261, the Center of Biomedical Research Excellence (COBRE) in Pharmaceutical Research and Innovation (CPRI, NIH P20 GM130456), the University of Kentucky College of Pharmacy, and the National Center for Advancing Translational Sciences (UL1TR000117 and UL1TR001998).

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Bull. Pharm. Sci., Assiut University, Vol. 47, Issue 1, 2024, pp. 151-168

نشرة العلوم الصيدلية
جامعة أسيوط

BULL. PHARM. SCI. Assiut Univ.

الماكرولاكتونات والماكروليدات من الفطريات النباتية والسقالات الكيميائية ، الأنشطة البيولوجية والتحليل الطيفي: مراجعة شاملة

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أظهرت جائحة كورونا مدى الحاجة الملحة لإيجاد علاجات جديدة ، الأمر الذي يحفز البحث عن مصادر جديدة للوصول إلى هذه العلاجات. وتعد الفطريات النباتية الداخلية أحد هذه المصادر ، حيث تقوم هذه الفطريات بتكوين أنواع مختلفة من المركبات ذات التأثيرات الحيوية الواعدة.

الهدف من الدراسة

أن هذه الدراسة المرجعية هي استقصاء لمركبات الماكروليد والماكرولاكتون الطبيعية التي تنتجها الفطريات الداخلية النباتية خلال الفترة من ٢٠١٣ إلى منتصف ٢٠٢٣ (وقت الانتهاء من البحث) ، مع ذكر الفطر المنتج والتركيب الكيميائي و التأثيرات الحيوية لكل مركب.

النتائج

خلال السنوات العشر الماضية تم التعرف على واحد وتسعين مركبا من هذه الفطريات ، منها ثمانون مركبا جديدا ، وكانت التأثيرات الحيوية لهذه المركبات تقع أغلبها في نطاق مضادات البكتريا ، مضادات الأورام ، التأثير القاتل للخلايا ، مضادات الفطريات ، مضادات الملاريا بالإضافة إلى التأثير المثبط لإنزيم ألفا-جلوكوسيداز. ولكن يبقى هذا العدد ضئيلا مقارنة بعدد المركبات التي تم فصلها والتعرف عليها من الفطريات البحرية أو من البكتريا (الأكتينومايسيتس و الاستربتومايسيس). ولذلك يجب الاهتمام بهذا المصدر المهم وإجراء المزيد من الأبحاث على الفطريات النباتية الغنية بالمركبات الواعدة ذات التأثيرات الحيوية المهمة. ملحق بهذه الدراسة بيانات تكميلية عن قيم الكربون الطيفية للمركبات المنشورة خلال هذه الفترة.