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Review on Fungi of Genus *Penicillium* a Producers of Biologically Active Polyketides

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ABSTRACT

Objectives: This review article highlights a remarkable class of compounds (polyketides) and their derivatives produced by fungi of genus *Penicillium* and the diversity of their biological activities, isolated, identified and biologically assessed. The species belong to this genus represent a large part of microbial diversity and one of the promising resources in the search of biologically active natural scaffolds. *Penicillium* genera are one of the most important sources of different secondary metabolites of a wide range of classes of chemical compounds, i.e., anthraquinones, benzodiazepines, coumarins, diketopiperazines, ergot alkaloids, polyketides, quinolines, quinazolines, steroids and terpenoids. Interest in these metabolites increases owing to their valuable pharmacological and therapeutic properties. **Methods:** This review includes articles between 1988 and 2018, reviewed by internationally accepted databases and scientific journals. **Results:** This review demonstrates the structural and biological diversity of fifty-three polyketides isolated from different *Penicillium* species highlighting the culture media used for fungal growth and solvent of extraction along with biological activities and the reported biological assays used to estimate the potential activities of the reviewed polyketides. **Conclusion:** The structural and biological diversity and potency of reviewed *Penicillium* polyketides along with the reproducibility of their production make them a perfect candidate for the discovery of new potent pharmaceuticals.

***Keywords**: Biodiversity; Fungi; Penicillium; Polyketides*

INTRODUCTION

The endophytic fungi are microorganisms that colonize in the internal tissues of plants, it represents a large kingdom of over 300,000 species on earth. Every plant is considered a host of one or more endophytes, which generally affect the hosts' abilities to survive in special environments[1]. It has been proved by several studies that microbes are not always harmful and a cause of infectious diseases: their secondary metabolites can also treat and often cure such infections. Ecologically, fungi and bacteria survive by their ability to kill or control other microorganisms with only their cell walls or cell membranes and chemical arsenals to defend them. These chemical arsenals have provided many of the important chemotherapeutics used to date[2]. Fungal endophytes are considered a diverse group of microorganisms that live between the living plant tissue in the arctic, Antarctic, coastal forests, deserts, mangrove swamps, oceans, and rainforests[3]. The versatile inhabitants of the tissues of higher plants may represent a rich source of yet undiscovered and unexplored genera to contribute to fungal diversity and secondary metabolite investigations[4]. The potent

antifungal agent; griseofulvin is of fungal origin[5], the antibiotic; streptomycin and the anticancer agent; calicheamicin are produced by actinomycetes[6], and the anticancer drug; taxol is produced by the fungus *Taxomyces andreanae*[7]. Several well-known fungi-derived pharmaceuticals such as the penicillin's; lovastatin, echinocandin B, and cyclosporin A serve to demonstrate the importance of the fungal secondary metabolites in drug discovery. The rich diversity of new bioactive compounds produced by these organisms pointed to their importance as potential sources of pharmaceutical leads.

Penicillium endophytic genera are considered the most widespread hyphomycetes among other different fungi. They are well-known as a source of a wide range of biologically active compounds such as alkaloids, diketopiperazines, sterols, terpenes and polyketides[8]. Some important biologically active compounds synthesized by *Penicillium* fungi are cyclic peptides diketopiperazines consisting of residues of two amino acids and mevalonic acid. Tryptophan, histidine and mevalonic acid are the biosynthetic precursors of roquefortine and related alkaloids such as meleagrine, glandicolines A and boxalin[9]. Different strains of genus *Penicillium* were reported to represent productive sources of a variety of bioactive mero-, other terpenoids and sesquiterpenes. These fungal secondary metabolites have been reported to exhibit a wide array of biological and pharmacological properties including antibacterial, anti-inflammatory, antitumor, antifungal, cholesterol-lowering, and immunosuppressive activities[10].

Polyketides are naturally occurring compounds characterized by the presence of alternating carbonyl and methylene groups ('*β*-polyketones'). Polyketides are a group of compounds not only produced extensively by microbes (both bacteria and fungi) but also produced by the host organisms including plants (e.g., flavonoids), algae (e.g., bromoallene and acetogenins), insects (e.g., hydroxyacetophenones), lichens (e.g., usnic acid), and sponges (e.g., mycothiazole)[11]. Polyketides and their derivatives have taken leads in the new discoveries for new anticancer, antifungal, antibiotics and therapeutic agents. Studies showed that around 1% of each 5000 to 10,000 discovered polyketides contributes to the medical society and used as active drugs[12]. Tetracycline, nystatin and erythromycin are biologically active polyketides used as antibiotics, moreover, doxorubicin is used as anticancer and lovastatin is used as anti-hypercholesterolemic agent. On the other hand, rapamycin is used as immunosuppressant.

This is a review of bioactive polyketides isolated from different species of genus *Penicillium* over the last thirty years covering the articles between 1988 to 2018, highlighting the new polyketides isolated and their biological benefits.

MATERIAL AND METHODS

The research strategy is focused on reviewing the polyketides and their derivatives isolated from *Penicillium* species arranged according to their reported biological activities depending on the published data in the internationally accepted databases like Science Direct, Scopus and Web of Science as well as scientific data collected from scientific journals.

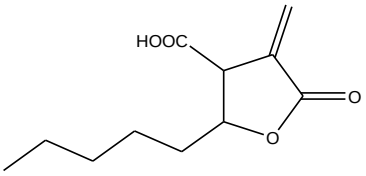
RESULTS AND DISCUSSION

Biologically active polyketides isolated from the genus Penicillium

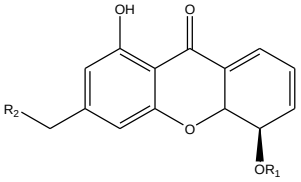
A variety of biologically active polyketides have been isolated from different species of genus *Penicillium* and several biological activities such as anticancer, antibacterial, antifungal, antioxidant, anthelmintic, antimycobacterial and antiviral were reported for these compounds.

Cytotoxic polyketides isolated from the genus Penicillium:

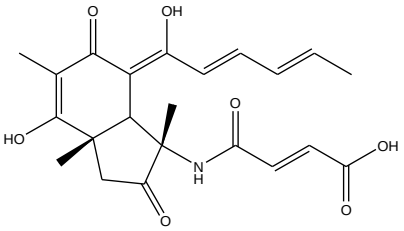
Methylenolactocin (**1**), an antitumor polyketide isolated from culture nitrate of *Penicillium* sp. Its antitumor activity was achieved with *in-vivo* study on female mice inoculated with Ehrlich carcinoma cells caused a prolongation of the life span of the treated mice bearing tumor cells[13]. Two cytotoxic polyketide derivatives were isolated from the mycelia extracts of two different *Penicillium* species, nidulaline A (**2**) from *Penicillium* sp. AJ117292 and nidulaline B (**3**) from *Penicillium* sp. AJ1 17291. Dihydroxanthone derivatives of compounds (**2** and **3**) exhibit potent cytotoxic activities against both murine and human tumor cell lines *in vitro*[14]. Sorbicillactone A (**4**) is a sorbicillin-derived compound isolated from a saltwater culture of a *P. chrysogenum* strain isolated from the Mediterranean sponge *Ircinia fasciculata*. Sorbicillactone A (**4**) was tested for its cytotoxic activity against several tumor cell lines, namely murine leukemic lymphoblasts L5178y, rat adrenal pheochromocytoma PC12 cells, human T lymphocytes H9 cells, and human cervix carcinoma HeLa S3 cells. Sorbicillactone A (**4**) had a selective activity against L5178y cells (IC_{50} of 2.2 mg/mL), however, for the other tested cell lines the IC_{50} was >10 mg/mL[15]. Nidurufin (**5**) is a cell cycle inhibitor isolated from culture media of marine-derived fungus *P. flavidorsum* SHK1-27. Nidurufin (**5**) cytotoxic activity was evaluated against Human myeloid leukemia (K562) cell line. Nidurufin (**5**) showed moderate cytotoxic activity with an IC_{50} value of 12.6 µM and the studied mechanism of action suggested that nidurufin (**5**) induced *in vitro* cell cycle arrest at G2/M transition in the K562 cell line in a concentration and time-



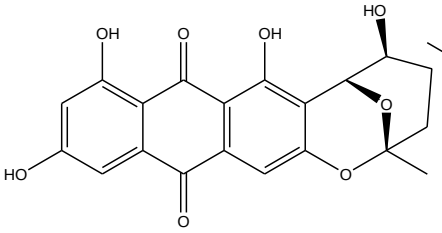
Methylenolactocin **(1)**



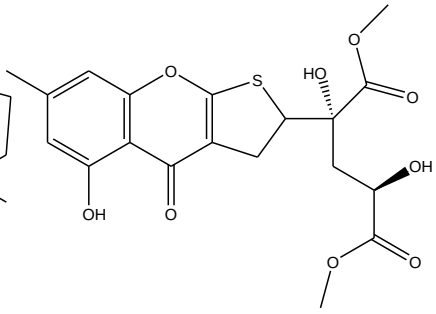
Nidulaline A R_1=Ac, R_2= H **(2)**
Nidulaline B R_1=H, R_2= OH **(3)**



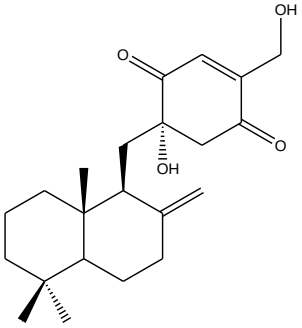
Sorbicillactone A **(4)**



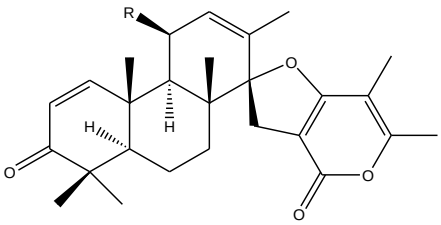
Nidurufin **(5)**



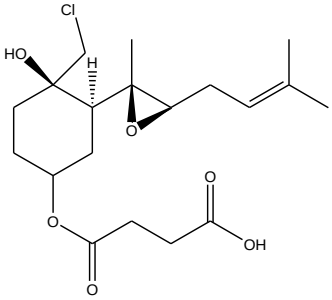
Oxalicumones A **(6)**



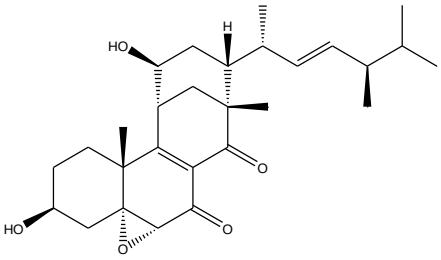
Penicilliumin A **(7)**



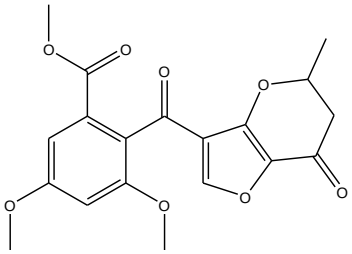
Brevione I R=OH **(8)**
Brevione A R=H **(9)**



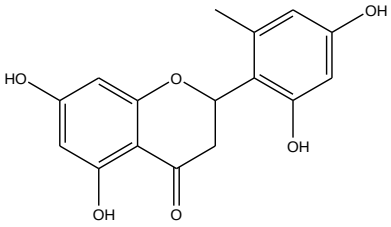
Ligerin **(10)**



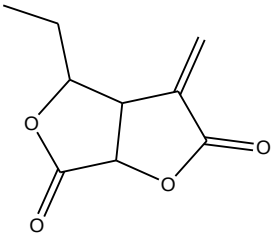
Penicillitone **(11)**



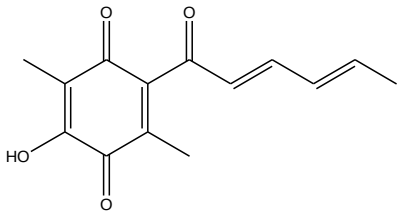
Penifupyrone **(12)**



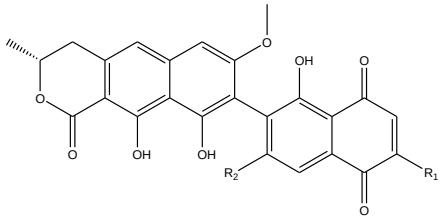
Penimethavone A **(13)**



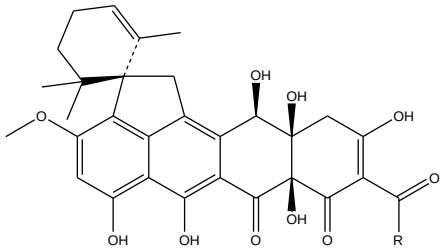
Ethisolide **(14)**



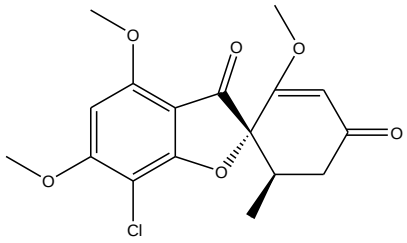
Sorrentanone **(15)**



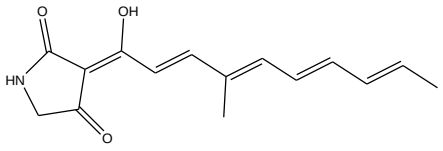
Xanthoradone A **(16)**
R_1=OCH_3, R_2=CH_3
Xanthoradone B **(17)**
R_1=CH_3, R_2=OCH_3



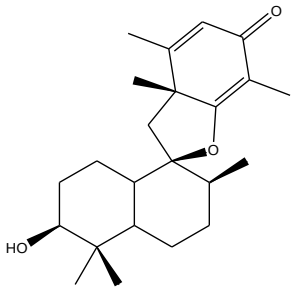
Spirohexaline **(18)**
R= CH_3
Viridicatumtoxin **(19)**
R= NH_2



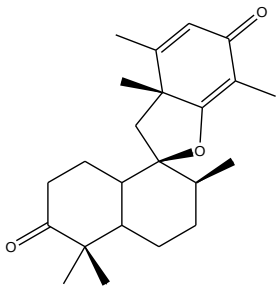
Griseofulvin **(20)**



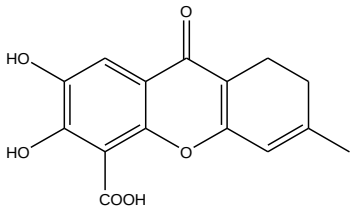
Ravynic acid **(21)**



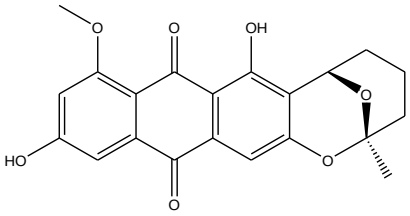
Chermesins A **(22)**



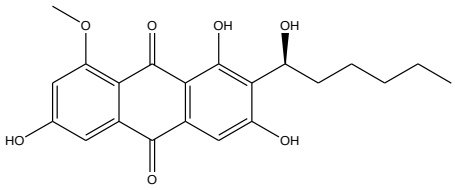
Chermesins B **(23)**



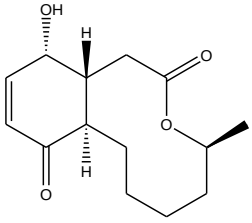
Penialidins C **(24)**



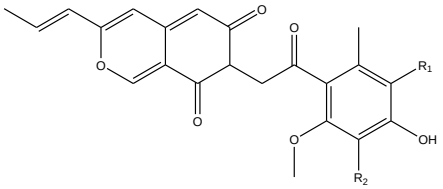
8-*O*-methylaverufin **(25)**



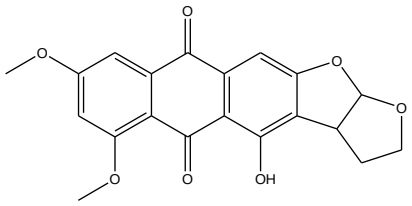
1,8-*O*-dimethylaverantin **(26)**



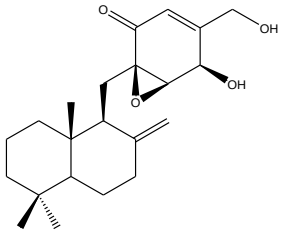
Sch 642305 **(27)**



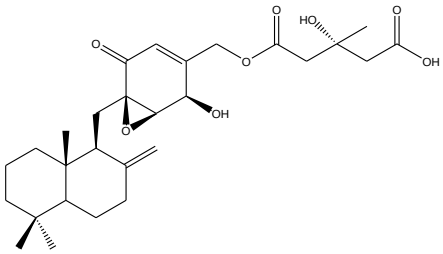
6`-hydroxy-3-methoxy-mitorubrin (R_1=OH, R_2= H) **(28)**
4`-hydroxy-3-methoxy-(S)-mitorubrin (R_1=H, R_2= OH) **(29)**
Monomethyl-(S)-mitorubrin (R_1=H, R_2= H) **(30)**



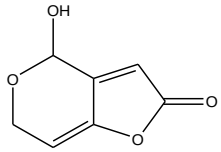
Aversin **(31)**



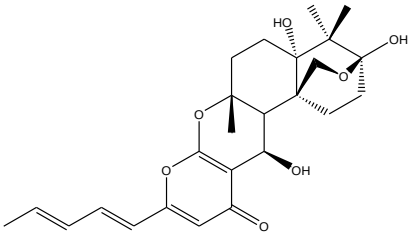
Macrophorin A **(32)**



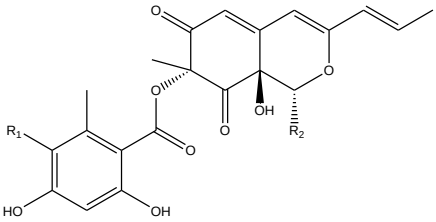
Macrophorin D **(33)**



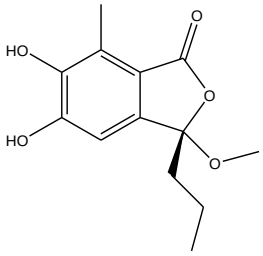
Sch 351633 **(34)**



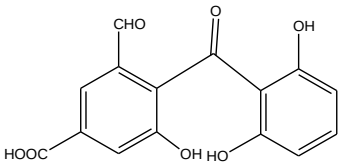
Hesseltin A **(35)**



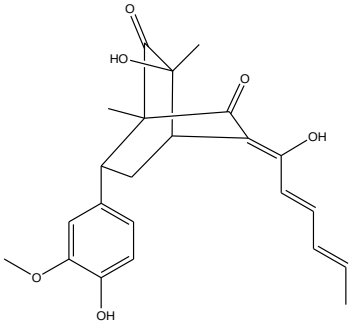
Purpurquinones B **(36)**
R_1=OH, R_2= OH
Purpurquinones C **(37)**
R_1=H, R_2= H



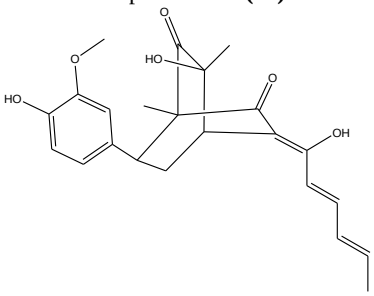
Purpuresters A **(38)**



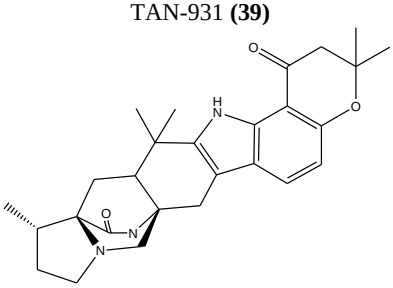
TAN-931 **(39)**



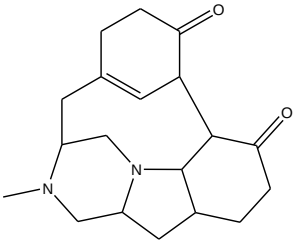
Sorbicatechols A **(40)**



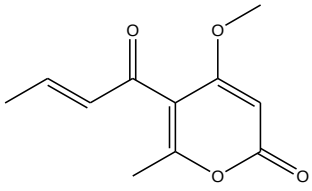
Sorbicatechols B **(41)**



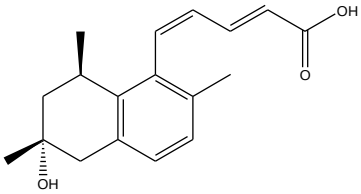
Peniciherquamide C **(42)**



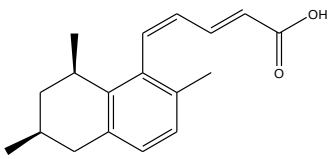
Herquline A **(43)**



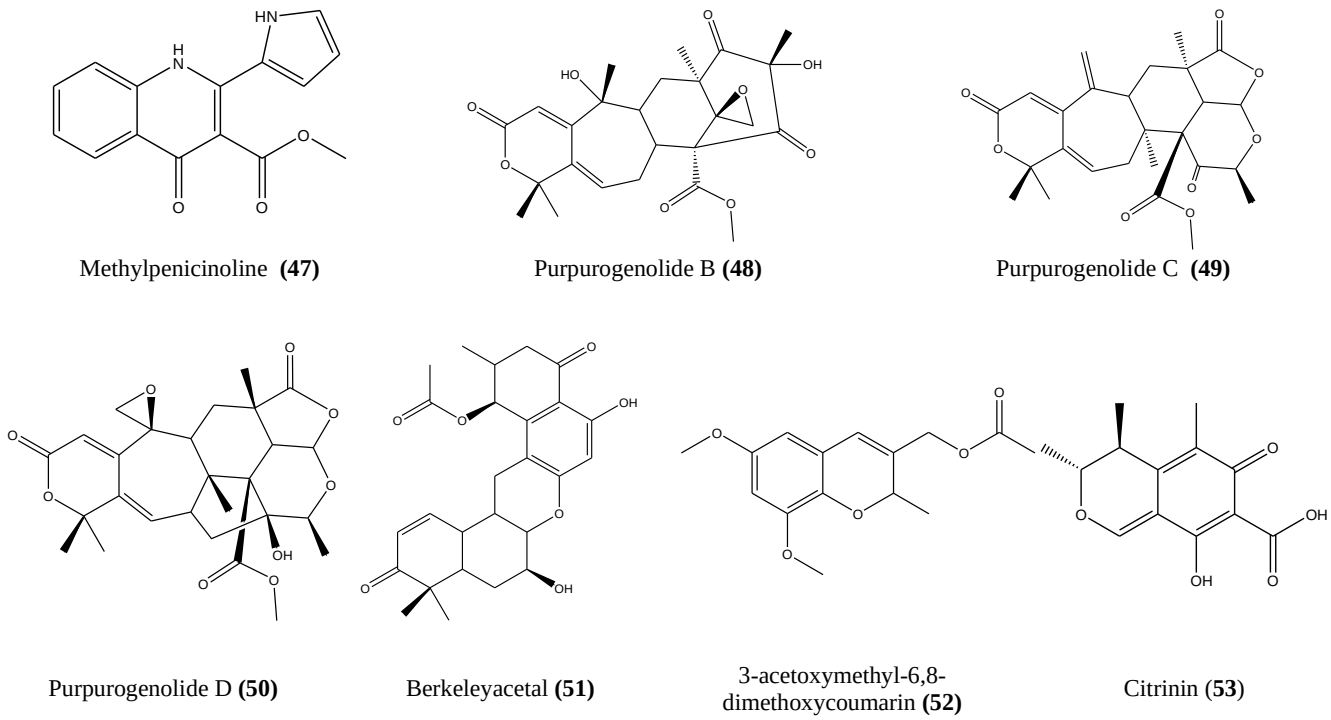
Pyrenocine A **(44)**



2*E*,4*Z*-tanzawaic acid D **(45)**



Tanzawaic acid A **(46)**



Methylpenicinoline **(47)** | Purpurogenolide B **(48)** | Purpurogenolide C **(49)**

Purpurogenolide D **(50)** | Berkeleyacetal **(51)** | 3-acetoxymethyl-6,8-dimethoxycoumarin **(52)** | Citrinin (**53**)

Figure 1. Biologically active polyketides isolated from genus Penicillium

dependent manner[16]. Oxalicumones A (**6**) is a natural chromone isolated from culture broth extract of marine-derived fungus, *P. oxalicum*. The acetylated derivative of Oxalicumones A (**6**) was tested for its cytotoxic activity against human melanoma A375, lung carcinoma A549, cervical carcinoma HeLa, liver hepatocellular carcinoma HepG2, colonic adenocarcinoma SW-620, and normal liver L-02 cell-lines showing a notable cytotoxic activity with an IC_{50} of 8.9 and 7.8 µM against A375 and SW-620 cell lines respectively. Whereas oxalicumones A (**6**) showed moderate cytotoxicity with an IC_{50} of 11.7 and 22.6 Mm against A375 and SW-620 respectively[17]. Penicilliumin A (**7**), a sesquiterpene quinone isolated from the ethyl acetate extract of the fungal culture of *Penicillium* F00120. Penicilliumin A (**7**) was tested for its cytotoxic activity against mouse melanoma (B16), human melanoma (A375), and human cervical carcinoma (Hela) cell lines. Penicilliumin A (**7**) exhibited potent cytotoxic activity against human melanoma (A375) with an IC_{50} of 22.88µg/mL[18]. Brevione I (**8**) and brevione A (**9**) are two breviane spiroditerpenoids isolated from the ethyl acetate extract of the fungal culture of *Penicillium* obtained from a sea sediment sample that was collected at a depth of 5115 m. Brevione I (**8**) and brevione A (**9**) were tested for their cytotoxic activity against MCF-7 breast cancer cell lines. Compound (**8**) and (**9**) showed cytotoxic activity with an IC_{50} values of 7.44 and 28.4 µM, respectively. Also, brevione I (**8**) was tested against A549 cell line (adenocarcinomic human alveolar basal epithelial cells) where it showed moderate activity with an IC_{50} value of 32.5 µM[19]. Ligerin (**10**) is a chlorinated sesquiterpenoid analogue was isolated from the ethyl acetate extract of a mixture of culture media and mycelia of fungal strain *Penicillium* MMS351 that was isolated from a seawater sample, gathered on the French Atlantic coast near the Loire river estuary in 1997. Ligerin (**10**) showed remarkable antiproliferative activity against murine osteosarcoma cell line (POS-1) as it showed an IC_{50} = 117 nM[20]. Penicillitone (**11**) was isolated from the ethyl acetate extract of a solid culture of *P. purpurogenum* SC0070. Penicillitone (**11**) was tested in an MTT assay for its growth inhibitory activity against A549, HepG2, and MCF-7 cells. Penicillitone (**11**) exhibited growth inhibitory activity with an IC_{50} ranges from 4-6 µM[21]. Penifupyrone (**12**) is a funicone derivative was isolated from the chloroform extract of rice culture media of the endophytic fungus *Penicillium* sp. HSZ-43. Penifupyrone (**12**) cytotoxic activity was tested against KB cells by using the MTT colorimetric method. The results showed a notable cytotoxic activity (IC_{50} = 4.7mM)[22]. Penimethavone A (**13**) is a flavone was isolated from the ethyl acetate extract of solid rice culture media of the fungus *P. chrysogenum* cultured for 45 days. Penimethavone A (**13**) was tested for its

Table 1. Cytotoxic polyketides isolated from the genus *Penicillium*

Number	Chemical constituents	Species	Cell line	Reported IC_{50}
1	Methylenolactocin	*Penicillium* sp. strain No. 24-4	Ehrlich carcinoma cells	0.2 mg per mouse *in vivo* study
2	Nidulaline A	*Penicillium* sp. AJ117292	HCT-116 K562 P388	0.042 µg/mL 0.096 µg/mL 0.0072 µg/mL
3	Nidulaline B	*Penicillium* sp. AJ1 17291	HCT-1 16 K562 P388	0.086 µg/mL 0.06 µg/mL 0.024 µg/mL
4	Sorbicillactone A	*Penicillium chrysogenum*	Murine leukemic lymphoblasts L5178y	2.2 mg/mL
5	Nidurufin	*Penicillium flavidorsum* SHK1-27	K562 cells (Human myeloid leukemia cell line)	12.6 µM
6	Oxalicumones A	*Penicillium oxalicum*	A375 SW-620	8.9 µM 7.8 µM
7	Penicilliumin A	*Penicillium* F00120	Human melanoma (A375)	22.88 µg/mL
8 **9**	Brevione I Brevione A	*Penicillium* 3A00005	MCF-7 breast cancer cell line	7.44 µM 28.4 µM
10	Ligerin	*Penicillium* MMS351	Murine osteosarcoma cell line (POS-1)	117 nM
11	Penicillitone	*Penicillium. purpurogenum* SC0070	A549. HepG2 MCF-7	5.57 µM 4.44 µM 5.98 µM
12	Penifupyrone	*Penicillium* sp. HSZ-43	KB cells	4.7mM
13	Penimethavone A	*Penicillium chrysogenum*	HeLa RD	8.41 µM 8.18 µM

Table 2. Antibacterial polyketides isolated from the genus *Penicillium*

Number	Chemical constituents	Species
14	Ethisolide	*Penicillium. capsulaturn*
15	Sorrentanone	*Penicillium chrysogenum*
16 **17**	Xanthoradone A Xanthoradone B	*Penicillium radicum* FKI-3765-2: I
18 **19**	Spirohexaline Viridicatumtoxin	*Penicillium brasilianum*
20	Griseofulvin	*Penicillium brasilianum*
21	Ravynic acid	*Penicillium* MINAP-9902
22 **23**	Chermesins A Chermesins B	*Penicillium chermesinum* EN-480
24	Penialidins C	*Penicillium sp.*
53	Citrinin	*Penicillium citrinum*

cytotoxic activity against HeLa and RD cell lines. Penimethavone A (**13**) exerted a notable activity with an IC_{50} values of 8.41 and 8.18 µM, respectively[23].

Antibacterial polyketides isolated from the genus Penicillium

Ethisolide (**14**) is a major bis-lactone component was isolated from chloroform extract of culture media of *P. capsulaturn.* Ethisolide (**14**) was tested for its antibiotic activity against *Escherichia coli, Salmonella, Shigella, Enterobacter, Proteus, Yersinia enterocolitica and Mycoplasma*. Upon testing (**14**) it showed a notable antibiotic activity with inhibition zone ranging from 13-22 mm[24]. Sorrentanone (**15**) is a tetrasubstituted quinone was isolated from the *n*-butanol extract of culture media broth of *P. chrysogenum.* The antimicrobial investigation of sorrentanone (**15**) against different Gram-positive and Gram-negative bacteria (*Staphylococcus pneumonia, Staphylococcus pyogene, Enterococcus faecalis, Staphylococcus Hetero, Staphylococcus epidermidis and Staphylococcus hemolytic*) showed a notable antimicrobial activity against *Staphylococcus pyogene* with MIC 16 µg/mL[25].Xanthoradone A (**16**) and xanthoradone B (**17**) were isolated from an acetone extract of rice culture media of *P. radicum* FKI-3765-2: I. They were tested against *S. aureus* and *Bacillus subtilis*. Xanthoradone A (**16**) exhibited inhibition zone 8 and 9 mm respectively and xanthoradone B (**17**) showed inhibition zone around 9 mm against *Bacillus subtilis.* Both showed moderate activities against methicillin-resistant *Staphylococcus aureus* but potentiate the activity of imipenem against the same strain[26]. Spirohexaline (**18**) and viridicatumtoxin (**19**) are two hexacycline structures produced by the fusion of a tetracycline-type ring with a spiro-type ring. Spirohexaline (**18**) and viridicatumtoxin (**19**) were isolated from the ethyl acetate extract of solid rice culture media of *P. brasilianum* FKI-3368. Spirohexaline (**18**) and viridicatumtoxin (**19**) showed an inhibitory activity to undecaprenyl pyrophosphate (UPP) synthase so inhibit the synthesis of undecaprenyl pyrophosphate the key lipid involved in the biosynthesis of peptidoglycan and another bacterial cell wall polysaccharide component in an enzyme-based assay[27]. Griseofulvin (**20**), is an antibiotic was isolated and identified from the culture extract of *P. brasilianum*. Griseofulvin (**20**) was tested *in vitro* for its antibacterial activity against *Escherichia coli, Bacillus subtilis, Bacillus cereus and Staphyloccocus aureus*. Griseofulvin (**20**) had an antibacterial activity with reported MICs of 3.13–25 µM. The most sensitivity was against *Staphyloccocus aureus* with MIC 3.13 µM[28]. Ravynic acid (**21**) is a 3-acyltetramic acid was isolated from CH_2Cl_2/ethyl acetate (1: 4) mycelia extract of *Penicillium* MINAP-9902 species. Ravynic acid (**21**) was examined for its antibacterial activity against *Staphyloccocus aureus* using Kirby Bauer bioassays. Ravynic acid (**21**) inhibited the culture growth down to approximately 2.5 µg mL^{-1} [29].Chermesins A (**22**) and chermesins B (**23**) are spiromeroterpenoids containing a drimane-type sesquiterpene skeleton was isolated from the ethyl acetate extract of culture filtrate of *P. chermesinum* EN-480 obtained from a marine red alga *Pterocladiella tenuis*[30]. The antibacterial activity of both chermesins A (**22**) and chermesins B (**23**) was tested against four human pathogens (*Candida albicans, Escherichia coli, Micrococcus luteus, and Pseudomonas aeruginosa*) and five aquatic bacteria (*Aeromonas hydrophila, Edwardsiella tarda, Vibrio alginolyticus, V. harveyi, and V. parahemolyticus*) both compounds showed a notable antimicrobial activity against *C. albicans, E. coli, M. luteus,* and *V. alginolyticus*, with MIC values ranging from 8 to 64 µg/mL[30]. Penialidins C (**24**) is an anti-tuberculosis polyketide was isolated from potato dextrose broth medium of an endophytic *Penicillium* species from leaves of *Garcinia nobilis* collected in Mount Etinde in the Southwest Region of Cameroon[31]. Penialidins C (**24**) was tested for its antimycobacterial activity against *Mycobacterium smegmatis* as (**24**) showed a remarkable antimycobacterial activity with MIC of 15.6 µg /mL[31]. Citrinin (**53**) is a polyketide mycotoxin, which is a secondary metabolite of some fungi species. Citrinin (**53**) was purified from the ethyl acetate extract of the culture media of *Penicillium citrinum* was isolated from olive tree fruit[32]. The agar diffusion test (Kirby–Bauer antibiotic testing) was used to test the antibacterial activity of citrinin (**53**) against several micro-organisms (*Bacillus subtilis* [G+], *Staphylococcus aureus* [G+], *Escherichia coli* [G-]). Citrinin (**53**) exerted marked antibiotic activity against the tested Gram (-) and Gram (+) bacteria with activity up to several-fold better than tetracycline which used as positive control[32].

Antifungal polyketides isolated from the genus Penicillium

8-*O*-methylaverufin (**25**) and 1,8-*O*-dimethylaverantin (**26**) are two quinone derivatives that were isolated from the ethyl acetate extract of a *P. chrysogenum*[33]. 8-*O*-methylaverufin (**25**) and 1,8-*O*-dimethylaverantin (**26**) were tested for their antimicrobial activities against *Staphylococcus aureus, Bacillus subtilis, and Mucor miehei.* They showed a notable antifungal activity with *Mucor miehei* with a noticed inhibition zone around 16mm[33]. Sch 642305 (**27**), a fungitoxic extrolites was isolated from the ethyl acetate extract of Czapek-Dox broth culture media of *P. canescens*. Sch 642305 (**27**) antifungal activity was measured against *Rhizoctonia solani*. Sch 642305 (**27**) inhibited the mycelial growth completely of isolates of *R. solani* and other plant pathogenic fungi *in vitro*[34].

Table 3. Antifungal polyketides isolated from the genus *Penicillium*

Number	Chemical constituents	Species
25	8-*O*-methylaverufin	*Penicillium chrysogenum*
26	1,8-*O*-dimethylaverantin	
27	Sch 642305	*Penicillium canescens*
28	6`-hydroxy-3_-methoxy-mitorubrin	*Penicillium radicum* fki-3765-2
29	4`-hydroxy-3-methoxy-(S)-mitorubrin	
30	Monomethyl-(S)-mitorubrin	
31	Aversin	*Penicillium purpurogenum* Stoll (CGMCC 3. 3708)
32	Macrophorin A	*Penicillium* YIM PH 30003
33	Macrophorin D	

Table 4. Antiviral polyketides isolated from the genus *Penicillium*

Number	Chemical constituents	Species
34	Sch 351633	*Penicillium griseofulvum*
35	Hesseltin A	*Penicillinum hesseltinei*
36	Purpurquinones B	*Penicillium purpurogenum* JS03-21
37	Purpurquinones C	
38	Purpuresters A	
39	TAN-931	
40	Sorbicatechols A	*Penicillium chrysogenum* PJX-17
41	Sorbicatechols B	
42	Peniciherquamide C	*Penicillium herquei*
43	Herquline A	*Penicillium herquei*

Table 5. Anti-inflammatory polyketides isolated from the genus *Penicillium*

Number	Chemical constituents	Species
44	Pyrenocine A	*Penicillium paxillin*
45	2*E*,4*Z*-tanzawaic acid D	*Penicillium* sp. SF-6013
46	Tanzawaic acids A	
47	Methylpenicinoline	*Penicillium* sp. (SF-5995)
48	Purpurogenolide B	*Penicillium purpurogenum*
49	Purpurogenolide C	
50	Purpurogenolide D	
51	Berkeleyacetal C	
52	3-acetoxymethyl-6,8-dimethoxycoumarin	*Penicillium purpurogenum*

6`-hydroxy-3-methoxy-mitorubrin (**28**), 4`-hydroxy-3-methoxy-(S)-mitorubrin (**29**), and monomethyl-(S)-mitorubrin (**30**), are three isochromene derivatives were isolated from acetone extract of culture broth of *P. radicum* fki-3765-2. The three compounds showed no antifungal activity against *Candida albicans* but interestingly they potentiated the miconazole antifungal activity against *C. albicans* in a dose-dependent manner[35] Aversin (**31**), is an anthraquinone was isolated from a methanol extract of solid cultures of the fungus *P. purpurogenum* Stoll (CGMCC 3. 3708). Aversin (**31**) antifungal activity was tested against three phytopathogens, *Botrytis cinerea*, *Magnaporthe oryzae* and *Gibberella saubinettii*. Aversin (**31**) showed a notable antifungal activity against *B. cinerea* with MIC 25 μM[36]. Macrophorin A (**32**) and macrophorin D (**33**) are cyclohexanone epoxides having a sesquiterpene residue was isolated from 80% acetone mycelia extract of the fungus *Penicillium* YIM PH 30003. Upon testing the antifungal activity of macrophorin A (**32**) and macrophorin D (**33**) against *Fusarium solani* fungal strain it had a significant antifungal activity with MICs at 16 and 32 mg/mL respectively[37].

Antiviral polyketides isolated from the genus Penicillium

Sch 351633 (**34**), is an antihepatitis C virus protease inhibitor was isolated from the ethyl acetate extract of fermentation broth of *P. griseofulvum* was isolated from a soil sample collected from desert terrain in the state of Arizona, USA. Sch 351633 (**34**) showed antiviral activity against hepatitis C virus (HCV) in an *in vitro* HCV protease scintillation proximity assay with an IC_{50} = 3.8 μg /mL[38]. Hesseltin A (**35**) is a polyketide-terpenoid compound was isolated from the ethyl acetate extract of the agar plate of *P. hesseltinei*. Upon testing of hesseltin A (**35**) against herpes simplex virus (HSV-1.) it showed inhibition of the viral growth by 25-50% at 300 μg[39]. Purpurquinones B (**36**), purpurquinones C (**37**), purpuresters A (**38**) and TAN-931(**39**), four polyketides were isolated from the ethyl acetate extract of culture broth of *P. purpurogenum* JS03-21. The antiviral activity of the four compounds was tested against influenza virus A (H1N1). The four isolated compounds (**36, 37, 38 and 39**) showed potent antiviral activity more than ribavirin used as positive control with an IC_{50} 61.3, 64.0, 85.3, 58.6, and 100.8 μM, respectively[40]. Sorbicatechols A (**40**) and sorbicatechols B (**41**) are two polyketides were isolated from the ethyl acetate extract of culture broth of fungal strain *P. chrysogenum* PJX-17. The antiviral activity of sorbicatechols A (**40**) and sorbicatechols B (**41**) was evaluated against the influenza virus (H1N1) using cytopathic effect (CPE) inhibition assay. Compounds (**40** and **41**) exhibited a significant antiviral activity with an IC_{50} values of 85 and 113 μM respectively[41]. Peniciherquamide C (**42**) is a diazabicyclooctane derivative was isolated from dichloromethane extract of potato dextrose broth of *P. herquei* fungal strain was isolated from Seaweeds collected in Toba, Mie, Japan. The anti-HCV activity of peniciherquamide C (**42**) was evaluated and it showed a notable anti-HCV activity with an IC_{50} value of 5.1 μM[42]. Herquline A (**43**) is an antiviral polyketide was isolated from 50% aqueous ethanol extract of culture broth media of *P. herquei* fungal strain. Herquline A (**43**) inhibited replication of influenza A virus (A/PR/8/34) strain in a dose-dependent manner giving an IC_{50} 10 μg/mL[43].

Anti-inflammatory polyketides isolated from the genus Penicillium:

Penicillitone (**11**) was tested for its anti-inflammatory activity using murine macrophage RAW 264.7 cell line test method.[44] Penicillitone (**11**) had an anti-inflammatory activity through a significant reduction in the secretion of two pro-inflammatory cytokines by 70.7% and 90% using dexamethasone as standard reference[21] Pyrenocine A (**44**), a polyketide was isolated from the ethyl acetate extract of the growth culture medium of the marine-derived fungus *P. paxillin*. Pyrenocine A (**44**) demonstrated an anti-inflammatory activity through inhibition of the nitrite production and synthesis of inflammatory prostaglandin E2 and cytokines[45]. 2*E*,4*Z*-tanzawaic acid D (**45**), a tanzawaic acid derivative along with tanzawaic acids A (**46**) were isolated from the ethyl acetate extract of growth culture medium of the marine-derived fungus *Penicillium* sp. SF-6013. Using lipopolysaccharide (LPS)-induced RAW264.7 murine macrophages model system, the anti-inflammatory activity of (**45**) and (**46**) was tested and significantly inhibited nitric oxide production with an IC_{50} values of 37.8 and 7.1lM, respectively[46]. Methylpenicinoline (**47**), was isolated from the ethyl acetate extract of agar *Penicillium* sp. (SF-5995) was isolated from an unidentified soft coral. Methylpenicinoline (**47**) was tested for its ant-inflammatory and anti-neuroinflammatory activities using RAW264.7 macrophages and BV2 microglia, respectively. The results suggested methylpenicinoline (**47**) as a promising therapeutic agent for its ant-inflammatory and anti-neuroinflammatory activities. The reported mechanism of action was through inhibition of nitric acid production stimulated by lipopolysaccharide through suppressing the expression of nitric oxide synthase in EAW264.7 macrophages along with inhibition of COX-2 expression decreasing the production of prostaglandin E2 in a dose-dependent manner along with reduction in cytokines production[47]. Purpurogenolide B (**48**), purpurogenolide C (**49**), purpurogenolide D (**50**) and berkeleyacetal C (**51**) were isolated from the ethyl acetate extract of the growth culture medium of *P. purpurogenum* MHZ 111. The

isolated meroterpenes (**48**), (**49**), (**50**) and (**51**) were tested for their anti-inflammatory activity in LPS-activated NO production in BV-2 microglial cells using the Griess assay. Compounds (**48**), (**49**), (**50**) and (**51**) showed a significant anti-inflammatory activity through inhibition nitric acid production stimulated by lipopolysaccharide with an IC_{50} values of 30, 15.5, 8 and 0.8 μM respectively[48]. 3-acetoxymethyl-6,8-dimethoxycoumarin (**52**), a coumarin derivative was isolated from the ethyl acetate extract of the growth culture medium of fungus *P. purpurogenum* MHZ 111. Compound (**52**) showed significant anti-inflammatory activity through inhibition nitric acid production in lipopolysaccharide-activated BV-2 microglial cells with an IC_{50} values of 26.5 μM[49].

CONCLUSION

This review demonstrates the functional and structural diversity of a wide range of polyketides natural products, a remarkable class of compounds isolated from genus *Penicillium* and describes the diversity of their biological activities such as cytotoxic, antibacterial, antifungal, antiviral and anti-inflammatory activities. Therefore, the understanding of polyketides structural diversity and their biosynthetic pathways has obvious academic importance in order to set the foundation for the future studies of the possible use of polyketide scaffolds as a chemical structural entity to prepare series of biosynthetic analogues to improve their biological activity with a better understanding of their mechanism of actions.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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