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Review

Secondary Metabolites of Endophytes Associated with the Zingiberaceae Family and Their Pharmacological Activities

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Abstract: Zingiberaceae is commonly known as the ginger family and has been extensively studied in the last decades for its pharmacological purposes. The study of ginger includes microorganisms known as endophytes, which raise interest for the research community because they can produce a wide range of secondary metabolites. This review discusses the secondary metabolites of endophytes from the Zingiberaceae family and their pharmacological activities. We detail the group of secondary metabolites, updated for its absolute structures, source and part origins, and, especially, pharmacological divided properties. Zingiberaceae endophytes have 106 volatile compounds and 52 isolated constituents, including 17 polyketides, five nonribosomal peptides, five aromatic compounds, three alkaloids, and 21 terpene-alkaloids. They have antimicrobial, anticancer, antioxidant, and anti-inflammatory activities. Secondary metabolites from plant endophytes of the Zingiberaceae family have the potential to be therapeutic drugs in the future. Research on endophytic bacteria or fungi has been little performed. Therefore, this study supports a new drug discovery from Zingiberaceae endophytes and compares them for future drug development.

Keywords: Zingiberaceae; endophytes; pharmacological activities; secondary metabolites

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1. Introduction

Zingiberaceae is commonly known as the ginger family. It is a flowering plant of more than 1300 species divided into 52 genera. The plant is distributed throughout tropical Africa, Asia, and America [1–4]. Some plant genera of this family are beneficial for use in medicinal products, dyes, condiments, and spices [5–8]. Over the last three decades, Zingiberaceae has been studied extensively for substantial pharmacological and clinical investigations [9–11]. Interestingly, the phytochemical study of Zingiberaceae continues to explore their endophytes [12,13]. Endophytes are living microorganisms inside internal plant tissue and they are a beneficial symbiont to their host. These microorganisms have emerged as potential pharmacological metabolites producers [14–17].

In the last 16 years, endophytes from Zingiberaceae have been reported as producing several metabolites. There are volatile compounds, polyketides, peptides, aromatics, alkaloids, and hybrid terpene alkaloids, and they also have antimicrobial, anticancer, antioxidant, and anti-inflammatory properties [18–27].

The study of Zingiberaceae endophytes so far includes (1) species identification of endophytes microorganisms using molecular and genomic tools, (2) pharmacological potential screening, and (3) compound isolation of the natural product chemistry field area. A comprehensive review of these studies has not been conducted.

For this reason, we discuss the secondary metabolites of Zingiberaceae-associated endophytes with special emphasis on pharmacological purposes. This review highlights

the chemical content of different strains classified by their biosynthesis chemical origins and their same activities. Furthermore, we add data on their parts, origin, function, biological roles, and absolute structure updates. All databases were concluded, including isolated secondary metabolites, species name, their host, absolute structures, volatile compounds, and their pharmacological activity from Scopus and SciFinder search engines. The keywords are "endophytes", "Zingiberaceae genus member", and "name of compound" collected from May 1975 to August 2022 [18–56]. This review might be helpful in future drug development, especially from Zingiberaceae endophytes.

2. Botany

Zingiberaceae is a large family, usually classified into four subfamilies: Hedychieae (leaves parallel to the rhizome, staminodes laterally petaloid, not fused with the labellum); Zingibereae (out of the anthers and covered by elongated anthers); Alpinieae (leaves perpendicular to the rhizome, lateral staminode absent or small and fused to the labellum); and Globbeae (elongated and curved filaments, l-locular gynoecium) [56–59]. Members of this family have distribution in tropical Asia, especially Indo-Malaysia. This family is an economic asset, an essential source of spice plants, such as *Curcuma domestica* (turmeric), *Elettaria cardamomum* (cardamom), and *Zingiber officinale* (ginger). Some species are grown as cultivated ornamental plants, for example, Alpinia and Hedychium [60–62].

Zingiberaceae grows from zero to more than 2000 m above sea level. It generally grows in areas with high rainfall and in humid places. Several other species are found in secondary forests, open forests, riverbanks, and swamps, and sometimes grow in open areas with full sun. Some species of Etlingera grow in secondary forests or open forest sites [63–66].

Zingiberaceae consists of several parts: rhizome, leaves, flowers, and fruit. These parts are used for several purposes by local communities. For example, ginger has been widely used over time because it has significant economic potential, such as traditional medicines for herbs, spices, cooking spices, hair toners, beverage ingredients, vegetables, and food seasonings. Others, such as *Etlingera elatior*, is used to make chili sauce or add seasoning to grilled rice. More than 60 species of Zingiberaceae are used from both cultivated and wild species from the forest [66–70].

3. Natural Product Diversity

Based on literature collected from May 1975 to August 2022, a total of 52 phytochemicals have been isolated from endophytic microorganisms living inside the Zingiberaceae family, including 17 polyketides, five nonribosomal peptides, five aromatics, three alkaloids, and 21 terpene-alkaloids. The isolated and identified phytochemicals are summarized in Table 1. Furthermore, the endophytic microorganism isolated from the Zingiberaceae family is rich in essential oil and volatile constituent. One hundred six volatile compounds, including 42% terpenes, 20% aromatic compounds, 12% organic acids, 5% esters, and 21 others, have been detected using gas chromatography–mass spectroscopy analysis. The volatile constituents are summarized in Table 2.

Table 1. Compounds isolated from Zingiberaceae endophytes.

Type	Name of Compound	Strain	Host Origin	Part of Host Origin	Reference
Polyketide	5,7-Dimethoxy-4-p-methoxylphenylcoumarin (1)	*Streptomyces aureofaciens* CMUAc130	*Z. officinale* Rosc.	Root	[18]
	5,7-Dimethoxy-4-phenylcoumarin (2)	*S. aureofaciens* CMUAc130	*Z. officinale* Rosc.	Root	[18]
	Umbelliferon (3)	*Streptomyces* sp. Tc052	*Alpinia galanga*	Root	[19]
	Chicorii (4)	*Streptomyces* sp. Tc052	*A. galanga*	Root	[19]
	Kaempferol (5)	*Streptomyces* sp. Tc052	*A. galanga*	Root	[19]
	Isoscutellarin (6)	*Streptomyces* sp. Tc052	*A. galanga*	Root	[19]
	7-methoxy-3, 3′,4′,6-tetrahydroxyflavone (7)	*Streptomyces* sp. BT01	*Boesenbergia rotunda* (L.) Mansf.	Root	[28]
	2′,7-dihydroxy-4′,5′-dimethoxyisoflavone (8)	*Streptomyces* sp. BT01	*B. rotunda* (L.) Mansf.	Root	[28]
	3,3′,4′,7-tetrahydroxyflavone (fisetin) (9)	*Streptomyces* sp. BT01	*B. rotunda* (L.) Mansf.	Root	[28]
	4′,5,7-trihydroxyflavanone (naringenin) (10)	*Streptomyces* sp. BT01	*B. rotunda* (L.) Mansf.	Root	[28]
	3′-hydroxydaidzein (11)	*Streptomyces* sp. BT01	*B. rotunda* (L.) Mansf.	Root	[28]
	xenognosin B (12)	*Streptomyces* sp. BT01	*B. rotunda* (L.) Mansf.	Root	[28]
	arugosin J (13)	*Xylaria* sp.	*Curcuma xanthorrhiza*	Leaves	[24]
	xylarugosin (14)	*Xylaria* sp.	*C. xanthorrhiza*	Leaves	[24]
	6-*n*-pentyl-2H-pyran-2-one (15)	*Trichoderma erinaceum* ST-KKU2	*Z. officinale*	Root	[23]
	1-hydroxy-2-methyl-6-methoxyanthraquinone (16)	*Streptomyces* sp. W08	*Amomum krervanh Pierre*	Root	[22]
	6-methoxy-2-methylquinizarin (17)	*Streptomyces* sp. W08	*A. krervanh Pierre*	Root	[22]
Nonribosomal Peptides	actinomycin D (18)	*Streptomyces* sp. Tc022	*A. galanga*	Root	[19]
	brevianamide F (19)	*Streptomyces omiyaensis* NBRC 11449T	*Zingiber spectabile*	Root	[25]
	2,2-dichloro-*N*-[(1r, 2r)-2-hydroxy-1-(hydroxymethyl)-2-(4-nitrophenyl) ethyl]-acetamide (20)	*S. omiyaensis* NBRC 11449T	*Z. spectabile*	Root	[25]
	pretrichodermamide G (21)	*Trichoderma harzianum*	*Z. officinale*	Leaves	[26]

Table 1. *Cont.*

Type	Name of Compound	Strain	Host Origin	Part of Host Origin	Reference
	pretrichodermamide A (22)	*T. harzianum*	*Z. officinale*	Leaves	[26]
Aromatic Compound	Vanillin (23)	*Streptomyces aureofaciens* CMUAc130	*Z. officinale Rosc.*	Root	[18]
	3-methoxy-4-hydroxytoluene (24)	*S. aureofaciens* CMUAc130	*Z. officinale Rosc.*	Root	[18]
	Resacetophenone (25)	*Xylaria* sp.	*C. xanthorrhiza*	Leaves	[24]
	3′-hydroxy-5-methoxy-3,4-methylenedioxybiphenyl (26)	*Streptomyces* sp. BO-07	*B. rotunda* (L.) Mansf A	Root	[21]
	3′-hydroxy-5,5′-dimethoxy-3,4-methylenedioxybiphenyl (27)	*Streptomyces* sp. BO-07	*B. rotunda* (L.) Mansf A	Root	[21]
Alkaloid	3-methylcarbazole (28)	*Streptomyces* sp. LJK109	*A. galanga* (L.) Willd.	Root	[29]
	1-methoxy-3-methylcarbazole (29)	*Streptomyces* sp. LJK109	*A. galanga* (L.) Willd.	Root	[29]
	Indole acetic acid (30)	*Bacillus subtilis* CL1, *Bacillus* sp. CL3, *Burkholderia thailandensis* CL4, *Agrobacterium tumefaciens* CL5, *Klebsiella* sp. CL6, *Bacillus cereus* CL7, *Pseudomonas putida* CL9, *Pseudomonas fluorescens* CLI2 and *Azotobacter chroococcum* CL13	*Curcuma longa* L.	Rhizome	[37]
		Paenibacillus favisporus Paenibacillus sp.	*C. longa* L.	Rhizome	[38]
		Pseudomonas sp.	*Z. officinale*	Rhizome	[39]
		Pseudomonas, *Pantoea agglomerans*, *Aeromonas*, *Serratia*, *Enterobacter asburiae*, and *Rhizobium*.	*Z. officinale* Roscoe	Root, stems, tubers, and Leaves	[40]

Table 1. *Cont.*

Type	Name of Compound	Strain	Host Origin	Part of Host Origin	Reference
		Ochrobactrum, *Agrobacterium*, *Acinetobacter*, *Stenotrophomonas*, *Serratia and Bacillus*	*Z. officinale* Roscoe		[41]
		Bacillus cereus (ECL1), *Bacillus thuringiensis (ECL2)*, *Bacillus* sp. *(ECL3)*, *Bacillus pumilis (ECL4)*, *Pseudomonas putida (ECL5)*, *and Clavibacter michiganensis (ECL6)*	*C. longa* L.		[37]
		T. harzianum *T. asperellum* *T. atroviride*	*C. longa* L.		[31]
		Aspergillus flavus	*Alpinia* sp.		[42]
Indole Diterpenoids	Shearilicine (31)	*Penicillium* sp. *(strain ZO-R1-1)*	*Z. officinale*	Root	[23]
	Paspalinine-13-ene (32)	*Penicillium* sp. *(strain ZO-R1-1)*	*Z. officinale*	Root	[23]
	7-Hydroxypaxilline-13-ene (33)	*Penicillium* sp. *(strain ZO-R1-1)*	*Z. officinale*	Root	[23]
	7-Methoxypaxilline (34)	*Penicillium* sp. *(strain ZO-R1-1)*	*Z. officinale*	Root	[23]
	Shearinine N (35)	*Penicillium* sp. *(strain ZO-R1-1)*	*Z. officinale*	Root	[23]
	Shearinine O (36)	*Penicillium* sp. *(strain ZO-R1-1)*	*Z. officinale*	Root	[23]
	Shearinine P (37)	*Penicillium* sp. *(strain ZO-R1-1)*	*Z. officinale*	Root	[23]
	7-Methoxyshearinine P (38)	*Penicillium* sp. *(strain ZO-R1-1)*	*Z. officinale*	Root	[23]
	Shearinine Q (39)	*Penicillium* sp. *(strain ZO-R1-1)*	*Z. officinale*	Root	[23]
	Emindole SB (40)	*Penicillium* sp. *(strain ZO-R1-1)*	*Z. officinale*	Root	[23]
	21-isopentenylpaxilline (41)	*Penicillium* sp. *(strain ZO-R1-1)*	*Z. officinale*	Root	[23]
	Paxilline (42)	*Penicillium* sp. *(strain ZO-R1-1)*	*Z. officinale*	Root	[23]
	Dehydroxypaxilline (43)	*Penicillium* sp. *(strain ZO-R1-1)*	*Z. officinale*	Root	[23]
	7-hydroxy-13-dehydroxypaxilline (44)	*Penicillium* sp. *(strain ZO-R1-1)*	*Z. officinale*	Root	[23]

Table 1. *Cont.*

Type	Name of Compound	Strain	Host Origin	Part of Host Origin	Reference
	Paspaline (45)	*Penicillium* sp. *(strain ZO-R1-1)*	*Z. officinale*	Root	[23]
	shearinine F (46)	*Penicillium* sp. *(strain ZO-R1-1)*	*Z. officinale*	Root	[23]
	Paspalicine (47)	*Penicillium* sp. *(strain ZO-R1-1)*	*Z. officinale*	Root	[23]
	Paspalinine (48)	*Penicillium* sp. *(strain ZO-R1-1)*	*Z. officinale*	Root	[23]
	paspalitrem A (49)	*Penicillium* sp. *(strain ZO-R1-1)*	*Z. officinale*	Root	[23]
	6,7-dehydropaxilline (50)	*Penicillium* sp. *(strain ZO-R1-1)*	*Z. officinale*	Root	[23]
	10β-hydroxy-13-desoxypaxilline (51)	*Penicillium* sp. *(strain ZO-R1-1)*	*Z. officinale*	Root	[23]
	Pyrapaxilline (52)	*Penicillium* sp. *(strain ZO-R1-1)*	*Z. officinale*	Root	[23]

Table 2. Volatile constituents from Zingiberaceae endophytes.

No.	Compound	Molecular Formula	Fungal Species	Host	Reference
Terpenoids					
1.	α fencho-camphorone	$C_9H_{14}O$	*Arthrinium* sp. MFLUCC16-1053	*Zingiber cassumunar*	[30]
2.	α-muurolol	$C_{15}H_{26}O$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
3.	α-sinensal	$C_{15}H_{22}O$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
4.	β-bisabolenol	$C_{15}H_{24}O$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
5.	β-chenopodiol	$C_{15}H_{26}O_2$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
6.	β-cyclocitral	$C_{10}H_{16}O$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
7.	β-isocomene	$C_{15}H_{24}$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
8.	γ-curcumene	$C_{15}H_{24}$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
9.	3-p-menthone	$C_{10}H_{18}O$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
10.	11,12-dihydroxy-valencene	$C_{18}H_{30}O$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
11.	13-manool oxide	$C_{20}H_{34}O$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
12.	2*Z*,6*E*-farnesol	$C_{15}H_{26}O$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
13.	3*E*-cembrene A	$C_{20}H_{32}$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
14.	5*E*,9*E*-farnesyl acetone	$C_{18}H_{30}O$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
15.	7-α-hydroxy manool	$C_{20}H_{34}O_2$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
16.	7-epi-α-selinene	$C_{15}H_{24}$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]

Table 2. *Cont.*

No.	Compound	Molecular Formula	Fungal Species	Host	Reference
17.	abienol	$C_{20}H_{34}O$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
18.	allocedrol	$C_{15}H_{26}O$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
19.	amorpha-4,9-dien-2-ol	$C_{15}H_{24}O$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
20.	bicyclogermacrene	$C_{15}H_{24}$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
21.	Bornyl acetate	$C_{12}H_{20}O_2$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
22.	caryophyllenyl alcohol	$C_{15}H_{26}O$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
23.	cembrene	$C_{20}H_{32}$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
24.	cis-cadin-4-en-7-ol	$C_{15}H_{26}O$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
25.	cis-vertocitral C	$C_9H_{14}O$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
26.	curzerenone	$C_{15}H_{18}O_2$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
27.	Dehydro-aromadendrene	$C_{15}H_{22}$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
28.	*E*,*E*-geranyl linalool	$C_{20}H_{34}O$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
29.	*E*-iso-γ-bisabolene	$C_{15}H_{24}$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
30.	*E*-phytol acatate	$C_{22}H_{42}O$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
31.	epi-α-bisabolol acetate	$C_{17}H_{28}O_2$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
32.	E-β-santalol acetate	$C_{17}H_{26}O$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
33.	himachalene epoxide	$C_{15}H_{24}O$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
34.	laurenan-2-one	$C_{20}H_{32}O$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
35.	Linalool acetate	$C_{12}H_{20}O_2$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
36.	Linalool isobutanoate	$C_{14}H_{24}O_2$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
37.	longiborneol	$C_{15}H_{26}O$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
38.	occidol	$C_{15}H_{22}O$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
39.	ophiobolin A	$C_{25}H_{36}O_4$	*Trichoderma harzianum* TharDOB-31	*C. longa* L.	[31]
40.	oplopanone	$C_{15}H_{26}O_2$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
41.	phyllocladanol	$C_{20}H_{34}O$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
42.	Punctaporin B	$C_{15}H_{24}O_3$	*T. harzianum* TharDOB-31	*C. longa* L.	[31]
43.	Sapindoside A	$C_{41}H_{66}O_{12}$	*T. harzianum* TharDOB-31	*C. longa* L.	[31]
44.	Sclareol	$C_{20}H_{36}O_2$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
45.	*Z*,*E*-geranyl linalool	$C_{20}H_{34}O$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
46.	*Z*,*Z*-farnesyl acetone	$C_{18}H_{30}O$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
Steroids					
47.	Calicoferol D	$C_{28}H_{42}O_2$	*T. harzianum* TharDOB-31	*C. longa* L.	[31]
48.	Ergosta-4, 6, 8(14), 22-tetraen-3-one (ergone)	$C_{28}H_{40}O$	GF6 (*Gliocladiopsis*)	*Z. officinale*	[12]

Table 2. *Cont.*

No.	Compound	Molecular Formula	Fungal Species	Host	Reference
Alkaloids					
49.	Diethanolamine	$C_4H_{11}NO_2$	*T. harzianum* TharDOB-31	*C. longa* L.	[31]
50.	Harmalol	$C_{12}H_{12}N_2O$	*T. harzianum* TharDOB-31	*C. longa* L.	[31]
51.	*N*-Aminopyrrolidine	$C_4H_{10}N_2$	GFM12 (Uncultured fungus clone/*Cerrena* sp.)	*Z. officinale*	[12]
Aromatics					
52.	2-Amino-3-methoxy-benzoic acid *Antifungal*	$C_8H_9NO_3$	*T. harzianum* TharDOB-31	*C. longa* L.	[31]
53.	2-Isopropyl-3-Methoxycinnamic acid	$C_{13}H_{16}O_3$	*T. harzianum* TharDOB-31	*C. longa* L.	[31]
54.	3-Nonaprenyl-4-hydroxybenzoic acid	$C_{52}H_{78}O_3$	*T. harzianum* TharDOB-31	*C. longa* L.	[31]
55.	4-hydroxy-stilbene	$C_{14}H_{12}O$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
56.	Benzene acetaldehyde	C_8H_8O	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
57.	Benzenacetic acid	C_6H_8O	GFV1 (*Fungal* sp.)	*Z. officinale*	[12]
58.	Benzeneethanol, 4-hydroxy-(tyrosol)	$C_8H_{10}O$	GFV1 (*Fungal* sp.) GFM12 (Uncultured fungus clone/*Cerrena* sp.)	*Z. officinale*	[12]
59.	Benzenemethanol, 2-(2-aminopropoxy)-3-methyl-	$C_{11}H_{16}O_3$	*T. harzianum* TharDOB-31	*C. longa* L.	[31]
60.	*E*-cinnamyl alcohol	$C_9H_{10}O$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
61.	*E*-isoeugenyl benzyl ether	$C_{17}H_{18}O_2$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
62.	*E*-methyl isoprenyl cinnamate	$C_{20}H_{32}$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
63.	Ellagic acid	$C_{14}H_6O_8$	*A. flavus*	*Kaempferia rotunda*	[33]
64.	Ferulic acid	$C_{10}H_{10}O_4$	*A. flavus*	*K. rotunda*	[33]
65.	Hydrocinnamyl acetate	$C_{11}H_{14}O_2$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
66.	Isoamyl benzoate	$C_{12}H_{16}O_2$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
67.	*p*-Coumaric acid	$C_9H_8O_3$	*A. flavus*	*K. rotunda*	[33]
68.	phenethyl cinnamate	$C_{17}H_{16}O_2$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
69.	Syringic acid	$C_9H_{10}O_5$	*A. flavus*	*K. rotunda*	[33]
70.	Vanillic acid	$C_8H_8O_4$	*T. harzianum* TharDOB-31	*C. longa* L.	[31]
71.	*Z*-cinnamyl acetate	$C_{11}H_{12}O_2$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
72.	*Z*-isoeugenyl phenyl acetate	$C_{18}H_{18}O_3$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
73.	*Z*-methyl isoprenyl cinnamate	$C_{20}H_{32}$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
Flavonoids					
74.	Kaempferol	$C_{15}H_{10}O_6$	*A. flavus*	*K. rotunda*	[33]
75.	Myricetin	$C_{15}H_{10}O_8$	*A. flavus*	*K. rotunda*	[33]
Ketones					
76.	Bicyclo[3.2.0]heptan-2-one, 6-hydroxy-5-methyl-6-vinyl	$C_{10}H_{14}O_2$	*B. specifera*	*Zingiber nimmonii* (J. Graham) Dalzell	[32]

Table 2. *Cont.*

No.	Compound	Molecular Formula	Fungal Species	Host	Reference
77.	trans-methyl dihydrojasmonate	$C_{13}H_{22}O_3$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
Lactone					
78.	Dehydromevalonic lactone	C_6H_8O	GFV1 (*Fungal* sp.)	*Z. officinale*	[12]
Quinones					
79.	1,4-Naphthoquinone, 6-acetyl-2,5-dihydroxy	$C_{12}H_8O_5$	*B. specifera*	*Z. nimmonii* (J. Graham) Dalzell	[32]
80.	catalpalactone	$C_{15}H_{14}O_4$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
81.	catalponone	$C_{15}H_{16}O_2$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
Anthraquinone					
82.	Danthron (1,8-dihydroxyanthraquinone)	$C_{14}H_8O_4$	*Paraconiotyrium* sp.	*Z. officinale* Rosc.	[34]
Macrolides					
83.	Dirithromycin *Antimicrobial*	$C_{42}H_{78}N_2O_{14}$	*T. harzianum* TharDOB-31	*C. longa* L.	[31]
Sugars					
84.	Acarbose	$C_{24}H_{40}O_{14}$	*T. harzianum* TharDOB-31	*C. longa* L.	[31]
85.	Topiramate	$C_{12}H_{21}NO_8S$	*T. harzianum* TharDOB-31	*C. longa* L.	[31]
Esters					
86.	(*Z*)-4-Hexenoic acid, 2-acetyl-2-methyl-, ethyl ester	$C_{11}H_{18}O_3$	*B. specifera*	*Z. nimmonii* (J. Graham) Dalzell	[32]
87.	Adipic acid divinyl ester	$C_{10}H_{14}O_4$	*B. specifera*	*Z. nimmonii* (J. Graham) Dalzell	[32]
88.	Butanoic acid, 2-acetyl-3-methyl-, methyl ester	$C_8H_{14}O$	*B. specifera*	*Z. nimmonii* (J. Graham) Dalzell	[32]
89.	Citronellyl formate	$C_{11}H_{20}O_2$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
90.	Decanedioic acid, 3,7-dimethyl-,dimethyl ester	$C_{12}H_{22}O_4$	*B. specifera*	*Z. nimmonii* (J. Graham) Dalzell	[32]
91.	Dihydro citronellol acetate	$C_{12}H_{22}O_3$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
92.	ethyl octadecanoate	$C_{20}H_{40}O_2$	*Arthrinium* sp. MFLUCC16-1053	*Z. cassumunar*	[30]
Organic Acids					
93.	2-Methyl-2*E*-hexenoic acid	$C_7H_{12}O_2$	*T. harzianum* TharDOB-31	*C. longa* L.	[31]
94.	2-Oxo-3-methylvaleric acid	$C_6H_{10}O_3$	*T. harzianum* TharDOB-31	*C. longa* L.	[31]
95.	2,3-Dihydroxy stearic acid	$C_{18}H_{36}O_4$	*T. harzianum* TharDOB-31	*C. longa* L.	[31]
96.	3-Hydroxy-tridecanoic acid	$C_{13}H_{26}O_3$	*T. harzianum* TharDOB-31	*C. longa* L.	[31]
97.	3-Methyl-tetradecanedioic acid	$C_{15}H_{28}O_4$	*T. harzianum* TharDOB-31	*C. longa* L.	[31]

Table 2. *Cont.*

No.	Compound	Molecular Formula	Fungal Species	Host	Reference
98.	9,12-Octadecadienoic acid (*Z*,*Z*)-, methyl ester (methyl linoleate)	$C_{16}H_{32}O_2$	GFV1 (*Fungal* sp.)	*Z. officinale*	[12]
99.	9,12-Octadecadienoic acid (*Z*,*Z*) (linoleic acid)	$C_{18}H_{32}O$	GFV1 (*Fungal* sp.), GFM12 (*Pseudolagarobasidium* sp.), GFM11 (Uncultured fungus clone/*Cerrena* sp.)	*Z. officinale*	[12]
100.	9*R*-hydroxy-10*E*-octadecenoic acid	$C_{18}H_{34}O_3$	*T. harzianum* TharDOB-31	*C. longa* L.	[31]
101.	12-Hydroxy-10-octadecynoic acid	$C_{18}H_{32}O_3$	*T. harzianum* TharDOB-31	*C. longa* L.	[31]
102.	Hexadecanoic acid (palmitic acid)	$C_{16}H_{32}O_2$	GFV1 (*Fungal* sp.), GFM10 (Uncultured fungus clone)	*Z. officinale*	[12]
103.	*n*-Hexadecanoic acid	$C_{16}H_{32}O_2$	GFV1 (*Fungal* sp.), GFM12 (Uncultured fungus clone/*Cerrena* sp.), GFM11 (*Pseudolagarobasidium* sp.), GFA1 (*Trichothecium* sp.), GFA2 (Uncultured fungus clone), GFM10 (Uncultured fungus clone)	*Z. officinale*	[12]
104.	Oleic acid	$C_{18}H_{34}O_2$	GFV1 (*Fungal* sp.), GFM12 (Uncultured fungus clone/*Cerrena* sp.)	*Z. officinale*	[12]
105.	palmitic acid methyl ester	$C_{17}H_{34}O_2$	GFV1 (*Fungal* sp.), GFM10 (Uncultured fungus clone)	*Z. officinale*	[12]
106.	Tetradecanoic acid (myristic acid)	$C_{14}H_{28}O_2$	GFV1 (*Fungal* sp.)	*Z. officinale*	[12]

3.1. Volatile Constituents

Volatile compounds are often used in many pharmaceuticals and for other products such as soaps, cosmetics, toiletry products, and perfumes [71–76]. Volatile oils are extracted from some plant organs, including flowers, bark, leaves, roots, seeds, and others [77–80]. Interestingly, a microorganism that lives inside a plant, known as an endophyte, also produces volatile compounds [81,82].

Some reported Zingiberaceae endophytes produce volatile constituents, including terpene, steroid, alkaloid, aromatic, flavonoid, and others. There are *Arthrinium* sp. from *Z. cassumunar*, *T. harzianum* from *C. longa*, *B. specifera* from *Z. nimmonii*, *A. flavus* from *K. rotunda*, etc. [12,30–34]. All the reported volatile compounds from the Zingiberaceae endophyte are summarized in Table 2.

Pharmacological activities of some endophyte genera from *Z. officinale* show antibacterial activities against *S. aureus B. subtilis S. typhimurium* identified as *Fusarium oxysporum* and *Fungal* sp., GFV1. Some major compounds from fungal crude extract using GC-MS analysis includes tyrosol, benzene acetic acid, ergone, dehydromevalonic lactone, *N*-aminopyrrolidine, and many bioactive fatty acids and their derivatives, which include linoleic acid, oleic acid, myristic acid, hexadecenoic acid, palmitic acid methyl ester, and methyl linoleate [12].

Anisha and her co-workers [34] performed research on endophyte genera from *Z. officinale* and found danthron, an anthraquinone derivate from *Paraconiothyrium* sp., which has broad-spectrum antimicrobial activity. The PCR analysis of this endophyte showed the existence of a non-reducing polyketide synthase gene and was responsible for synthesizing anthraquinone.

The ethyl extract from *Aspergillus terreus* and *B. specifera* has shown antibacterial activity against six pathogenic bacterial strains viz., *B. subtilis* (MTCC 121), *Staphylococcus aureus* (MTCC 7443), *Pseudomonas aeruginosa* (MTCC 7093), *Escherichia coli* (MTCC 729), *Enterobacter aerogenes* (MTCC 111), and *Klebsiella pneumoniae* (MTCC 661), with minimum inhibitory concentrations (MIC) of 0.04–0.14 mg/mL. Seven major compounds with antibacterial activity were detected with GC–MS: (1) bicyclo[3.2.0]heptan-2-one, 6-hydroxy-5-methyl-6-vinyl; (2) adipic acid divinyl ester; (3) 1,4-naphthoquinone, 6-acetyl-2,5-dihydroxy; (4) decanedioic acid, 3,7-dimethyl ester; (5) (*Z*)-4-hexenoic acid 2-acetyl- 2-methyl-ethyl ester, and (6) butanoic acid 2-acetyl-3-methyl-methyl ester. These compounds are volatile esters and phenolic and adipic acid [32].

The *Arthrinium* sp. MFLUCC16-1053, an endophyte from *Z. cassumunar*, has shown antibacterial activity against *S. aureus* and *E. coli* with MIC 31.25 and 7.81 µg/mL, respectively. This fungus also has antioxidant activity with DPPH, scavenging at an IC_{50} value of 28.47 µg/mL. The major volatile compound was tested using gas chromatography–mass spectrometry and analysis revealed β-cyclocitral, 3*E*-cembrene A, laurenan-2-one, sclareol, 2*Z*,6*E*-farnesol, cembrene, β-isocomene, and γ-curcumene [30]. The volatile constituent from the Zingiberaceae endophytes has shown potential uses as an antibacterial and antioxidant. This information can be helpful for further development in the future in the field of drug discovery.

3.2. Polyketides

A total of 17 polyketides have been isolated from endophytic microorganisms living inside the Zingiberaceae plant. Polyketides are a large family of natural products that are known to exhibit a high degree of structural diversity with fascinating activities. Plants, bacteria, and fungi can produce polyketides through polyketide synthases enzymes [83–86]. Polyketides of fungal origin have diverse structures, ranging from antibiotics to toxins [87], which are widely used in pharmacological aspects. Taechowisan et al. [18] isolated two coumarins from the ethyl acetate extract of *Streptomyces aureofaciens* living inside the root tissue of *Z. officinale*, namely 5,7-Dimethoxy-4-p-methoxylphenylcoumarin (**1**) and 5,7-Dimethoxy-4-phenylcoumarin (**2**). Three years later, Taechowisan et al. [19] isolated another two coumarin, umbelliferone (**3**) and chicorii (**4**), together with two flavonoids,

kaempferol (**5**) and isoscutellarin (**6**), from endophytic *Streptomyces* sp. Tc052 on the roots of *A. galanga*. Afterward, Taechowisan et al. [28] isolated two new flavonoids, 7-methoxy-3, 3′,4′,6-tetrahydroxyflavone (**7**) and 2′,7-dihydroxy-4′,5′-dimethoxyisoflavone (**8**) along with four known flavonoids, fisetin (**9**), naringenin (**10**), 3′-hydroxydaidzein (**11**), and xenognosin B (**12**) from endophytic *Streptomyces* sp. BT01 living inside the root tissue of *B. rotunda* (L.). These new compound structures were characterized using infrared, mass spectra, NMR spectroscopic data, and a polarimeter. In addition, the absolute configuration of **10** has been determined using VCD and DFT calculations [35]. Flavonoids were mentioned to prevent injury caused by free radicals and direct scavenging of free radicals [88].

Hammerschidt et al. [24] isolated two new polyketides from the endophytic fungus *Xylaria* sp. (healthy leaves of *C. xanthorrhiza*), that are rugosin J (**13**) and xylarugosin (**14**). These two new compounds were characterized using NMR data and mass spectral analysis, and the ECD spectrum confirmed the absolute structures. Five years later, Suebrasri and his co-workers [23] isolated 6-n-pentyl-2H-pyran-2-one **(15)** for the first time from *Trichoderma erinaceum* ST-KKU2 living inside *Z. officinale*. More recently, Taechowisan et al. [22] isolated 1-hydroxy-2-methyl-6-methoxyanthraquinone (**16**) and 6-methoxy-2-methylquinizarin (**17**) from endophytic *Streptomyces* sp. W08 from the pseudostem tissue of *Amomum krevanh*. The chemical structures of polyketides isolated from the endophytic microorganism of the Zingiberaceae family are shown in Figure 1.

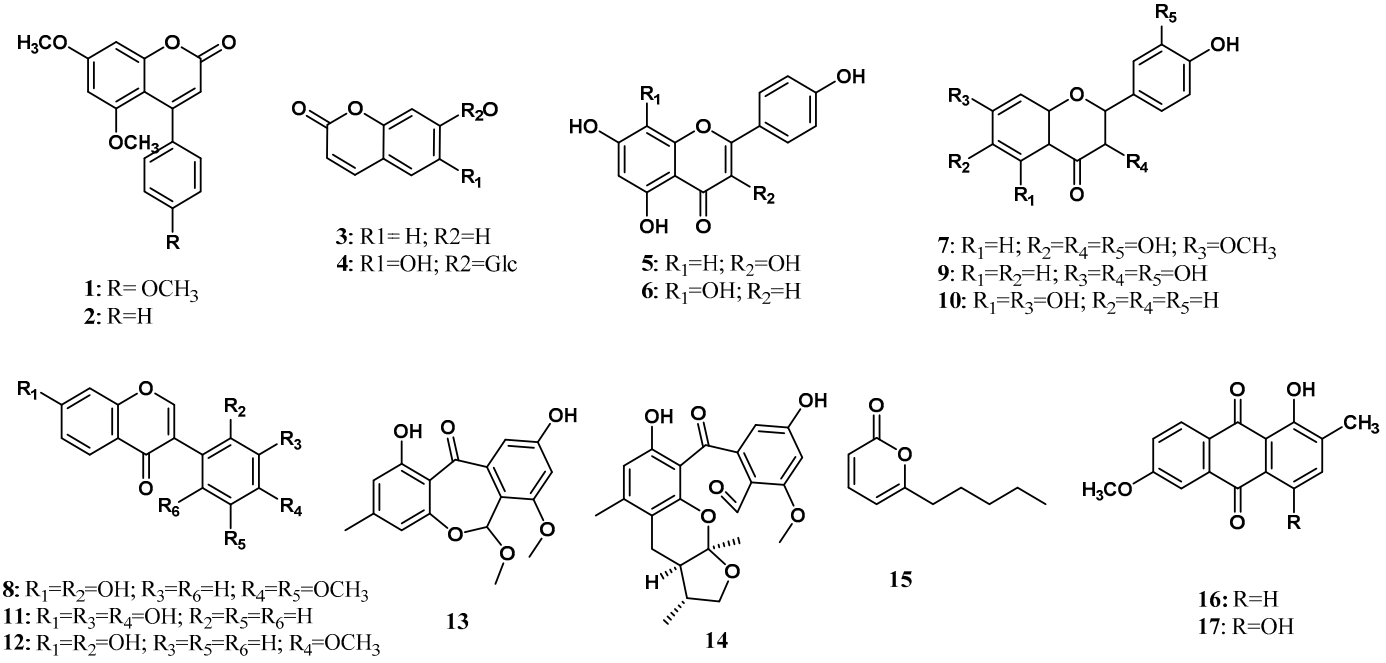

Figure 1. Polyketides from Zingiberaceae endophytes.

3.3. Nonribosomal Peptides

Ribosomes are molecular tools that translate mRNA into protein. the independent ribosomal tools of amide bond formation are called nonribosomal peptide synthesis [87,89–91]. The nonribosomal peptide consists of amino acid proteinogenic or non-proteinogenic linked with a peptide bond [92]. Each domain of NRPs provides a specific function, such as recognizing amino acids, activation with amino acids, bonding in between, and releasing the peptide [93]. The nonribosomal peptide was first isolated from the endophytic microorganism Zingiberaceae family by Taechowisan et al. [19]. Actinomycin D (**18**) was isolated from *Streptomyces* sp. Tc022 from the plant *A. galanga*. Over the next ten years, Alshaibani [25] isolated cyclic peptides that are brevianamide F (**19**) and 2,2-dichloro-*N*-[(1r,2r)-2-hydroxy-1-(hydroxymethyl)-2-(4-nitrophenyl) ethyl]-acetamide (**20**) from *Streptomyces omiyaensis* NBRC 11449T living inside *Z. spectabile*. Harwoko et al. [26] isolated two dithiodiketopiperazine derivatives from endophytic fungi *T. harzianum* associated with medicinal plants

Z. officinale, namely pretrichodermamide G (**21**) and pretrichodermamide A (**22**). The absolute structure of **21** was determined to be the same as pretrichodermamide D, according to the common biosynthetic origin and its optical rotation value [26]. Meanwhile, the absolute stereostructure of **22** was previously determined using X-ray crystallographic analysis [36]. Compound **18** was first isolated and characterized by mass spectra analysis, 1D, and 2D NMR data. The chemical structures of nonribosomal peptides isolated from the endophytic microorganism Zingiberaceae family are shown in Figure 2.

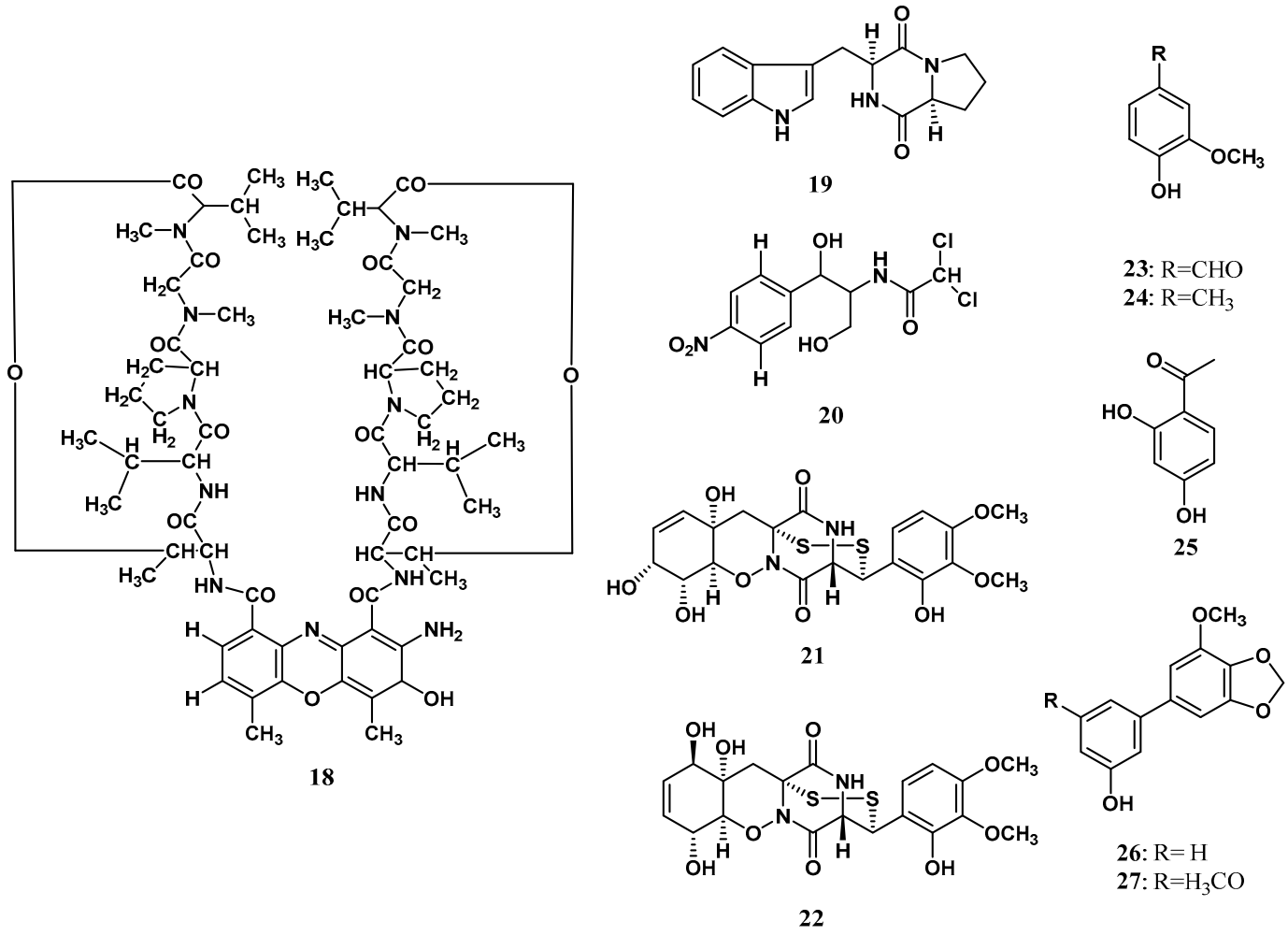

Figure 2. Nonribosomal peptides and aromatic compounds from Zingiberaceae endophytes.

3.4. Aromatic Compounds

Aromatic compounds are found as essential oils that are volatile at room temperature [94]. In plants, aromatics are responsible for altering the odor and flavoring [95], attracting pollinators and seed dispersers and providing defense against pathogens [96,97]. Aromatic fragrance compounds are of great commercial interest in research, health, food, cosmetic, and health industries [96]. The first aromatic derivatives isolated from endophytic microorganisms living inside Zingibereacae were vanillin (**23**) and 3-methoxy-4-hydroxytoluene (**24**) by Taechowisan et al. [18] from *Streptomyces aureofaciens* SMUAc130 of the roots tissue of *Z. officinale* Rosc. The research followed the finding of resacetophenone (**25**) that was isolated by Hammerschmidt et al. [24] from *Xylaria* sp. living inside *C. xanthorrhiza*. Two years later, Taechowisan et al. [21] isolated 3′-hydroxy-5-methoxy-3,4-methylenedioxybiphenyl (**26**) and 3′-hydroxy-5,5′-dimethoxy-3,4-methylenedioxybiphenyl (**27**) from *Streptomyces* sp. BO-07 associated with the plant *B. rotunda* (L.). The structure of aromatic compounds is shown in Figure 2.

3.5. Alkaloids

Alkaloids are mainly characterized by nitrogen atoms on the structure [98–101]. Alkaloids are familiar additive drugs to pharmacological relevance. The commercial value of alkaloids is primarily as medicines, flavorings, and poisons [102]. Alkaloids are produced by various organisms, including plants, animals, bacteria, and fungi. They are responsible as protective agents for biotic and abiotic stress [98]. Two alkaloids were isolated by Taechowisan et al. [29] from the endophytic *Streptomyces* sp. LJK109 from the roots of *A. galanga* (L.) Wild, which are 3-methylcarbazole (**28**) and 1-methoxy-3-methylcarbazole (**29**). Indole acetic acid (**30**) was characterized to be produced in various endophytic microorganisms, including *B. subtilis* CL1, *Bacillus* sp. CL3, *Burkholderia thailandensis* CL4, *Agrobacterium tumefaciens* CL5, *Klebsiella* sp. CL6, *Bacillus cereus* CL7, *Pseudomonas putida* CL9, *Pseudomonas fluorescens* CLI2, and *Azotobacter chroococcum* CL13; living inside the medicinal plant *C. longa* L. [37], *Paenibacillus favisporus*, and *Paenibacillus* sp. associated with the rhizome of *C. longa* L. [38], *Pseudomonas* sp.; living inside *Z. officinale* [39], *Pseudomonas*, *Pantoea agglomerans*, *Aeromonas*, *Serratia*, *Enterobacter asburiae*, and *Rhizobium* inside the roots, stem, tubers, and leaves of *Z. officinale* Roscoe [40], *Ochrobactrum*, *Agrobacterium*, *Acinetobacter*, *Stenotrophomonas*, *Serratia and Bacillus* associated inside *Z. officinale* Roscoe [41], *Bacillus cereus* (ECL1), *Bacillus thuringiensis* (ECL2), *Bacillus* sp. (ECL3), *Bacillus pumilis* (ECL4), *Pseudomonas putida* (ECL5), and *Clavibacter michiganensis* (ECL6); living inside *C. longa* L. [37], *T. harzianum*, *T. asperellum*, *T. atroviride*; and associated with the plant *C. longa* L. [31], *A. flavus* inside *Alpinia* sp. [42]. The structure of the isolated alkaloids is shown in Figure 3.

3.6. Indole Diterpenoids

Indole terpenoids are fungal secondary metabolites with diverse structures and a broad range of biological activities [40,103,104]. Indole diterpenoids, a subclass of the indole terpenoids, have recently caught interest due to their promising biological properties [105]. Arianti and her co-workers [23] isolated nine indole diterpenoids along with 13 known congeners from the endophytic fungi *Penicillium* sp ZO-R1-1 associated with the roots of the medicinal plant *Z. officinale*. Nine new indole diterpenoids, namely shearilicine (**31**), paspalinine-13-ene (**32**), 7-hydroxypacilline-13-ene (**33**), 7-methoxypaxilline (**34**), shearinine N (**35**), shearinine O (**36**), shearinine P (**37**), 7-methoxyshearinine P (**38**), and shearinine Q (**39**), along with known indole diterpenoids, including emindole SB (**40**), 21-isopentenylpaxilline (**41**), paxilline (**42**), dehydroxypaxilline (**43**), 7-hydroxy-13-dehydroxyp axilline (**44**), paspaline (**45**), shearinine F (**46**), paspalicine (**47**), paspalinine (**48**), paspalitrem A (**49**), 6,7-dehydropaxilline (**50**), 10β-hydroxy-13-desoxypaxilline (**51**), and pyrapaxilline (**52**), were characterized and identified using mass spectra analysis and 1D and 2D NMR data. Meanwhile, the absolute configuration of the new natural products was determined using the TDDFT-ECD approach and confirmed by single-crystal X-ray determination through anomalous dispersion. The total synthesis of **41** has confirmed its structural assignment and absolute stereochemistry [43]. The absolute configuration of **42** was first reported by Springer et al. [44], using X-ray crystallography analysis. Based on that, **43** was determined to have the same absolute configuration as **42** [45]. Recently, the absolute configuration of **44** was determined by ECD calculation [46]. In addition, the absolute structures of **45** and **46** [47], as well as **50** [48], have been determined using comprehensive spectroscopic data analysis and circular dichroism (CD) calculation. The structure of indole diterpenoids isolated from *Penicillium* sp. ZO-R1-11 is shown in Figure 3.

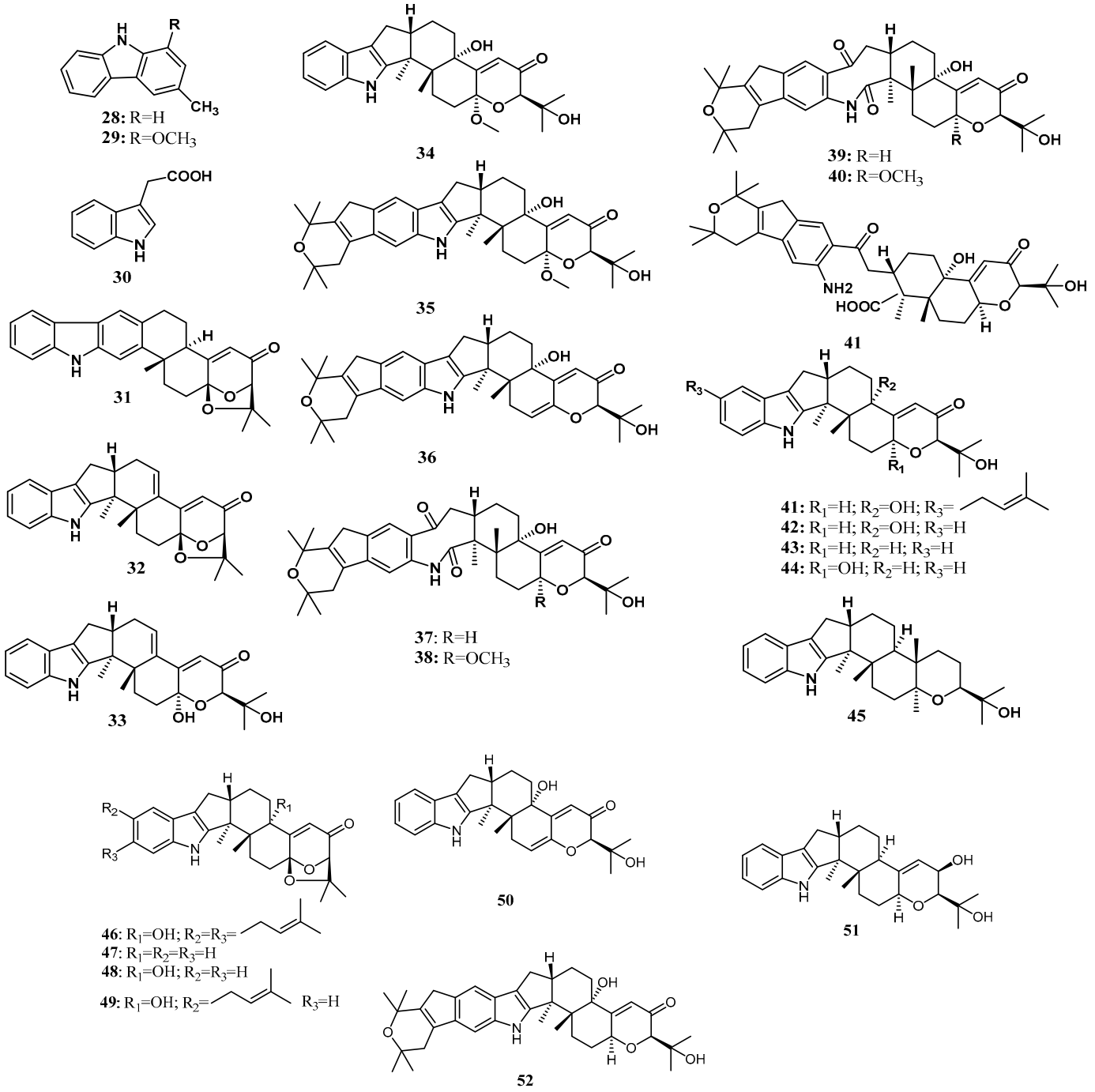

Figure 3. Alkaloid and indole diterpenoids from Zingiberaceae endophytes.

4. Pharmacological Activities

4.1. Antimicrobial Activity

Compounds **1**, **2**, **23**, and **24** were evaluated for their antifungal activity by 14 using a paper-disc assay method against *C. musae* and *F. oxysporum*. Compounds **1** and **2** give the same percentage for inhibiting the growth of *C. musae* and *F. oxysporum*, namely 66% and 72%, respectively. The MIC values of **1** and **2** for inhibition of *C. musae* were 120 and 150 µg/mL, respectively. Meanwhile, **23** and **24** showed weak inhibition, i.e., 32% and 35% for **23** and 26% and 30% for **24** [18]. Ten years later, El-Gendy & El-Bondkly [49] conducted the antimycotic activity of compound **1** against several dermatophytes and other pathogenic fungi, namely *T. rubrum*, *T. mentagrophytes*, *M. gypseum*, *E. floccosum*, *A. niger*,

A. fumigatus, *F. oxysporum*, *C. albicans*, and *C. humicolus*. The results give the MIC values of 7.5, 90, 100, 50, 20, 10, 22, 15, and 10 μg/mL, respectively and give the MFC values of 100, 90, 150, 66, 50, 35, 49, 20, and 32 μg/mL, respectively [49].

Compound **4** was evaluated for its antibacterial effectiveness against *S. aureus*, *E. coli*, and *P. aeruginosea*, and antifungal activity against *C. albicans* with the observation by measuring the inhibited zones (IZ) in mm with DMF as a control. The results showed the IZ values of **4** are 14, 20, 14, and 20 mm, respectively, compared with the IZ values of DMF being 14, 18, 12, and 17, respectively. However, the MIC and MBC values of **4** against *S. aureus* and *E. coli* showed an inactive result; meanwhile, the activity of **4** against *P. aeroginosea* gives the same MIC and MBC values of 62.5 μg/mL, respectively. In addition, the antifungal activity of **4** against *C. albicans* gives a MIC value of 62.5 μg/mL, but a weak MBC value of >500 μg/mL [50]. In 2008, Taechowisan et al. [20] evaluated the antibacterial and antifungal activities of compounds **3**, **4**, **5**, and **6** against *S. aureus*, *E. coli*, *P. aeruginosa*, *B. subtilis*, *C. albicans*, and *C. musae*. The MIC values lower or equal to 128 μg/mL were obtained with compounds **3**, **5**, and **6** on all tested microbial species; meanwhile, with compound **4**, they were only obtained on *S. aureus*. The lowest MIC value of 16 μg/mL was obtained by compound **5** against *S. aureus* and *C. albicans*, and also on compound **6** against *C. albicans*. The MMC determinations of compounds **3**, **5**, and **6** against the tester microorganisms were 40%, 100%, and 80%, respectively, within the tested interval (0.50–256 μg/mL) [20]. On the previous research, compound **18** was also tested for its antifungal activity against *C. albicans* and *C. musae*, with MIC values of 20 and 10 mg/mL, respectively [19].

The antibacterial activity of **7**, **8**, **9**, **10**, **11**, and **12** were evaluated against *S. aureus* ATCC25932, *B. cereus* ATCC7064, *B. subtilis* ATCC6633, *E. coli* ATCC10536, and *P. aeruginosa* ATCC27853. Compound **8** demonstrated strong activity with MIC values of 32 μg/mL against *S. aureus*, *B. cereus*, and *B. subtilis*. Compounds **7** and **9** gave MIC values of 32, 64, and 64 μg/mL against *S. aureus*, *B. cereus*, and *B. subtilis*, respectively. However, compounds **7** and **8** had weak activity against *E. coli*, with MIC values of 128 μg/mL. MIC values of 64 μg/mL were also obtained with compound **10** against *S. aureus* and compound **11** against *S. aureus*, *B. cereus*, and *B. subtilis*. MIC values of 128 μg/mL were obtained with compound **10** against *B. cereus* & *B. subtilis* and compound **12** against *S. aureus*, *B. cereus*, and *B. subtilis*. Compounds **9**, **10**, and **11** had weak activity against *E. coli*, with MIC values of 256 μg/mL. Meanwhile, **12** had the weakest activity against *E. coli*, with MIC values of 512 μg/mL. All of the tested compounds showed weak activity against *P. aureginosa*, with MIC values of 256–512 μg/mL [28].

The in vitro antibacterial activity of **19** and **20** were evaluated by Alshaibani [25] against MRSA with MIC and MBC calculation. Compound **19** gives MIC and MBC values of 16 μg/mL and 32 μg/mL; meanwhile, compound **20** gives MIC and MBC values of 8 and 64 μg/mL (21). Compound **22** was evaluated for its antifungal activity against the pathogenic fungus *U. maydis* with MIC values of 1 mg/mL (2 mM). In addition, **22** displayed antibacterial activity against the human pathogenic bacterium *M. tuberculosis* with MIC values of 25 μg/mL (50 μM) [26].

Compounds **26** and **27** were evaluated for their antibacterial activity against *S. aureus* ATCC25932, *B. cereus* ATCC7064, *B. subtilis* ATCC6633, *E. coli* ATCC10536, *Salmonella typhi* ATCC19430, *P. aeruginosa* ATCC27853, and *Serratia marcescens* ATCC8100 compared with ampicillin and chloramphenicol as a positive control. Based on the IZ calculation, compounds **26** and **27** showed the highest activity against *S. aureus*, *B. cereus*, and *B. subtilis* (35.0 mm, 34.0 mm & 35.5 mm, and 33.0 mm, 32.5 mm & 33.5 mm, respectively). These results showed more potent activity than the positive control. However, compounds **26** and **27** showed moderate activity against *E. coli*, *S. typhi*, and *S. marcescens* (14.8 mm, 17.5 mm & 15.5 ± 1.65 mm, and 13.0 mm, 15.5 mm & 14.5 mm, respectively) and had weak activity against *P. aeruginosa* (12.0 mm and 10.0 mm, respectively). These results were also confirmed with the calculation of high MIC values of **26** and **27** against *E. coli*, *S. typhi*, *S. marcescens*, and *P. aeruginosa* (256 to 512 μg/mL), indicating **26** and **27** as moderate

inhibitors against Gram-negative bacteria and the MBC values >512 μg/mL indicating no bactericidal activity against Gram-negative bacteria. On the other hand, MIC values of 0.5 μg/mL were obtained from both **26** and **27** against *S. aureus*, *B. cereus*, and *B. subtilis*. In addition, compound **26** showed the lowest MBC values of 2 μg/mL against Gram-positive bacteria, whereas compound **27** showed greater MBC varies in 4–16 μg/mL [21].

In 2012, Taechowisan et al. [29] also evaluated the antifungal activity of **28** and **29** against nine phytopathogenic fungi, namely *A. porri*, *C. gloeosporioides*, *C. musae*, *Curvularia* sp., *Drechsler* sp., *Exserohilum* sp., *F. oxysporum*, *Verticillium* sp., and *S. rolfsii* using the paper disk method. Based on the percentage of growth inhibition calculation, compound **28** showed growth inhibition of all tested fungi in 20.5%, 16.4%, 35.6%, 28.9%, 27.2%, 22.9%, 40.0%, 30.6%, and 28.6%, respectively; meanwhile, compound **29** showed the growth inhibition of all tested fungi in 24.1%, 20.2%, 33.8%, 31.2%, 36.1%, 34.3%, 36.2%, 29.4%, and 26.7%, respectively. Furthermore, the MIC values of 60 μg/mL were obtained from both **28** and **29** against *A. porri*, *Curvularia* sp., *Drechsler* sp., and *Verticilllium* sp., and from **29** against *C. gloeosporioides* and *S. rolfsii*. Meanwhile, MIC values of 120 μg/mL were obtained from both **28** and **29** against *C. musae* & *Exserohilum* sp. and from **28** against *S. rolfsii*. The weak MIC values of 240 were obtained from both **28** and **29** against *F. oxysporum*. However, compound **28** displayed the strongest activity against *C. gloeosporioides* with MIC values of 30 μg/mL [29].

Hu et al. [51] evaluated the antibacterial activity of **40** and **45**. Compound **40** showed potent activity against the aquatic pathogens *P. aeruginosa*, *V. parahaemolyticus*, and *V. alginolyticus*, with MIC values of 1.0, 2.0, and 1,0 μg/mL, respectively, compared with the positive control chloromycetin (0.5 μg/mL on the tested microbial). In addition, compounds **40** and **45** displayed activity against the human pathogen *E. coli*, with MIC values of 4.0 and 0.5 μg/mL, respectively, compared with the positive control chloromycetin, with MIC values of 1.0 μg/mL. The result show that compound **45** has more potent activity than the positive control against *E. coli* [51].

4.2. Anticancer Activity

Compounds **31**, **32**, **33**, **36**, **37**, **40**, **41**, **44**, and **52** were evaluated for their cytotoxic activity toward the murine L5178Y cell lines with the IC_{50} values of 3.6, 5.3, 5.3, 8.1, 7.6, 18.3, 12.9, 6.2, and 10.9 μM, respectively. Compound **31** exhibited more potent activity than the positive control kahalalide F (IC_{50} 4.3 μM) [23]. In addition, compounds **31**, **32**, **34**, **35**, **36**, **37**, **38**, **39**, **40**, **43**, **45**, **49**, **51**, and **52** were evaluated for their cytotoxic activity against the A2780 human ovarian cancer cell line with the IC_{50} values of 9.7, 12.2, 12.2, 32.2, 7.8, 11.9, 19.4, 51.5, 8.2, 17.1, 5.3, 19.8, 28.5, and 12.8 μM, respectively [23]. The results indicated strong potential activity from **31**, **36**, **40**, and **45**. Compounds **31**, **32**, **34**, **35**, **36**, **37**, and **38** were also evaluated for their cytotoxicity against human urothelial bladder cancer cell line J82. The compounds active in bladder cancer cell lines are of high scientific interest regarding the rapid chemoresistance development of the cell. The tested compounds gave IC_{50} values of 40.6, 42.1, 55.3, 96.7, 31.7, 29.4, and 73.0 μM, respectively. These results indicate a lower potency than their activity against L5178Y and/or A2780 cell lines [23]. Furthermore, compounds **31**, **32**, **33**, **36**, **37**, **40**, **44**, and **45** were tested toward the human embryonic kidney cell line HEK-293 with the IC_{50} values of 28.5, 21.7, 27.9, 37.4, 28.3, 44.6, 39.8, and 43.0 μM, respectively [23]. In addition, compound **44** gave inhibitory activity against protein tyrosine phosphatases with IC_{50} values of 13 and 17 μg/mL against PTP1B and TCPTP, respectively [52].

The cytotoxic and anticancer activities of **26** and **27** were evaluated against the three tumor cell lines: HepG2, HeLa, and Huh7, and one murine fibroblast cell line, L929, using the MTT assay. The results show that compounds **26** and **27** exhibited significant anticancer activity against HeLa cells with IC_{50} values of 3.04 and 3.96 μg/mL, respectively. The anticancer activity of **26** and **27** against HepG2 and Huh7 cells also showed high potential, with IC_{50} values of 15.42 & 17.52 μg/mL and 18.73 & 20.30 μg/mL, respectively. However,

these compounds showed the weakest cytotoxic activity toward the L929 cell line, with IC_{50} values of 182.28 and 216.33 μg/mL, respectively [21].

4.3. Antioxidant Activity

In 2009, compounds **5** and **6** were evaluated for their protective effects on glutamate-induced cytotoxicity in mouse hippocampal HT22 cells. This cell line lacks ionotropic glutamate receptors, resulting in a high concentration of glutamate that inhibits cysteine uptake and depletes intracellular glutathione, which leads to the accumulation of reactive oxygen species (ROS). The effective protection ratios of **5** and **6** at a concentration of 100 μM are 62.4 ± 2.8% and 55.3 ± 3.4%, respectively, compared to the positive control, Trolox, with a protection ratio of 92.5 ± 2.5% at the same concentration [53]. Furthermore, the free radical scavenging activity of **5** and **6** was also measured by the interaction with stable free radical DPPH. The results exhibited potent scavenging effects on DPPH radical with the IC_{50} value of 60.74 and 75.65 μM, respectively, compared with L-Ascorbic acid as a positive control, with an IC_{50} value of 72.35 μM [53].

Compounds **26** and **27** were evaluated for their antioxidant activity using the decoloration of the ethanolic solution of DPPH. The absorption disappears in the presence of an active radical scavenger, and the subsequent decolorization is stoichiometric at a chosen range about the degree of reduction. The antioxidant activity of **26** and **27** gave the SC_{50} values of 85.84 and 88.26 μg/mL, respectively, compared with the positive control L-ascorbic acid, with an SC_{50} value of 50.25 μg/mL [21].

4.4. Anti-Inflammatory Activity

Compound **12** was evaluated for its anti-inflammatory activity against the release of β-glucuronidase and lysozyme from rat neutrophils. The result showed the IC_{50} value of 80.9 and >100 μM, respectively, compared to the positive control trifluoperazine against the release of β-glucuronidase and lysozyme, with IC_{50} values of 16.9 and 12.8 μM, respectively [54]. In 2014, the anti-inflammatory activity of compounds 42 and 52 was reported with the inhibition of LPS-induced NO production of mouse macrophage cell line RAW264.7. As a result, 52 inhibited the LPS-induced NO production at 10–30 μg/mL. On the other hand, compound 42 inhibited the NO production at 10 μg/mL. In addition, compound 52 inhibited with lower toxicity than 42 [55].

5. Future Perspectives

Some compounds from Zingiberaceae endophytes have the potency for further development. For example, for antimicrobials, there are 2′,7-dihydroxy-4′,5′-dimethoxyisoflavone demonstrating strong activity against *S. aureus*, *B. cereus*, and *B. subtilis*, and pretrichodermamide A show activity as an antimycobacterial with MIC values of 25 μg/mL. Paspaline shows more potent activity than the positive control (chloromycetin) against human pathogenic *E. coli*. Meanwhile, 3-methylcarbazole and 1-methoxy-3-methylcarbazole have activity against nine phytopathogenic fungi, namely *A. porri*, *C. gloeosporioides*, *C. musae*, *Curvularia* sp., *Drechsler* sp., *Exserohilum* sp., *F. oxysporum*, *Verticillium* sp., and *S. rolfsii*. A mechanism of antimicrobials can further examine these compounds: cell wall interference, protein, and nucleic acid synthesis, as well as inhibition of the metabolic pathway, membrane function, and ATP synthase [106]. In vivo studies of antimicrobial compounds in antiseptic efficacy are needed for antiseptic development. These studies of in vivo models are necessary at more advanced development stages, while the in vitro models are essential at the discovery stages [107].

Some cancer lines have been tested from a Zingiberaceae endophytes compound: murine L5178Y cell lines, A2780 human ovarian cancer cell line, human urothelial bladder cancer cell line J82, human embryonic kidney cell line HEK-293, HepG2, HeLa, Huh7, and one murine fibroblast cell line. The potent anticancer compound includes 3′-hydroxy-5-methoxy-3,4-methylenedioxybiphenyl, 3′-hydroxy-5,5′-dimethoxy-3,4 methylenedioxyphenyl, shearilicine, shearinine O, emindole SB, 7-hydroxy-13-dehydroxypaxilline, and paspaline.

However, these compounds are needed for mechanism action studies, such as mitochondria-dependent cytochrome C, caspase activation, and extrinsic mechanisms of apoptosis (activation of tumor necrotic factor) [108]. Such studies could lead to new perspectives on how these compounds can induce apoptosis.

The antioxidant and anti-inflammatory activity have also been tested. For antioxidants, there is reactive oxygen species protection from glutamate-induced cytotoxicity in mouse hippocampal HT22 cells and DPPH. Two methylenedioxyphenyl from *Streptomyces* sp. BO-07 has potent as an antioxidant. The anti-inflammatory activities were reported to inhibit LPS-induced NO production of the mouse macrophage cell line RAW264.7 with the potent compound pyrapaxilline. However, further studies are needed on this compound, such as the production of nitrite, iNOS (inducible nitric oxide synthase) mRNA, and protein expression [109].

There are several methods to enhance the chemical diversity of bacterial and fungal endophyte metabolites. According to Betrand et al. [110], the co-culture of endophytes with other microorganisms can stimulate the activation of the silent gene. The genome approach strategy can be used, such as mutasynthesis, metabolic engineering, and heterologous expression. Also, fermentation media modification with the principle of one strain of many compounds can be performed [111]. Because of the complexity of microbial extraction, the analytical method (e.g., mass spectrometry methods and metabolomics) is the key to the successful detection and identification of new compounds [110]. The discoveries of new compounds from endophytes, such as Zingiberaceae endophytes, are interesting for pharmacological studies and natural product diversity.

6. Conclusions

In summary, Zingiberaceae plant endophytes have been studied thus far for secondary metabolites in *Alipinia*, *Amomoum*, *Boesenbergia*, *Curcuma*, and *Zingiber* genus. There are different strains of bacteria and fungi endophytes, including *Streptomyces* sp., *Bacillus* sp., *Agrobacterium* sp., *Xylaria* sp., *Trichoderma* sp., *Aspergillus* sp., *Penicillium* sp., etc. This endophyte produced many secondary metabolites such as polyketide, peptide, aromatic, alkaloid, and hybrid terpene alkaloid. The volatile constituent has been identified from GC–MS Spectra, produced by endophyte genera of *Curcuma*, *Kaempferia*, *Zingiber*, and other plants, such as terpene, steroid, alkaloid, aromatic, flavonoid, and others. These compounds have pharmacological activities for antibacterial, antifungal, anticancer, antioxidant, and anti-inflammatory. A comprehensive review of secondary metabolites from Zingiberaceae endophytes and their pharmacology activities has filled the gaps in information between the studies: species identification of endophytes compounds isolation and pharmacological potency. Hopefully, this review will increase knowledge for the development of endophytic research, especially in plants of the Zingiberaceae family.

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Abbreviations

DFT	Density Functional Theory
DMF	Dimethylformamide
DPPH	2,2-diphenyl-1-picrylhydrazyl
ECD	Electronic Circular Dichroism
GC–MS	Gas Chromatography–Mass Spectroscopy
IC_{50}	Inhibitory Concentration 50
IZ	Inhibition Zones
LPS-induced NO	Lipopolysaccharide-Induced Nitric Oxide
MBC	Minimum Bactericidal Concentration
MFC	Minimum Fungicidal Concentration
MIC	Minimum Inhibitory Concentration
MMC	Minimum Microbicidal Concentration
MRSA	Methicillin-Resistant *Staphylococcus aureus*
MTT	(3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) tetrazolium
NMR	Nuclear Magnetic Resonance
PCR	Polymerase Chain Reaction
PTP1B	Protein Tyrosine Phosphatase 1B
ROS	Reactive Oxygen Species
SC_{50}	Scavenging Concentration 50
TCPTP	T-Cell Protein Tyrosine Phosphatase
TDDFT	Time-Dependent Density-Functional Theory
VCD	Vibrational Circular Dichroism

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