Prospective Leads from Endophytic Fungi for Anti-Inflammatory Drug Discovery

Authors
Pragya Paramita Pal[1], Ameer Basha Shaik[2], A. Sajeli Begum[1]

Affiliations
1 Department of Pharmacy, Birla Institute of Technology and Science–Pilani, Hyderabad Campus, Jawahar Nagar, Hyderabad, Telangana State, India
2 Department of Plant Pathology, Professor Jeyashanker Telangana State Agricultural University, Rajendra Nagar, Hyderabad, Telangana State, India

Key words
endophytes, fungi, anti-inflammation, cytokines, herbarin, periconianone, phytochemicals

received December 2, 2019
accepted after revision March 17, 2020
published online April 25, 2020

Bibliography
Planta Med 2020; 86: 941–959
DOI 10.1055/a-1140-8388
ISSN 0032-0943

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Correspondence
Dr. A. Sajeli Begum
Department of Pharmacy, Birla Institute of Technology and Science-Pilani, Hyderabad Campus, Jawahar Nagar
Kapra Mandal, Hyderabad 500078, Telangana State, India
Phone: + 91 40 66 30 35 78, Fax: + 91 40 66 30 39 98
sajeli@hyderabad.bits-pilani.ac.in

ABSTRACT

A wide array of therapeutic effects has been exhibited by compounds isolated from natural sources. “Bio-actives of endophytic origin” is a recently explored area that came into recognition over the last 2 decades. Literature search on the secondary metabolites of endophytes have shown several pharmacologically active compounds especially anti-inflammatory compounds, which have been reviewed in the present paper. The article is structured based on the chemical classification of secondary metabolites. The compounds were identified to possess activity against a total of 16 anti-inflammatory targets. The most common targets involved were NO, TNF-α, and inhibition of total ROS. Further, the article gives a detailed insight into the compounds, their endophytic source, and anti-inflammatory target as well as potency. The contents of the article cover all the scientific reports published until Feb. 2019. Thus 118 compounds and 6 extracts have been reported to be obtained from endophytic sources showing anti-inflammatory activities. Amongst these, herbarin, periconianone A, and periconianone B were identified as the most potent compounds in terms of their IC_{50} values against NO inhibition.

ABBREVIATIONS

AI	anti-inflammatory
COX	cyclooxygenase
IFN-γ	interferon gamma
IL	interleukin
LOX	lipoxygenase
LPS	lipo polysaccharide
PG	prostaglandin.
ROS	reactive oxygen species
TNF-α	tumor necrosis factor alpha

Introduction

Endophytes are the nonpathogenic fungi or bacteria that reside and colonize the inner tissues of plants by maintaining a symbiotic relationship with their host plants. They provide immunity to the plants during biotic and abiotic stresses by providing better adaptability to them. Microbial natural products of endophytic origin is a less explored field, yet it has immense possibilities to provide a huge library of novel bioactive lead molecules for drug discovery [1]. Also, endophytes are found to contribute largely to the production of bioactive plant secondary metabolites. Thus en-

▶ **Table 1** Anti-inflammatory metabolites, and their source endophytes.

S. No.	Compound name	Source endophyte	Host plant of endophyte	Reference
1.	(3*R*,4*S*)-3,8-dihydroxy-3-hydroxy methyl-6-methoxy-4,5-dimethyl isochroman-1-one (**117**)	*Phoma sp.* PF2	*Artemisia princeps* Pamp.	[9]
2.	(3*S*,4*S*)-3,8-dihydroxy-6-methoxy-3,4,5-trimethylisochroman-1-one (**118**)	*Phoma sp.* PF2	*Artemisia princeps* Pamp.	[9]
3.	1,2 seco-trypacidin (**70**)	*Aspergillus fumigatus*	*Rumex patientia*	[10]
4.	1,8-dimethoxynaphthalene (**102**)	*Hypoxylon investiens*	*Litsea akoensis var. chitouchiaoensis*	[11]
5.	11-epichaetomugilin I (**57**)	*Wikstroemia uva-ursi*	*Chaetomium globosum*	[12]
6.	1-methoxy-3-methylcarbazole (**3**)	*Streptomyces sp.* LJK109	*Alpinia galanga Swartz*	[13]
7.	1-*O*-methyl emodin (**64**)	*Aspergillus fumigatus, Gaeumannomyces sp.*	*Rumex patientia, Phragmites communis*	[10, 14]
8.	1-*O*-methyl-6-*O*-(α-D-ribofuranosyl)-emodin (**63**)	*Gaeumannomyces sp.*	*Phragmites communis*	[14]
9.	1α-isopropyl-4α,8-dimethylspiro dec-8-ene-3β,7α-diol (**26**)	*Trichoderma sp.* Xy24	*Xylocarpus granatum*	[15]
10.	3-methylcarbazole (**2**)	*Streptomyces sp.* LJK109	*Alpinia galanga Swartz*	[13]
11.	3β,5α-dihydroxy-6β-methoxyergosta-7,22-diene (**39**)	*Trichoderma sp.* Xy24	*X. granatum*	[16]
12.	4′,5,7-trihydroxyisoflavone-7-*O*-(4′′-*O*-methyl)-β-D-glucopyranoside (**84**)	*Cordyceps ninchukispora*	*Beilschmiedia erythrophloia* (Seeds)	[17]
13.	4′,7-dihydroxy-6-methoxyisoflavone-7-*O*-(4′′-*O*-methyl)-β-D-glucopyranoside (**83**)	*Cordyceps ninchukispora*	*Beilschmiedia erythrophloia* (Seeds)	[17]
14.	4′,7-dihydroxyisoflavone-7-*O*(4′′-*O*-methyl)-β-D-glucopyranoside (**85**)	*Cordyceps ninchukispora*	*Beilschmiedia erythrophloia* (Seeds)	[17]
15.	5,7-dimethoxy-4-phenylcoumarin (**28**)	*Streptomyces aureofaciens CMUAc130*	*Zingiber officinale Rosc.* (Root Tissues)	[18]
16.	5,7-dimethoxy-4-p-methoxylphenylcoumarin (**29**)	*Streptomyces aureofaciens CMUAc130*	*Zingiber officinale Rosc.* (Root Tissues)	[18]
17.	5α,8α-epidioxy-(22*E*,24 *R*)-23-methylergosta-6,22-dien-3β-ol (**44**)	*Gaeumannomyces sp.*	*Phragmites communis*	[14]
18.	5α,8α-epidioxyergosta-6,22-dien-3β-ol (**38**)	*Colletotrichum sp.* GDMU-1	*Santalum album*	[19]
19.	5α,8α-epidioxyergosta-6,9(11),22-trien-3-ol (**43**)	*Gaeumannomyces sp.*	*Phragmites communis*	[14]
20.	8-methoxy naphthalene-1,7-diol (**100**)	*Hypoxylon investiens*	*Litsea akoensis var. chitouchiaoensis*	[11]
21.	8-methoxynaphthalen-1-ol (**101**)	*Hypoxylon investiens*	*Litsea akoensis var. chitouchiaoensis*	[11]
22.	Aloe emodin (**68**)	*Aspergillus fumigatus*	*Rumex patientia*	[10]
23.	Alternariol (**99**)	*Phomopsis sp.*	*Senna spectabilis* (Leaves)	[20]
24.	Amestolkolide A (**112**)	*Talaromyces amestolkiae* YX1	*Kandelia obovata* (Leaves)	[21]
25.	Amestolkolide B (**111**)	*Talaromyces amestolkiae* YX1	*Kandelia obovata* (Leaves)	[21]
26.	Andasperfumin (**72**)	*Aspergillus fumigatus*	*Rumex patientia*	[10]
27.	Asperimide C (**97**)	*Aspergillus terreus*	*Suriana maritima* L.	[22]
28.	Asperimide D (**98**)	*Aspergillus terreus*	*Suriana maritima* L.	[22]
29.	Aspernolide A (**92**)	*Aspergillus terreus*	*Camellia sinensis var. assamica*	[23]
30.	Asperteretal A (**87**)	*Aspergillus terreus*	*Camellia sinensis var. assamica*	[23]
31.	Asperteretal C (**88**)	*Aspergillus terreus*	*Camellia sinensis var. assamica*	[23]
32.	Botryoisocoumarin A (**36**)	*Botryosphaeria sp.* KcF6	*Kandelia candel*	[5]
33.	Botryosphaerin B (**115**)	*Botryosphaeria sp.* SCSIO KcF6	*Kandelia candel*	[24]
34.	Butyrolactone I (**89**)	*Aspergillus terreus*	*Suriana maritima L., Camellia sinensis var. assamica*	[22, 23]
35.	Butyrolactone II (**90**)	*Aspergillus terreus*	*Camellia sinensis var. assamica*	[23]
36.	Butyrolactone III (**91**)	*Aspergillus terreus*	*Camellia sinensis var. assamica*	[23]
37.	Chaetoglobosin Fex (Cha Fex) (**7**)	*Chaetomium globosum* QEN-14	*Ulva pertusa*	[25]

continued

▶ **Table 1** *Continued*

S. No.	Compound name	Source endophyte	Host plant of endophyte	Reference
38.	Chaetomugulin E (**60**)	*Wikstroemia uva-ursi*	*Chaetomium globosum*	[12]
39.	Chaetomugulin F (**61**)	*Wikstroemia uva-ursi*	*Chaetomium globosum*	[12]
40.	Chaetomugulin I (**58**)	*Wikstroemia uva-ursi*	*Chaetomium globosum*	[12]
41.	Chaetomugulin J (**59**)	*Wikstroemia uva-ursi*	*Chaetomium globosum*	[12]
42.	Chrysophanol (**65**)	*Aspergillus fumigatus*	*Rumex patientia*	[10]
43.	Chrysophanol-8-*O*-*β*-D- glucopyranoside (**73**)	*Aspergillus fumigatus*	*Rumex patientia*	[10]
44.	Conioxanthone A (**48**)	*Penicillium sp.* ZJ-SY2	*Sonneratia apetala*	[26]
45.	Cordycepiamide B (**82**)	*Cordyceps ninchukispora*	*Beilschmiedia erythrophloia* (Seeds)	[17]
46.	Cordycepiamides D (**86**)	*Cordyceps ninchukispora*	*Beilschmiedia erythrophloia* (Seeds)	[17]
47.	Corynesidone A (**103**)	*Corynespora cassicola*	*Gongronema latifolium*	[27]
48.	Corynesidone C (**104**)	*Corynespora cassicola*	*Gongronema latifolium*	[27]
49.	Corynesidone D (**105**)	*Corynespora cassicola*	*Gongronema latifolium*	[27]
50.	Corynether A (**106**)	*Corynespora cassicola*	*Gongronema latifolium*	[27]
51.	Cyclonerodiol B (**25**)	*Trichoderma sp.* Xy24	*X. granatum*	[15]
52.	Cytochalasin H (**13**)	*Phomopsis sp*	*Senna spectabilis* (Leaves)	[20]
53.	Cytochalasin J (**12**)	*Phomopsis sp*	*Senna spectabilis* (Leaves)	[20]
54.	Desmethyldichloro diaportin (**32**)	*Ascomycota sp.*	*Pluchea indica*	[28]
55.	Desmethyldichlorodiaportintone (**31**)	*Ascomycota sp.*	*Pluchea indica*	[28]
56.	Diaporindenes A (**8**)	*Diaporthe sp.*	*Excoecaria agallocha* (branches)	[29]
57.	Diaporindenes B (**9**)	*Diaporthe sp.*	*Excoecaria agallocha* (branches)	[29]
58.	Diaporindenes C (**10**)	*Diaporthe sp.*	*Excoecaria agallocha* (branches)	[29]
59.	Diaporindenes D (**11**)	*Diaporthe sp.*	*Excoecaria agallocha* (branches)	[29]
60.	Diaporisoindoles A (**5**)	*Diaporthe sp.*	*Excoecaria agallocha* (branches)	[29]
61.	Diaporisoindoles B (**6**)	*Diaporthe sp.*	*Excoecaria agallocha* (branches)	[29]
62.	Dichlorodiaportin (**33**)	*Ascomycota sp.*	*Pluchea indica*	[28]
63.	Dichlorodiaportintone (**30**)	*Ascomycota sp.*	*Pluchea indica*	[28]
64.	Emodin (**66**)	*Aspergillus fumigatus*	*Rumex patientia*	[10]
65.	Emodin-8-*O*-*β*-D- glucopyranoside (**75**)	*Aspergillus fumigatus*	*Rumex patientia*	[10]
66.	Emodin-8-*O*-*β*-D-*O*-acetyl glucopyranoside (**74**)	*Aspergillus fumigatus*	*Rumex patientia*	[10]
67.	Ergoflavin (**47**)	*Ascomycetes sp.*	*Mimosops elengi* (Leaves)	[30]
68.	Ergosterol-3-*O*-*β*-D-glucopyranoside (**37**)	*Colletotrichum sp.* GDMU-1	*Santalum album*	[19]
69.	Fusaristerol A (**45**)	*Fusarium sp.*	*Mentha longifolia L. roots*	[31]
70.	Fusaristerol B (**46**)	*Fusarium sp.*	*Mentha longifolia L. roots*	[31]
71.	Glomeremophilanes A (**22**)	*Glomerella cingulata*	*Gelsemium elegans*	[32]
72.	Glomeremophilanes C (**23**)	*Glomerella cingulata*	*Gelsemium elegans*	[32]
73.	Glomeremophilanes D (**24**)	*Glomerella cingulata*	*Gelsemium elegans*	[32]
74.	Herbarin (**62**)	*Dendryphion nanum* (Nees) S. Hughes	*Ficus religiosa*	[33]
75.	Isoprenylisobenzofuran A (**109**)	*Diaporthe sp.*	*Excoecaria agallocha* (branches)	[29]
76.	Koninginin E (**107**)	*Trichoderma koningii*	*Strychnos cogens plant*	[34]
77.	Koninginin F (**108**)	*Trichoderma koningii*	*Strychnos cogens plant*	[34]
78.	Lansai C (**4**)	*Streptomyces sp.* SUC1	*Ficus benjamina* (roots)	[35]
79.	Lasiodiplactone A (**52**)	*Lasiodiplodia theobromae* ZJ-HQ1	*Acanthus ilicifolius*	[36]
80.	Montagnuphilone B (**53**)	*Montagnulaceae sp.* DM0194	*Persicaria amphibia*	[37]
81.	Montagnuphilones E (**54**)	*Montagnulaceae sp.* DM0194	*Persicaria amphibia*	[37]
82.	Nepalenside A (**76**)	*Aspergillus fumigatus*	*Rumex patientia*	[10]

continued

▶ **Table 1** *Continued*

S. No.	Compound name	Source endophyte	Host plant of endophyte	Reference
83.	Palmaerones A (**34**)	*Lachnum palmae*	*Przewalskia tangutica*	[38]
84.	Palmaerones E (**35**)	*Lachnum palmae*	*Przewalskia tangutica*	[38]
85.	Patientoside A (**77**)	*Aspergillus fumigatus*	*Rumex patientia*	[10]
86.	Patientoside B (**78**)	*Aspergillus fumigatus*	*Rumex patientia*	[10]
87.	Peniphenone (**110**)	*Penicillium sp.* ZJ-SY2	*Sonneratia apetala*	[26]
88.	Periconianone A (**20**)	*Periconia sp.*	*Annonsa muricata*	[39]
89.	Periconianone B (**21**)	*Periconia sp.*	*Annonsa muricata*	[39]
90.	Pestaloporinate B (**27**)	*Pestalotiopsis sp.*	*Melia azedarach*	[40]
91.	Phomol (**51**)	*Phomopsis sp.*	*Erythrina crista-galli*	[41]
92.	Phomopchalasin C (**15**)	*Phomopsis sp.*	*Isodon eriocalyx var. laxiflora*	[42]
93.	Phomopsterones B (**40**)	*Phomopsis sp.* TJ507A	*Phyllanthus glaucus*	[43]
94.	Physcion (**67**)	*Aspergillus fumigatus*	*Rumex patientia*	[10]
95.	Piniphenol A (**116**)	*Pinus sp.*	*Porodaedalea pini*	[44]
96.	Pinselin (**50**)	*Penicillium sp.* ZJ-SY2	*Sonneratia apetala*	[26]
97.	Pseurotin A (**1**)	*Aspergillus fumigatus*	*Erythrophloeum fordii Oliv.* (Stem)	[45]
98.	Questin (**69**)	*Aspergillus fumigatus*	*Rumex patientia*	[10]
99.	Rubiginosins B (**55**)	*Montagnulaceae sp.* DM0194	*Persicaria amphibia*	[37]
100.	Sorrentanone (**113**)	*Trichoderma sp.* Xy24	*Xylocarpus granatum*	[16]
101.	Stemphol C (**80**)	*Gaeumannomyces sp.*	*Phragmites communis*	[14]
102.	Stemphol D (**81**)	*Gaeumannomyces sp.*	*Phragmites communis*	[14]
103.	Sydowinin A (**49**)	*Penicillium sp.* ZJ-SY2	*Sonneratia apetala*	[26]
104.	Terrusnolides A (**93**)	*Aspergillus sp.*	*Tripterygium wilfordii* (Roots)	[46]
105.	Terrusnolides B (**94**)	*Aspergillus sp.*	*Tripterygium wilfordii* (Roots)	[46]
106.	Terrusnolides C (**95**)	*Aspergillus sp.*	*Tripterygium wilfordii* (Roots)	[46]
107.	Terrusnolides D (**96**)	*Aspergillus sp.*	*Tripterygium wilfordii* (Roots)	[46]
108.	Trichodimerol (**114**)	*Trichoderma sp.* Xy24	*Xylocarpus granatum*	[16]
109.	Trypacidin (**71**)	*Aspergillus fumigatus*	*Rumex patientia*	[10]
110.	Xylapapuside A (**79**)	*Xylaria papulis*	*Lepidagathis stenophylla*	[47]
111.	Xylarenones C (**16**)	*Camarops sp.*	*Alibertia macrophylla*	[48]
112.	Xylarenones D (**17**)	*Camarops sp.*	*Alibertia macrophylla*	[48]
113.	Xylarenones F (**18**)	*Camarops sp.*	*Alibertia macrophylla*	[48]
114.	Xylarenones G (**19**)	*Camarops sp.*	*Alibertia macrophylla*	[48]
115.	Xylariphilone (**56**)	*Annulohypoxylon truncatum*	*Zizania caduciflora*	[49]
116.	Yamchaetoglobosin A (**14**)	*Chaetomium globosum*	*Hydrocharis dubia*	[50]
117.	*β*-sitosterol (**41**)	*Gaeumannomyces sp.*	*Phragmites communis*	[14]
118.	*β*-sitosterone (**42**)	*Cordyceps ninchukispora*	*Beilschmiedia erythrophloia* (Seeds)	[17]

dophytic bacteria and fungi can serve as an alternative natural source for the production of bioactive metabolites [2].

Recently, research interest toward endophytic fungi has increased due to the novelty of molecules that are secreted by them. Such molecules have been reported to possess a wide variety of pharmacological activities including anti-bacterial, anti-fungal, cytotoxic, AI, proliferative, antioxidant, antiviral, anti-tubercular, etc. [1].

Inflammation, a local response to chemical/physical irritants, infection, or injury to tissues, can lead to a series of processes involving tissue repair, proliferation, collagen and elastin production, and cytokines release [3]. Cytokines such as IL-1, IL-6, IL-12, IL-18, INF-γ, TNF-α and the granulocyte macrophage colony-stimulating factor promote inflammation and are termed as pro-inflammatory cytokines. On the other hand, those that suppress the pro-inflammatory cytokines expressions such as IL-4, IL-10, IL-13, IFN-α, and transforming growth factor are termed as AI cytokines. A balance between these 2 is essential, and any disruption in the balance can lead to the promotion of inflammation, tissue destruction, or loss of essential functionality of tissues [4]. Pro-inflammatory cytokines including IL and TNF mediate a variety of hyperalgesic states. They are also related to various illness re-

▶ **Table 2** Anti-inflammatory efficacy of compounds isolated from endophytic fungi.

S. No.	Compound name	Anti-inflammatory activity	Reference
1.	(3*R*,4*S*)-3,8-dihydroxy-3-hydroxy methyl-6-methoxy-4,5-dimethyl isochroman-1-one (**117**)	NO (Nitric oxide) inhibition	[9]
2.	(3*S*,4*S*)-3,8-dihydroxy-6-methoxy-3,4,5-trimethyl-isochroman-1-one (**118**)	NO inhibition	[9]
3.	1,2 seco-trypacidin (**70**)	IL-6 inhibition (diabetic nephropathy)	[10]
4.	1,8-dimethoxynaphthalene (**102**)	NO and IL-6 inhibition [IC_{50} 2.0 μM and 13.3 μM for IL-6 and NO respectively]	[11]
5.	11-epichaetomugilin I (**57**)	NO inhibition [IC_{50} 0.8 μM]	[12]
6.	1-methoxy-3-methylcarbazole (**3**)	NO, PGE-2, TNF-α, IL-1β, IL-6, and IL-10 inhibition	[13]
7.	1-*O*-methyl emodin (**64**)	IL-6 inhibition (diabetic nephropathy), NO inhibition [31%]	[10, 14]
8.	1-*O*-methyl-6-*O*-(α-D-ribofuranosyl)-emodin (**63**)	NO inhibition [43%]	[14]
9.	1α-isopropyl-4α,8-dimethylspiro dec-8-ene-3β,7α-diol (**26**)	NO inhibitor (neural anti-inflammatory) [39.2%]	[15]
10.	3-methylcarbazole (**2**)	NO, PGE-2, TNF-α, IL-1β, IL-6, and IL-10 inhibition	[13]
11.	3β,5α-dihydroxy-6β-methoxyergosta-7,22-diene (**39**)	NO inhibition (neural anti-inflammatory) [108.2%]	[16]
12.	4′,5,7-trihydroxyisoflavone-7-*O*-(4′′-*O*-methyl)-β-D-glucopyranoside (**84**)	NO inhibition [10.8%]	[17]
13.	4′,7-dihydroxy-6-methoxyisoflavone-7-*O*-(4′′-*O*-methyl)-β-D-glucopyranoside (**83**)	NO inhibition [14.8%]	[17]
14.	4′,7-dihydroxyisoflavone-7-*O* (4′′-*O*-methyl)-β-D-glucopyranoside (**85**)	NO inhibition [14.0%]	[17]
15.	5,7-dimethoxy-4-phenylcoumarin (**28**)	NO, PGE2, TNF-α, IL-6, IL-1, and COX-2 inhibition	[18]
16.	5,7-dimethoxy-4-p-methoxylphenylcoumarin (**29**)	NO, PGE2, TNF-α, IL-6, IL-1, and COX-2 inhibition	[18]
17.	5α,8α-epidioxy-(22*E*,24 *R*)-23-methylergosta-6,22-dien-3β-ol (**44**)	NO inhibition	[14]
18.	5α,8α-epidioxyergosta-6,22-dien-3β-ol (**38**)	NO inhibition [IC_{50} 8.9 μM]	[19]
19.	5α,8α-epidioxyergosta-6,9(11),22-trien-3-ol (**43**)	NO inhibition [IC_{50} 8.94 μM]	[14]
20.	8-methoxy naphthalene-1,7-diol (**100**)	NO and IL-6 inhibition [IC_{50} 9.2 μM and 11.8 μM for IL-6 and NO respectively]	[11]
21.	8-methoxynaphthalen-1-ol (**101**)	NO and IL-6 inhibition [IC_{50} 18.0 μM and 17.8 μM for IL-6 and NO respectively]	[11]
22.	Aloe emodin (**68**)	IL-6 inhibition (diabetic nephropathy)	[10]
23.	Alternariol (**99**)	Total ROS inhibition	[20]
24.	Amestolkolide A (**112**)	NO inhibition [IC_{50} 30 mM]	[21]
25.	Amestolkolide B (**111**)	NO inhibition [IC_{50}1.6 μM]	[21]
26.	Andasperfumin (**72**)	IL-6 inhibition (diabetic nephropathy)	[10]
27.	Asperimide C (**97**)	NO inhibition [IC_{50} 0.78 μM]	[22]
28.	Asperimide D (**98**)	NO inhibition [IC_{50} 1.26 μM]	[22]
29.	Aspernolide A (**92**)	NO inhibition [IC_{50} 45.37 μM]	[23]
30.	Asperteretal A (**87**)	NO inhibition [IC_{50} 26.64 μM]	[23]
31.	Asperteretal C (**88**)	NO inhibition [IC_{50}16.80 μM]	[23]
32.	Botryoisocoumarin A (**36**)	COX-2 inhibition [IC_{50} 6.51 μM]	[5]
33.	Botryosphaerin B (**115**)	COX-2 inhibition [IC_{50} 1.12 μM]	[24]
34.	Butyrolactone I (**89**)	NO inhibition [IC_{50} 24.2 μM and 17.21 μM as per Ref [22] and [23], respectively]	[22, 23]
35.	Butyrolactone II (**90**)	NO inhibition [IC_{50} 44.37 μM]	[23]
36.	Butyrolactone III (**91**)	NO inhibition [IC_{50} 20.60 μM]	[23]
37.	Chaetoglobosin Fex (Cha Fex) (**7**)	TNF-α, IL-6, MCP-1, and MAPKs [TNF-α inhibition 15.2% 0.5 μg/ml, 21.3% 1 μg/ml, 56.7% 2 μg/ml; IL-6 inhibition 30.9% 0.5 μg/ml, 37.1% 1 μg/ml, and 50.1% 2 μg/ml]	[25]

continued

▶ **Table 2** *Continued*

S. No.	Compound name	Anti-inflammatory activity	Reference
38.	Chaetomugulin E (**60**)	NO inhibition [IC_{50} 5.8 µM]	[12]
39.	Chaetomugulin F (**61**)	NO inhibition [IC_{50} 1.9 µM]	[12]
40.	Chaetomugulin I (**58**)	NO inhibition [IC_{50} 0.3 µM]	[12]
41.	Chaetomugulin J (**59**)	NO inhibition [IC_{50} 4.2 µM]	[12]
42.	Chrysophanol (**65**)	IL-6 inhibition (diabetic nephropathy)	[10]
43.	Chrysophanol-8-*O*-*β*-D- glucopyranoside (**73**)	IL-6 inhibition (diabetic nephropathy)	[10]
44.	Conioxanthone A (**48**)	Splenic lymphocytes inhibition [IC_{50} 8.1 (Con-A) and 9.3 µg/mL (LPS)]	[26]
45.	Cordycepiamide B (**82**)	NO inhibition [11.2%]	[17]
46.	Cordycepiamides D (**86**)	NO inhibition [17.4%]	[17]
47.	Corynesidone A (**103**)	NO and TNF-*α* inhibition [IC_{50} 1.88 µM (NO) and 8.16 µM (TNF-*α*)]	[27]
48.	Corynesidone C (**104**)	NO and TNF-*α* inhibition [IC_{50} 3.99 µM (NO) and 9.49 µM (TNF-*α*)]	[27]
49.	Corynesidone D (**105**)	NO and TNF-*α* inhibition [IC_{50} 7.48 µM (NO) and 15.29 µM (TNF-*α*)]	[27]
50.	Corynether A (**106**)	NO [IC_{50} 37.22 µM] and TNF-*α* [IC_{50} 26.52 µM] inhibition	[27]
51.	Cyclonerodiol B (**25**)	NO inhibition (neural anti-inflammatory) [75.0%]	[15]
52.	Cytochalasin H (**13**)	Total ROS inhibition	[20]
53.	Cytochalasin J (**12**)	Total ROS inhibition	[20]
54.	Desmethyldichloro diaportin (**32**)	NO inhibition [IC_{50} 33.6 µM]	[28]
55.	Desmethyldichlorodiaportintone (**31**)	NO inhibition [IC_{50} 15.8 µM]	[28]
56.	Diaporindenes A (**8**)	NO inhibition [IC_{50} 8.5 µM]	[29]
57.	Diaporindenes B (**9**)	NO inhibition [IC_{50} 5.9 µM]	[29]
58.	Diaporindenes C (**10**)	NO inhibition [IC_{50} 4.2 µM]	[29]
59.	Diaporindenes D (**11**)	NO inhibition [IC_{50} 4.2 µM]	[29]
60.	Diaporisoindoles A (**5**)	NO inhibition [IC_{50} 22.7 µM]	[29]
61.	Diaporisoindoles B (**6**)	NO inhibition [IC_{50} 18.2 µM]	[29]
62.	Dichlorodiaportin (**33**)	NO inhibition [IC_{50} 67.2 µM]	[28]
63.	Dichlorodiaportintone (**30**)	NO inhibition [IC_{50} 41.5 µM]	[28]
64.	Emodin (**66**)	IL-6 inhibition (diabetic nephropathy)	[10]
65.	Emodin-8-*O*-*β*-D-glucopyranoside (**75**)	IL-6 inhibition (diabetic nephropathy)	[10]
66.	Emodin-8-*O*-*β*-D-*O*-acetyl glucopyranoside (**74**)	IL-6 inhibition (diabetic nephropathy)	[10]
67.	Ergoflavin (**47**)	TNF-*α* and IL-6 inhibition [IC_{50} 1.9 µm (TNF-*α*) and 1.2 µm (IL-6)]	[30]
68.	Ergosterol-3-*O*-*β*-D-glucopyranoside (**37**)	NO inhibition [IC_{50} 30.4 µM]	[19]
69.	Fusaristerol A (**45**)	5-LOX inhibition [IC_{50} 2.4 µM]	[31]
70.	Fusaristerol B (**46**)	5-LOX inhibition [IC_{50} 3.6 µM]	[31]
71.	Glomeremophilanes A (**22**)	NO inhibition (neural anti-inflammatory) [50.6%]	[32]
72.	Glomeremophilanes C (**23**)	NO inhibition (neural anti-inflammatory) [36.1%]	[32]
73.	Glomeremophilanes D (**24**)	NO inhibition (neural anti-inflammatory) [29.4%]	[32]
74.	Herbarin (**62**)	TNF-*α* and IL-6 inhibition [IC_{50} 0.06 µM (TNF-*α*) and 0.01 µM (IL-6)]	[33]
75.	Isoprenylisobenzofuran A (**109**)	NO inhibition [IC_{50} 9.0 µM]	[29]
76.	Koninginin E (**107**)	Phospholipase A2 inhibition [90.2%]	[34]
77.	Koninginin F (**108**)	Phospholipase A2 inhibition [91.8%]	[34]
78.	Lansai C (**4**)	NO, PGE2, TNF-*α*, IL-1*α*, IL-6, and IL-10 inhibition	[35]
79.	Lasiodiplactone A (**52**)	NO inhibition [IC_{50} 23.5 µM]	[36]
80.	Montagnuphilone B (**53**)	NO inhibition [IC_{50} 39.6 µM]	[37]
81.	Montagnuphilones E (**54**)	NO inhibition [IC_{50} 25.5 µM]	[37]
82.	Nepalenside A (**76**)	IL-6 inhibition (diabetic nephropathy)	[10]
83.	Palmaerones A (**34**)	NO inhibition [IC_{50} 26.3 µM]	[38]

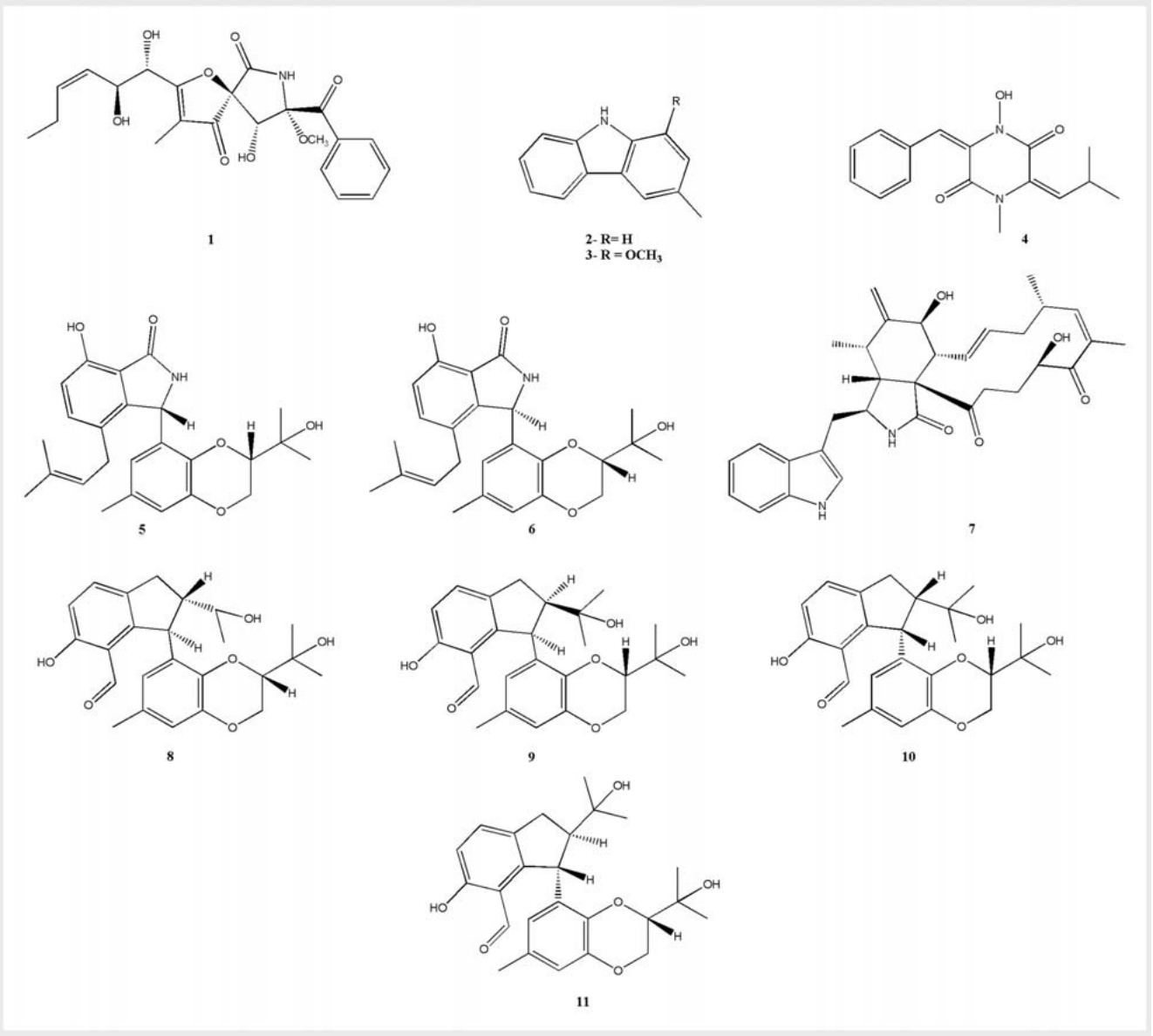
continued

▶ **Table 2** *Continued*

S. No.	Compound name	Anti-inflammatory activity	Reference
84.	Palmaerones E (**35**)	NO inhibition [IC_{50} 38.7 μM]	[38]
85.	Patientoside A (**77**)	IL-6 inhibition (diabetic nephropathy)	[10]
86.	Patientoside B (**78**)	IL-6 inhibition (diabetic nephropathy)	[10]
87.	Peniphenone (**110**)	Splenic lymphocytes inhibition [IC_{50} 6.5 (Con-A) 7.1 μg/mL (LPS)]	[26]
88.	Periconianone A (**20**)	NO inhibition (neural anti-inflammatory) [IC_{50} 0.15 μM]	[39]
89.	Periconianone B (**21**)	NO inhibition (neural anti-inflammatory) [IC_{50} 0.38 μM]	[39]
90.	Pestaloporinate B (**27**)	NO inhibition [IC_{50} 19.0 μM]	[40]
91.	Phomol (**51**)	*In vivo* anti-inflammatory activity in mouse ear edema model [53.20%]	[41]
92.	Phomopchalasin C (**15**)	NO inhibition [IC_{50} 11.2 μM]	[42]
93.	Phomopsterones B (**40**)	NO inhibition [IC_{50} 4.65 μM]	[43]
94.	Physcion (**67**)	IL-6 inhibition (diabetic nephropathy)	[10]
95.	Piniphenol A (**116**)	NO inhibition [IC_{50} 60.0 μM]	[44]
96.	Pinselin (**50**)	Splenic lymphocytes inhibition [IC_{50} 8.2 (Con-A) and 7.5 μg/mL (LPS)]	[26]
97.	Pseurotin A(**1**)	NO inhibition [IC_{50} 5.20 μM]	[45]
98.	Questin (**69**)	IL-6 inhibition (diabetic nephropathy)	[10]
99.	Rubiginosins B (**55**)	NO inhibition [IC_{50} 9.2 μM]	[37]
100.	Sorrentanone (**113**)	NO inhibition (neural anti-inflammatory) [100%]	[16]
101.	Stemphol C (**80**)	NO inhibition	[14]
102.	Stemphol D (**81**)	NO inhibition	[14]
103.	Sydowinin A (**49**)	Splenic lymphocytes inhibition[IC_{50} 5.9 (Con-A) and 7.5 μg/mL (LPS)]	[26]
104.	Terrusnolides A (**93**)	IL-1β, TNF-α, and NO inhibition [IC_{50} 35.23 (IL-1β, 42.57 (TNF-α), and 38.15 μM (NO)]	[46]
105.	Terrusnolides B (**94**)	IL-1β, TNF-α, and NO inhibition [IC_{50} 17.89 (IL-1β, 23.53 (TNF-α), and 21.45 μM (NO)]	[46]
106.	Terrusnolides C (**95**)	IL-1β, TNF-α, and NO inhibition [IC_{50} 16.21 (IL-1β), 20.45 (TNF-α), and 19.34 μM (NO)]	[46]
107.	Terrusnolides D (**96**)	IL-1β, TNF-α, and NO inhibition [IC_{50} 21.16 (IL-1β), 19.83 (TNF-α), and 16.78 μM (NO)]	[46]
108.	Trichodimerol (**114**)	NO inhibition (neural anti-inflammatory) [75.1%]	[16]
109.	Trypacidin (**71**)	IL-6 inhibition (diabetic nephropathy)	[10]
110.	Xylapapuside A (**79**)	NO inhibition [Emax 34.3 μM]	[47]
111.	Xylarenones C (**16**)	Total ROS inhibition [IC_{50} 6.13 μM]	[48]
112.	Xylarenones D (**17**)	Total ROS inhibition [IC_{50} 5.73 μM]	[48]
113.	Xylarenones F (**18**)	Total ROS inhibition [IC_{50} 5.90 μM]	[48]
114.	Xylarenones G (**19**)	Total ROS inhibition [IC_{50} 4.17 μM]	[48]
115.	Xylariphilone (**56**)	TNF-α, IL-6, and IL-12 p40 inhibition [IC_{50} IL-65.3, IL-12 p4019.4, and TNF-α 37.6 μM]	[49]
116.	Yamchaetoglobosin A (**14**)	NO inhibition [92.5%]	[50]
117.	β-Sitosterol (**41**)	NO inhibition [35.0%]	[14]
118.	β-Sitosterone (**42**)	NO inhibition [10.3%]	[17]

sponses such as endocrinal, behavioral, neural, and physiological changes. These responses are a direct or indirect consequence of the production of IL such as IL-1 and IL-6 and TNF released during inflammation, injury, and infection [3].

PG, and cyclooxygenases 1 and 2 (COX-1 and COX-2) have been synonymously linked to inflammation and cause major inflammation-related disorders. COX-2 is a well-known target for AI and analgesic drug discovery. The well-established NSAIDs work through the pathway of inhibition of COX enzyme. COX-2 is an enzyme that gets activated by cytokines and endotoxins. Thus compounds displaying inhibition of COX can serve as promising AI agents [5]. The enzyme COX-2 is believed to trigger inflammatory responses in the CNS by a series of complex reactions in the neurons of the spinal cord and other associated parts of the CNS. This, in turn, results in the elevation of PGE-2 levels in cerebrospinal fluid [6].

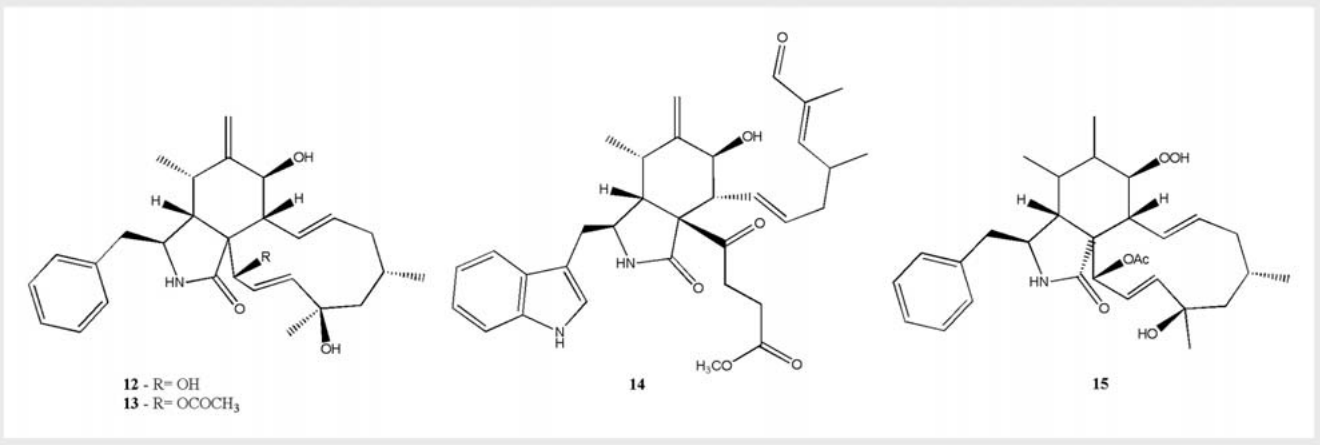


▶ **Fig. 1** Structures of anti-inflammatory alkaloids and benzophenones obtained from endophytic fungi.

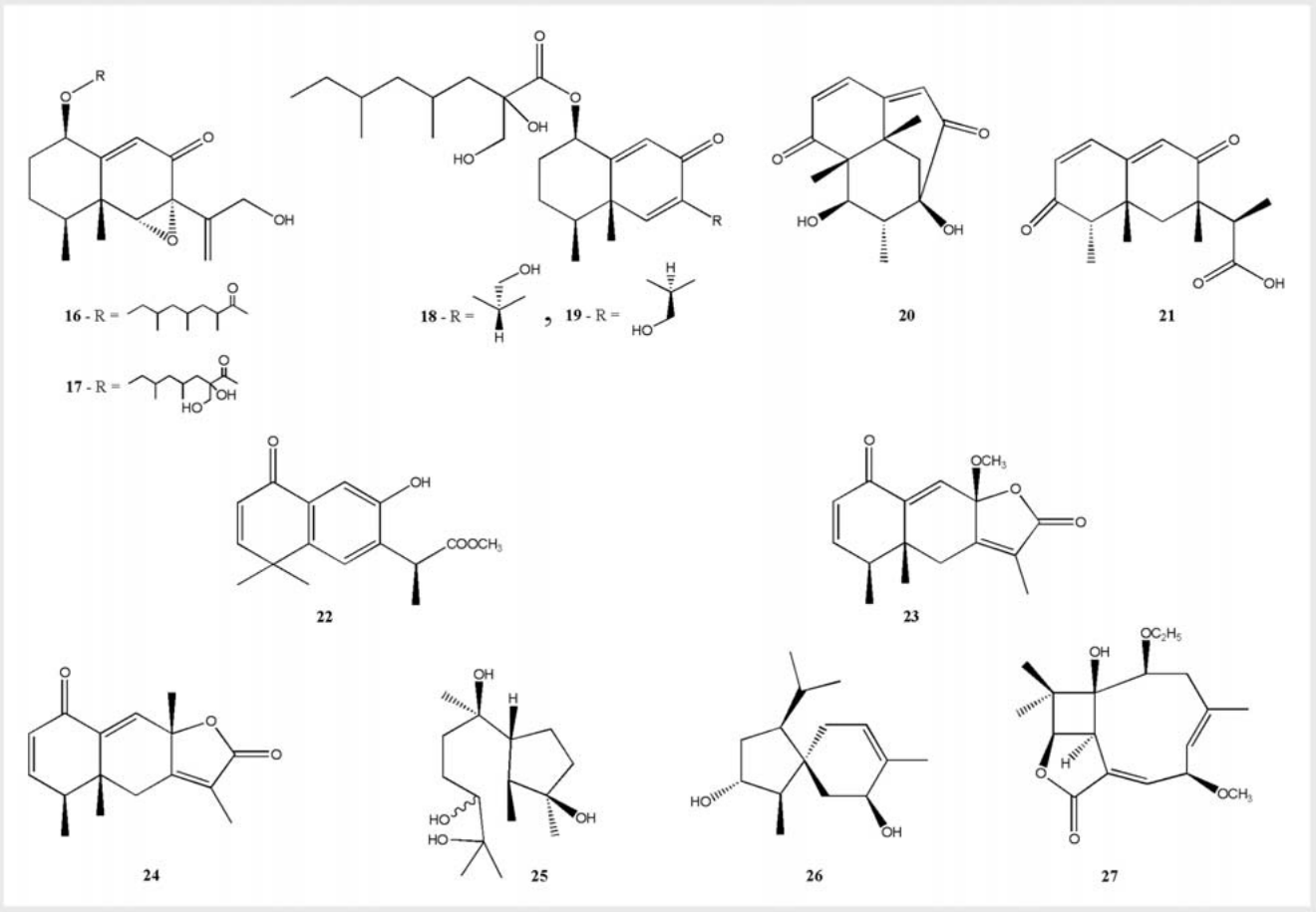
ROS like superoxides, hydroxyl, and hydrogen peroxide anions have been responsible for several degenerative diseases like rheumatoid arthritis, inflammation, the progression of cancers, etc. Thus, inhibitors of the total ROS concentration could be probable leads for the design of AI drugs [7].

Further, reports had revealed that inflammation can directly lead to the progression of a tumor. Cancers have been reported to arise from the sites of chronic irritation, infections, and inflammation. The tumor microenvironment is controlled considerably by inflammatory cells and can be correlated to the neoplastic process, encouraging the development of proliferation. Further, tumor cells have signaling mediators similar to that of the innate immune system (chemokines and their receptors) for migration and metastasis. These facts lead to the path of new AI therapy as another possible way of treating cancer [8].

Given the interest in AI therapy, and the structural and pharmacological diversity of endophytic secretions, an attempt was made to present comprehensive data on the AI compounds isolated from endophytic fungi. The review has covered all the scientific reports published on the identified topic until Feb. 2019. The literature search was done through Sci-Finder Scholar search engine using different combination of key words, and 72 and 124 hits were obtained using “inflammation+endophytic fungi” and “anti-inflammatory+endophytes”, respectively. Also, reports on the crude extracts obtained from endophytic fungi showing AI activity have been included. The literature search revealed the evaluation of AI properties of endophytic extracts and compounds using various parameters based on *in vitro* and *in vivo* studies, which included LOX, COX, ROS, albumin denaturation, membrane stabilization, proteinase inhibition, etc.



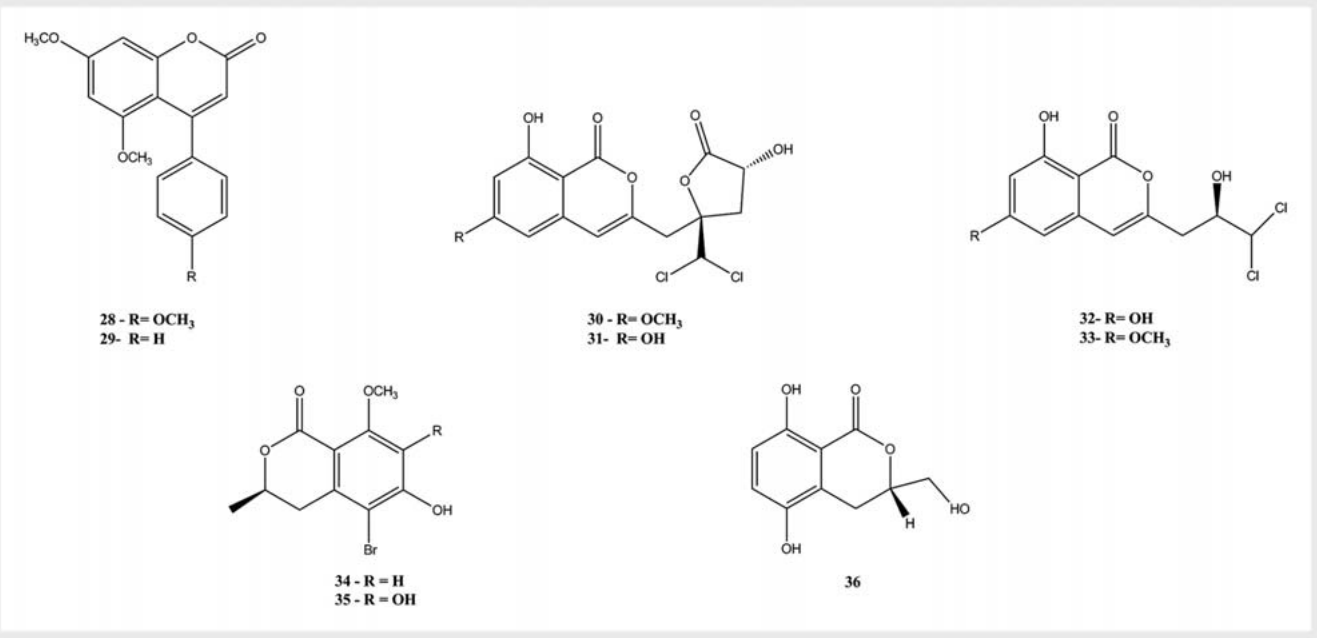
▶ **Fig. 2** Structures of anti-inflammatory cytochalasans obtained from endophytic fungi.



▶ **Fig. 3** Structures of anti-inflammatory sesquiterpenes obtained from endophytic fungi.

Endophytic Fungi as a Source for AI Leads

Secondary metabolites from diverse genera of endophytic fungi had been researched for AI properties. No study reporting the AI activity of compounds of endophytic bacterial origin was found in the literature. The information on various AI compounds, their endophytic fungal sources along with the host plants are listed in ▶ **Table 1**. Research on 29 endophytic fungi had yielded 118 compounds belonging to different phytochemical classifications such as alkaloids, benzophenones, cytochalasans, sesquiterpenes, cou-



▶ **Fig. 4** Structures of anti-inflammatory coumarins obtained from endophytic fungi.

marins, steroids, xanthones, butenolides, lactones, glycosides, azaphilones, quinones, etc. The more explored genera included *Aspergillus, Streptomyces, Penicillium, Phomopsis, Trichoderma, and Ascomycota* (▶ **Table 1**).

General Procedures for the Isolation and Characterization of Endophytic Fungi

Fresh parts of the plant material are thoroughly washed using water and soap solution if required, then surface sterilized by immersing in 70% ethanol, 5% sodium hypochlorite, and 96% ethanol, followed by rinses in sterile distilled water. The sample tissues are then cut into small dimensions of 2 × 2 cm pieces and placed onto separate petri dishes containing the media suitable for the growth of the endophytes. The grown microorganisms are then transferred to fresh plates, and several subculturing are carried out to obtain a pure culture [51]. After incubating the culture for 14–21 days (in case of fungi) at room temperature (around 25 °C), the culture broth of the selected strain is added with a suitable solvent like ethyl acetate or methanol. The fungal matter is separated by a process of filtration or macerated along with the broth, and the liquid broth is extracted several times using a suitable organic solvent. The organic layer is then evaporated under reduced pressure to obtain the crude extract, which can be purified by column chromatography to obtain pure compounds [50]

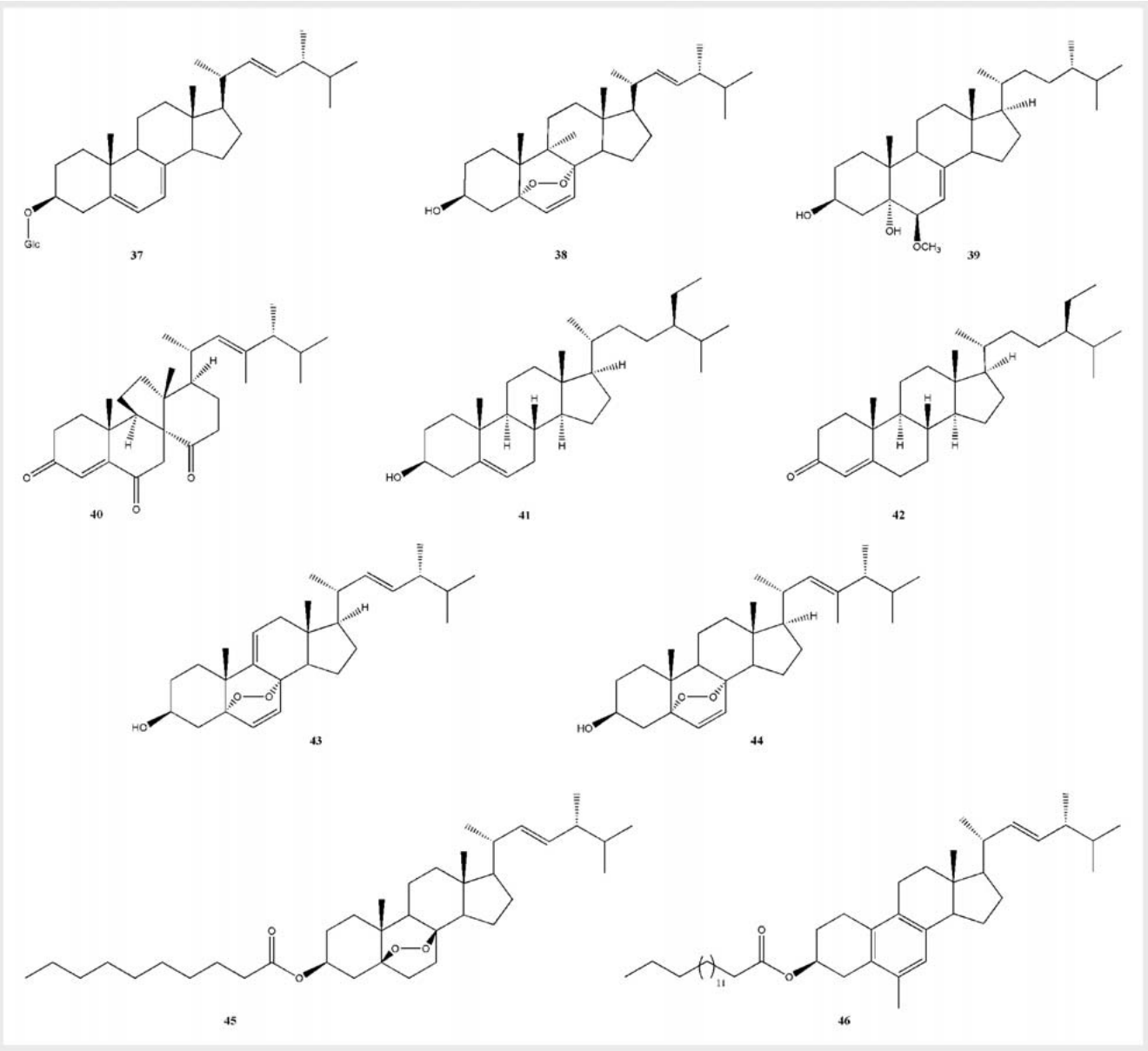
The molecular identification involves the extraction of the fungal genomic DNA. The internal transcribed spacer (ITS) region of the fungus is amplified by PCR using the universal ITS primers ITS1 and ITS4 [52]. PCR is performed and the product can be visualized by agarose gel electrophoresis for confirmation of amplification. The isolated DNA is further purified and used as template for sequencing PCR using Big Dye Terminator Sequence Reaction Ready Mix. The sequence is then subjected to a basic local alignment search tool (BLAST) analysis [37]. For the phylogenetic analysis, related sequences are retrieved from NCBI and aligned with ClustalW. The aligned data could be used for further phylogenetic analysis with the neighbor-joining method using MEGA 5 with 1000 bootstrap replicates.

AI Compounds Produced by Endophytic Fungi

The first AI metabolite of endophytic origin was phomol (**51**), reported by Weber et al., in 2004 [41]. Phomol, a polyketide lactone, was isolated from *Phomopsis sp*., an endophyte of the medicinal plant *Erythrina crista-galli*. It exhibited interesting AI activity in the mouse ear assay [41]. ▶ **Table 2** presents a list of reported AI compounds from endophytic fungi arranged alphabetically together with their structure numbers, AI target, and references.

AI Alkaloids and Benzophenones

Alkaloids are widely distributed among various families in the plant kingdom and generally found to possess diverse biological activities [53]. Isolation of 11 AI alkaloids from different endophytes had been reported with the genus *Streptomyces* as a major source. Interestingly, the alkaloids were found to be effective on diverse AI targets ranging from NO, PGE-2, IL-1β, IL-6, IL-10, TNF-α, IL-1α, etc. The structure of the reported compounds pseurotin A (**1**), 3-methylcarbazole (**2**), 1-methoxy-3-methylcarbazole (**3**), lansai C (**4**), diaporisoindoles A–B (**5–6**), chaetoglobosin Fex (**7**), and diaporindene A–D (**8–11**) are presented in ▶ **Fig. 1**. These compounds were found to possess excellent AI activities on diverse targets. Among the 11 reported compounds, diaporindene C (**10**) (IC_{50} 4.2 µM) and D (**11**) (IC_{50} 4.2 µM) were the most potent inhibitors of LPS-induced NO production in raw 264.7 cell



▶ **Fig. 5** Structures of anti-inflammatory steroids and related derivatives obtained from endophytic fungi.

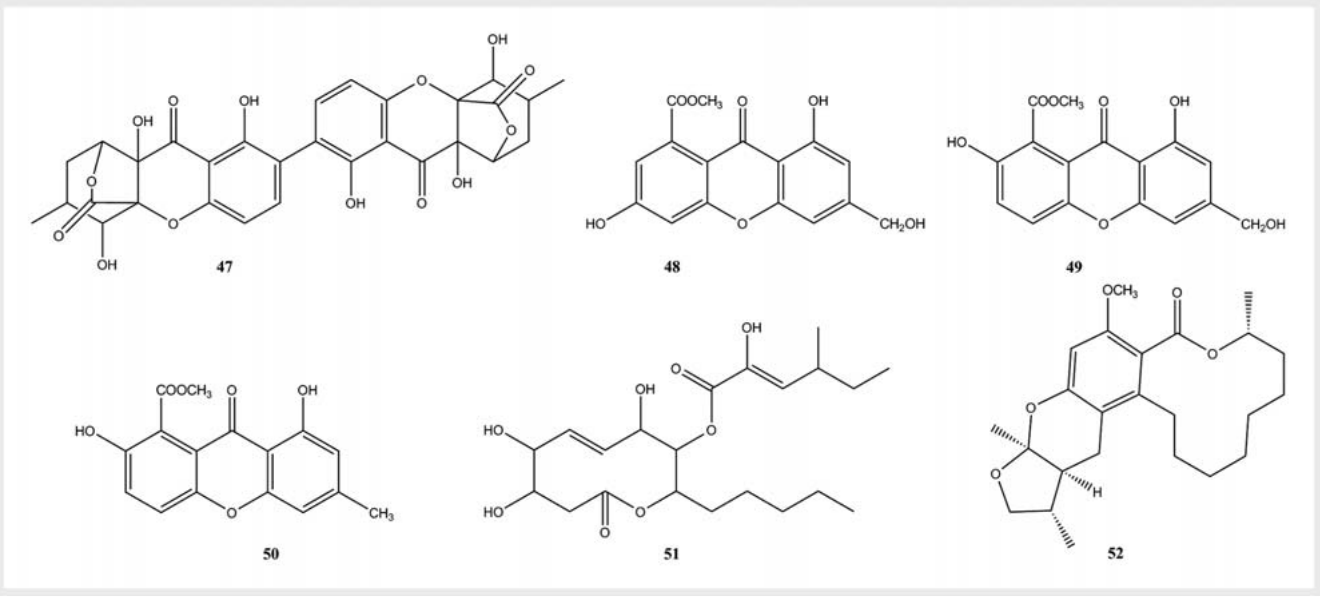
lines. Pseurotin A (**1**) was also found to be highly inhibitory (IC_{50} 5.20 µM) exhibiting indirect AI activity by suppressing the LPS-induced pro-inflammatory factors in BV2 microglial cells [13, 25, 29, 35, 45].

AI Cytochalasans

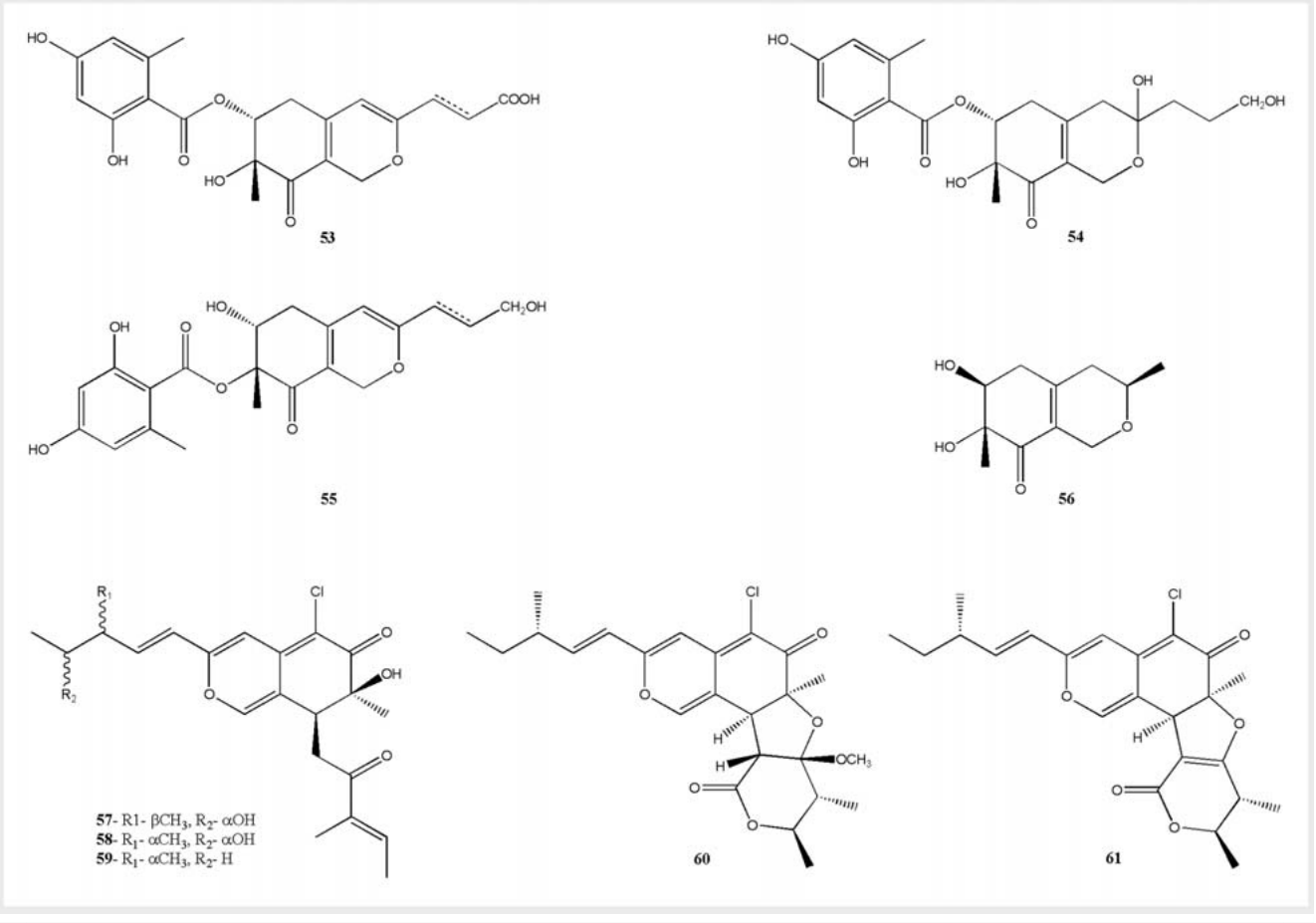
Cytochalasans represent a group of polyketide amino acid hybrid metabolites having diverse biological and pharmacological activities. They are characterized by a highly substituted per hydro-isoindolone moiety to which a macrocyclic ring like a carbocycle, a lactone, or a cyclic carbonate is fused [54]. Four AI cytochalasan derivatives [cytochalasin J (**12**) and H (**13**), yamchaetoglobosin A (**14**), and phomopchalasin C (**15**)] from endophytic fungal sources were reported (▶ **Fig. 2**). *Phomopsis* fungi were found to yield 3 out of the 4 reported cytochalasans. The compounds exhibited activities through inhibition of NO and total ROS. Phomopchalasin C (**15**) was identified as the most active inhibitor of NO production in LPS-induced raw cells with an IC_{50} value of 11.2 µM (▶ **Table 2**) [20, 42, 50].

AI Sesquiterpenes and Sesquiterpenoids

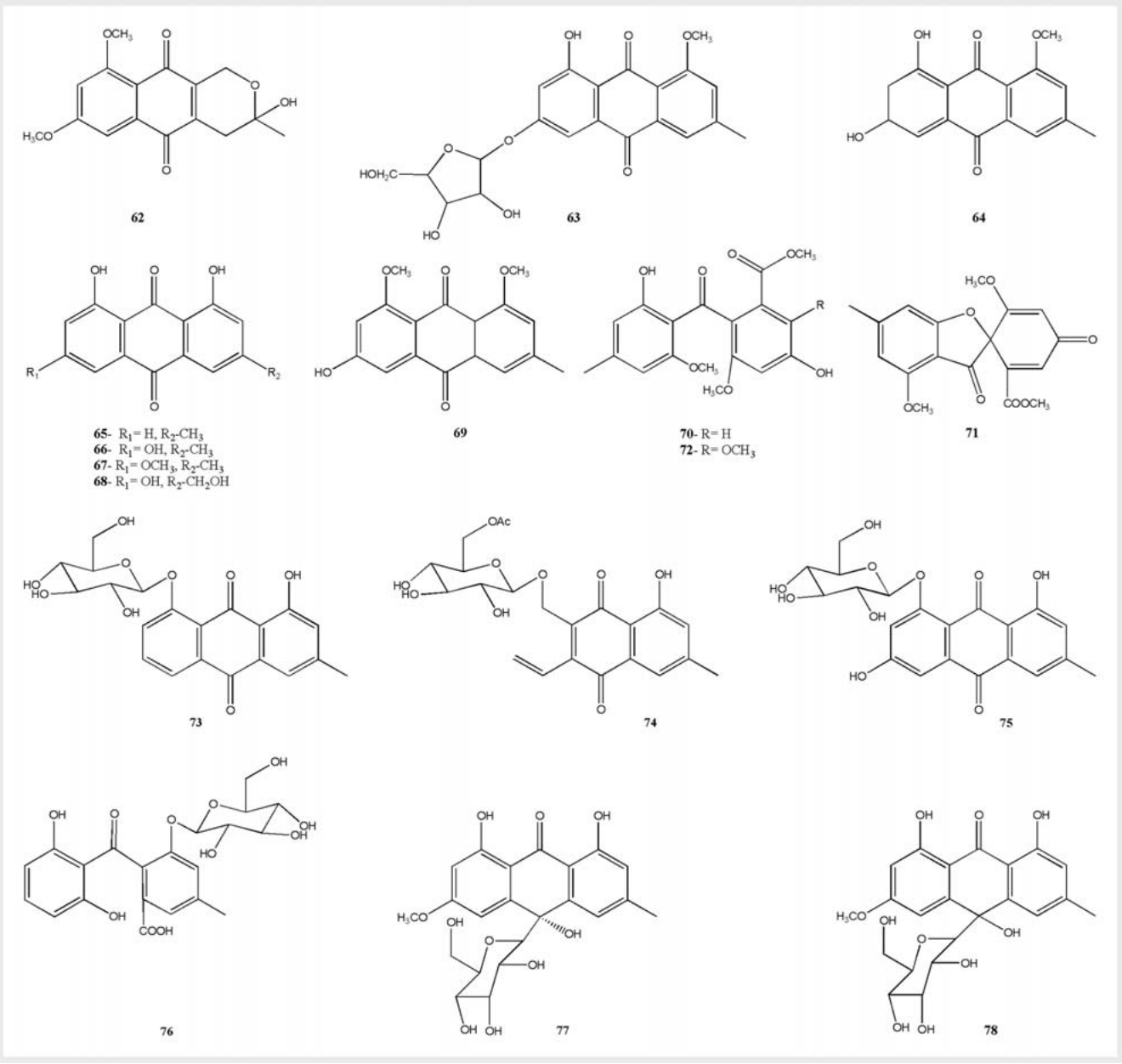
Sesquiterpenes and sesquiterpenoids were found to be the prominent class of compounds possessing AI properties, with a total of 12 compounds isolated from endophytic fungal sources. The compounds were isolated from a variety of fungi and were found to exhibit ROS and NO inhibition effect. The compounds included xylarenones C, D, F and G (**16**–**19**), periconianone A and B (**20**–**21**), glomeremophilane A, C and D (**22**–**24**), cyclonerodiol B (**25**), 1α-isopropyl-4α,8-dimethylspiro[4.5]dec-8-ene-2β,7α-diol (**26**), and pestaloporinate B (**27**) (▶ **Fig. 3**). Periconianone A (**20**)



▶ **Fig. 6** Structures of anti-inflammatory xanthenes and lactones obtained from endophytic fungi.



▶ **Fig. 7** Structures of anti-inflammatory azaphilones obtained from endophytic fungi.



▶ **Fig. 8** Structures of anti-inflammatory anthraquinones, quinones and related glycosides obtained from endophytic fungi.

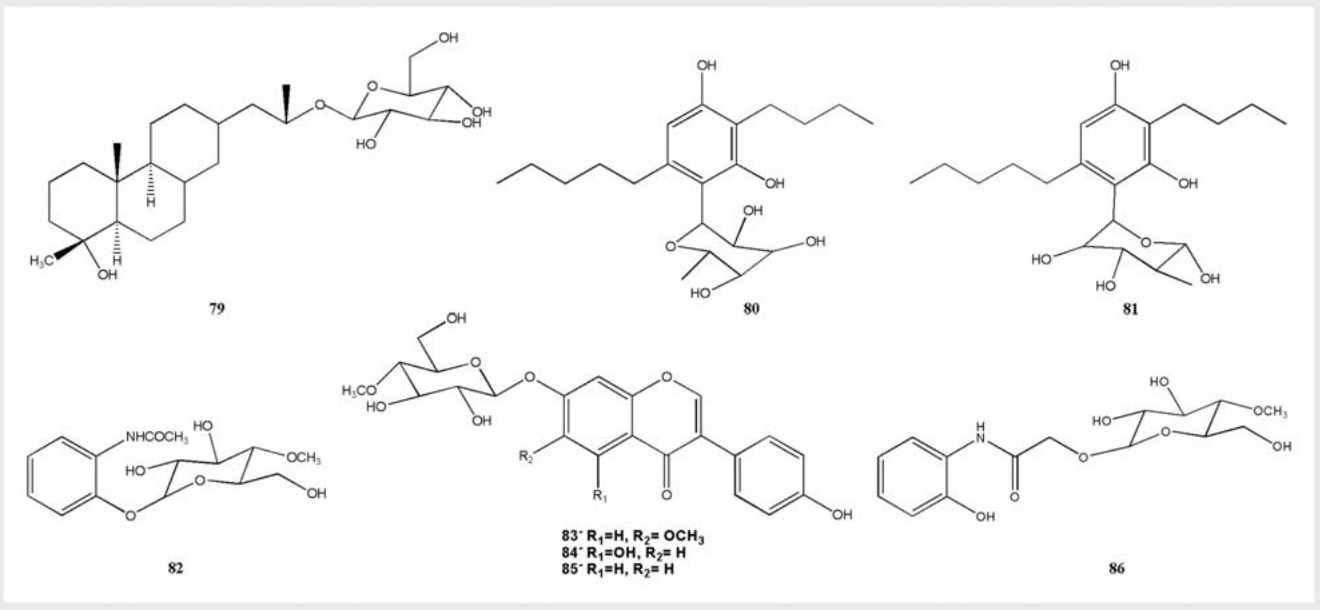
and periconianone B (**21**) were found to inhibit LPS-induced NO production in mouse microglia BV2 cells with IC_{50} values of 0.15 and 0.38 µM, respectively. Nevertheless, all the sesquiterpenes were proven to possess good AI activity (▶ **Table 2**) [15, 31, 38, 39, 47].

AI Coumarin Derivatives

Nine secondary metabolites having the basic coumarin nucleus (*i.e.,* benzo-*α*-pyrone structure [55]) had been reported from different endophytic fungi. Such compounds possessing AI activity included 5,7-dimethoxy-4-phenyl coumarin (**28**), 5,7-dimethoxy-4-*p*-methoxyl phenyl coumarin (**29**), dichlorodiaportintone(**30**), desmethyldichlorodiaportintone (**31**), desmethyldichlorodiaportin (**32**), dichlorodiaportin (**33**), palmaerones A (**34**) and E (**35**), and botryoisocoumarin A (**36**) (▶ **Fig. 4**). These compounds were effective against targets ranging from IL-6, IL-1*β*, TNF-*α*, NO, PGE-2, COX-2, and iNOS enzyme in raw 264.7 cells stimulated with LPS. The most potent compound reported among the coumarins was botryoisocoumarin A (**36**), displaying inhibition of COX-2 enzyme with IC_{50} value of 6.51 µM (▶ **Table 2**) [5, 18, 28, 38].

AI Steroids and Related Compounds

Ten compounds containing cyclopentanoperhydrophenanthrene as the basic nucleus (*i.e.*, steroids [56]) had been reported from endophytic fungi, which belong to different genus. They were ergosterol-3-O-*β*-*D*-glucopyranoside (**37**), 5*α*,8*α*-epidioxyergosta-6,22-dien-3*β*-ol (**38**), 3*β*,5*α*-dihydroxy-6*β*-methoxy ergosta-7,22-diene (**39**), phomopsterone B (**40**), *β*-sitosterol (**41**), *β*-sitosterone



▶ **Fig. 9** Structures of anti-inflammatory glycosides obtained from endophytic fungi.

(**42**), 5α,8α-epidioxyergosta-6,9(11),22-trien-3-ol (**43**), 5α,8α-epidioxy-(22*E*,24 *R*)-23-methylergosta-6,22-dien-3β-ol (**44**), and fusaristerol A and B (**45**–**46**) (▶ **Fig. 5**). These compounds had been reported as NO and IL-6 inhibitors. Compound phomopsterone B (**40**) was found to be potentially active exhibiting IC_{50} value of 4.65 µM (▶ **Table 2**) [14–17, 43].

AI Xanthone and Xanthenes

These are a group of important compounds that are oxygenated heterocycles. Most xanthones are mono- or polymethyl esters found as glycosides [57]. The biological activities of this class of compounds are associated with their tricyclic scaffold but vary depending on the nature and/or position of the different substituents [57]. From endophytic fungi, so far 4 compounds [ergoflavin (**47**), conioxanthone A (**48**), sydowinin A (**49**), and pinselin (**50**)] having xanthene or xanthone nucleus were reported for AI properties (▶ **Fig. 6**). They were isolated from the *Ascomycetes* and *Penicillium* genus. They were active against TNF-α and IL-6 in the LPS-induced human monocytic cell line (THP-1) (▶ **Table 2**). Ergoflavin (**47**) was found to be highly active showing IC_{50} values of 1.9 µM and 1.2 µM against TNF-α and IL-6, respectively [26, 30].

AI Lactones

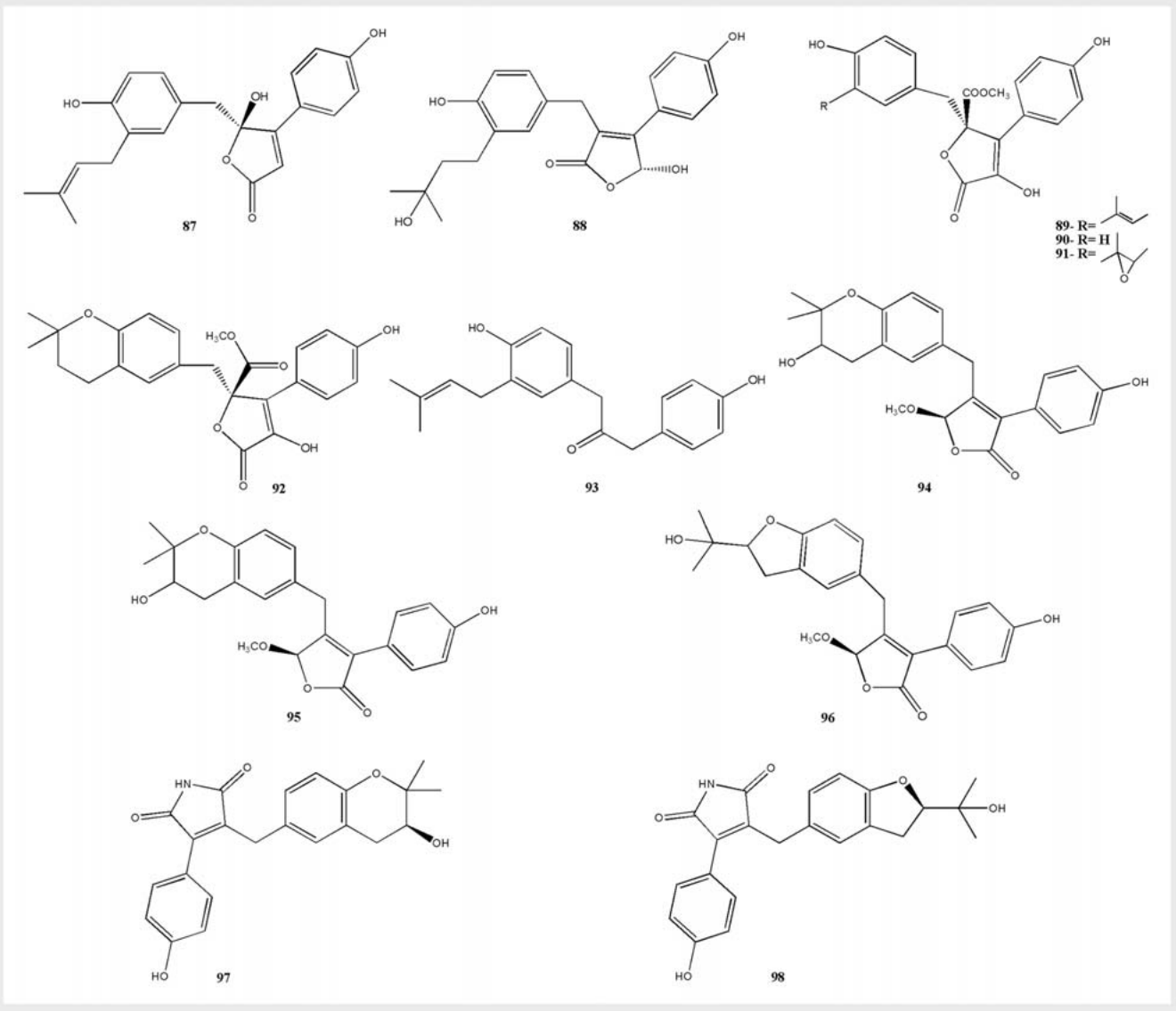
Two lactones *viz*., phomol (**51**) and lasiodiplactone A (**52**) isolated from endophytic fungi, *Phomopsis sp*., and *Lasiodiplodia theobromae* ZJ-HQ1 respectively, were reported as AI compounds. Phomol (**51**) was effective under *in vivo* mice ear edema model having inhibition of 53.20%, whereas Lasiodiplactone A(**52**) was found to inhibit NO production in LPS-stimulated RAW 264.7 cell lines showing IC_{50} value of 23.5 µM (▶ **Fig. 6** and **Table 2**) [36, 41].

AI Azaphilones

Azaphilones are generally pigments that are polyketides in nature, having pyrone-quinone structures with a highly oxygenated bicyclic core and a chiral quaternary center [59]. Nine azaphilones isolated from endophytic fungi had been reported as AI compounds by acting on a variety of targets such as IL-6, IL-12p40, NO, and TNF-α. Pure characterized compounds include montagnuphilone B (**53**), montagnuphilones E (**54**), rubiginosins B (**55**), xylariphilone (**56**), 11-epichaetomugilin I (**57**), chaetomugulin I (**58**), chaetomugulin J (**59**), chaetomugulin E, (**60**) and chaetomugulin F (**61**) (▶ **Fig. 7**). The most potent compound was chaetomugulin I (**58**) reported with an IC_{50} value of 0.3 µM against NO inhibitory assay (▶ **Table 2**) [12, 37, 49].

AI Anthaquinones, Quinones, and Related Glycosides

Search resulted in 17 AI quinone derivatives from endophytes. Generally, quinones are derived from aromatic compounds such as benzene or naphthalene by conversion of an even number of −CH= groups into −C(=O)− groups with any required rearrangement of double bonds, resulting in a fully conjugated cyclic dione structure [60]. Effective compounds include herbarin (**62**), 1-*O*-methyl-6-*O*-(α-D-ribofuranosyl)-emodin (**63**), 1-*O*-methylemodin (**64**), chrysophanol (**65**), emodin (**66**), physcion (**67**), aloe emodin (**68**), questin (**69**), 1,2-seco-trypacidin (**70**), trypacidin (**71**) and dandasperfumin (**72**) chrysophanol-8-O-β-D-glucopyranoside (**73**), emodin-8-O-β-D-(6)-O-acetyl) glucopyranoside (**74**), emodin-8-O-β-D-glucopyranoside (**75**), nepalenside A(**76**), patientoside A (**77**), patientoside B (**78**) (▶ **Fig. 8**). These quinone derivatives were found to be effective inhibitors of TNF-α and IL-6 in THP-1 cells, NO in LPS-stimulated BV-2 microglia cells, and IL-6 in diabetic nephropathy. Compound 1-O-methylemodin (**64**) had been isolated from 2 plant sources, one being *Rumex patientia* and the other *Phragmites communis*, which were obtained from



▶ **Fig. 10** Structures of anti-inflammatory butenolides obtained from endophytic fungi.

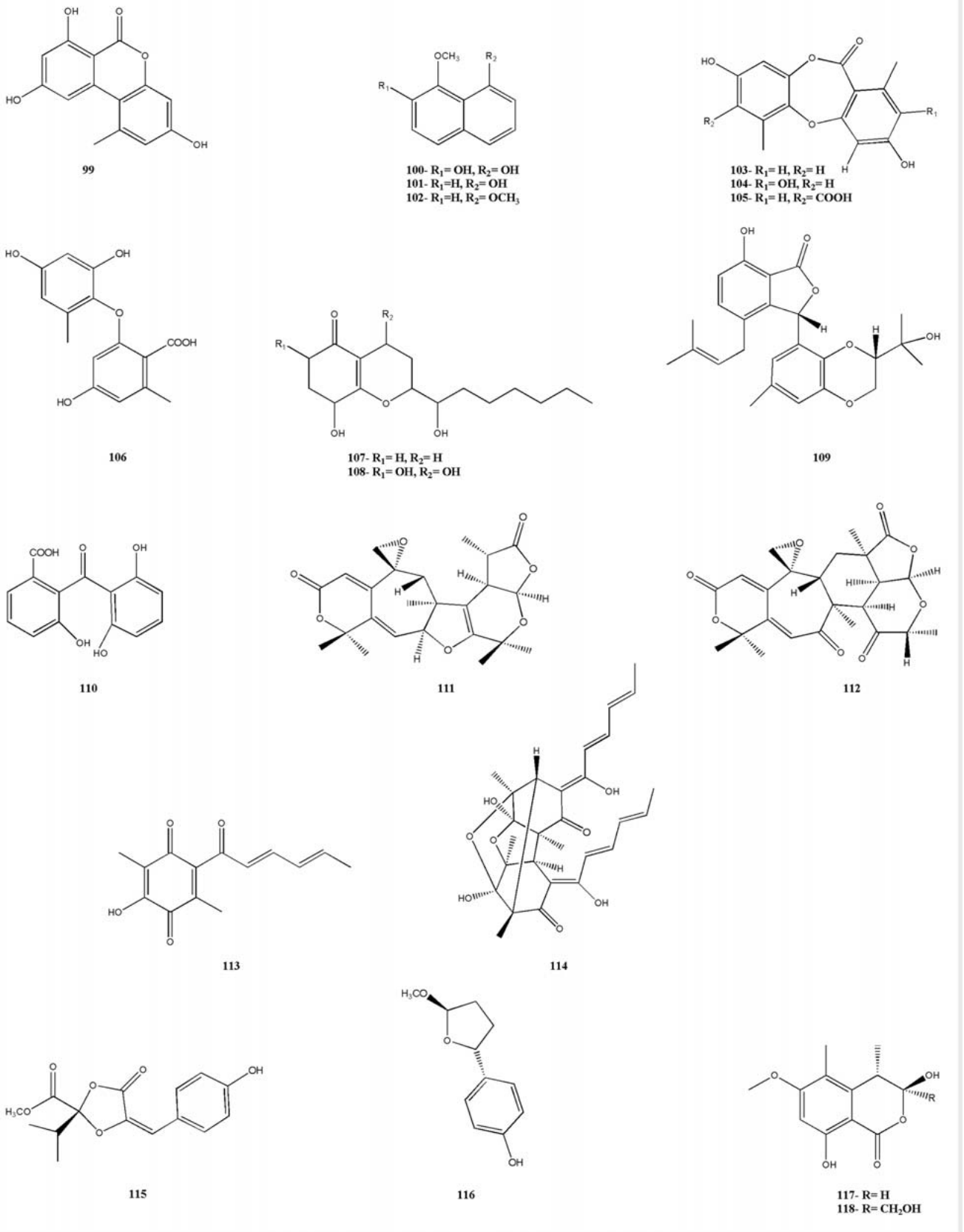
Aspergillus fumigatus and *Gaeumannomyces sp.*, respectively. Herbarin (**62**) was found to be most active among the quinines showing an IC_{50} value of 0.06 µM and 0.01 µM, respectively in inhibiting TNF-α and IL-6 (▶ **Table 2**) [10, 14, 33].

AI Glycosides

Around 10 compounds containing sugar moieties attached through glycosidic linkage were found to be reported as inhibitors of NO and IL-6 expressions. Endophyte-derived glycosides include xylapapuside A (**79**), stemphol C (**80**), stemphol D (**81**), cordycepiamideB (**82**), 4′,7-dihydroxy-6-methoxyisoflavone-7-O-(4′′-O-methyl)-β-D-glucopyranoside (**83**), 4′,5,7-trihydroxyisoflavone-7-O-(4′′-O-methyl)-β-D-glucopyranoside (**84**), 4′,7-dihydroxyisoflavone-7-O-(4′′-O-methyl)- β-D-glucopyranoside (**85**), and Cordycepiamides D (**86**) (▶ **Fig. 9**) [10, 14, 17, 47].

AI Butenolides

Butenolides are unsaturated γ-lactone also known as furan derivatives. Alkyl-substituted butenolides having no exocyclic double bond are usually liquids. α-Arylidene-γ-aryl- (or alky1) butenolides are usually solids with the color varying from yellow to brown [58]. During the study, butenolides emerged as a major class of compounds possessing AI effects. Around 12 compounds were reported from various endophytic fungi, which included asperteretal A (**87**), asperteretal C (**88**), butyrolactone I (**89**), butyrolactone II (**90**), butyrolactone III (**91**), aspernolide A (**92**), terrusnolides A–D (**93–96**), asperimide C (**97**), and asperimide D (**98**) (▶ **Fig. 10**). The compounds possessed *in vitro* AI activity against IL-1, TNF-α, and NO secretions. The most active compound in terms of LPS-induced NO production was asperimide C (**97**) with IC_{50} value of 0.78 µM (▶ **Table 2**). Another compound, butyrolactone II (**90**), was isolated from multiple plant sources. *Aspergillus terreus* iso-



▶ **Fig. 11** Structures of miscellaneous anti-inflammatory compounds obtained from endophytic fungi.

▶ **Table 3** Anti-inflammatory efficacy of culture broth extracts of endophytic fungi.

S. No.	Endophyte [type of extract]	Host plant	Anti-inflammatory activity	Ref.
1.	*Rhizoctonia* sp. [Methanolic extract]	*Schinu sterebinthifolius* (seeds)	*In vivo* mice paw edema [Inhibition at dose of 10 mg/kg i.p.]	[61]
2.	*Talaromyces wortmannii* [Crude extract and isolated fractions]	*Aloe vera*	IL-8 inhibition	[62]
3.	*Myrothecium sp.* [Crude extract and fraction]	*Calophyllum apetalum*	Extract: COX-2 (8 µg/mL) and LOX (IC_{50}: 58 µg/mL) inhibition Fraction: COX-2 (50 µg/mL) and LOX (IC_{50}: 25 µg/mL) inhibition	[63]
4.	*Aspergillus niger, Penicillium* sp., *Alternaria alternate* *Aspergillus flavus* [Methanolic and aqueous extracts]	*Loranthus* sp.	Albumin denaturation, membrane stabilisation, proteinase inhibition [85–32%]	[64]
5.	*Penicillium citrinum* *Geotrichum candidum* [Ethanol, hexane, methanol, and ethyl acetate extract]	*Phoenix dactylifera* L.	Protein denaturation method [EtOAc extract (*Geotrichum* sp.) [IC_{50} = 0.47 mg/ml] EtOH extract (*Geotrichum* sp.) [IC_{50} = 1.37 mg/ml] EtOH extract (*Penicillium sp.*) [IC_{50} = 1.88 mg/ml] EtOAc extract (*Penicillium sp.*) [IC_{50} = 3.67 mg/ml]	[65]
6.	*Penicillium species* [Silver nanoparticles of extract]	*Glycosmis mauritiana*	Albumin denaturation. membrane stabilization, proteinase inhibition [83.63%, 89.41%, and 87.49%, respectively]	[66]

lated from *Suriana maritima L.* and *Camellia sinensis var. assamica* had yielded butyrolactone II (**88**) [22, 23, 46].

Miscellaneous Compounds

Apart from the above discussed 98 compounds, 20 other compounds belonging to different categories of secondary metabolites had been reported. These include alternariol (**99**), 8-methoxynaphthalene-1,7-diol (**100**), 8-methoxynaphthalen-1-ol (**101**), 1,8-dimethoxynaphthalene (**102**), corynesidone A, C and D (**103–105**), cornether A (**106**), koninginin E and F (**107–108**), isoprenylisobenzofuran A (**109**), peniphenone (**110**), amestolkolide A and B (**112–111**), sorrentanone (**113**), botryosphaerin B (**115**), piniphenol A (**116**), (3*R*,4*S*)-3,8-dihydroxy-3-hydroxy methyl-6-methoxy-4,5-dimethyl isochroman-1-one (**117**), and (3*S*,4*S*)-3,8-dihydroxy-6-methoxy-3,4,5-trimethylisochroman-1-one (**118**). Chemical structures of these compounds are presented in ▶ **Fig. 11**. These compounds were found to be effective inhibitors of NO, COX-2, IL-6, 5- LOX, proliferation of mouse splenic lymphocytes, and TNF-α. Corynesidone A (**103**) was found to be significantly active against NO production, exhibiting an IC_{50} value of 1.88 µM. Compound 1,8-dimethoxynaphthalene (**102**) showed an IC_{50} value of 2.0 µM against the secretion of IL-6 (▶ **Table 2**) [9, 11, 16, 18, 20, 21, 24, 26, 27, 29, 31, 34, 44].

AI Crude Extracts

Apart from the AI effect by pure compounds isolated from the various endophytic fungi, efficacy by crude extracts was also recorded (▶ **Table 3**). Around 6 reports on extracts obtained from a variety of endophytic fungal sources were reported in the literature. Interestingly, an extract of *Penicillium species* incorporated in the form of silver nanoparticles was found to enhance the AI activity [66]. The efficacy had been tested against IL-8, COX-2, LOX, *in vivo* mice paw edema, albumin denaturation, membrane stabilization, and proteinase inhibitor [61–66]. The EtOAc extract of *Geotrichum* sp. exhibited AI effect displaying an IC_{50} value of 0.47 mg/mL under protein denaturation method [65].

Conclusion

Endophytic fungi can serve as an alternative source for the production of AI metabolites. In all, 118 metabolites, which are chemically and pharmacologically characterized for AI activity, had been reported since the first report in 2004. Both *in vitro* and *in vivo* studies had been performed to evaluate the AI effects. Several classes of endophytic fungi had been investigated from a wide variety of plant sources with the most explored genus being *Aspergillus, Streptomyces, Penicillium, Phomopsis, Trichoderma, and Ascomycota* which produced several AI compounds. The compounds obtained from these endophytes further displayed a wide diversity in their chemical structures incorporating themselves under alkaloids, cytochalasans, sesquiterpenes, steroids, coumarins, glycosides, lactones, butenolides, xanthenes, quinones, azaphilones, etc. Thus, endophytic fungi-derived AI secondary metabolites reviewed under this article could further serve as lead molecules in the production of AI drugs.

Acknowledgements

The authors would like to thank DST-SERB [EMR/2016/002460] (Department of Science and Technology, Science and Engineering Research Board) for providing the financial support.

Conflict of Interest

The authors declare that they have no conflict of interest.

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