

Review

Natural Dibenzo- α -Pyrones and Their Bioactivities

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Abstract: Natural dibenzo- α -pyrones are an important group of metabolites derived from fungi, mycobionts, plants and animal feces. They exhibit a variety of biological activities such as toxicity on human and animals, phytotoxicity as well as cytotoxic, antioxidant, antiallergic, antimicrobial, antinematodal, and acetylcholinesterase inhibitory properties. Dibenzo- α -pyrones are biosynthesized via the polyketide pathway in microorganisms or metabolized from plant-derived ellagitannins and ellagic acid by intestinal bacteria. At least 53 dibenzo- α -pyrones have been reported in the past few decades. This mini-review aims to briefly summarize the occurrence, biosynthesis, biotransformation, as well as their biological activities and functions. Some considerations related to synthesis, production and applications of dibenzo- α -pyrones are also discussed.

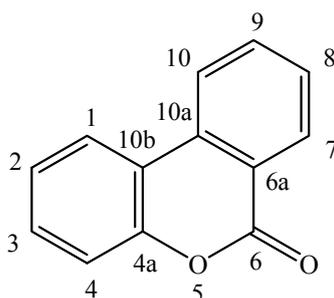
Keywords: dibenzo- α -pyrones; dibenzo- α -pyranones; 6*H*-benzo[*c*]chromen-6-ones; 6*H*-dibenzo[*b,d*]pyran-6-ones; biological activities

1. Introduction

Dibenzo- α -pyrones (also named dibenzo- α -pyranones, 6*H*-benzo[*c*]chromen-6-ones, and 6*H*-dibenzo[*b,d*]pyran-6-ones) are an important group of heptaketide coumarin derivatives that have a fused tricyclic nucleus (Figure 1). They are usually isolated from fungi [1], mycobionts [2,3], plants [4,5], and animal feces containing the transformed products of plant-derived ellagitannins and ellagic acid by intestinal bacteria [6,7]. Many of them possess a wide spectrum of biological activities, spanning from toxicity on human and animals [8], cytotoxic activity [9], phytotoxicity [10], antioxidant [6],

antiallergic [11], antimicrobial [12], to acetylcholinesterase inhibitory activities [13]. In addition, dibenzo- α -pyrones are key intermediates in the synthesis of cannabinoids [14], and other pharmaceutically interesting compounds such as progesterone, androgen, glucocorticoid receptor agonists [15,16], as well as endothelial proliferation inhibitors [17], and antidyslipidemic agents [18]. This review mainly presents the occurrence, biosynthesis, biotransformation, and biological activities of the dibenzo- α -pyrones from bioorganisms. We also discuss and prospect their synthesis, production and applications.

Figure 1. The basic skeleton of dibenzo- α -pyrones.



2. Occurrence

2.1. Dibenzo- α -pyrones from Fungi

Dibenzo- α -pyrones are mainly distributed in the *Alternaria* species and mycobionts. Other dibenzo- α -pyrone-producing fungi include *Botrytis allii*, *Cephalosporium acremonium*, *Hyalodendriella* sp. Ponipodef12, *Microsphaeropsis olivacea*, *Penicillium verruculosum*, and *Phoma* sp. TC 1674 (Table 1). From the biosynthetic pathway, fungal dibenzo- α -pyrones have a polyketide origin via acetyl-CoA and malonyl-CoA. They are usually toxic to plants and animals. Typical examples include alternariol (**10**), alternariol 9-methyl ether (**11**), botrallin (**16**), and 2-chloro-4,6-dihydro-1,7-dihydroxy-3,9-dimethoxy-1-methyl-1*H*-dibenzo[*b,d*]pyran-4,6-dione (TMC-264, **28**). The structures of the dibenzo- α -pyrones from fungi are shown in Figure 2.

Table 1. Occurrence of the dibenzo- α -pyrones in fungi.

Dibenzo- α -pyrone	Fungal Species	Reference
Altenuene = ATL (1)	Endophytic <i>Alternaria</i> sp. isolated from <i>Polygonum senegalense</i>	[9]
	<i>Alternaria alternata</i>	[10]
	Unidentified freshwater fungus belong to Tubeufiaceae	[19]
Isoaltenuene (2)	<i>Alternaria alternata</i>	[20]
	Unidentified freshwater fungus belong to Tubeufiaceae	[19]
2-Epialtenuene (3)	<i>Alternaria alternata</i>	[21]
	Unidentified freshwater fungus belong to Tubeufiaceae	[19]

Table 1. Cont.

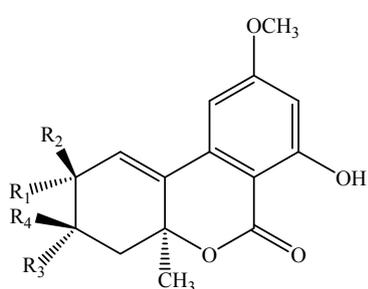
Dibenzo- α -pyrone	Fungal Species	Reference
3-Epialtenuene (4)	Endophytic <i>Alternaria</i> sp. isolated from <i>Polygonum senegalense</i>	[9]
Neoaltenuene (5)	<i>Alternaria alternata</i>	[21]
Dehydroaltenuene A (6)	Unidentified freshwater fungus belong to Tubeufiaceae	[19]
Dehydroaltenuene B (7)	Unidentified freshwater fungus belong to Tubeufiaceae	[19]
Dihydroaltenuene A (8)	Unidentified freshwater fungus belong to Tubeufiaceae	[19]
Dihydroaltenuene B (9)	Unidentified freshwater fungus belong to Tubeufiaceae	[19]
Alternariol = AOH (10)	Endophytic <i>Acremonium</i> sp. isolated from <i>Plantago lanceolata</i>	[22]
	Endophytic <i>Alternaria</i> sp. isolated from <i>Polygonum senegalense</i>	[9]
	Endophytic <i>Alternaria</i> no.28 isolated from <i>Ginkgo biloba</i>	[23]
	Endophytic <i>Alternaria</i> sp. PR-14 isolated from <i>Paeonia delavayi</i>	[24]
	Endophytic <i>Alternaria</i> sp. isolated from <i>Datura stramonium</i>	[25]
	Endophytic <i>Alternaria</i> sp. N.SBA10 isolated from <i>Scutellaria baicalensis</i>	[26]
	<i>Alternaria alternata</i>	[27]
	<i>Alternaria alternata</i>	[10]
	Endophytic <i>Alternaria brassicicola</i> ML-P08 isolated from <i>Malus halliana</i>	[28]
	Endophytic <i>Alternaria tenuissima</i> EN-192 isolated from <i>Rhizophora stylosa</i>	[29]
	Endophytic <i>Colletotrichum</i> sp. isolated from <i>Aristolochia</i> sp.	[30]
Alternariol 9-methyl ether = AME = Djalonsone (11)	Endophytic <i>Acremonium</i> sp. isolated from <i>Plantago lanceolata</i>	[22]
	Endophytic <i>Alternaria</i> sp. isolated from <i>Polygonum senegalense</i>	[9]
	Endophytic <i>Alternaria</i> sp. PR-14 isolated from <i>Paeonia delavayi</i>	[24]
	Endophytic <i>Alternaria</i> sp. isolated from <i>Datura stramonium</i>	[25]
	Endophytic <i>Alternaria</i> sp. N.SBA10 isolated from <i>Scutellaria baicalensis</i>	[26]
	<i>Alternaria alternata</i>	[27]
	<i>Alternaria alternata</i>	[31]
	<i>Alternaria alternata</i>	[10]
	Endophytic <i>Alternaria</i> no.28 isolated from <i>Ginkgo biloba</i>	[23]
	Endophytic <i>Alternaria brassicicola</i> ML-P08 isolated from <i>Malus halliana</i>	[28]
	Endophytic <i>Alternaria linicola</i> isolated from <i>Linum ustiatissimum</i>	[32]
	<i>Alternaria tenuis</i>	[33]

Table 1. Cont.

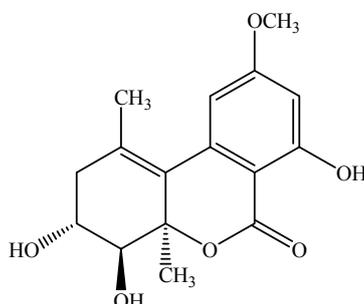
Dibenzo- α -pyrone	Fungal Species	Reference
Alternariol 9-methyl ether = AME = Djalonsone (11)	Endophytic <i>Alternaria tenuissima</i> isolated from <i>Acacia mangium</i>	[34]
	Endophytic <i>Alternaria tenuissima</i> EN-192 isolated from <i>Rhizophora stylosa</i>	[29]
	Endophytic <i>Cephalosporium acremonium</i> IFB-E007 isolated from <i>Trachelospermum jasminoides</i>	[35]
	Endophytic <i>Colletotrichum</i> sp. isolated from <i>Aristolochia</i> sp.	[30]
	Endophytic <i>Hyalodendriella</i> sp. Ponipodef12 isolated from the hybrid 'Neva' of <i>Populus deltoides</i> \times <i>P. nigra</i>	[12]
Alternariol 9-methyl ether-3- <i>O</i> -sulfate (12)	Endophytic <i>Alternaria</i> sp. isolated from <i>Polygonum senegalense</i>	[9]
	Endophytic <i>Alternaria</i> sp. isolated from <i>Polygonum senegalense</i>	[9]
	Endophytic <i>Alternaria</i> sp. isolated from <i>Polygonum senegalense</i>	[9]
4-Hydroxyalternariol 9-methyl ether (14)	Endophytic <i>Alternaria</i> sp. isolated from <i>Datura stramonium</i>	[25]
	Endophytic <i>Alternaria</i> sp. isolated from <i>Datura stramonium</i>	[25]
Altertenuol = Altenuisol = Alternuisol (15)	<i>Alternaria</i> sp.	[37]
	<i>Alternaris tenuis</i>	[38]
	<i>Alternaris tenuis</i>	[39,40]
	<i>Alternaris tenuis</i>	[41]
Botrallin (16)	<i>Botrytis allii</i>	[42]
	Endophytic <i>Hyalodendriella</i> sp. Ponipodef12 isolated from the hybrid 'Neva' of <i>Populus deltoides</i> \times <i>P. nigra</i>	[12,43]
	Endophytic <i>Microsphaeropsis olivacea</i> isolated from <i>Pilgerodendron uviferum</i>	[13]
Dehydroaltenusin (17)	<i>Acremonium</i> sp.	[44]
	<i>Alternaria tenuis</i>	[45]
	<i>Penicillium verruculosum</i>	[46]
Graphislactone A (18)	Mycobiont of <i>Graphis scripta</i> var. <i>pulverulenta</i>	[2]
	Endophytic <i>Cephalosporium acremonium</i> IFB-E007 isolated from <i>Trachelospermum jasminoides</i>	[35]
	Endophytic <i>Microsphaeropsis olivacea</i> isolated from <i>Pilgerodendron uviferum</i>	[13]
Graphislactone B (19)	Mycobiont of <i>Graphis scripta</i> var. <i>pulverulenta</i>	[2]
Graphislactone C (20)	Mycobiont of <i>Graphis scripta</i> var. <i>pulverulenta</i>	[2]
Graphislactone D (21)	Mycobiont of <i>Graphis scripta</i> var. <i>pulverulenta</i>	[2]
Graphislactone E (22)	Mycobiont of <i>Graphis scripta</i>	[3]
	Mycobiont of <i>Graphis prunicola</i>	[3]
Graphislactone F (23)	Mycobiont of <i>Graphis prunicola</i>	[3]

Table 1. Cont.

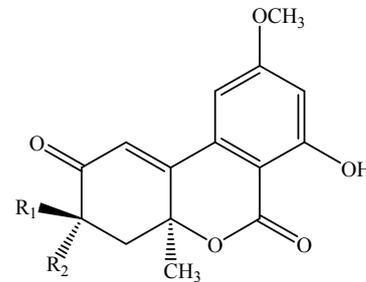
Dibenzo- α -pyrone	Fungal Species	Reference
Graphislactone G (24)	Endophytic <i>Cephalosporium acremonium</i> IFB-E007 isolated from <i>Trachelospermum jasminoides</i>	[35]
Graphislactone H (25)	Endophytic <i>Cephalosporium acremonium</i> IFB-E007 isolated from <i>Trachelospermum jasminoides</i>	[35]
Palamriol A (26)	<i>Lachnum palmae</i>	[36]
Palmariol B (27)	<i>Lachnum palmae</i>	[36]
	Endophytic <i>Hyalodendriella</i> sp. Ponipodef12 isolated from the hybrid 'Neva' of <i>Populus deltoides</i> \times <i>P. nigra</i>	[12]
TMC-264 (28)	<i>Phoma</i> sp. TC 1674	[47]

Figure 2. Structures of dibenzo- α -pyrones isolated from fungi.

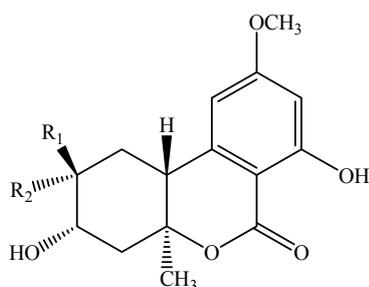
1. Altenuene, $R_1 = \text{OH}$, $R_2 = \text{H}$, $R_3 = \text{H}$, $R_4 = \text{OH}$
2. Isoaltenuene, $R_1 = \text{H}$, $R_2 = \text{OH}$, $R_3 = \text{OH}$, $R_4 = \text{H}$
3. 2-Epialtenuene, $R_1 = \text{OH}$, $R_2 = \text{H}$, $R_3 = \text{OH}$, $R_4 = \text{H}$
4. 3-Epialtenuene, $R_1 = \text{H}$, $R_2 = \text{OH}$, $R_3 = \text{H}$, $R_4 = \text{OH}$



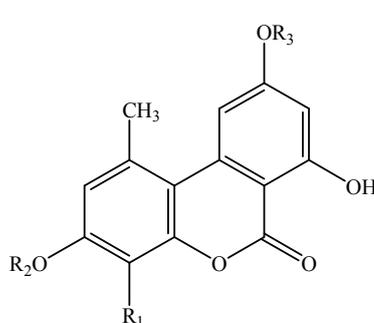
5. Neoaltenuene



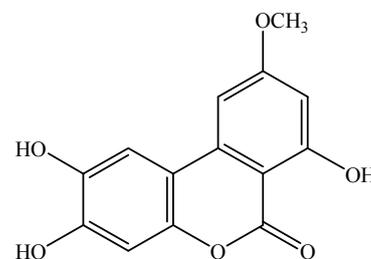
6. Dehydroaltenuene A, $R_1 = \text{OH}$, $R_2 = \text{H}$
7. Dehydroaltenuene B, $R_1 = \text{H}$, $R_2 = \text{OH}$



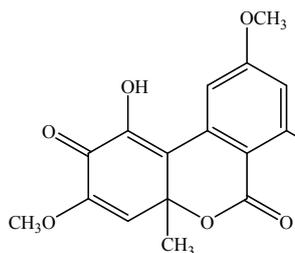
8. Dihydroaltenuene A, $R_1 = \text{H}$, $R_2 = \text{OH}$
9. Dihydroaltenuene B, $R_1 = \text{OH}$, $R_2 = \text{H}$



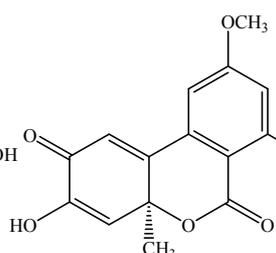
10. Alternariol, $R_1 = \text{H}$, $R_2 = \text{H}$, $R_3 = \text{H}$
11. Alternariol 9-methyl ether, $R_1 = \text{H}$, $R_2 = \text{H}$, $R_3 = \text{CH}_3$
12. Alternariol 9-methyl ether-3-O-sulfate, $R_1 = \text{H}$, $R_2 = \text{SO}_3\text{H}$, $R_3 = \text{CH}_3$
13. Alternariol 9-O-sulfate, $R_1 = \text{H}$, $R_2 = \text{H}$, $R_3 = \text{SO}_3\text{H}$
14. 4-Hydroxyalternariol 9-methyl ether, $R_1 = \text{OH}$, $R_2 = \text{H}$, $R_3 = \text{CH}_3$



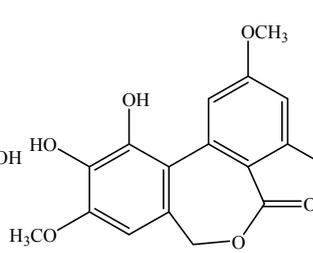
15. Alvertenuol



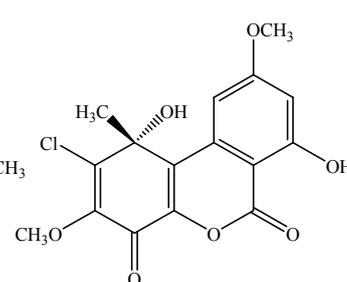
16. Botrallin



17. Dehydroaltenusin

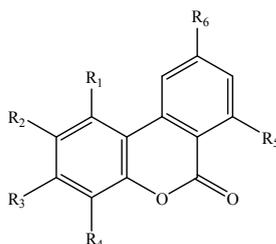


21. Graphislactone D



28. TMC-264

Figure 2. Cont.



18. Graphislactone A, R₁ = CH₃, R₂ = H, R₃ = OCH₃, R₄ = OH, R₅ = OH, R₆ = OCH₃
 19. Graphislactone B, R₁ = CH₃, R₂ = H, R₃ = OCH₃, R₄ = OH, R₅ = OCH₃, R₆ = OCH₃
 20. Graphislactone C, R₁ = CH₂OH, R₂ = H, R₃ = OCH₃, R₄ = OH, R₅ = OH, R₆ = OCH₃
 22. Graphislactone E, R₁ = OH, R₂ = H, R₃ = OCH₃, R₄ = OH, R₅ = OH, R₆ = OCH₃
 23. Graphislactone F, R₁ = OH, R₂ = H, R₃ = OCH₃, R₄ = OH, R₅ = OH, R₆ = OH
 24. Graphislactone G, R₁ = CH₃, R₂ = Cl, R₃ = OCH₃, R₄ = H, R₅ = OH, R₆ = OCH₃
 25. Graphislactone H, R₁ = CH₃, R₂ = H, R₃ = OCH₃, R₄ = OCH₃, R₅ = OH, R₆ = OCH₃
 26. Palmariol A, R₁ = CH₃, R₂ = H, R₃ = OH, R₄ = Cl, R₅ = OH, R₆ = OCH₃
 27. Palmariol B, R₁ = CH₃, R₂ = Cl, R₃ = OH, R₄ = H, R₅ = OH, R₆ = OCH₃

2.2. Dibenzo- α -pyrones from Plants

The dibenzo- α -pyrones from plants are listed in Table 2. One dibenzo- α -pyrone, namely djalonensone (**11**), was isolated from the roots of *Anthocleista djalonensis* (Loganiaceae). The authors postulated djalonensone to be a significant taxonomic marker of the plant species [48]. However, djalonensone is identical to alternariol 9-methyl ether (AME) which has been isolated from a series of fungi including pathogenic and endophytic fungi [1]. Thus, the significance of djalonensone (**11**) as an important taxonomic marker of the plant species should be reconsidered. The possibility that djalonensone (**11**) was produced by an endophytic fungus residing in the healthy roots of *A. djalonensis*, needs further investigation [49].

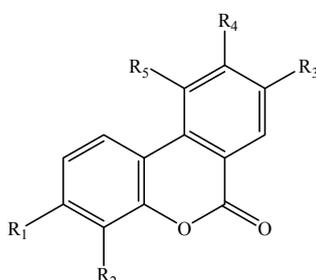
Three dibenzo- α -pyrones, namely (2'*S*,3'*R*)-3,10-dihydroxy-9-*O*-(6'-hydroxy-2'-hydroxymethyl-dihydrofuran-3-yl)-dibenzo[*b,d*]pyran-6-one (**31**), (2'*S*,3'*R*)-3,10-dihydroxy-9-*O*-(5',6'-dihydroxy-2'-hydroxymethyldihydrofuran-3-yl)-dibenzo[*b,d*]pyran-6-one (**32**), and fasciculiferol (**33**) were isolated from the heartwood of *Umtiza listerana* [50]. Fasciculiferol (**33**) was previously isolated from the heartwood of *Acacia fasciculifera* [51]. Two dibenzo- α -pyrones, autumnariniol (**29**) and autumnariol (**30**), were isolated from the bulbs of *Eucomis autumnalis* (Liliaceae) [52]. Four urolithins, namely urolithin A (**40**), isourolithin A (**41**), urolithin B (**42**) and urolithin C (**43**) were isolated from *Trapa natans* (Trapaceae) [4] and *Caesalpinia sappan* (Caesalpiniaceae) [53]. These urolithins (Figure 3) were also isolated from animal feces [6,7]. Other dibenzo- α -pyrones isolated from plants included sabilactone (**38**) from *Sabina vulgaris* [54] and sarolactone (**39**) from *Hypericum japonicum* [55]. The structures of the dibenzo- α -pyrones from plants are shown in Figure 4.

Table 2. Occurrence of dibenzo- α -pyrones in plants.

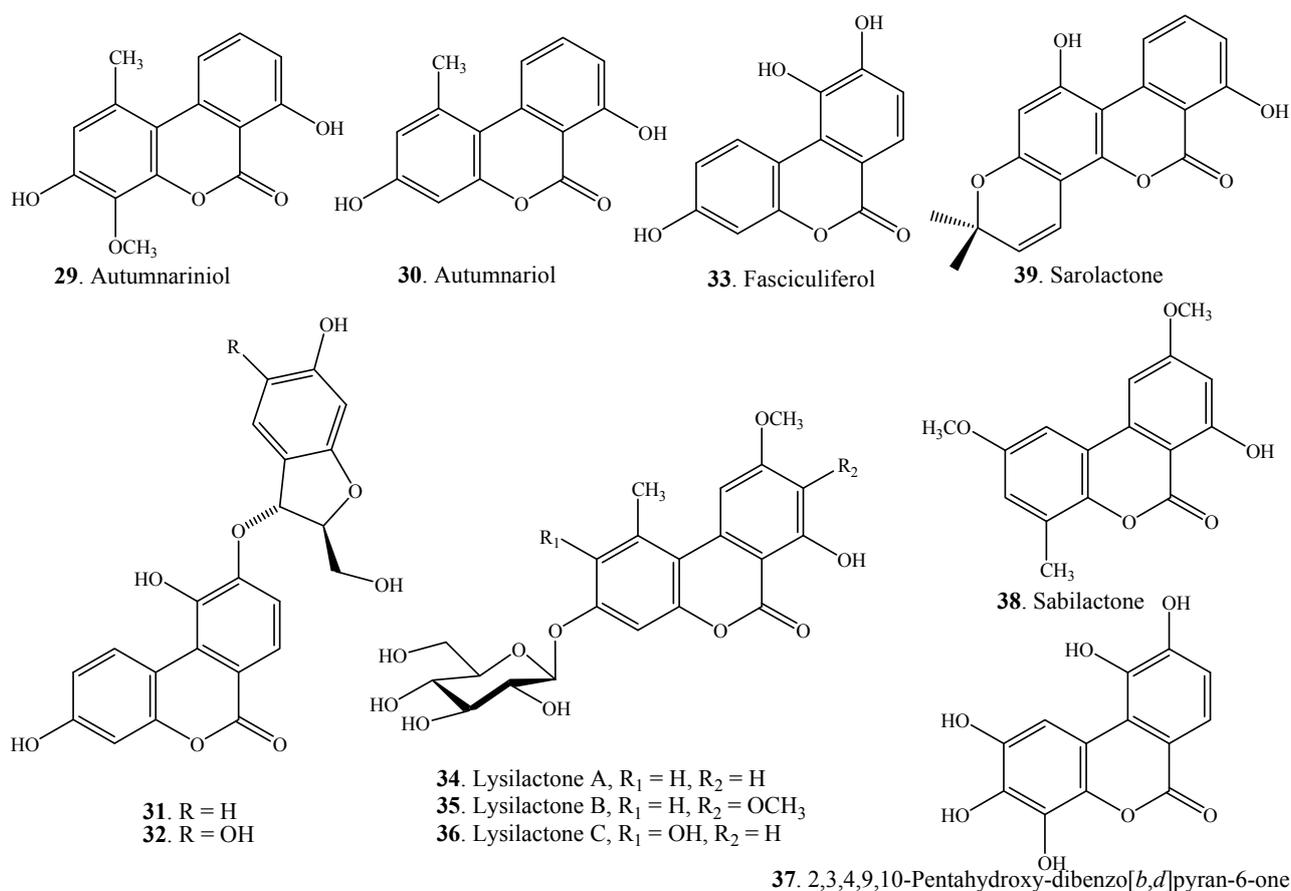
Dibenzo- α -pyrone	Plant species (Family)	Reference
Alternariol 9-methyl ether (11)	<i>Anthocleista djalonensis</i> (Loganiaceae)	[48]
Autumnariniol (29)	<i>Eucomis autumnalis</i> Graeb (Liliaceae)	[52]
Autumnariol (30)	<i>Eucomis autumnalis</i> Graeb (Liliaceae)	[52]
(2' <i>S</i> ,3' <i>R</i>)-3,10-Dihydroxy-9- <i>O</i> -(6'-hydroxy-2'-hydroxymethyldihydrofuran-3-yl)-dibenzo[<i>b,d</i>]pyran-6-one (31)	<i>Umtiza listerana</i> (Caesalpiniaceae)	[50]

Table 2. Cont.

Dibenzo- α -pyrone	Plant species (Family)	Reference
(2'S,3'R)-3,10-Dihydroxy-9-O-(5',6'-dihydroxy-2'-hydroxymethyldihydrofuran-3-yl)-dibenzo[<i>b,d</i>]pyran-6-one (32)	<i>Umtiza listerana</i> (Caesalpiniaceae)	[50]
Fasciculiferol (33)	<i>Acacia fasciculifera</i> (Mimosaceae)	[51]
Lysilactone A (34)	<i>Umtiza listerana</i> (Caesalpiniaceae)	[50]
Lysilactone B (35)	<i>Lysimachia clethroides</i> (Primulaceae)	[5]
Lysilactone C (36)	<i>Lysimachia clethroides</i> (Primulaceae)	[5]
2,3,4,9,10-Pentahydroxy-6 <i>H</i> -dibenzo[<i>b,d</i>]pyran-6-one (37)	<i>Chrozophora senegalensis</i> (Euphorbiaceae)	[56]
	<i>Polygonum chinense</i> (Polygonaceae)	[57]
	<i>Sebastiania chamaelea</i> (Euphorbiaceae)	[56]
	<i>Tamarix nilotica</i> (Tamaricaceae)	[58]
Sabilactone (38)	<i>Sabina vulgaris</i> (Cupressaceae)	[54]
Sarolactone (39)	<i>Hypericum japonicum</i> (Guttiferae)	[55]
Urolithin A (40)	<i>Trapa natans</i> (Trapaceae)	[4]
Isourolithin A (41)	<i>Trapa natans</i> (Trapaceae)	[4]
Urolithin B (42)	<i>Trapa natans</i> (Trapaceae)	[4]
Urolithin C (43)	<i>Caesalpinia sappan</i> (Caesalpiniaceae)	[53]

Figure 3. Dibenzo- α -pyrones produced by transformation of intestinal bacteria.

Dibenzo- α -pyrone	R ₁	R ₂	R ₃	R ₄	R ₅	Reference
Urolithin A (40)	OH	H	OH	H	H	[6]
Urolithin B (42)	OH	H	H	H	H	[6]
Urolithin C (43)	OH	H	OH	OH	H	[6]
Urolithin D (44)	OH	OH	OH	OH	H	[59]
Urolithin E (45)	OH	OH	OH	H	OH	[59]
Urolithin M-5 (46)	OH	OH	OH	OH	OH	[7]
Urolithin M-6 (47)	OH	H	OH	OH	OH	[7,59]
Urolithin M-7 (48)	OH	H	OH	H	OH	[7,11]
Isourolithin A (41)	OH	H	H	OH	H	[7]
Isourolithin B (49)	H	H	H	OH	H	[7]
8-O-Methylurolithin A (50)	OH	H	OCH ₃	H	H	[6]
8,9-Di-O-methylurolithin C (51)	OH	H	OCH ₃	OCH ₃	H	[6]
8,9-Di-O-methylurolithin D (52)	OH	OH	OCH ₃	OCH ₃	H	[6]

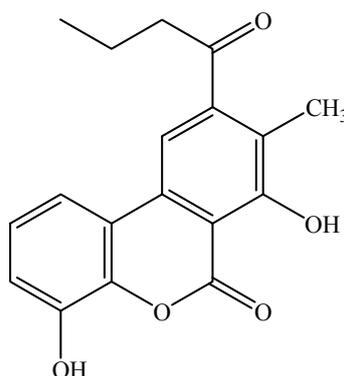
Figure 4. Structures of the dibenzo- α -pyrones from plants.

2.3. Dibenzo- α -pyrones Produced by Transformation of Intestinal Bacteria

A group of dibenzo- α -pyrones **40–52**, namely urolithins with different phenolic hydroxylation patterns, have been isolated from animal feces. Ellagitannins and ellagic acid (EA) are plant secondary metabolites that have relevant antioxidant activities *in vitro*, potential cardiovascular protection, anticarcinogenic and anti-inflammatory effects [59–61]. These dibenzo- α -pyrones are important constituents in different foods including pomegranates, berries (*i.e.*, strawberry, raspberry, blackberry, and camu-camu), nuts (*i.e.*, walnuts, acorns, and chestnuts), muscadine grapes, oak-aged wines, medicinal plants and tisanes (*i.e.*, geranium and oak leaves). They are not absorbed in the gut and are metabolized *in vivo* by the intestinal bacteria to produce a series of metabolites known as urolithins [62,63]. Some urolithins such as urolithins A (**40**), B (**42**) and C (**43**) as well as isourolithin A (**41**) were previously isolated from plants (Table 2) [4,53]. The structures of the isolated urolithins are shown in Figure 3.

2.4. Dibenzo- α -pyrones from Bacteria

Up to now, only one dibenzo- α -pyrone called murayalactone (**53**) has been isolated from *Streptomyces murayamaensis* [64]. The structure of murayalactone is shown in Figure 5.

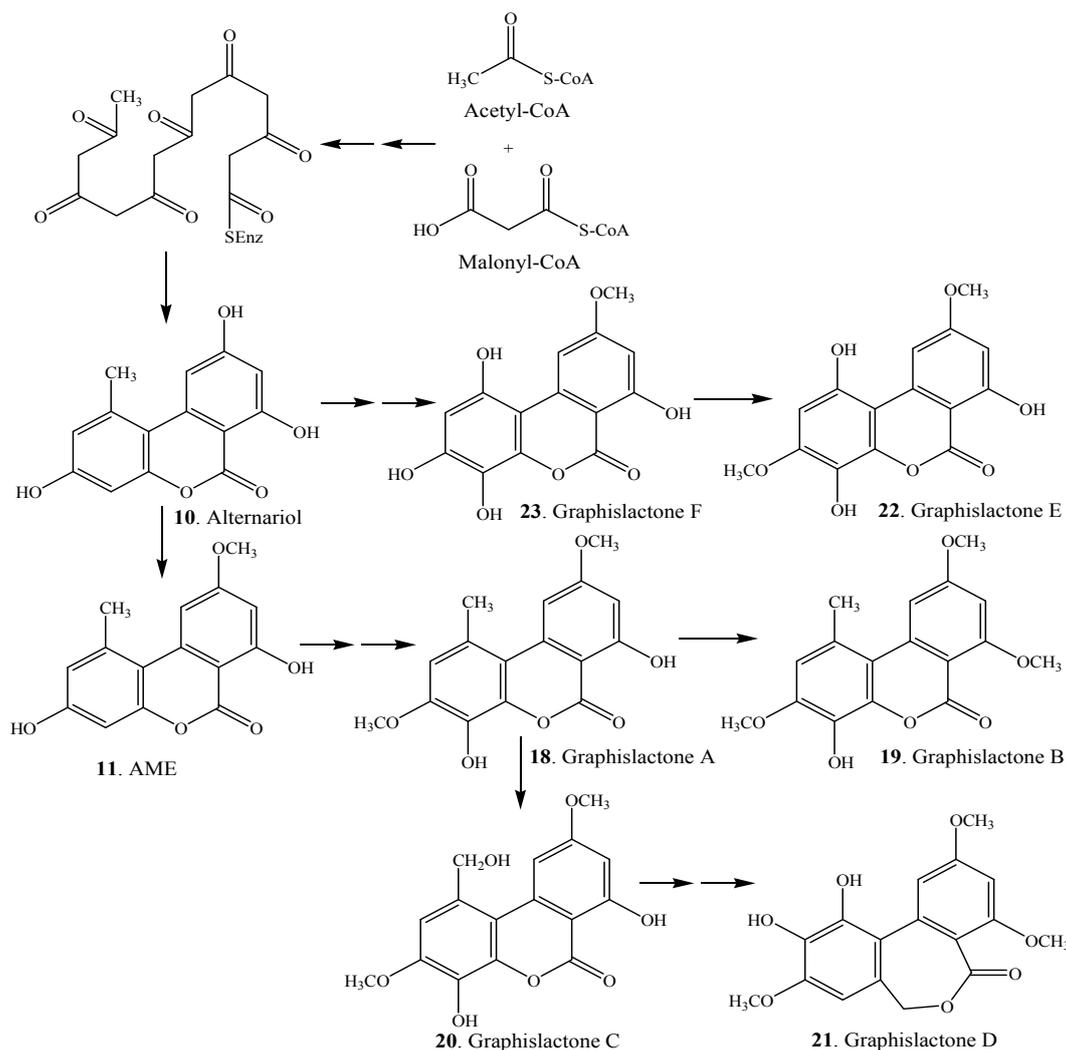
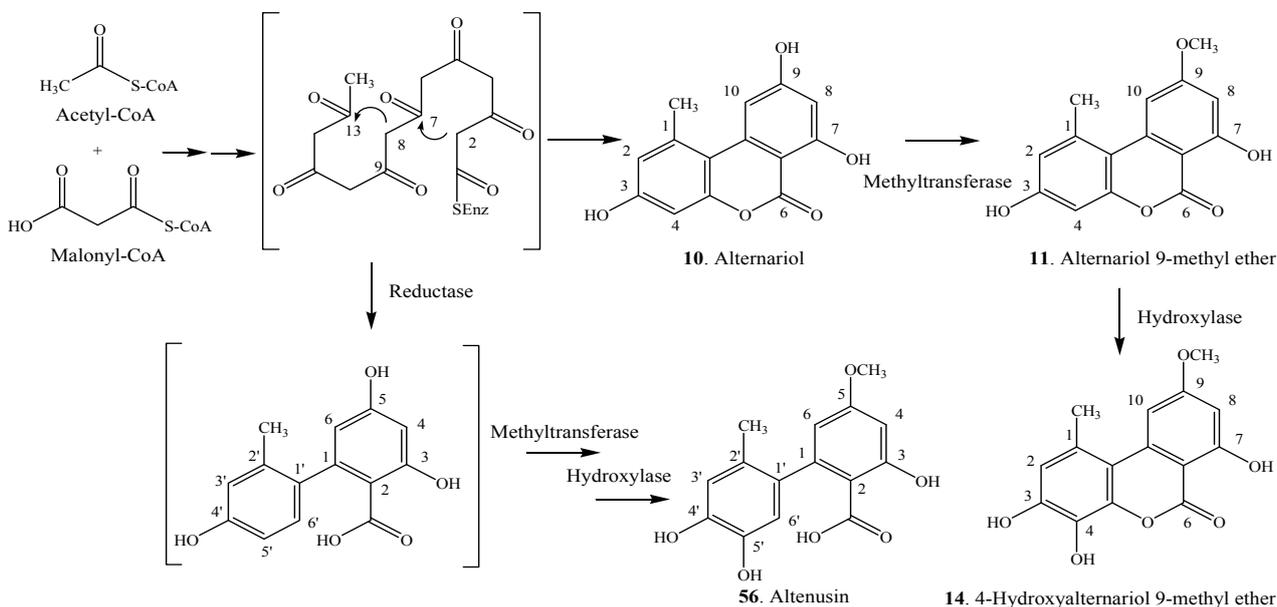
Figure 5. The structure of murayalactone (**53**).**53.** Murayalactone

3. Biosynthesis and Biotransformation

We know very little about the biosynthesis of dibenzo- α -pyrones in living organisms, including their genetics, biochemistry and biosynthetic pathways [2,25,65,66]. In plants, gallic acid (**54**), which is biosynthesized via the shikimate pathway [67], was considered as the precursor of ellagitannins [68]. The ellagitannins would be transformed into ellagic acid (**55**), and then into a series of urolithins (Scheme 1) [6,7,63]. However, in microorganisms, dibenzo- α -pyrones are biosynthesized via the polyketide pathway [3,25]. Polyketide synthase (PKS) is one of the postulated core enzymes in the biosynthesis of 6*H*-dibenzo[*b,d*]pyran-6-ones (*i.e.*, alternariol, AME) in *Alternaria alternata* [66]. In a draft genome sequence of *A. alternata*, 10 putative PKS-encoding genes were identified. The timing of the expression of two PKS genes, *pksJ* and *pksH*, was found to correlate with the production of AOH and AME [66].

Alternariol (**10**) was first thought to be biosynthesized via norlichexanthone [65], which was ruled out later, and it was proven that alternariol (**10**) could be biosynthesized by simple cyclization and aromatization of a polyketide precursor [69]. After administration of [1-¹³C]acetate and [1,2-¹³C]acetate to cultured lichen mycobionts of *Graphis* spp., acetate units were incorporated into the 6*H*-dibenzo[*b,d*]pyran-6-one derivatives including alternariol (**10**), AME (**11**) and graphislactones A-F (**18–23**) [3]. Alternariol (**10**) could suffer oxidative demethylation at C-1, hydroxylation at C-4, and *O*-methylation at C-9 to lead formation of graphislactones E (**22**) and F (**23**). On the other hand, alternariol (**10**) could be transformed to graphislactones A-D (**18–21**) without demethylation via AME (**11**) [3]. The biosynthetic pathways of graphislactones A-F (**18–23**) in the cultured lichen mycobionts of *Graphis* spp. are shown in Scheme 2.

Epigenetic modifiers, including DNA methyltransferase (DNMT) inhibitors (*i.e.*, 5-azacytidine, abbreviated as 5-AC) and histone deacetylase (HDAC) inhibitors (*i.e.*, suberoylanilide hydroxamic acid, abbreviated as SBHA) are useful to induce the expression of otherwise silent biosynthetic genes under standard laboratory conditions [70]. Supplementation of a DNMT inhibitor 5-AC or a HDAC inhibitor SBHA to the medium induced the production of alternariol (**10**), alternariol 9-methyl ether (**11**), 4-hydroxyalternariol 9-methyl ether (**14**) and altenusin (**56**) [25]. The proposed biosynthesis of the aromatic polyketides **10**, **11**, **14** and **56** involves the condensation of seven molecules of malonyl-CoA, followed by aldol-type cyclizations between C-2 and C-7, and C-8 and C-13, and the subsequent

Scheme 2. Biosynthetic pathways of graphislactones in the cultured lichen mycobionts [3].**Scheme 3.** Hypothetical biosynthetic pathways of alternariol (10) and its derivatives (11, 14) in an endophytic fungus from *Datura stramonium* [25].

Urolithins include a family of metabolites of dibenzo- α -pyrone structures with different phenolic hydroxylation patterns. They are produced in different animals after the intake of ellagitannins and ellagic acid (EA) [71,72]. Ellagitannins are hydrolyzed to ellagic acid (**55**) in the acidic environment of the stomach by the action of the intestinal bacteria. The proposed transformation from ellagic acid to urolithins by the intestinal bacteria [6,7,63] is shown in Scheme 1.

4. Biological Activities and Functions

Dibenzo- α -pyrones and their derivatives with diverse chemical properties have been clarified (Figures 1–5, Tables 1 and 2). Some of them act as mycotoxins to humans and animals or as phytotoxins to plants. They have been examined to have a variety of biological activities and functions, which mainly include the cytotoxic, antioxidant, antiallergic, antimicrobial, antinematodal, and acetylcholinesterase inhibitory activities.

4.1. Toxicity on Human and Animals

The association of mycotoxins from *Alternaria* fungi with human and animal health is not a recent phenomenon. *Alternaria* toxins have been linked to a variety of adverse effects (*i.e.*, genotoxic, mutagenic, and carcinogenic) on human and animal health [8]. Altenuene (**1**), alternariol (**10**), and alternariol 9-methyl ether (**11**) were studied for their toxicity to chickens. Addition of these compounds in chicken feed from sublethal to lethal levels progressively reduced feed efficiency, suppressed weight gain and increased internal haemorrhaging [27,73].

There were a few reports about the toxicity of *Alternaria* metabolites on brine shrimp (*Artemia salina* L.) [74,75]. The LC₅₀ values of altenuene (**1**) and alternariol (**10**) were 375 and 100 $\mu\text{g/mL}$, respectively, to brine shrimp larvae by using the disk method of inoculation and an exposure period of 18 h [75]. Altenuene (**1**) and alternariol (**10**) along with alternariol 9-methyl ether (**11**) were also verified to be toxic to brine shrimp [74].

4.2. Cytotoxic Activity

Among *Alternaria* dibenzo- α -pyrones, alternariol (**10**) was the most active metabolite to have cytotoxic activity on L5178Y mouse lymphoma cells [9], as well as to have inhibitory activity on protein kinase and xanthine oxidase [28]. Further investigation showed that alternariol (**10**) was a topoisomerase I and II poison which might contribute to the impairment of DNA integrity in human colon carcinoma cells [73,76]. It induced cell death by activation of the mitochondrial pathway of apoptosis in human colon carcinoma cells [76]. Alternariol (**10**) and its 9-methyl ether (**11**) induced cytochrome P450 1A1 and apoptosis in murine hepatoma cells dependent on the aryl hydrocarbon receptor [77]. Other alternariol derivatives such as alternariol 9-methyl ether (**11**), alternariol 9-*O*-sulfate (**13**), and altenusin (**56**) were also screened to be cytotoxic [9].

Dehydroaltenusin (**17**), isolated from *A. tenuis*, was found to be a specific inhibitor of eukaryotic DNA polymerase α to show its strong cytotoxic activity on tumor cells [45,78]. This compound also exhibited strong inhibitory activity on mammalian DNA polymerase α *in vitro* [79]. It was further

proved to abrogate cell proliferation of the cultured mammalian cells to show its potential as an effective chemotherapeutic agent against tumors [44].

Alternariol 9-methyl ether (**11**), graphis lactone A (**18**), graphis lactone G (**24**), and graphis lactone H (**25**) from the endophytic fungus *Cephalosporium acremonium* IFB-E007 derived from *Trachelospermum jasminoides* showed pronounced activity against SW1116 cell with IC₅₀ values of 14.0, 21.0, 12.0 and 8.5 µg/mL, respectively [35].

Urolithins derived from ellagic acid (**55**) were screened to have cytotoxic and anti-tumor activities. Urolithin A (**40**) inhibited cell growth of human colon cancer cell lines HT29 by inhibiting the canonical wnt signal pathway and interfere with β-catenin/TCF-dependent transcription [80], and inhibited growth of 22Rv1 prostate cancer cells by interfered with the expression of CYP1B1 protein [81]. Urolithin A (**40**), urolithin B (**42**), and 8-*O*-methylurolithin A (**50**) also showed antiproliferative effect on human bladder cancer T24 cells [82].

4.3. Phytotoxicity

The metabolites from fungal pathogens are usually toxic to plants and are called phytotoxins which are divided into host-specific [83,84] and host non-specific toxins [85,86]. Some *Alternaria*-derived dibenzo- α -pyrones were approved as the host-specific phytotoxins including altenuene (**1**), alternariol (**10**), alternariol 9-methyl ether (**11**), alternuisol (**15**), and dehydroaltenuin (**17**) [9,10,37,39,41,45].

4.4. Antioxidant Activity

Urolithin A (**40**), isourolithin A (**41**), and urolithin B (**42**) from the fruits of *Trapa natans* showed antioxidant activity. Among them, isourolithin A (**41**) showed the strongest, and urolithin B (**42**) showed weak antioxidative effect [4]. As ellagic acid and ellagitannins are extremely poorly absorbed in gut, urolithins appear to be responsible for biological activities related to the intake of ellagitannins. Most of urolithins (*i.e.*, urolithins A, C, and D) exhibited antioxidant activity in a cell-based assay [6]. However, there have been contradictory reports on their antioxidant capacity [62,87]. Recently, urolithins were revealed to display both antioxidant and pro-oxidant activities depending on assay system and conditions by using oxygen radical absorbance capacity (ORAC) assay, three cell-based assays, copper-initiated pro-oxidant activity (CIPA) assay, and cyclic voltammetry. Urolithins were screened to be the strong antioxidants in the ORAC assay, but mostly pro-oxidants in cell-based assays [88]. The antioxidant activity of urolithins is very likely mediated exclusively by the hydrogen atom transfer (HAT) mechanism. The hydrogen atom is donated by the phenolic hydroxyl group [88].

4.5. Antiallergic Activity

Urolithin A (**40**), isourolithin A (**41**), and urolithin B (**42**), from the feces of *Trogopterus xanthipes* showed hyaluronidase inhibitory activities with IC₅₀ values of 1.33, 1.07 and 2.33 mM, respectively that indicated their antiallergic activity [11]. TMC-264 (**28**) from the fungus *Phoma* sp. TC 1674 [47] selectively inhibited tyrosine phosphorylation of STAT6, and also inhibited the complex formation of phosphorylated STAT6 and its recognition sequence. Therefore, TMC-264 (**28**) would inhibit IL-4 signaling and would be useful in the treatment of allergic disease [47,89,90].

4.6. Other Bioactivities

Other biological activities of dibenzo- α -pyrones include antimicrobial, antimalarial, antinematodal activities as well as calmodulin-dependent, estrogenic and antiestrogenic, and acetylcholinesterase (AChE) inhibitory activities. Alternariol 9-methyl ether (**11**) from endophytic *Alternaria* spp. exhibited inhibitory activity on the appressorium formation of *Magnaporthe grisea* (*M. oryzae*) with IC₅₀ value of 51.0 $\mu\text{g/mL}$ [34]. Alternariol 9-methyl ether (**11**), botrallin (**16**) and palmariol B (**27**) from endophytic fungus *Hyalodendriella* sp. Ponipodef12 showed moderate antimicrobial activity [12,43].

2,3,4,9,10-Pentahydroxy-6H-dibenzo[*b,d*]pyran-6-one (**37**) from the plants *Chrozophora senegalensis* (Euphorbiaceae) and *Sebastiania chamaelea* (Euphorbiaceae) showed moderate antimalarial activity (IC₅₀ > 10 $\mu\text{g/mL}$) on *Plasmodium falciparum* [56]. Alternariol 9-methyl ether (**11**), botrallin (**16**) and palmariol B (**27**) from endophytic fungus *Hyalodendriella* sp. Ponipodef12 also showed moderate antinematodal inhibitory activity on *Caenorhabditis elegans* [12].

Dehydroaltenusin (**17**) from *Penicillium verrucosum* IAM-13756 inhibited the calmodulin-dependent activity of myosin light chain kinase (MLCK) with IC₅₀ value of 0.69 μM [46].

Both urolithins A (**40**) and B (**42**) from human feces exhibited estrogenic and antiestrogenic activities, which suggested that consumption of ellagitannin-containing foodstuffs such as pomegranate, walnuts, berries, and oak-aged wines may exert some proestrogenic/antiestrogenic effects [91].

Alternariol 9-methyl ether (**11**), botrallin (**16**) and palmariol B (**27**) from endophytic fungus *Hyalodendriella* sp. Ponipodef12 showed moderate AChE inhibitory activity [12]. Botrallin (**16**) from the endophytic fungus *Microsphaeropsis olivacea* was also screened to have AChE inhibitory activity with IC₅₀ value as 6.1 $\mu\text{g/mL}$ [13].

5. Conclusions and Future Perspectives

We have just clarified one part of the dibenzo- α -pyrones from fungi, plants and bacteria. The remaining dibenzo- α -pyrones in bioorganisms need to be further identified. In recent years, more and more dibenzo- α -pyrones have been isolated from plant endophytic fungi. These endophytic fungi could be the rich sources of biologically active compounds that are indispensable for medicinal and agricultural applications [92,93]. In most cases, biological activities, structure-activity relationships, and modes of action of dibenzo- α -pyrones were only primarily investigated.

The potential applications of dibenzo- α -pyrones as antitumor agents, antiallergics, antioxidants, and antimicrobials have attracted considerable interest within the pharmaceutical community. Chemical syntheses have been achieved for a few bioactive dibenzo- α -pyrones such as altenuene (**1**) [94], isoaltenuene (**2**) [94], neoaltenuene (**5**) [95], alternariol (**10**) [96], alternariol 9-methyl ether (**11**) [96], altertenuol (**15**) [97], dehydroaltenusin (**17**) [98], graphisactones A (**18**), C (**20**), D (**21**) and H (**25**) [99], TMC-264 (**28**) [90], lysilactone A (**34**) [5], urolithins A-C (**40**, **42** and **43**) [100], and urolithin M-7 (**48**) [101]. In addition, some dibenzo- α -pyrones are the important precursors of many synthetic drugs [14–18].

With comprehensive understanding of the biosynthetic pathways of some dibenzo- α -pyrones in the next few years, we may be able to effectively not only increase the yields of bioactive dibenzo- α -

pyrones, but also block the biosynthesis of some toxic dibenzo- α -pyrones (*i.e.*, phytotoxins and mycotoxins) [1].

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Author Contributions

Ziling Mao performed bibliographic researches, drafted and corrected manuscript. Weibo Sun, Linyun Fu and Haiyu Luo participated in the discussions and supported manuscript corrections. Daowan Lai reviewed manuscript and helped to revised it. Ligang Zhou conceived the idea, designed the structure of review article, supervised manuscript drafting, and revised manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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