

Prospective Leads from Endophytic Fungi for Anti-Inflammatory Drug Discovery

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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 IC₅₀ values against NO inhibition.

ABBREVIATIONS

AI	anti-inflammatory
COX	cyclooxygenase
IFN- γ	interferon gamma
IL	interleukin
LOX	lipoxigenase
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.	(3R,4S)-3,8-dihydroxy-3-hydroxy methyl-6-methoxy-4,5-dimethyl isochroman-1-one (117)	<i>Phoma</i> sp. PF2	<i>Artemisia princeps</i> Pamp.	[9]
2.	(3S,4S)-3,8-dihydroxy-6-methoxy-3,4,5-trimethylisochroman-1-one (118)	<i>Phoma</i> sp. PF2	<i>Artemisia princeps</i> Pamp.	[9]
3.	1,2 seco-trypacidin (70)	<i>Aspergillus fumigatus</i>	<i>Rumex patientia</i>	[10]
4.	1,8-dimethoxynaphthalene (102)	<i>Hypoxyylon investiens</i>	<i>Litsea akoensis</i> var. <i>chitouchiaoensis</i>	[11]
5.	11-epichaetomuginin I (57)	<i>Wikstroemia uva-ursi</i>	<i>Chaetomium globosum</i>	[12]
6.	1-methoxy-3-methylcarbazole (3)	<i>Streptomyces</i> sp. LJK109	<i>Alpinia galanga</i> Swartz	[13]
7.	1-O-methyl emodin (64)	<i>Aspergillus fumigatus</i> , <i>Gaeumannomyces</i> sp.	<i>Rumex patientia</i> , <i>Phragmites communis</i>	[10, 14]
8.	1-O-methyl-6-O-(α -D-ribofuranosyl)-emodin (63)	<i>Gaeumannomyces</i> sp.	<i>Phragmites communis</i>	[14]
9.	1 α -isopropyl-4 α ,8-dimethylspiro dec-8-ene-3 β ,7 α -diol (26)	<i>Trichoderma</i> sp. Xy24	<i>Xylocarpus granatum</i>	[15]
10.	3-methylcarbazole (2)	<i>Streptomyces</i> sp. LJK109	<i>Alpinia galanga</i> Swartz	[13]
11.	3 β ,5 α -dihydroxy-6 β -methoxyergosta-7,22-diene (39)	<i>Trichoderma</i> sp. Xy24	<i>X. granatum</i>	[16]
12.	4',5,7-trihydroxyisoflavone-7-O-(4''-O-methyl)- β -D-glucopyranoside (84)	<i>Cordyceps ninchukispora</i>	<i>Beilschmiedia erythrophloia</i> (Seeds)	[17]
13.	4',7-dihydroxy-6-methoxyisoflavone-7-O-(4''-O-methyl)- β -D-glucopyranoside (83)	<i>Cordyceps ninchukispora</i>	<i>Beilschmiedia erythrophloia</i> (Seeds)	[17]
14.	4',7-dihydroxyisoflavone-7-O(4''-O-methyl)- β -D-glucopyranoside (85)	<i>Cordyceps ninchukispora</i>	<i>Beilschmiedia erythrophloia</i> (Seeds)	[17]
15.	5,7-dimethoxy-4-phenylcoumarin (28)	<i>Streptomyces aureofaciens</i> CMUAc130	<i>Zingiber officinale</i> Rosc. (Root Tissues)	[18]
16.	5,7-dimethoxy-4-p-methoxyphenylcoumarin (29)	<i>Streptomyces aureofaciens</i> CMUAc130	<i>Zingiber officinale</i> Rosc. (Root Tissues)	[18]
17.	5 α ,8 α -epidioxy-(22E,24R)-23-methylergosta-6,22-dien-3 β -ol (44)	<i>Gaeumannomyces</i> sp.	<i>Phragmites communis</i>	[14]
18.	5 α ,8 α -epidioxyergosta-6,22-dien-3 β -ol (38)	<i>Colletotrichum</i> sp. GDMU-1	<i>Santalum album</i>	[19]
19.	5 α ,8 α -epidioxyergosta-6,9(11),22-trien-3-ol (43)	<i>Gaeumannomyces</i> sp.	<i>Phragmites communis</i>	[14]
20.	8-methoxy naphthalene-1,7-diol (100)	<i>Hypoxyylon investiens</i>	<i>Litsea akoensis</i> var. <i>chitouchiaoensis</i>	[11]
21.	8-methoxynaphthalen-1-ol (101)	<i>Hypoxyylon investiens</i>	<i>Litsea akoensis</i> var. <i>chitouchiaoensis</i>	[11]
22.	Aloe emodin (68)	<i>Aspergillus fumigatus</i>	<i>Rumex patientia</i>	[10]
23.	Alternariol (99)	<i>Phomopsis</i> sp.	<i>Senna spectabilis</i> (Leaves)	[20]
24.	Amestolkolide A (112)	<i>Talaromyces amestolkiae</i> YX1	<i>Kandelia obovata</i> (Leaves)	[21]
25.	Amestolkolide B (111)	<i>Talaromyces amestolkiae</i> YX1	<i>Kandelia obovata</i> (Leaves)	[21]
26.	Andasperfumin (72)	<i>Aspergillus fumigatus</i>	<i>Rumex patientia</i>	[10]
27.	Asperimide C (97)	<i>Aspergillus terreus</i>	<i>Suriana maritima</i> L.	[22]
28.	Asperimide D (98)	<i>Aspergillus terreus</i>	<i>Suriana maritima</i> L.	[22]
29.	Aspernolide A (92)	<i>Aspergillus terreus</i>	<i>Camellia sinensis</i> var. <i>assamica</i>	[23]
30.	Asperteretal A (87)	<i>Aspergillus terreus</i>	<i>Camellia sinensis</i> var. <i>assamica</i>	[23]
31.	Asperteretal C (88)	<i>Aspergillus terreus</i>	<i>Camellia sinensis</i> var. <i>assamica</i>	[23]
32.	Botryoisocoumarin A (36)	<i>Botryosphaeria</i> sp. KcF6	<i>Kandelia candel</i>	[5]
33.	Botryosphaerin B (115)	<i>Botryosphaeria</i> sp. SCSIO KcF6	<i>Kandelia candel</i>	[24]
34.	Butyrolactone I (89)	<i>Aspergillus terreus</i>	<i>Suriana maritima</i> L., <i>Camellia sinensis</i> var. <i>assamica</i>	[22, 23]
35.	Butyrolactone II (90)	<i>Aspergillus terreus</i>	<i>Camellia sinensis</i> var. <i>assamica</i>	[23]
36.	Butyrolactone III (91)	<i>Aspergillus terreus</i>	<i>Camellia sinensis</i> var. <i>assamica</i>	[23]
37.	Chaetoglobosin Fex (Cha Fex) (7)	<i>Chaetomium globosum</i> QEN-14	<i>Ulva pertusa</i>	[25]

continued

► **Table 1** Continued

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

continued

► Table 1 Continued

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

uction, 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 <i>R</i> ,4 <i>S</i>)-3,8-dihydroxy-3-hydroxy methyl-6-methoxy-4,5-dimethyl isochroman-1-one (117)	NO (Nitric oxide) inhibition	[9]
2.	(3 <i>S</i> ,4 <i>S</i>)-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- <i>O</i> -methyl emodin (64)	IL-6 inhibition (diabetic nephropathy), NO inhibition [31%]	[10, 14]
8.	1- <i>O</i> -methyl-6- <i>O</i> -(α- <i>D</i> -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- <i>O</i> -(4''- <i>O</i> -methyl)-β- <i>D</i> -glucopyranoside (84)	NO inhibition [10.8%]	[17]
13.	4',7-dihydroxy-6-methoxyisoflavone-7- <i>O</i> -(4''- <i>O</i> -methyl)-β- <i>D</i> -glucopyranoside (83)	NO inhibition [14.8%]	[17]
14.	4',7-dihydroxyisoflavone-7- <i>O</i> -(4''- <i>O</i> -methyl)-β- <i>D</i> -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- <i>p</i> -methoxyphenylcoumarin (29)	NO, PGE2, TNF-α, IL-6, IL-1, and COX-2 inhibition	[18]
17.	5α,8α-epidioxy-(22 <i>E</i> ,24 <i>R</i>)-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- <i>O</i> -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 diaporitin (32)	NO inhibition [IC ₅₀ 33.6 μM]	[28]
55.	Desmethyldichlorodiaporitintone (31)	NO inhibition [IC ₅₀ 15.8 μM]	[28]
56.	Diaporindenones A (8)	NO inhibition [IC ₅₀ 8.5 μM]	[29]
57.	Diaporindenones B (9)	NO inhibition [IC ₅₀ 5.9 μM]	[29]
58.	Diaporindenones C (10)	NO inhibition [IC ₅₀ 4.2 μM]	[29]
59.	Diaporindenones 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.	Dichlorodiaporitin (33)	NO inhibition [IC ₅₀ 67.2 μM]	[28]
63.	Dichlorodiaporitintone (30)	NO inhibition [IC ₅₀ 41.5 μM]	[28]
64.	Emodin (66)	IL-6 inhibition (diabetic nephropathy)	[10]
65.	Emodin-8- <i>O</i> -β-D-glucopyranoside (75)	IL-6 inhibition (diabetic nephropathy)	[10]
66.	Emodin-8- <i>O</i> -β-D- <i>O</i> -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- <i>O</i> -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.	Koningin E (107)	Phospholipase A2 inhibition [90.2%]	[34]
77.	Koningin F (108)	Phospholipase A2 inhibition [91.8%]	[34]
78.	Lansai C (4)	NO, PGE2, TNF-α, IL-1α, IL-6, and IL-10 inhibition	[35]
79.	Lasiodiactone A (52)	NO inhibition [IC ₅₀ 23.5 μM]	[36]
80.	Montagnuphilonone B (53)	NO inhibition [IC ₅₀ 39.6 μM]	[37]
81.	Montagnuphilonones 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

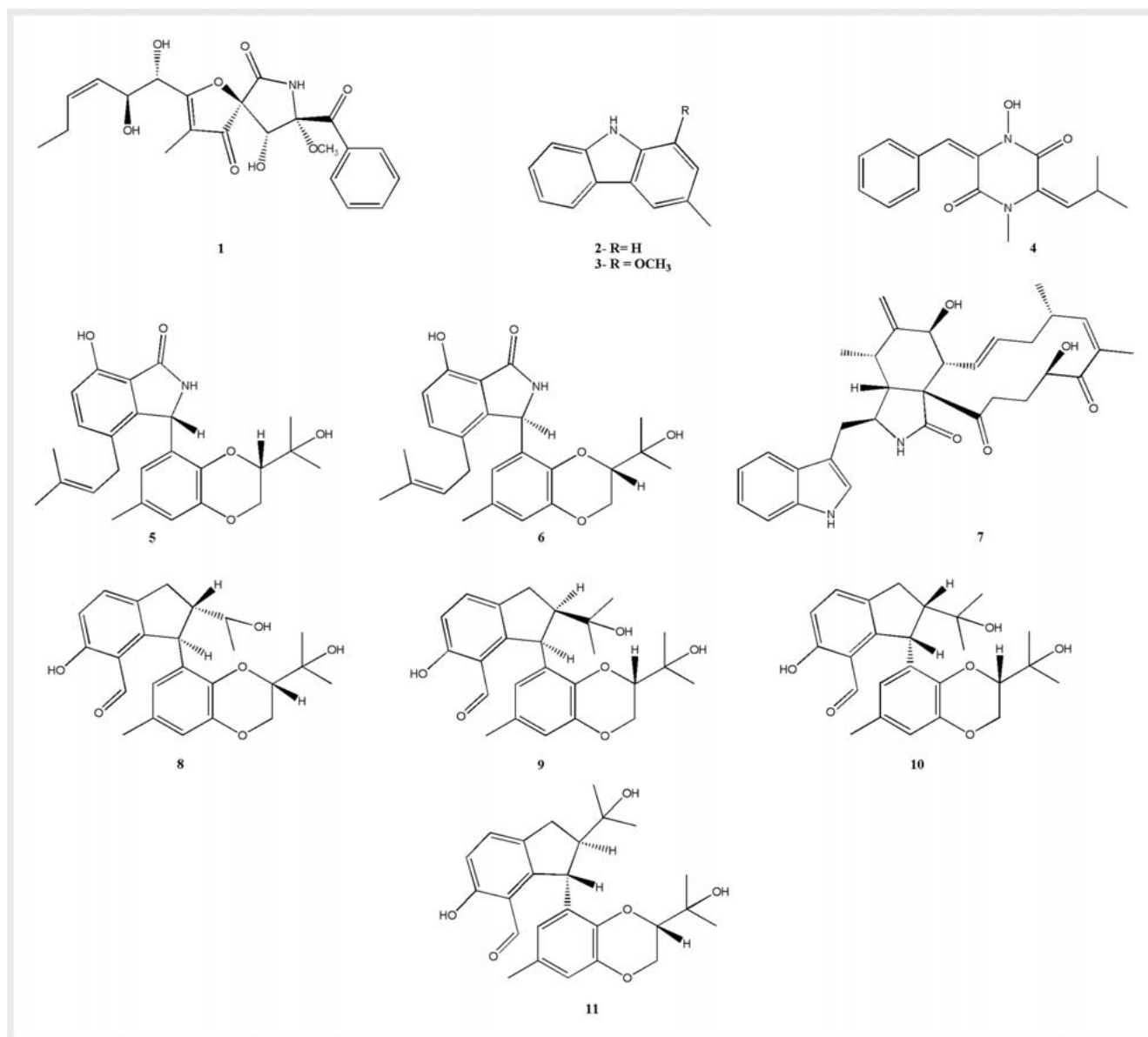
► **Table 2** Continued

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)	<i>In vivo</i> anti-inflammatory activity in mouse ear edema model [53.20%]	[41]
92.	Phomopchalsin 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.	Pinselins (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 [E _{max} 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-6 5.3, IL-12 p40 19.4, 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].

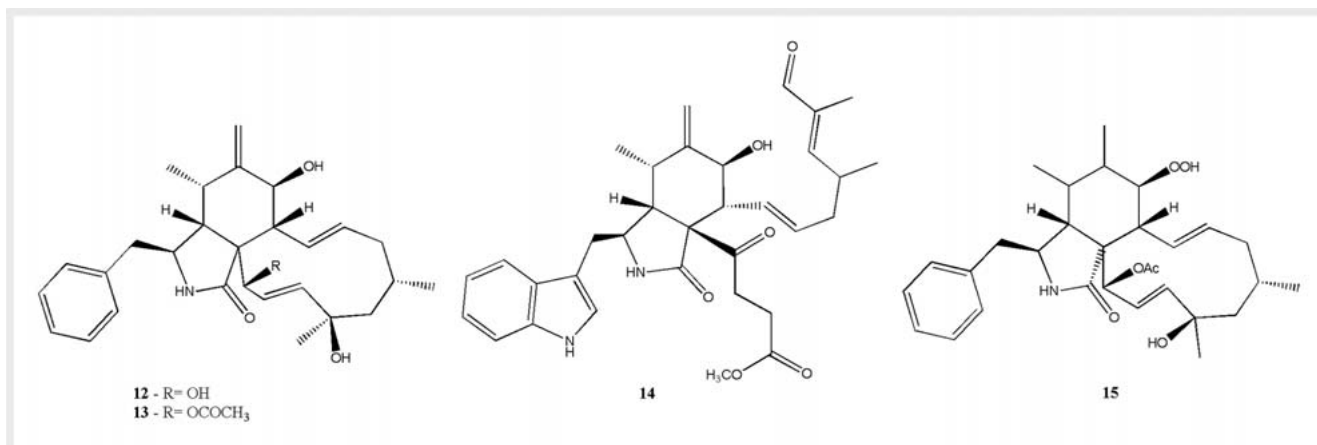


► **Fig. 1** Structures of anti-inflammatory alkaloids and benzophenones obtained from endophytic fungi.

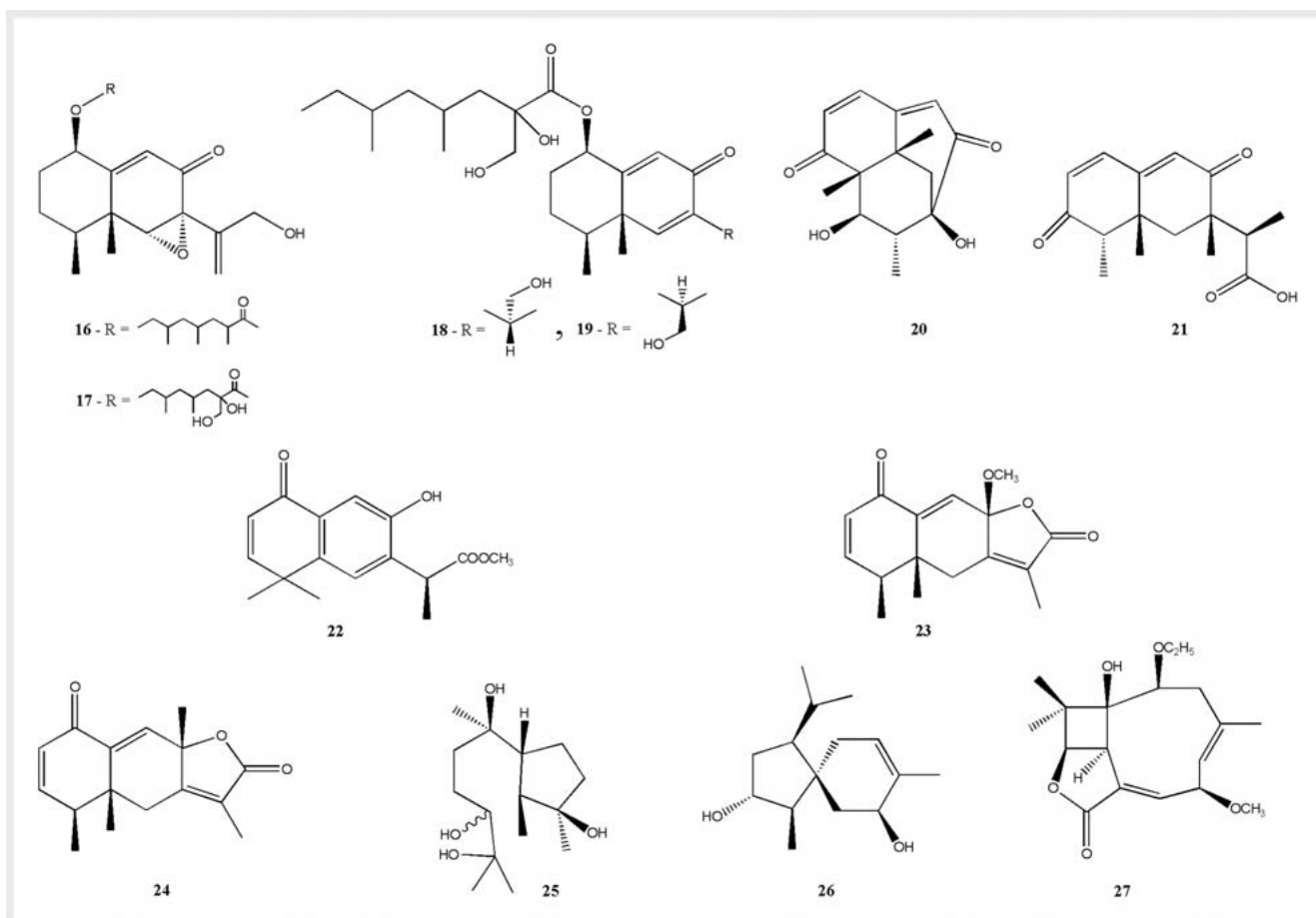
ROS like superoxides, hydroxyl, and hydrogen peroxide anions have been responsible for several degenerative diseases like rheumatoid arthritis, inflammation, the progression of cancers, etc. Thus, inhibitors of the total ROS concentration could be probable leads for the design of AI drugs [7].

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.

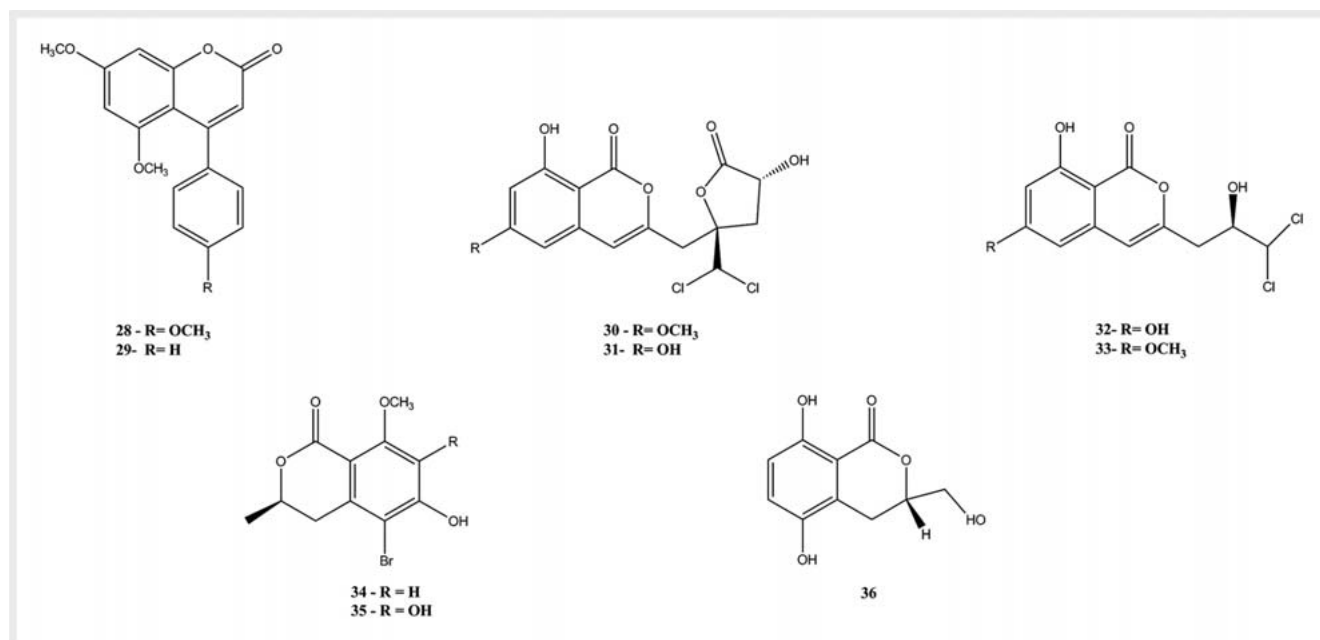


► **Fig. 3** Structures of anti-inflammatory sesquiterpenes obtained from endophytic fungi.

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, xanthenes, 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

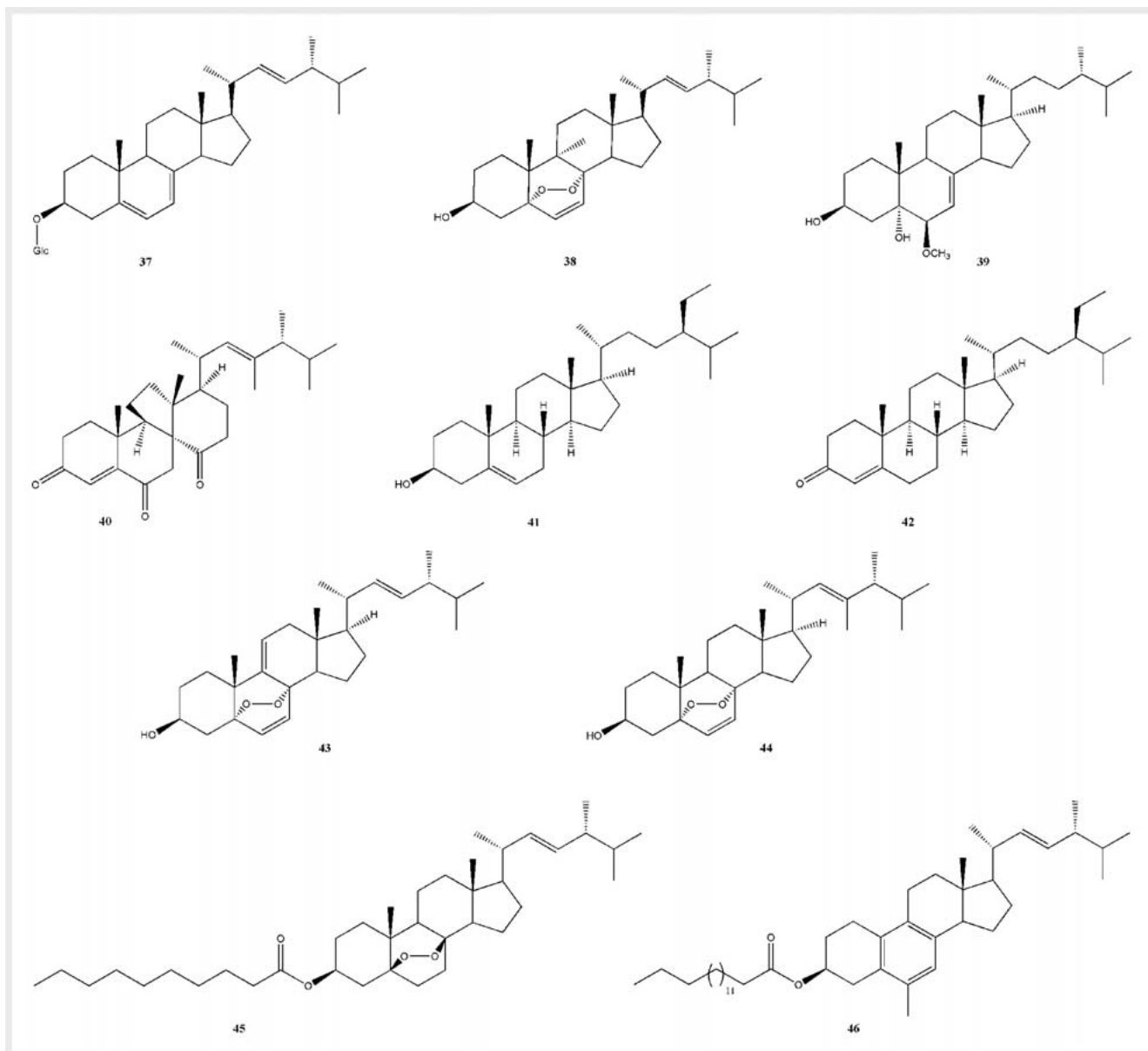
Mix. The sequence is then subjected to a basic local alignment search tool (BLAST) analysis [37]. For the phylogenetic analysis, related sequences are retrieved from NCBI and aligned with ClustalW. The aligned data could be used for further phylogenetic analysis with the neighbor-joining method using 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-1 β , IL-6, IL-10, TNF- α , IL-1 α , 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) (IC₅₀ 4.2 μ M) and D (11) (IC₅₀ 4.2 μ M) 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 μ M) exhibiting indirect AI activity by suppressing the LPS-induced pro-inflammatory factors in BV2 microglial cells [13, 25, 29, 35, 45].

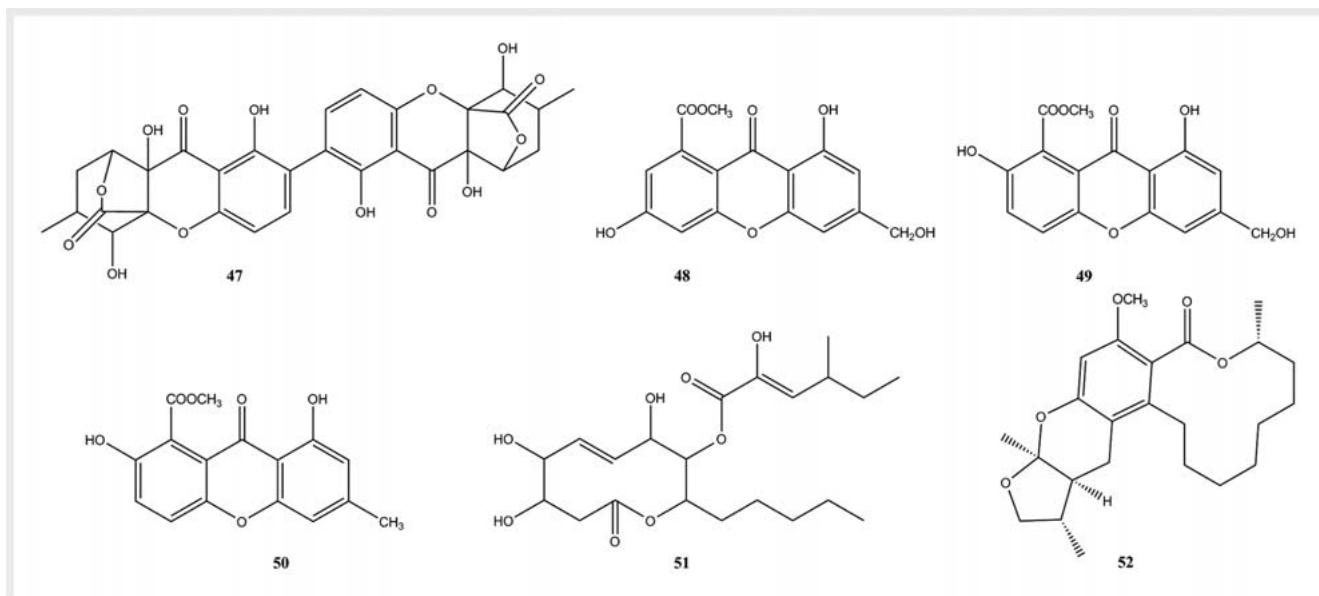
AI Cytochalasans

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-isindolone 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 phomopchalsin 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

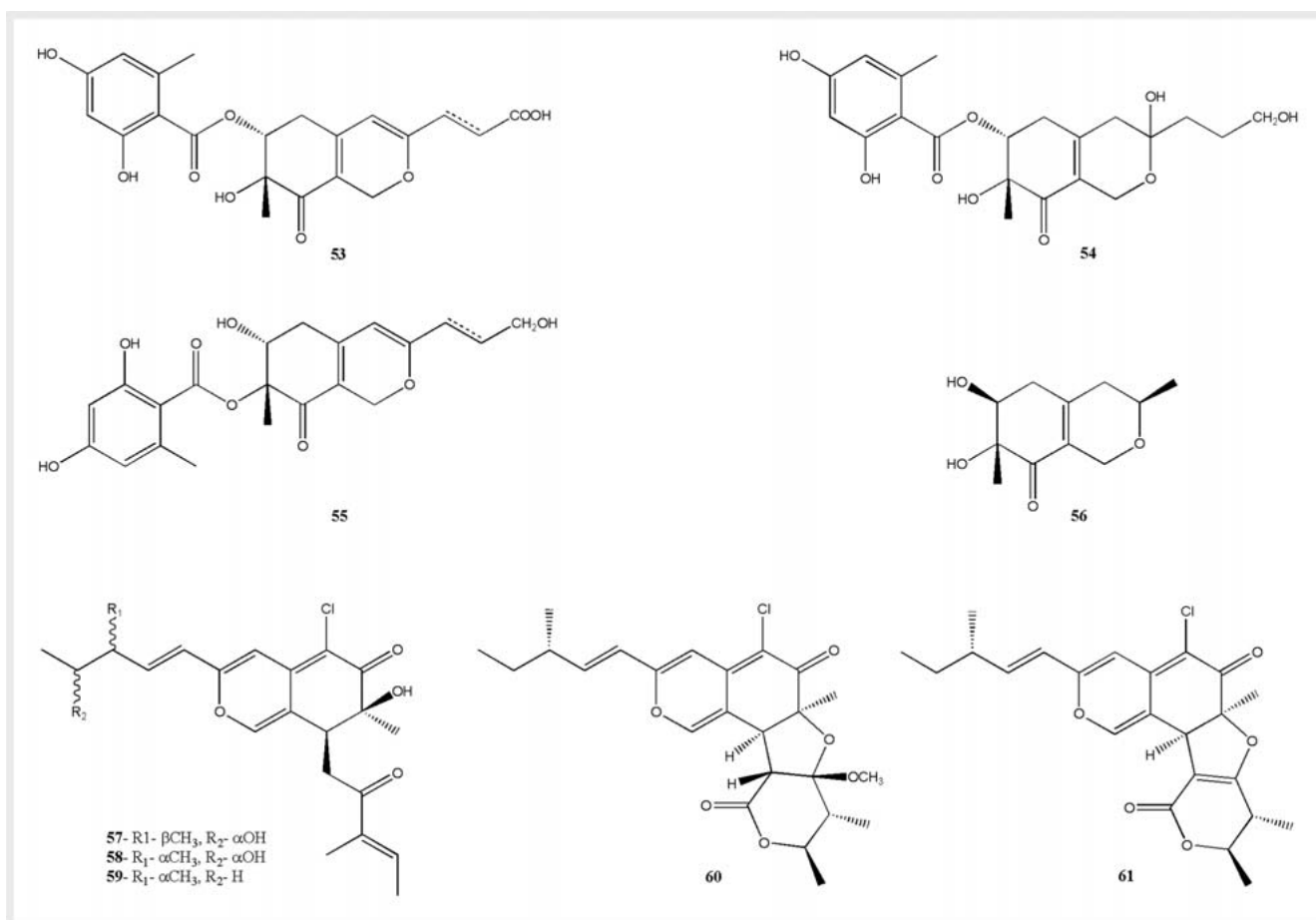
activities through inhibition of NO and total ROS. Phomopchalsin C (15) was identified as the most active inhibitor of NO production in LPS-induced raw cells with an IC_{50} value of 11.2 μ M (► **Table 2**) [20, 42, 50].

AI Sesquiterpenes and Sesquiterpenoids

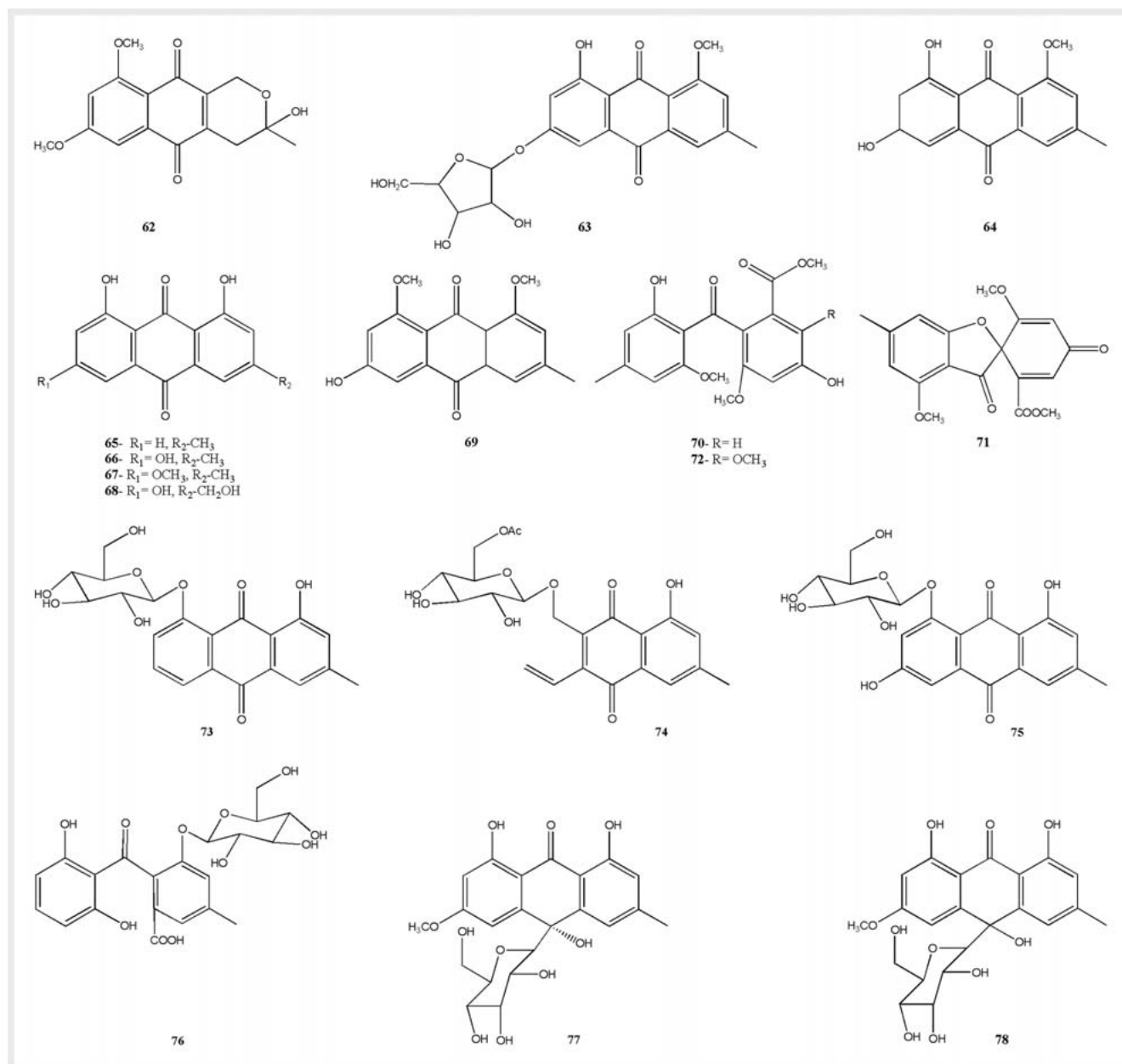
Sesquiterpenes and sesquiterpenoids were found to be the prominent class of compounds possessing AI properties, with a total of 12 compounds isolated from endophytic fungal sources. The compounds were isolated from a variety of fungi and were found to exhibit ROS and NO inhibition effect. The compounds 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), 1 α -isopropyl-4 α ,8-dimethylspiro[4.5]dec-8-ene-2 β ,7 α -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 IC₅₀ 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].

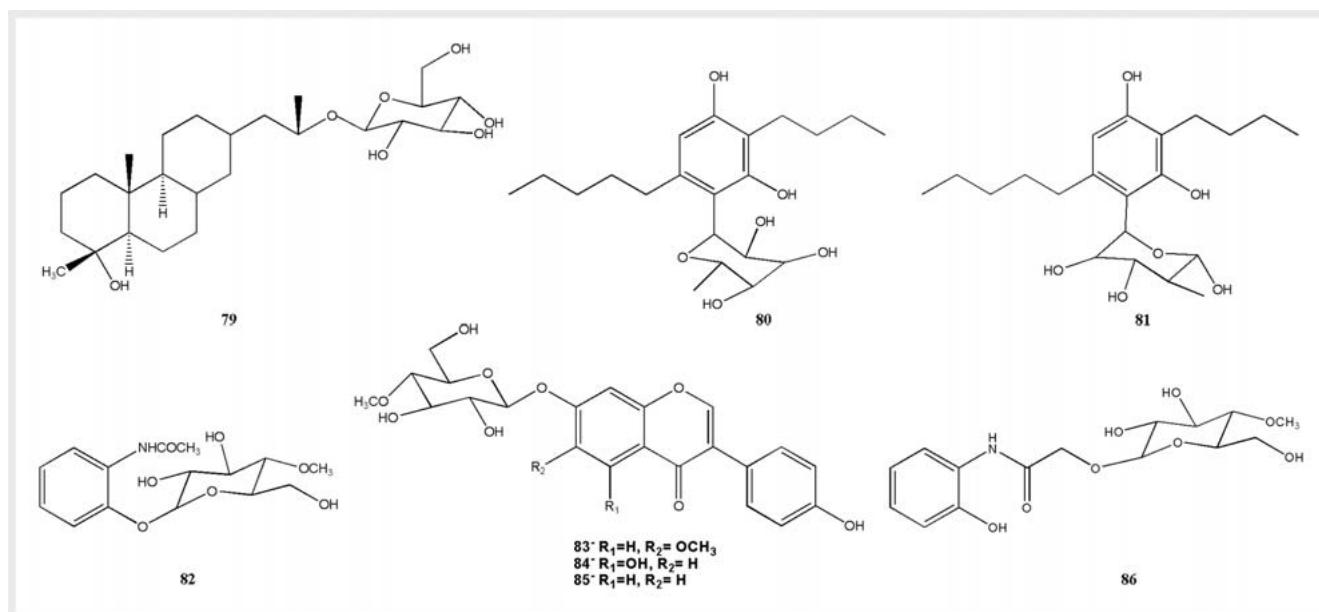
AI Coumarin Derivatives

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 IC₅₀ 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-glucoopyranoside (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), 5 α ,8 α -epidioxyergosta-6,9(11),22-trien-3-ol (43), 5 α ,8 α -epidioxy-(22E,24 R)-23-methylergosta-6,22-dien-3 β -ol (44), and fusaristerol A and B (45–46) (► Fig. 5). These compounds had been reported as NO and IL-6 inhibitors. Compound phomosterone B (40) was found to be potentially active exhibiting IC₅₀ value of 4.65 μ M (► Table 2) [14–17, 43].

AI Xanthone and Xanthenes

These are a group of important compounds that are oxygenated heterocycles. Most xanthenes 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 xanthone 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 IC₅₀ values of 1.9 μ M and 1.2 μ M against TNF- α and IL-6, respectively [26, 30].

AI Lactones

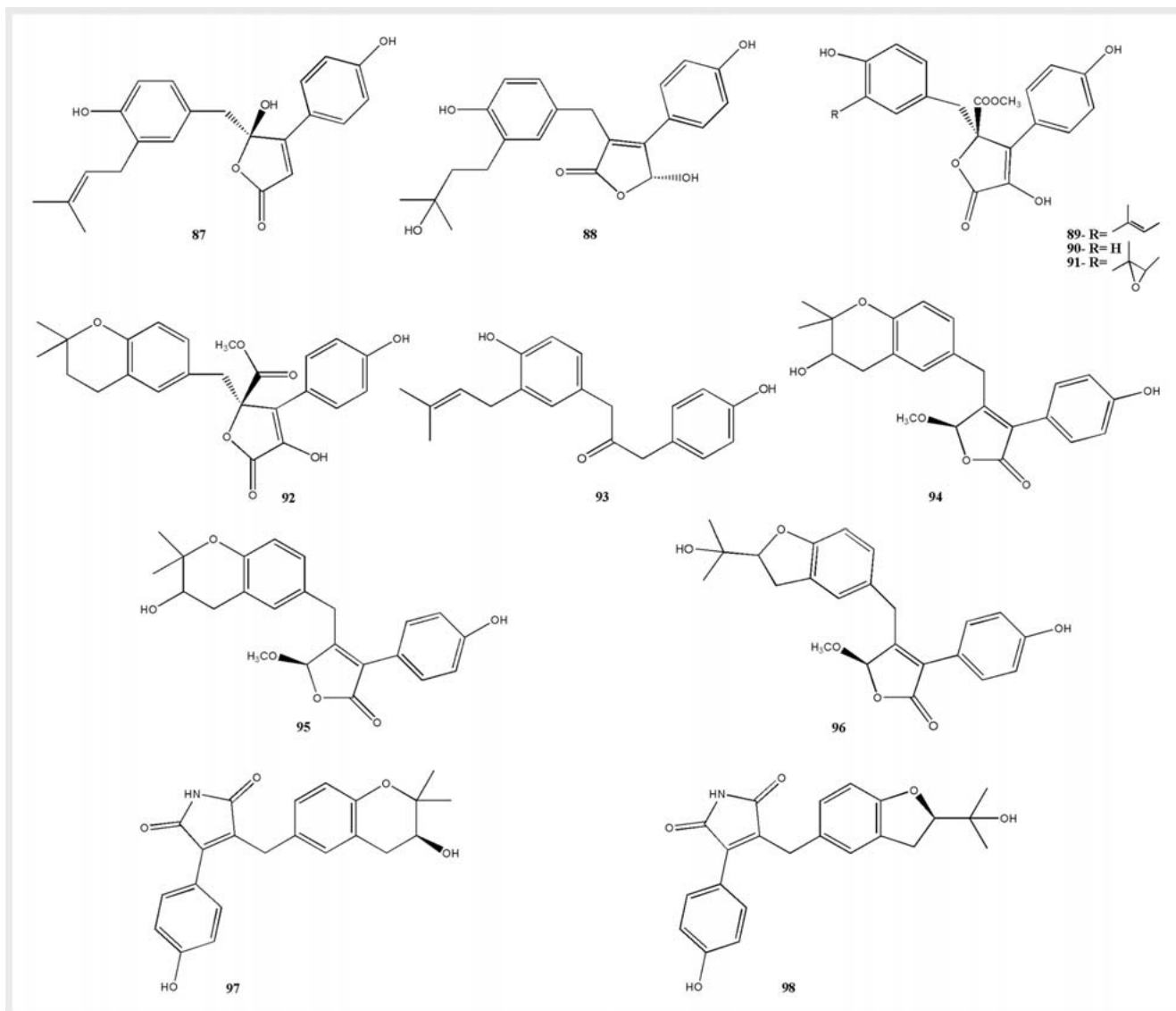
Two lactones viz., phomol (51) and lasiodiplactone A (52) isolated from endophytic fungi, *Phomopsis* sp., and *Lasiodiplodia theobromae* ZJ-HQ1 respectively, were reported as AI compounds. Phomol (51) was effective under *in vivo* mice ear edema model having inhibition of 53.20%, whereas Lasiodiplactone A(52) was found to inhibit NO production in LPS-stimulated RAW 264.7 cell lines showing IC₅₀ value of 23.5 μ M (► 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 montagnophilone B (53), montagnophilones E (54), rubiginosins B (55), xylariphilone (56), 11-epichaetomugilin I (57), chaetomugilin 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 IC₅₀ value of 0.3 μ M against NO inhibitory assay (► Table 2) [12, 37, 49].

AI Anthraquinones, 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 andasperfum (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), patientside A (77), patientside 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.

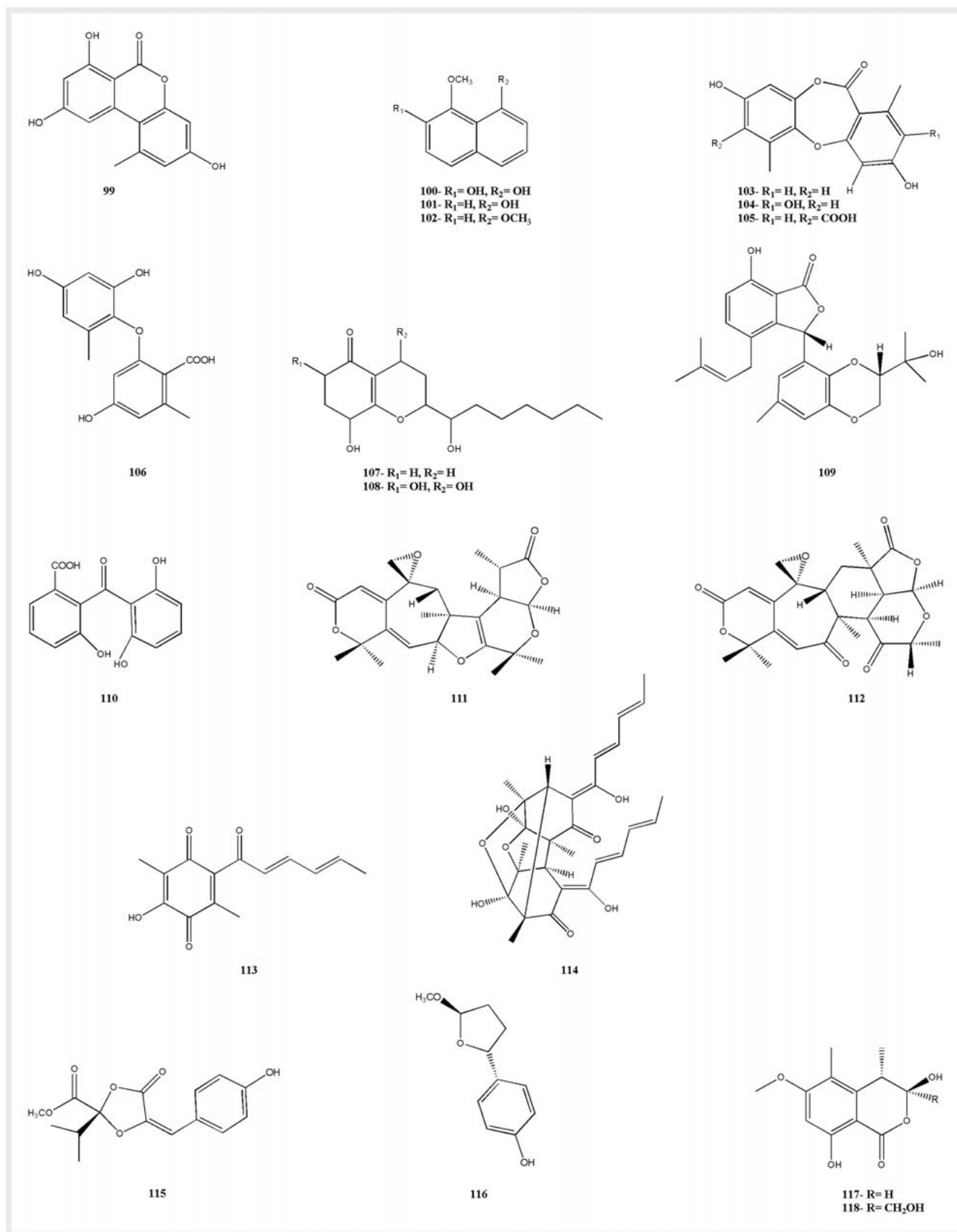
Aspergillus fumigatus and *Gaeumannomyces sp.*, respectively. Herbarin (**62**) was found to be most active among the quinines showing an IC_{50} value of 0.06 μ M and 0.01 μ M, respectively in inhibiting TNF- α and IL-6 (► **Table 2**) [10, 14, 33].

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**), cordycepiamide B (**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 alkyl) 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 μ M (► **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.	<i>Rhizoctonia</i> sp. [Methanolic extract]	<i>Schinu sterebinthifolius</i> (seeds)	<i>In vivo</i> mice paw edema [Inhibition at dose of 10 mg/kg i.p.]	[61]
2.	<i>Talaromyces wortmannii</i> [Crude extract and isolated fractions]	<i>Aloe vera</i>	IL-8 inhibition	[62]
3.	<i>Myrothecium</i> sp. [Crude extract and fraction]	<i>Calophyllum apetalum</i>	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.	<i>Aspergillus niger</i> , <i>Penicillium</i> sp., <i>Alternaria alternate</i> <i>Aspergillus flavus</i> [Methanolic and aqueous extracts]	<i>Loranthus</i> sp.	Albumin denaturation, membrane stabilisation, proteinase inhibition [85–32%]	[64]
5.	<i>Penicillium citrinum</i> <i>Geotrichum candidum</i> [Ethanol, hexane, methanol, and ethyl acetate extract]	<i>Phoenix dactylifera</i> L.	Protein denaturation method [EtOAc extract (<i>Geotrichum</i> sp.) [IC ₅₀ = 0.47 mg/ml] EtOH extract (<i>Geotrichum</i> sp.) [IC ₅₀ = 1.37 mg/ml] EtOH extract (<i>Penicillium</i> sp.) [IC ₅₀ = 1.88 mg/ml] EtOAc extract (<i>Penicillium</i> sp.) [IC ₅₀ = 3.67 mg/ml]	[65]
6.	<i>Penicillium species</i> [Silver nanoparticles of extract]	<i>Glycosmis mauritiana</i>	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), corynether A (106), koniginin 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 IC₅₀ value of 1.88 µM. Compound 1,8-dimethoxynaphthalene (102) showed an IC₅₀ 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 IC₅₀ 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.

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Conflict of Interest

The authors declare that they have no conflict of interest.

References

- [1] Gutierrez RM, Gonzalez AM, Ramirez AM. Compounds derived from endophytes: a review of phytochemistry and pharmacology. *Curr Med Chem* 2012; 19: 2992–3030
- [2] Jia M, Chen L, Xin HL, Zheng CJ, Rahman K, Han T, Qin LP. A friendly relationship between endophytic fungi and medicinal plants: a systematic review. *Front Microbiol* 2016; 7: 1–14
- [3] Watkins LR, Maier SF, Goehler LE. Immune activation: the role of pro-inflammatory cytokines in inflammation, illness responses and pathological pain states. *Pain* 1955; 63: 289–302
- [4] Dinarello CA. Proinflammatory cytokines. *Chest* 2000; 118: 503–508
- [5] Ju Z, Lin X, Lu X, Tu Z, Wang J, Kaliyaperumal K, Liu Y. Botryoisocoumarin A, a new COX-2 inhibitor from the mangrove *Kandelia candel* endophytic fungus *Botryosphaeria* sp. KcF6. *J Antibiot* 2015; 68: 653–656
- [6] Samad TA, Moore KA, Sapirstein A, Billet S, Allchorne A, Poole S, Woolf CJ. Interleukin-1 β -mediated induction of COX-2 in the CNS contributes to inflammatory pain hypersensitivity. *Nature* 2001; 410: 471–475
- [7] Kang HS, Chung HY, Kim JY, Son BW, Jung HA, Choi JS. Inhibitory phlorotannins from the edible brown algae *Ecklonia stolonifera* on total reactive oxygen species (ROS) generation. *Arch Pharm Res* 2004; 27: 194–198
- [8] Coussens LM, Werb Z. Inflammation and cancer. *Nature* 2002; 420: 860–867
- [9] Kim JW, Choi HG, Song JH, Kang KS, Shim SH. Bioactive secondary metabolites from an endophytic fungus *Phoma* sp. PF2 derived from *Artemisia princeps* Pamp. *J Antibiot* 2019; 72: 174–177
- [10] Yang Y, Yan YM, Wei W, Luo J, Zhang LS, Zhou XJ, Cheng YX. Anthraquinone derivatives from *Rumex* plants and endophytic *Aspergillus fumigatus* and their effects on diabetic nephropathy. *Bioorg Med Chem Lett* 2013; 23: 3905–3909
- [11] Chang CW, Chang HS, Cheng MJ, Liu TW, Hsieh SY, Yuan GF, Chen IS. Inhibitory effects of constituents of an endophytic fungus *Hypoxylon investiens* on nitric oxide and interleukin-6 production in RAW 264.7 macrophages. *Chem Biodivers* 2014; 11: 949–961
- [12] Youn UJ, Sripisut T, Park EJ, Kondratyuk TP, Fatima N, Simmons CJ, Chang LC. Determination of the absolute configuration of chaetoviridins and other bioactive azaphilones from the endophytic fungus *Chaetomium globosum*. *Bioorg Med Chem Lett* 2015; 25: 4719–4723
- [13] Taechowisan T, Chanaphat S, Ruensamran W, Phutdhawong WS. Anti-inflammatory effect of 3-methylcarbazoles on RAW 264.7 cells stimulated with LPS, polyinosinic-polycytidylic acid and Pam3CSK. *Adv Microbiol* 2012; 2: 98
- [14] Lee C, Kim S, Li W, Bang S, Lee H, Lee HJ, Shim SH. Bioactive secondary metabolites produced by an endophytic fungus *Gaeumannomyces* sp. JS0464 from a maritime halophyte *Phragmites communis*. *J Antibiot* 2017; 70: 737
- [15] Zhang M, Zhao JL, Liu JM, Chen RD, Xie KB, Chen DW, Dai JG. Neural anti-inflammatory sesquiterpenoids from the endophytic fungus *Trichoderma* sp. Xy24. *J Asian Nat Prod Res* 2017; 19: 651–658
- [16] Zhao JL, Zhang M, Liu JM, Tan Z, Chen RD, Xie KB, Dai JG. Bioactive steroids and sorbicillinoids isolated from the endophytic fungus *Trichoderma* sp. Xy24. *J Asian Nat Prod Res* 2017; 19: 1028–1035
- [17] Chang HS, Cheng MJ, Wu MD, Chan HY, Hsieh SY, Lin CH, Yech YJ, Chen IS. Secondary metabolites produced by an endophytic fungus *Cordyceps ninchukispora* from the seeds of *Beilschmiedia erythrophloia* Hayata. *Phytochem Lett* 2017; 22: 179–184
- [18] Taechowisan T, Lu C, Shen Y, Lumyong S. *In vitro* anti-inflammatory activity of 4-arylcoumarins from endophytic *Streptomyces aureofaciens* CMUAc130 in murine macrophage RAW 264.7 cells. *Nat Prod Res* 2007; 21: 1104–1113
- [19] Liu W, Chen S, Li J, Yang X, Yan C, Liu H. A new β -tetralonyl glucoside from the *Santalum album* derived endophytic fungus *Colletotrichum* sp. GDMU-1. *Nat Prod Res* 2019; 33: 354–359
- [20] Chen S, Ding M, Liu W, Huang X, Liu Z, Lu Y, Liu H, She Z. Anti-inflammatory meroterpenoids from the mangrove endophytic fungus *Talaromyces amestolkiae* YX1. *Phytochemistry* 2018; 146: 8–15
- [21] Chapla VM, Zeraik ML, Ximenes VF, Zanardi LM, Lopes MN, Cavalheiro AJ, Silva DH, Young MC, Fonseca LM, Bolzani VS, Araújo AR. Bioactive secondary metabolites from *Phomopsis* sp., an endophytic fungus from *Senecio spectabilis*. *Molecules* 2014; 19: 6597–6608
- [22] Liao G, Wu P, Xue J, Liu L, Li H, Wei X. Asperimides A–D, anti-inflammatory aromatic butenolides from a tropical endophytic fungus *Aspergillus terreus*. *Fitoterapia* 2018; 131: 50–54
- [23] Guo F, Li Z, Xu X, Wang K, Shao M, Zhao F, Wang H, Hua H, Pei Y, Bai J. Butenolide derivatives from the plant endophytic fungus *Aspergillus terreus*. *Fitoterapia* 2016; 113: 44–50
- [24] Ju ZR, Qin X, Lin XP, Wang JF, Kaliyaperumal K, Tian YQ, Liu J, Liu F, Tu Z, Xu SH, Liu Y. New phenyl derivatives from endophytic fungus *Botryosphaeria* sp. SCSIO KcF6 derived of mangrove plant *Kandelia candel*. *Nat Prod Res* 2016; 30: 192–198
- [25] Dou H, Song Y, Liu X, Gong W, Li E, Tan R, Hou Y. Chaetoglobosin Fex from the marine-derived endophytic fungus inhibits induction of inflammatory mediators via toll-like receptor 4 signaling in macrophages. *Biol Pharm Bull* 2011; 34: 1864–1873
- [26] Liu H, Chen S, Liu W, Liu Y, Huang X, She Z. Polyketides with immunosuppressive activities from mangrove endophytic fungus *Penicillium* sp. ZJ-SY2. *Mar Drugs* 2016; 14: 217–224
- [27] Okoye FB, Nworu CS, Akah PA, Esimone CO, Debbab A, Proksch P. Inhibition of inflammatory mediators and reactive oxygen and nitrogen species by some depsidones and diaryl ether derivatives isolated from *Corynespora cassiicola*, an endophytic fungus of *Gongronema latifolium* leaves. *Immunopharmacol Immunotoxicol* 2013; 35: 662–668
- [28] Chen Y, Liu Z, Liu H, Pan Y, Li J, Liu L, She Z. Dichloroisocoumarins with potential anti-inflammatory activity from the mangrove endophytic fungus *Ascomycoata* sp. CYSK-4. *Mar Drugs* 2018; 16: 54–63
- [29] Cui H, Liu Y, Li J, Huang X, Yan T, Cao W, Liu H, Long Y, She Z. Diaporindenes A–D: four unusual 2,3-dihydro-1H-indene analogues with anti-inflammatory activities from the mangrove endophytic fungus *Diaporthe* sp. SYSU-HQ3. *J Org Chem* 2018; 83: 11804–11813
- [30] Deshmukh SK, Mishra PD, Kulkarni-Almeida A, Verekar S, Sahoo MR, Periyasamy G, Goswami H, Khanna A, Balakrishnan A, Vishwakarma R. Anti-inflammatory and anticancer activity of ergoflavin isolated from an endophytic fungus. *Chem Biodivers* 2009; 6: 784–789
- [31] Khayat MT, Ibrahim SR, Mohamed GA, Abdallah HM. Anti-inflammatory metabolites from endophytic fungus *Fusarium* sp. *Phytochem Lett* 2019; 29: 104–109
- [32] Liu Y, Li Y, Liu Z, Li L, Qu J, Ma S, Chen R, Dai J, Yu S. Sesquiterpenes from the endophyte *Glomerella cingulata*. *J Nat Prod* 2017; 80: 2609–2614
- [33] Mishra PD, Verekar SA, Kulkarni-Almeida A, Roy SK. Anti-inflammatory and anti-diabetic naphthaquinones from an endophytic fungus *Dendryphion nanum* (Nees) S. Hughes. *Indian J Chem* 2013; 52B: 565–567
- [34] Souza AD, Rodrigues-Filho E, Souza AQ, Pereira JO, Calgarotto AK, Maso V, Marangoni S, Da Silva SL. Koninginins, phospholipase A2 inhibitors from endophytic fungus *Trichoderma koningii*. *Toxicon* 2008; 51: 240–250
- [35] Taechowisan T, Wanbanjob A, Tuntiwachwuttikul P, Liu J. Anti-inflammatory activity of lansais from endophytic *Streptomyces* sp. SUC1 in LPS-induced RAW 264.7 cells. *Food Agr Immunol* 2009; 20: 67–77
- [36] Chen S, Liu Z, Liu H, Long Y, Chen D, Lu Y, She Z. Lasiodiplactone A, a novel lactone from the mangrove endophytic fungus *Lasiodiplodia theobromae* ZJ-HQ1. *Org Biomol Chem* 2017; 15: 6338–6341
- [37] Luo JG, Xu YM, Sandberg DC, Arnold AE, Gunatilaka AL. Montagnuphilonones A–G, azaphilones from *Montagnulaceae* sp. DM0194, a fungal en-

- dophyte of submerged roots of *Persicaria amphibia*. *J Nat Prod* 2017; 80: 76–81
- [38] Zhao M, Yuan LY, Guo DL, Ye Y, Da-Wa ZM, Wang XL, Ma FW, Chen L, Gu YC, Ding LS, Zhou Y. Bioactive halogenated dihydroisocoumarins produced by the endophytic fungus *Lachnum palmae* isolated from *Przewalskia tangutica*. *Phytochemistry* 2018; 148: 97–103
- [39] Zhang D, Ge H, Zou JH, Tao X, Chen R, Dai J. Periconianone A, a new 6/6/6 carbocyclic sesquiterpenoid from endophytic fungus *Periconia* sp. with neural anti-inflammatory activity. *Org Lett* 2014; 16: 1410–1413
- [40] Liu Y, Yang MH, Wang XB, Li TX, Kong LY. Caryophyllene sesquiterpenoids from the endophytic fungus, *Pestalotiopsis* sp. *Fitoterapia* 2016; 109: 119–124
- [41] Weber D, Sterner O, Anke T, Gorzalczancy S, Martino V, Acevedo C. Phomol, a new antiinflammatory metabolite from an endophyte of the medicinal plant *Erythrina crista-galli*. *J Antibiot* 2004; 57: 559–563
- [42] Yan BC, Wang WG, Hu DB, Sun X, Kong LM, Li XN, Du X, Luo SH, Liu Y, Li Y, Sun HD. Phomopchalasins A and B, two cytochalasans with polycyclic-fused skeletons from the endophytic fungus *Phomopsis* sp. shj2. *Org Lett* 2016; 18: 1108–1111
- [43] Hu Z, Wu Y, Xie S, Sun W, Guo Y, Li XN, Liu J, Li H, Wang J, Luo Z, Xue Y. Phomosterones A and B, two functionalized ergostane-type steroids from the endophytic fungus *Phomopsis* sp. TJ507A. *Org Lett* 2016; 19: 258–261
- [44] Yang SS, Ming-jen C, Hing-Yuen C, Sung-Yuan H, Ho-Cheng W, Yuan GF, Chu-Hung L, Chang HS, Chen IS. New secondary metabolites from an endophytic fungus in *Porodaedalea pini*. *Rec Nat Prod* 2017; 11: 251–257
- [45] Shi YS, Chen XZ, Zhang N, Liu YB. Metabolites produced by the endophytic fungus *Aspergillus fumigatus* from the stem of *Erythrophloeum fordii* Oliv. *Molecules* 2015, 20: 10793–10799
- [46] Qi C, Gao W, Wang J, Liu M, Zhang J, Chen C, Hu Z, Xue Y, Li D, Zhang Q, Lai Y. Terrusnolides AD, new butenolides with anti-inflammatory activities from an endophytic *Aspergillus* from *Tripterygium wilfordii*. *Fitoterapia* 2018; 130: 134–139
- [47] Chen YS, Chang HS, Cheng MJ, Chan HY, Wu MD, Hsieh SY, Wang HC, Chen IS. New chemical constituents from the endophytic fungus *Xylaria papulis* cultivated on Taiwanese *Lepidagathis stenophylla*. *Rec Nat Prod* 2016; 10: 735–743
- [48] Gubiani JR, Zeraik ML, Oliveira CM, Ximenes VF, Nogueira CR, Fonseca LM, Silva DH, Bolzani VS, Araujo AR. Biologically active eremophilane-type sesquiterpenes from *Camarops* sp., an endophytic fungus isolated from *Alibertia macrophylla*. *J Nat Prod* 2014; 77: 668–672
- [49] Li W, Lee C, Bang SH, Ma JY, Kim S, Koh YS, Shim SH. Isochromans and related constituents from the endophytic fungus *Annulohyphoxylon truncatum* of *Zizania caduciflora* and their anti-inflammatory effects. *J Nat Prod* 2016; 80: 205–209
- [50] Ruan BH, Yu ZF, Yang XQ, Yang YB, Hu M, Zhang ZX, Zhou QY, Zhou H, Ding ZT. New bioactive compounds from aquatic endophyte *Chaetomium globosum*. *Nat Prod Res* 2017; 32: 1050–1055
- [51] Chithra S, Jasim B, Sachidanandan P, Jyothis M, Radhakrishnan E. Piperine production by endophytic fungus *Colletotrichum gloeosporioides* isolated from *Piper nigrum*. *Phytomedicine* 2014; 21: 534–540
- [52] White TJ, Bruns TD, Lee SB, Taylor JW. Amplification and direct Sequencing of fungal ribosomal RNA Genes for Phylogenetics. In: Innis MA, Gelfand DH, Sninsky JJ, White TJ, eds. *PCR Protocols: A Guide to Methods and Applications*. Cambridge: Academic Press; 1990: 315–322
- [53] Lu JJ, Bao JL, Chen XP, Huang M, Wang YT. Alkaloids isolated from natural herbs as the anticancer agents. *Evid Based Complement Alternat Med* 2012; 2012: 485042. doi:10.1155/2012/485042
- [54] Scherlach K, Boettger D, Remme N, Hertweck C. The chemistry and biology of cytochalasans. *Rec Nat Prod* 2010; 27: 869–886
- [55] Sethna SM, Shah NM. The chemistry of coumarins. *Chem Rev* 1945; 36: 1–62
- [56] Kasal A. Structure and Nomenclature of Steroids. In: Makin HLJ, Gower DB, eds. *Steroid Analysis*. Dordrecht: Springer; 2010: 1–25
- [57] Šiler B, Mišić D. Biologically active compounds from the genus *Centaureium* sp (Gentianaceae): current knowledge and future prospects in medicine. *Studies in Natural Product Chemistry* 2016; 49: 363–397
- [58] Rao YS. Chemistry of butenolides. *Chem Rev* 1964; 64: 353–388
- [59] Osmanova N, Schultze W, Ayoub N. Azaphilones: a class of fungal metabolites with diverse biological activities. *Phytochem Rev* 2010; 9: 315–342
- [60] McNaught AD, McNaught AD. *Compendium of chemical Terminology*. Oxford: Blackwell Science; 1997
- [61] de Barros BS, da Silva JP, de Souza Ferro JN, Agra IK, de Almeida Brito F, Albuquerque ED, Caetano LC, Barreto E. Methanol extract from mycelium of endophytic fungus *Rhizoctonia* sp. induces antinociceptive and anti-inflammatory activities in mice. *J Nat Med* 2011; 65: 526–531
- [62] Pretsch A, Nagl M, Schwendinger K, Kreiseder B, Wiederstein M, Pretsch D, Genov M, Hollaus R, Zinssmeister D, Debbab A, Hundsberger H. Antimicrobial and anti-inflammatory activities of endophytic fungi *Talaromyces wortmannii* extracts against acne-inducing bacteria. *PLoS One* 2014; 9: e97929
- [63] Ruma K, Sunil K, Prakash HS. Bioactive potential of endophytic *Myrothecium* sp. isolate M1-CA-102, associated with *Calophyllum apetalum*. *Pharm Biol* 2014; 52: 665–676
- [64] Govindappa M, Channabasava R, Sowmya DV, Meenakshi J, Shreevidya MR, Lavanya A, Santoyo G, Sadananda T. Phytochemical screening, antimicrobial and in vitro anti-inflammatory activity of endophytic extracts from *Loranthus* sp. *J Pharmacogn* 2011; 3: 82–90
- [65] Ben Mefteh F, Daoud A, Chenari Bouket A, Thissera B, Kadri Y, Cherif-Silini H, Eshelli M, Alenezi F, Vallat A, Oszako T, Kadri A. Date palm trees root-derived endophytes as fungal cell factories for diverse bioactive metabolites. *Int J Mol Sci* 2018; 19: 1986–2107
- [66] Govindappa M, Farheen H, Chandrappa CP, Rai RV, Raghavendra VB. Mycosynthesis of silver nanoparticles using extract of endophytic fungi, *Penicillium* species of *Glycosmis mauritiana*, and its antioxidant, antimicrobial, anti-inflammatory and tyrosinase inhibitory activity. *Adv Nat Sci-Nanosci* 2016; 7: 035014–035023