Review

Secondary Metabolites from Genus *Eurotium* and Their Biological Activities

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Review

Secondary Metabolites from Genus *Eurotium* and Their Biological Activities

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Abstract: *Eurotium* is the teleomorph genus associated with section Aspergillus. *Eurotium* comprises approximately 20 species, which are widely distributed in nature and human environments. *Eurotium* is usually the key microorganism for the ferment ation of traditional food, such as Fuzhuan brick tea, Liupao tea, Meju, and Karebushi, thus *Eurotium* is an important fungus in food industry. *Eurotium* has been extensively studied because they contain a series of interesting, structurally diverse, and biologically important secondary metabolites, including anthraquinones, benzaldehyde derivatives, and indol diketopiperazine alkaloids. These secondary metabolites have shown multiple biological activities, including antioxidative, antimicrobial, cytotoxic, antitumor, insecticidal, antimalarial, and anti-inflammatory activities. This study presents an up-to-date review of the phytochemistry and biological activities of all *Eurotium* species. This review will provide the recent advances on the secondary metabolites and their bioactivities in genus *Eurotium* for the first time and serve as a database for future research and drug development from the genus *Eurotium*.

Keywords: *Eurotium*; *Eurotium* cristatum; secondary metabolites; anthraquinones; benzaldehyde derivatives; biological activity

1. Introduction

Eurotium (Eurotiaceae) is the teleomorph genus associated with section *Aspergillus*. While most of *Aspergillus* species are asexual, sexual *Aspergillus* species have been separately summarized and named *Eurotium* [1,2]. *Eurotium* is characterized by its golden cleistothecia, lenticular ascospores, uniseriate conidial heads in shades of green or blue, and yellow-, orange- or red-encrusted hyphae [2,3]. The genus *Eurotium* comprises approximately 20 species [2], of which *Eurotium amstelodami*, *Eurotium cristatum*, and *Eurotium repens* have received the most attention [4,5]. All species of *Eurotium* are hypertonic fungi, which are widely distributed in nature and human environments, especially in environments of high salt, high sugar, and low water, such as salt lake, desert, plateau, and mangrove. *Eurotium* species are generally considered to be benign fungi without mycotoxins [6–10]. Moreover, *Eurotium* species are usually the key microorganism for the fermentation of traditional food, such as Fuzhuan brick tea, Liupao tea, Meju, and Karebushi [11–13].

Eurotium contains abundant secondary metabolites, which attract increasing attention. The investigation of secondary metabolites in *Eurotium* began with the identification of chemical structure of *Eurotium's* pigment, which dates back to the 19th century. Great progress has been made on the secondary metabolites of *Eurotium* over the past few decades [4,5]. Notably, marine environment and fermented food and drink have become important sources of *Eurotium* species in recent years, leading to the discovery of a variety of new secondary metabolites [14]. Compounds isolated from *Eurotium* species mainly include anthraquinones, benzaldehyde derivatives, and indol diketopiperazine

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alkaloids. These secondary metabolites exhibit various bioactivities, such as antioxidative, antimicrobial, cytotoxic, antitumor, insecticidal, antimalarial, and anti-inflammatory activities [13,15–20]. However, as far as we know, there is no English review article to systematically summarize the secondary metabolites and their biological activities in the genus *Eurotium.*

In this context, this review will provide the recent advances in the secondary metabolites and their bioactivities in the genus *Eurotium* for the first time. Meanwhile, future perspectives and challenges are also outlined in this review.

2. Secondary metabolites from *Eurotium*

Nearly 180 compounds have been isolated and identified from *Eurotium* species by nuclear magnetic resonance (NMR) spectroscopy. These compounds mainly include anthraquinones, benzaldehyde derivatives, and indol diketopiperazine alkaloids.

2.1. Anthraquinones

Anthraquinones, which are formed by the merger of three benzene rings, are the largest group of natural pigments of quinoids [21]. Anthraquinones are usually produced by plants and microorganisms [22]. They often give a color (usually yellow, orange, or brown) to the lichens and the mycelium and fruiting bodies of fungi. Usually, there are several side substituents in the benzene ring of fungal anthraquinones. The most widespread in fungi are 1,8 dihydroxy and 1,5,8 or 1,6,8 trihydroxy anthraquinone derivatives [23]. Anthraquinones have shown a variety of pharmacological activities, including antibacterial, antiviral, insecticidal, diuretic, diarrhoeal, immunomodulatory, and anticancer effects [10,24,25].

Research on anthraquinones of *Eurotium* began in 1980. Anke et al. systematically investigated the structures of pigments in 20 *Eurotium* species, including *Eurotium aeutum, Eurotium glabrum, Eurotium herbariorum, Eurotium pseudoglaucum, E. repens, Eurotium rubrum, Eurotium tonophihtm, Eurotium umbrosum, Eurotium appendiculatum, Eurotium carnoyi, Eurotium echinulatum, Eurotium niveoglaucum, E. amstelodami, Eurotium chevalieri, E. cristatum, Eurotium heterocaryoticum, Eurotium intermedium, Eurotium leucocarpum, Eurotium montevidensis,* and *Eurotium spiculosum*. They found that these pigments were polyhydroxy anthraquinones, including questin **(1)**, physcion **(2)**, erythroglaucin **(3)**, emodin **(4)**, catenarin **(5)**, rubrocristin **(6)**, rubrocristin-8-methylether **(7)**, rubrocristin-6-acetate **(8)** and querstin-6-methylether **(9)**. Further, rubrocristin, a new yellow pigment, was first discovered in nature. The production of these pigments was seriously affected by the concentrations of glucose and salt in culture medium. It has been proved that the number of hydroxyl groups and their position plays an essential role in the antibacterial activity of these polyhydroxy anthraquinones [21]. In addition, physcion was supposed to play a role in iron transport or metabolism of fungal cell [26]. Three anthraquinones, including 2-*O*-methyleurotinone **(10)**, 2,12-dimethyleurotinone **(11)**, and eurotinone **(12)** were isolated from *E. echinulatum* by Eder et al. These compounds were found to have an antiangiogenic effect; thus, they might be used for preventing and treating malignant diseases [27]. Miyake et al. isolated a strain of *E. herbariorum* NU-2 during the manufacturing process of Karebushi (a traditional food in Japan), and then identified physcion-10,10'-bianthrone **(13)**, questinol **(14)**, asperflavin **(15)**, as well as questin, physcion**,** and catenarin in this fungus [15]. Additionally, some pigments of anthraquinones, including variecolorquinone A **(16)**, questin, physcion, erythroglaucin, emodin, catenarin, questinol, and asperflavin, were also found in other *Eurotium* strains, such as *Eurotium sp.* M30 XS-2012 [10] or *E. cristatum* KUFC 7356 [28].

The study of bioactive substances in marine microorganisms has become a hot topic in recent years [1]. Li and co-workers isolated the *E. rubrum* strain from a marine mangrove plant *Hibiscus Tiliaceus*, and then identified four new anthraquinones, as well as three known anthraquinones (questin, 2-*O*-methyleurotinone, and asperflavin) in this fungus. These four new anthraquinones were 2-*O*-methyl-4-*O*-(*α*-D-ribofuranosyl)-9-dehydroxyeurotinone **(17**; colorless amorphous powder**)**, 2-*O*-methyl-9-dehydroxyeurotinone **(18**; colorless amorphous powder**)**, eurorubrin **(19**; brown amorphous powder**)**, and 3-*O*-(*α*-D-ribofuranosyl)-questin **(20**; orange amorphous powder**)**. Based on the spectral data, 2-*O*-methyl-9-dehydroxyeurotinone is a 9-dehydroxyl derivative of 2-*O*-

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methyleurotinone; eurorubrin is a symmetrical dimeric compound composed of two molecules of asperflavin through a methylene group; 3-*O*-(*α*-D-ribofuranosyl)-questin is a glycoside consisted of questin as aglycone and one sugar unit [29]. In addition, Du et al. isolated an endophytic fungus (*E. cristatum* EN-220) from the marine alga *Sargassum thunbergii*, and identified one new anthraquinone glycoside named 3-*O*-(*α*-D-ribofuranosyl)-questinol **(21**; red amorphous powder**)**, as well as asperflavin ribofuranoside **(22)**, asperflavin, (+)-variecolorquinone A, eurorubrin, and 3-*O*-(*α*-D-ribofuranosyl)-questin. 3-*O*-(*α*-D-ribofuranosyl)-questinol and 3-*O*-(*α*-D-ribofuranosyl)-questin have the same ribose residue [30]. A new anthraquinone named 9-dehydroxyeurotinone **(23**; colorless amorphous powder**)** was also found in the *E. rubrum* [31]. Zin et al. isolated a new compound named acetylquestinol **(24**; yellow crystal**)**, as well as four known anthraquinones including questin**,** physcion, emodin, and questinol from the culture of the mangrove plant *Rhizophora mucronata*-derived endophytic fungus *E. chevalieri* KUFA 0006. Acetylquestinol is a 1,3,6,8-tetrasubsituted 9,10-anthraquinone, similar to questinol [19]. Further, the metabolites vary greatly between the *E. chevalieri* KUFA 0006 and soil-derived strain of *E.chevalier* [32]. Additionally, questinol was also isolated from the marine-derived *E. amstelodami* [33].

The endophytes derived from the saline-alkali plants are attracting increasing attention due to the extreme environment of high osmolarity and nutrient deprivation. The chemical investigation of saline-alkali plant-derived endophytic fungi has just begun compared with those of marine mangrove plant-derived endophytes. Zhang et al. found a new anthraquinone named rubrumol **(25)**, as well as emodin, catenarin, rubrocristin, and 2-*O*-methyleurotinone in a halo-tolerant endophytic fungus *E. rubrum.* This fungus is derived from the salt-tolerance wild plant *Suaeda salsa.* These anthraquinones displayed topoisomerase inhibitory activity, which implied that endophytic *Eurotium* fungus from saline-alkali plants may be one new reservoir for natural products in the future [25] (Figure 1).

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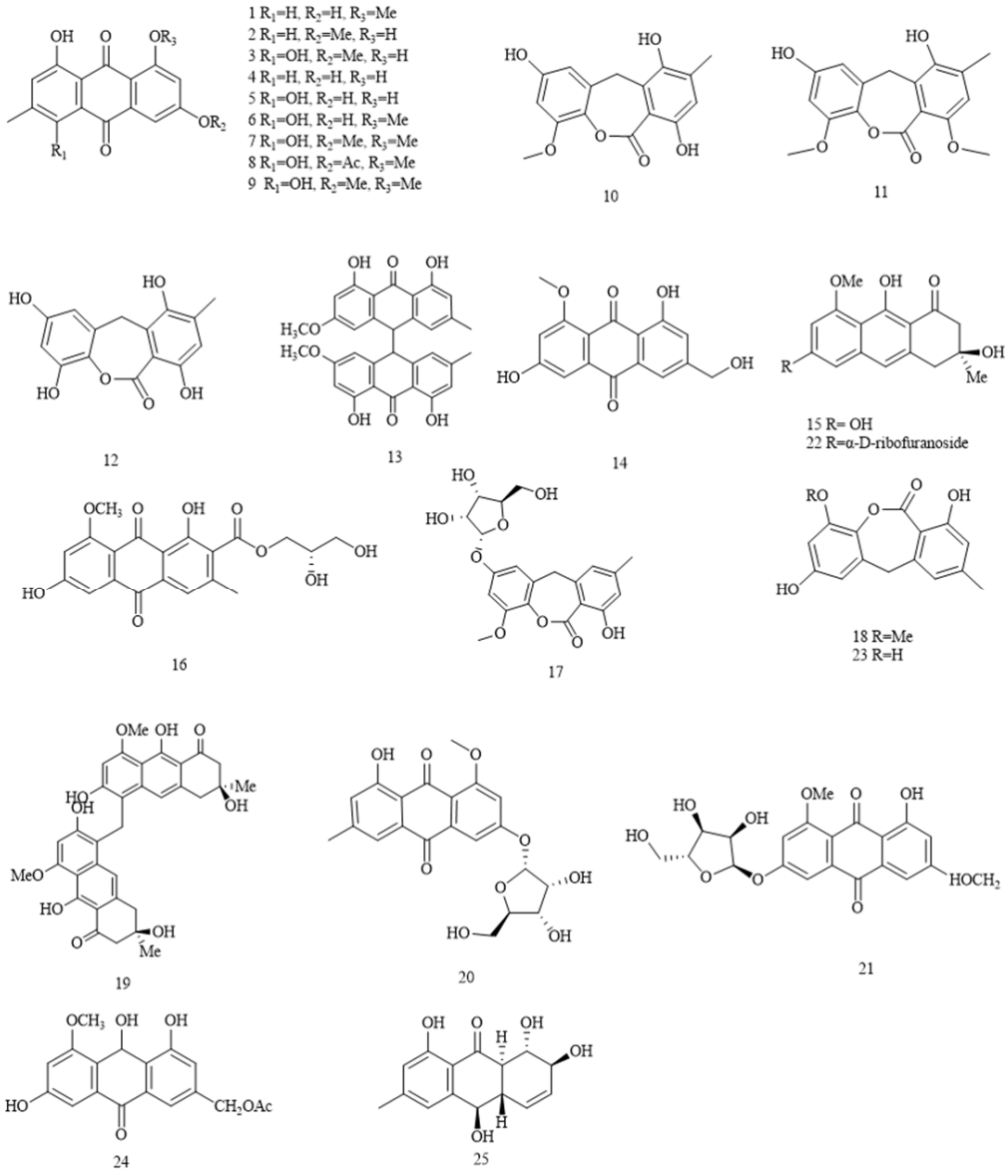

Figure 1. Structures of anthraquinones (compounds 1-25).

2.2. Benzaldehyde derivatives

Benzaldehyde derivatives are a class of polyketides that synthesized by the combination of polyketone and terpenoid pathways [34]. It has been reported that benzaldehyde derivatives have various bioactivities, including, antioxidative, antibacterial, antifungal, antitumor, antimalarial, and antileishmanial activities [35–37]. Benzaldehyde derivatives, which are a kind of natural pigments, are a class of main metabolites in genus *Eurotium* [13]. More than 20 benzaldehyde derivatives have been identified in *Eurotium*.

Four new and seven known benzaldehyde derivatives were identified from *E. rubrum*, an endophytic fungus isolated from the inner tissue of stems in the mangrove plant *Hibiscus tiliaceus* by Li et al. These four benzaldehyde derivatives were 2-(2',3-epoxy-1'-heptenyl)-6-hydroxy-5-(3''-methyl-2''-butenyl)-benzaldehyde **(26**; yellowish amorphous powder**)**, (*E*)-6-hydroxy-7-(3-methyl-2-

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butenyl)-2-(3-oxobut-1-enyl)-chroman-5-carbaldehyd **(27**; yellowish amorphous powder**)**, 2-(1',5'-heptadienyl)-3,6-dihydroxy-5-(3''-methyl-2''-butenyl)-benzaldehyde **(28**; yellowish amorphous powder**)**, and eurotirumin **(29**; yellowish amorphous powder**)**. These seven known benzaldehyde derivatives were chaetopyranin **(30)**, flavoglaucin **(31)**, aspergin **(32)**, isotetrahydroauroglaucin **(33)**, isodihydroauroglaucin **(34)**, 2-(2',3-epoxy-1',3'-heptadienyl)-6-hydroxy-5-(3-methyl-2-butenyl)-benzaldehyde **(35)**, and 2-(2',3-epoxy-1',3',5'-heptatrienyl)-6-hydroxy-5-(3-methyl-2-butenyl)-benzaldehyde **(36)**. These four benzaldehyde derivatives possess a penta-substituted benzene ring system bearing a 3-methyl-2-butenyl at C-5 and a phenolic hydroxyl group at C-6. The structures of compounds **26** and **35** are similar, except that two olefinic carbon signals of C-3' and C-4' in the ^{13}C-NMR of compound **35** are replaced by two methylene signals at C-3' and C-4' in compound **26**. The structures of compounds **27** and **30** are similar, except that the signals at H-6' and C-6' in compound **30** are replaced by a carbonyl signal at C-6' in compound **27**. The structures of compounds **28** and **34** are similar, and the inconsistent position for the two double bonds in the heptadienyl side chain is the only difference [36]. Li et al. also isolated two new benzaldehyde derivatives, eurotirubrin A **(37)** and eurotirubrin B **(38**; yellow powder**)** in *E. rubrum* in another research [38]. In addition, auroglaucin **(39)**, tetrahydroauroglaucin **(40)**, dihydroauroglaucin **(41)**, flavoglaucin, and isodihydroauroglaucin were identified from Karebushi-derived *Eurotium* fungi. All four benzaldehyde derivatives are disubstituted gentisaldehyde (2,5-dihydroxybenzaldehyde) derivatives with a prenyl group at C-3 and a seven-carbon unbranched aliphatic chain at C-6 [11]. Bioassay-guided fractionation of *E. repens* leads to the isolation of two new benzaldehyde compounds, (*E*)-2-(hept-1-enyl)-3-(hydroxymethyl)-5-(3-methylbut-2-enyl)-benzene-1,4-diol **(42**; yellow solid**)** and (*E*)-4-(hept-1-enyl)-7-(3-methylbut-2-enyl)-2,3-dihydrobenzofuran-2,5-diol **(43**; yellow oil**)**, along with five known benzaldehyde derivatives, including flavoglaucin, 2-(2',3-epoxy-1',3'-heptadienyl)-6-hydroxy-5-(3-methyl-2-butenyl)-benzaldehyde, auroglaucin, tetrahydroauroglaucin, and dihydroauroglaucin. Compounds **42** and **43** showed high structural similarities except that the carbinol group at C-7 in compound **42** was replaced by a hemiacetal group in compound **43** [39]. Gao et al. also isolated flavoglaucin, 2-(2',3-epoxy-1',3'-heptadienyl)-6-hydroxy-5-(3-methyl-2-butenyl)-benzaldehyde, auroglaucin, tetrahydroauroglaucin, dihydroauroglaucin**,** and (*E*)-2-(hept-1-enyl)-3-(hydroxymethyl)-5-(3-methylbut-2-enyl)-benzene-1,4-diol from the fungus *E. repens* [18].

Two new benzaldehyde derivatives named (3'*S**, 4'*R**)-6-(3',5-epoxy-4'-hydroxy-1'-heptenyl)-2-hydroxy-3-(3''-methyl-2''-butenyl)-benzaldehyde **(44**; yellow oil**)** and 3'-OH-tetrahydroauroglaucin **(45**; yellow oil**)** were isolated from a gorgonian-derived *Eurotium sp*. These two compounds could non-enzymatically transform into pairs of enantiomers or epimers, respectively, with opposite configurations at C-3', thus, they are possibly artefacts formed during the extraction/isolation process [34]. Two new benzaldehyde derivatives named cristaldehyde A **(46**; yellow powder**)** and cristaldehyde B **(47**; yellow powder**)** were isolated from the fungus *E. cristatum* in 2019. Compound **46** contains a dibenzannulated 6,6-spiroketal skeleton and is a racemic mixture of easily interconvertible enantiomers [37]. It's worth noting that six benzaldehyde derivatives, including flavoglaucin, isodihydroauroglaucin, 2-(2',3-epoxy-1',3'-heptadienyl)-6-hydroxy-5-(3-methyl-2-butenyl)-benzaldehyde, 2-(2',3-epoxy-1',3',5'-heptatrienyl)-6-hydroxy-5-(3-methyl-2-butenyl)-benzaldehyde, tetrahydroauroglaucin, and dihydroauroglaucin were discovered in Fuzhuan brick tea-derived *E. cristatum*. *E. cristatum* is the only dominant fungus in Fuzhuan brick tea, which is responsible for the color, taste, and health benefits of Fuzhuan brick tea [40–43]. These benzaldehyde derivatives may have a major impact on the sensory quality and health benefits of Fuzhuan brick tea [13] (Figure 2).

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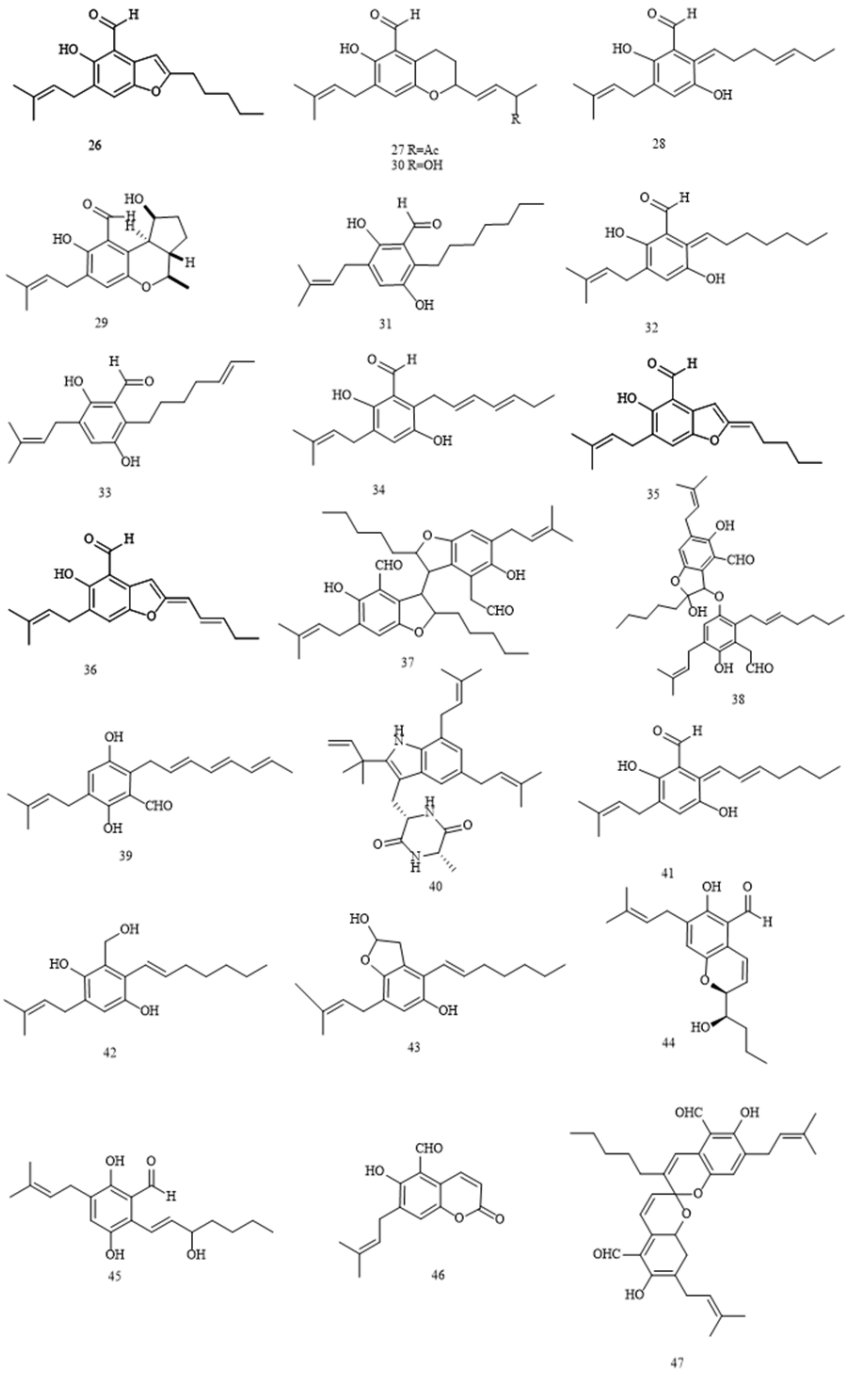

Figure 2. Structures of benzaldehyde derivatives (compounds 26-47).

2.3. Indole diketopiperazine alkaloids

Indole diketopiperazine alkaloids are a class of important secondary metabolites, which are widely distributed in filamentous fungi, especially in genus *Eurotium* [17]. Indole diketopiperazine alkaloids are formed by the condensation of some amino acids, including tryptophan, proline, and leucine [44]. Due to their significant biological activities including antimicrobial, antiviral, anticancer, immunomodulatory, antioxidative, and insecticidal activities, indole diketopiperazine alkaloids in genus *Eurotium* is attracting increasing attention [45,46].

Feed refused by swine contained a high-propagule density of *Eurotium sp.* Further, echinulin **(48)** was detected in this feed, and also isolated from this feed-derived *E. repens* [47]. Although significant differences in the metabolite composition were observed between the feed-derived and

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marine-derived *E. repens*, the biosynthesis of echinulin was conserved in *E. repens* regardless of its origin [48]. Kimoto et al. isolated neoechinulin A **(49)** from marine fungus *E. rubrum* Hiji 025, and further synthesized this compound by the natural configuration [49]. Slack et al. investigated the metabolites in *E. herbariorum*, *E. amstelodami*, and *E. rubrum* that are common in the built environment of Canadian homes. Neoechinulin B **(50)** and neoechinulin A were the major metabolites, but preechinulin **(51)**, neoechinulin E **(52)**, and echinulin were the minor metabolites in *E. amstelodami* and *E. rubrum*. *E. herbariorum* also produced a small amount of neoechinulin E [50]. In addition, a new spirocyclic diketopiperazine alkaloid, 7-*O*-methylvariecolortide A **(53**; yellow amorphous powder**)** was isolated from the mangrove plant *Hibiscus tiliaceus*-derived *E. rubrum*, along with variecolortides A-C **(54-56)**. Structurally, compounds **53**-**56** represent the unique spiro-anthronopyranoid diketopiperazine skeleton with a stable hemiaminal functional group. Further, a hydroxyl group in compound **54** is replaced by a methoxyl group at C-7 in compound **53** [51]. Fructigenine A **(57)** bearing a reverse-prenyl group was isolated from *Eurotium sp*. SF-5130 [52].

A new diketopiperazine dimer, namely, eurocristatine **(58**; white crystals**)** was isolated and identified from *E. cristatum*, along with previously reported dioxopiperazine alkaloids including variecolorin J **(59)**, echinulin, neoechinulin A, and neoechinulin E [28]. Yan et al. cultivated the semi-mangrove plant *Hibiscus tiliaceus*-derived *E. rubrum*, and further isolated one new dioxopiperazine alkaloid, 12-demethyl-12-oxo-eurotechinulin B **(60**; colorless amorphous powder**)** from this fungal strain, together with six known compounds, including variecolorin J, variecolorin G **(61)**, eurotechinulin B **(62)**, cryptoechinuline G **(63)**, alkaloid E-7 **(64)**, and isoechinulin B **(65)**. The structures of compounds **60** and **62** are similar, except that Me-C (12) of compound **62** is replaced by a C (12)=O group in compound **60** [31]. Du et al. also found four new alkaloids named cristatumins A-D **(66-69)** in the culture extract of *E. cristatum* EN-220, along with six known congeners including isoechinulin A **(70)**, tardioxopiperazine A **(71)**, echinulin, neoechinulin A, preechinulin, and variecolorin G. This is the first report that the alanine residue in the 2,5-diketopiperazine moiety of compound **49** is replaced by the serine residue in compound **66**. The C-20 Me group in compound **48** is replaced by CH_2OH group in compound **67**. Compound **68** is an almost symmetrical molecule consisting of two indole diketopiperazine moieties. Compound **69** is a ring-opened diketopiperazine derivative of compound **52** [45]. Besides, a pyrrolidinoindoline diketopiperazine alkaloid named cristatumin E **(72**; yellow amorphous powder**)** was isolated from the alga-derived *E. herbariorum* HT-2 [53].

In 2018, three new indole diketopiperazine alkaloids of isoechinulin type named rubrumazines A-C **(73-75)** and 13 related analogues were isolated and identified from *E. rubrum* MA-150, a fungus obtained from mangrove-derived rhizospheric soil collected from the Andaman Sea coastline, Thailand. These 13 related analogues were dehydroechinulin **(76)**, variecolorin E **(77)**, dihydroxyisoechinulin A **(78)**, variecolorin L **(79)**, tardioxopiperazine **(80)**, L-alanyl-L-tryptophan anhydride **(81)**, echinulin, neoechinulin A, neoechinulin E, variecolortide B, variecolortide C, variecolorin G, and isoechinulin A. Compounds **73-75** possess an oxygenated prenyl group either at C-7 **(73** and **74)** or at C-5 **(75)** [54]. A new prenylated indole diketopiperazine alkaloid named cristatumin F **(82**; colorless powder**)** was isolated from the Fuzhuan brick tea-derived *E. cristatum*, along with four known compounds including variecolorin O **(83)**, echinulin, neoechinulin A, and dehydroechinulin. Structurally, compound **82** is a diketopiperazine congener to compound **48**. An alanine unit in compound **48** is replaced by a valine unit in the 2,5-diketopeperazine moiety in compound **82** [46]. Four new indole diketopiperazine derivatives **(84-87)** and nine known congeners **(88-91**, **48**, **50**, **64**, **74**, **76)** were identified from the culture extract of *E. cristatum* EN-220. Compounds **84-91** were *N*-(4'-hydroxyprenyl)-cyclo(alanyltryptophyl) **(84)**, isovariecolorin I **(85)**, 30-hydroxyechinulin **(86)**, 29-hydroxyechinulin **(87)**, rubrumline M **(88)**, neoechinulin C **(89)**, didehydroechinulin **(90)**, and variecolorin H **(91)** [55]. In addition, (11*R*,14*S*)-3-(1*H*-indol-3ylmethyl)6-isopropyl-2,5-piperazinedione **(92)** was isolated from the culture of *E. chevalieri* KUFA 0006 [19].

Zhong et al. isolated three pairs of spirocyclic diketopiperazine enantiomers named variecolortins A-C **(93-95)** from marine-derived fungus *Eurotium sp*. SCSIO F452. Compound **93**

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possesses an unprecedented highly functionalized benzo[*f*]pyrazino[2,1-*b*][1,3]oxazepine new carbon skeleton comprising a 2-oxa-7-azabicyclo[3.2.1]octane core. Compounds **94-95** represent rare examples of a 6/6/6/6 tetracyclic cyclohexene-anthrone carbon scaffold [56]. Further, Zhong et al. isolated and characterized three new prenylated indole 2,5-diketopiperazine alkaloids named eurotiumins A-C **(96-98**; white crystals, white solid, and yellow oil, respectively**)** from *Eurotium sp*. SCSIO F452 in the same year. Compounds **96** and **97** are a pair of diastereomers presenting a hexahydropyrrolo[2,3-*b*]indole skeleton. The structures of compounds **96** and **97** are assigned as *2S,3R,9S,12S-cyclo*-2-dimethylallyl-3-hydroxy-L-Trp-L-Ala and *2R,3S,9S,12S-cyclo*-2-dimethylallyl-3-hydroxy-L-Trp-L-Ala, respectively. The structures of compounds **98** and **50** are similar, except that an olefinic methylene in compound **50** is transformed into an olefinic methine substituted by a doublet methyl in compound **98** [57]. In 2021, Elsebai et al. found a diketopiperazine indole alkaloid named fintiamin **(99)** in marine sponge *Ircinia variabilis*-derived *Eurotium sp*. Compound **99** is a lipophilic terpenoid-dipeptide hybrid molecule, which has similar synthetic pathways to compound **48** [58] (Figure 3).

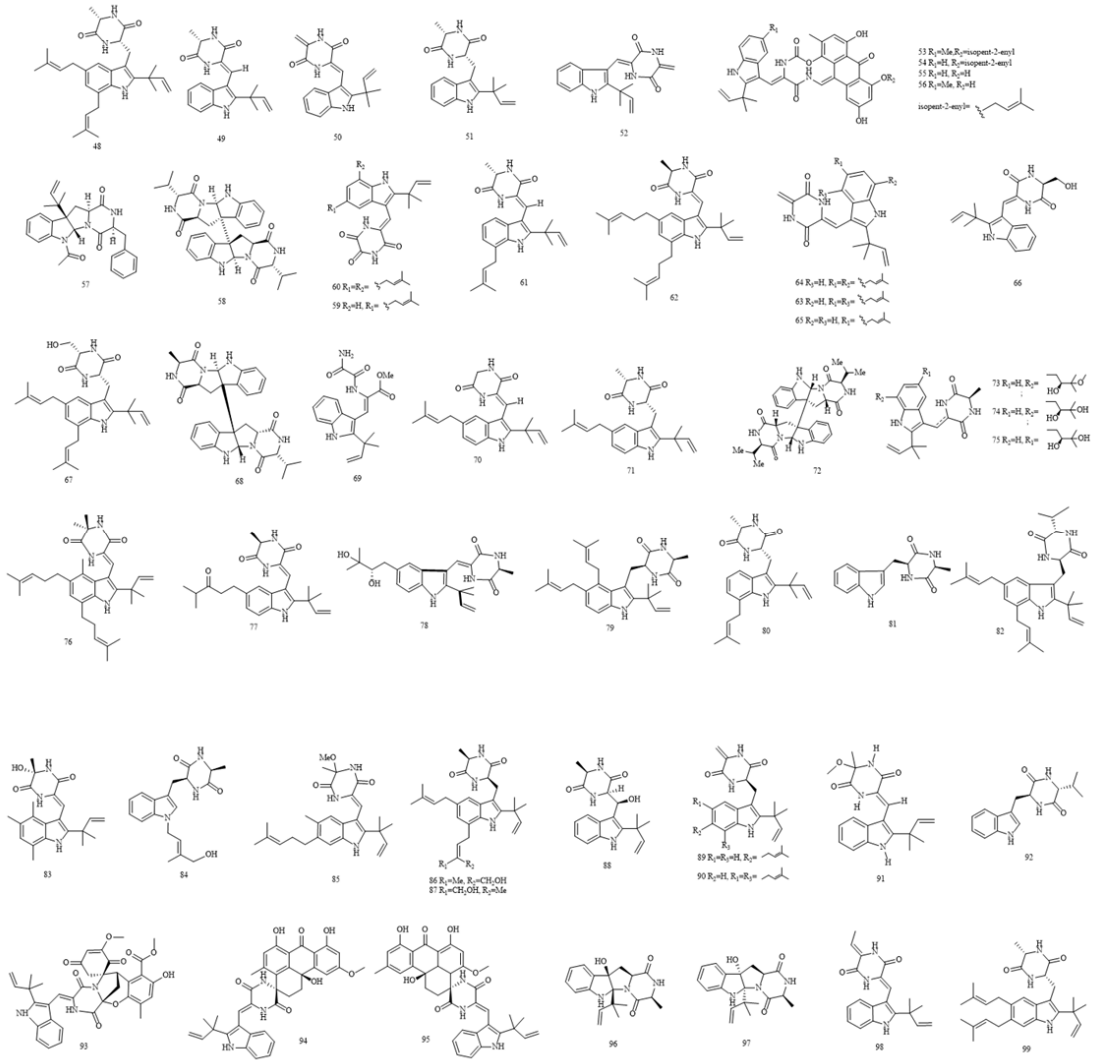

Figure 3. Structures of indole diketopiperazine alkaloids (compounds 48-99).

2.4. Other compounds

Six meroterpenoid-type terpenoids named chevalones A-D **(100-103**; colorless crystals, colorless crystals, white solid and white solid, respectively**)** and aszonapyrones A-B **(104-105)**, and terpenoid pyrrolobenzoxazine named CJ-12662 **(106)** have been isolated from *E. chevalieri* [32]. Eleven steroids were isolated from *E. rubrum*: 3*β*,5*α*-dihydroxy-10*α*-methyl-6*β*-acetoxy-ergosta-7,22-diene **(107**;

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colorless crystals**)**, 3*β*,5*α*-dihydroxy-6*β*-acetoxyergosta-7,22-diene **(108)**, (22*E*,24*R*)-ergosta-7,22-dien-3*β*-ol **(109)**, (22*E*,24*R*)-ergosta-7,22-dien-6*β*-methoxy-3*β*,5*α*-diol **(110)**, (22*E*,24*R*)-ergosta-7,22-dien-3*β*,5*α*,6*β*-triol **(111)**, (22*E*,24*R*)-ergosta-7,22-dien-3*β*,5*α*,6*α*-triol **(112)**, (22*E*,24*R*)-3*β*,5*α*,9*α*-trihydroxyergosta-7,22-dien-6-one **(113)**, (22*E*,24*R*)-3*β*,5*α*-dihydroxyergosta-7,22-dien-6-one **(114)**, (22*E*,24*R*)-5*α*,8*α*-epidioxyergosta-6,22-dien-3*β*-ol **(115)**, (22*E*,24*R*)-5*α*,8*α*-epidioxyergosta-6,22-dien-3*β*-acetate **(116)**, and (22*E*,24*R*)-ergosta-4,6,8(14),22-tetraen-3-one **(117)** [59]. Thirteen salicylaldehyde derivatives, including euroticins A-I **(118-126)**, salicylaldehydiums A-B **(127-128)**, and asperglaucins A-B **(129-130)** were isolated from *Eurotium sp*. SCSIO F452 [14,60–62] or *E. chevalieri* SQ-8 [16]. In addition, eight mycotoxins isolated from Eurotium species contain citrinin **(131)**, ochratoxin A **(132)**, gliotoxin **(133)**, aflatoxins **(134),** and sterigmatocystin **(135)** from *Eurotium* group [63]; a benzodiazepine-type mycotoxin cyclopenol **(136)** from *Eurotium sp*. SF-5130 [52]; and mycophenolic acid **(137)** from *E. repens* [64]. Three indole alkaloids, 2-(2-methyl-3-en-2-yl)-1*H*-indole-3-carbaldehyde **(138)** and (2,2-dimethylcyclopropyl)-1*H*-indole-3-carbaldehyde **(139)** were isolated from *E. chevalieri* KUFA 0006 [19], and 2-(1,1-dimethyl-2-propen-1-yl)-1*H*-indole-3-carboxaldehyde **(140)** was isolated from *Eurotium sp*.SCSIO F452 [65].

Other compounds isolated from *Eurotium* species contain ergosterol **(141)** [32], 2[(2,2-dimethylbut-3-enoyl)amino]benzoic acid **(142**; yellow viscous liquid**)**, 6,8-dihydroxy-3-(2-hydroxypropyl)-7-methyl-1*H*-isochromen-1-one **(143**; yellow viscous liquid**)**, palmitic acid, ergosterol 5,8-endoperoxide **(144)** [19], (11*S*,14*R*)-cyclo(tryptophylvalyl) **(145**; white crystal**)**, cinnalutein **(146)**, *cyclo*-L-Trp-L-Ala **(147)** [66], eurochevalierine **(148**; yellow needles**)** and sequiterpene **(149)** [32] from *E. chevalieri*; zinniol **(150)**, butyrolactone I **(151)**, aspernolide D **(152)**, vermistatin **(153)**, methoxyvermistatin **(154)**, eurothiocin A **(155**; colorless oil**)**, eurothiocin B **(156**; white amorphous solid**)** [67], and 7-isopentenylcryptoechinuline D **(157)** [31] from *E. rubrum*; methyl linoleate **(158**; yellow oil**)** [65], *cyclo*-(L-Pro-L-Phe) **(159)** [57], eurotinoids A-C **(160-162)**, dihydrocryptoechinulin D **(163)** [68], and (±)-Eurotone A **(164)** [69] from *Eurotium sp*. SCSIO F452; 5,7-dihydroxy-4-methylphthalide **(165)** from *E. repens* [39]; cristatumside A **(166)** from *E. cristatum* EN-220 [30]; (±)-eurotiumides A-G **(167-173)** from *Eurotium sp.* XS-200900E6 [20]; alkaloid viridicatol **(174)** from *Eurotium sp.* SF-5130 [52]; a β-hydroxy acid named monacolin K **(175)** [70] and a quinone derivative, cristaquinone A **(176)** [37] from *E. cristatum*; a glycoside isotorachrysone 6-*O*-*α*-D–ribofuranoside **(177)** from *E. cristatum* EN-220 [30] (Figure 4).

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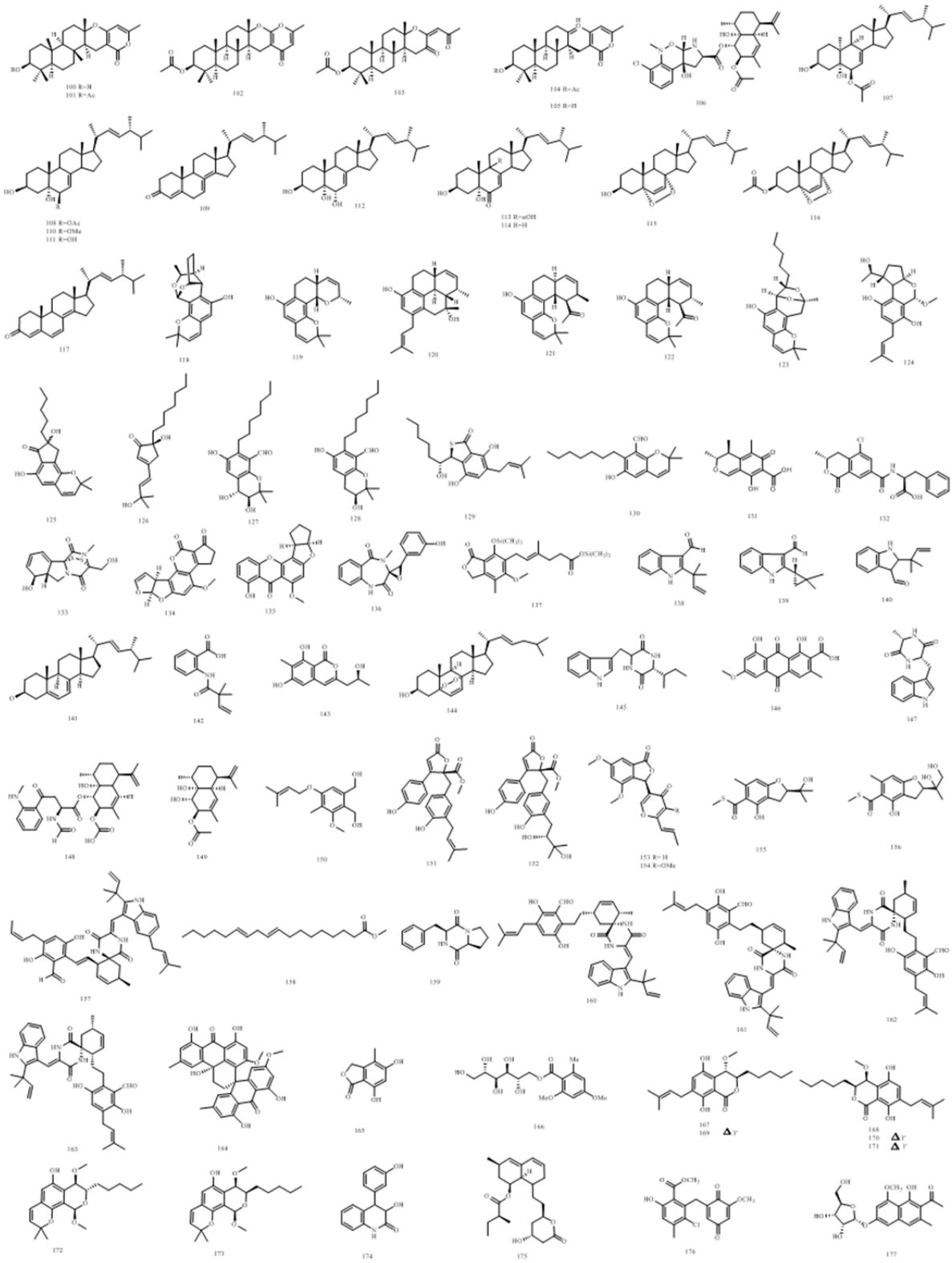

Figure 4. Structures of other compounds (compounds 100-177).

3. Bioactivities of secondary metabolites from *Eurotium*

Pharmacological studies have confirmed that the structurally unique compounds isolated from *Eurotium* species have multiple biological activities, including antioxidative, antimicrobial, cytotoxic, antitumor, insecticidal, antimalarial, and anti-inflammatory activities.

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3.1. Antioxidative activity

Numerous studies have proved that the metabolites isolated from *Eurotium* species showed excellent antioxidative activity. Further, the absolute and stereoscopic configurations affect the antioxidative activity of these compounds [56,57]. Ishikawa et al. found that flavoglaucin **(31)** was an excellent antioxidant and synergist with tocopherol. The antioxidative and synergistic effects of flavoglaucin and its derivatives largely depend on their hydroxy group, which does not form hydrogen bonds with the formyl group in the molecule [71]. Li et al. evaluated the antioxidative activity of metabolites isolated from a marine mangrove plant-derived endophytic fungus *E. rubrum* by using the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging assay. They found that neoechinulin E **(52)** showed a strong radical scavenging activity with half maximal inhibitory concentration (IC_{50}) values of 46.0 μM, which were stronger than that of well-known synthetic antioxidants butylated hydroxytoluene (IC_{50} = 82.6 μM) [72]. Eurorubrin **(19)** and 2-*O*-methyleurotinone **(10)** also displayed strong radical scavenging activity with IC_{50} values of 44.0 and 74.0 μM, respectively, while 2-*O*-methyl-4-*O*-(α-D-ribofuranosyl)-9-dehydroxyeurotinone **(17)**, 3-*O*-(α-D-ribofuranosyl)-questin **(20)**, 2-*O*-methyl-9-dehydroxyeurotinone **(18)**, asperflavin **(15)**, and questin **(1)** only showed weak or moderate activity [29]. In 2009, a study by Miyake et al. demonstrated that isodihydroauroglaucin **(34)**, auroglaucin **(39)**, dihydroauroglaucin **(41)**, tetrahydroauroglaucin **(40)**, and flavoglaucin exhibited high radical scavenging capacities of DPPH and superoxide when compared to α-tocopherol (a standard antioxidant for the scavenging capacity). The structures of 1'-monoene or 1',3'-diene in the substituent formed by the seven-carbon aliphatic chain of dihydroauroglaucin and tetrahydroauroglaucin may be related to their high radical scavenging activity [11]. Subsequently, Miyake et al. found that isoechinulin A **(70)** exhibited higher radical scavenging activity than α-tocopherol. Asperflavin, isoechinulin B, neoechinulin B **(50)**, and variecolorin O **(83)** were found to have the similar activity to α-tocopherol in respect of DPPH-radical scavenging [15].

Compounds eurotiumin C **(98)**, dehydroechinulin **(76)**, variecolorin G **(61)**, isoechinulin A, variecolorin O, neoechinulin B, and echinulin **(48)** showed significant radical scavenging activity against DPPH with IC_{50} values of 13, 19, 4, 3, 24, 13, and 18 μM, respectively, which were comparable or superior to that of ascorbic acid (Vc) (IC_{50} = 23 μM). Further, diprenylated analogs (compounds **61** and **70**) were found to have higher radical scavenging activity than the monoprenylated ones (compounds **96-98**, **83**, and **50**) and triprenylated ones (compounds **76** and **48**). The absolute configurations of the C-2 and C-3 in eurotiumin A **(96)** and B **(97)** may affect their radical scavenging activity [57]. (+)-variecolortin A **(93)** showed the radical scavenging activity against DPPH with an IC_{50} value of 58.4 μM, while the IC_{50} value of (-)-variecolortin A **(93)** was 159.2 μM. This implied that the stereoscopic configuration affects the biological activities of these two compounds [56]. In addition, the compounds (±)-eurotinoids A-C **(160-162)** and dihydrocryptoechinulin D **(163)** showed significant antioxidative activity against DPPH with IC_{50} values ranging from 3.7 to 24.9 μM, which were more potent than that of the positive control Vc [68]. The compounds (+)-euroticins B and (-)-euroticins B **(119)** showed remarkable DPPH radical scavenging activity with concentration for 50% of maximal effect (EC_{50}) values of 37.5 and 21.6 μM, which were superior or comparable to that of the positive control Vc (EC_{50} = 27.9 μM) [14]. In 2021, Zhong et al. found that (+)-euroticin C and (-)-euroticin C **(120)** showed the significant DPPH radical scavenging activity with EC_{50} values of 27.00 and 30.27 μM [60], but (±)-euroticin F **(123)** and G **(124)** showed week activity with EC_{50} values ranging from 41.40 to 77.07 μM [62]. In addition, compound Neoechinulin A **(49)** showed antioxidative activity against peroxynitrite derived from SIN-1 in the neuronal PC12 cells [49]. Nonetheless, the antioxidative activity of the metabolites isolated from *Eurotium* species was mainly measured by in vitro experiments, in vivo tests in animal models should be encouraged.

3.2. Antimicrobial activity

Microbial interference is an important threat to human health. Screening for antimicrobial compounds from *Eurotium* species is a promising way to overcome the increasing threat of human and plant pathogen, especially drug-resistant strains. Further, the antimicrobial activity of *Eurotium*

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species may be related to anthraquinones [73–75]. As early as in 1980, erythroglaucin **(3)** was found to have slight antibacterial activity against *Bacillus brevis*, *Bacillus subtilis*, and *Streptomyces viridochromogenes*. However, rubrocristin **(6)** and physcion **(2)** had no significant antimicrobial activity, indicating that the number and location of hydroxyl groups might play an important role in the antibacterial activity of polyhydroxyanthraquinones [21]. Chevalone C **(102)**, eurochevalierine **(148)**, and CJ-12662 **(106)** also showed the antimycobacterial activity against *Mycobacterium tuberculosis* with the minimal inhibitory concentration (MIC) values of 6.3, 50.0, and 12.5 μg/mL, respectively [32]. In 2012, Du et al. evaluated the antimicrobial activities of compounds isolated from *E. cristatum* against two bacteria (*Staphylococcus aureus* and *Escherichia coli*) and five plant-pathogenic fungi (*Valsa mali*, *Sclerotinia miyabeana*, *Alternaria brassicae*, *Physalospora obtuse* and *Alternaria solania*). The MIC value of positive control chloramphenicol against *E. coli* and *S. aureus* was 4 μg/mL. Cristatumin A **(66)** and tardioxopiperazine A **(71)** displayed potent inhibitory activity against *E. coli* and *S. aureus* with the MIC values of 64 and 8 μg/mL, whereas cristatumin D **(69)** and echinulin showed weak activity against *S. aureus*, each giving the inhibition zone of 8 mm at 100 μg/disk (MICs were not determined) [45]. In addition, the compound 9-dehydroxyeurotinone **(23)** isolated from *E. rubrum* showed a weak antibacterial activity against *E. coli* with an inhibition zone of 7.0 mm at 100 μg/disk, while amphotericin B had an inhibition zone of 11.0 mm at 20 μg/disk as control [31].

Gao et al. evaluated the antimicrobial activities of isolated metabolites from *E. repens* against five bacteria (*S. aureus*, *methicillin-resistant S. aureus*, *P. aeruginosa*, *M. intracellulare,* and *E. coli*) and five pathogenic fungi (*Candida. albicans*, *Candida glabrata*, *Candida krusei*, *Cryptococcus neoformans*, and *Aspergillus fumigatus*). Flavoglaucin, tetrahydroauroglaucin, and 2-(2',3-epoxy-1',3'-heptadienyl)-6-hydroxy-5-(3-methyl-2-butenyl)-benzaldehyde **(35)** exhibited antibacterial activity against *S. aureus* with IC_{50} values of 14.32, 13.51, and 7.75 μg/mL, respectively; (*E*)-2-(hept-1-enyl)-3-(hydroxymethyl)-5-(3-methylbut-2-enyl)-benzene-1,4-diol **(42)** and compounds **31** and **35** were active against *S. aureus* with IC_{50} values of 11.97, 10.41, and 5.40 μg/mL, respectively; auroglaucin, dihydroauroglaucin, and compound **35**, **40**, and **42** showed antifungal activity against *C. glabrata* with IC_{50} values of 7.33, 2.39, 1.13, 6.15, and 7.17 μg/mL, respectively. Compound **35** and 5,7-dihydroxy-4-methylphthalide **(165)** showed antifungal activity against *C. neoformans* with IC_{50} values of 5.31 and 18.08 μg/mL, respectively; only auroglaucin exhibited moderate antifungal activity against *C. krusei* with an IC_{50} value of 10.93 μg/mL [18]. In addition, cristatumin E **(72)** showed weak antibacterial activity against *E. aerogenes* and *E. coli* with IC_{50} and MIC values of 8.3, 44.0, and 44.0 μM, respectively [53]. Compounds 3-*O*-(*α*-D-ribofuranosyl)-questinol **(21)** and eurorubrin showed a weak inhibitory activity against *E. coli* with the MIC values of 32 and 64 μg/mL, while chloramphenicol had a MIC value of 4 μg/mL as control [30]. Emodin **(4)** not only showed moderate antibacterial activity against the Gram-positive bacteria but also exhibited a strong synergistic association with oxacillin against methicillin-resistant *S. aureus* (MRSA) [19]. In 2019, asperflavin was found to be active against *S. aureus* (MIC of 64 μg/mL) and *S. pneumoniae* Monza-82 (MIC of 32 μg/mL). Dihydroauroglaucin was active against the Gram-positive bacteria with MIC values of 128 μg/mL, 64 μg/mL, and 8 μg/mL on *S. aureus*, *E. faecalis*, and *S. pneumoniae*, respectively. Compound **41** was previously considered inactive against reference and MRSA *S. aureus* strains [66]. Neoechinulin A, L-alanyl-L-tryptophan anhydride **(81)**, dihydroxyisoechinulin A **(78),** and questin showed obvious antibacterial activity against *B. cereus* and *P. vulgaris* with the MIC values of 1.56 to 25 μM when ciprofloxacin (MIC values of 0.78 and 0.20 μM, respectively) was used as the positive control and DMSO (25 μM) was used as the negative control [10]. Asperglaucins A **(129)** and B **(130)** exhibited potent antibacterial activities against *Pseudomonas syringae* pv *actinidae* and *B. cereus*, with all MIC values of 6.25 μM. Compound **129** also exhibited a weak inhibitory effect against MRSA with a MIC value of 25 μM. The activity of compounds **129** and **130** is probably due to their heterocyclic fraction [16]. Notably, the above intriguing new compounds, which exhibit excellent antimicrobial properties, could be used as the leading compounds for the development of new drugs in the future.

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3.3. Cytotoxicity and antitumour activities

The cytotoxicity and antitumor activities of *Eurotium* species have been extensively studied since the 1970s. Podojil et al. reported that physcion had cytotoxicity towards HeLa cells with an IC_{50} value of 0.1 μg/mL [3]. Smetanina et al. found that physcion, asperflavin, and tetrahydroauroglaucin exhibited cytotoxic activity against sex cells of sea urchin *Strongylocentrotus intermedius* at a concentration of 25 μg/mL, 10 μg/mL, and 0.5 μg/mL, respectively [48]. In addition, compounds chevalone C, chevalone D, eurochevalierine, and CJ-12662 had respective IC_{50} values against the BC1 human breast cancer cells of 8.7, 7.8, 5.9, and 7.6 μg/mL, respectively. Compounds chevalone B **(101)** and eurochevalierine exhibited cytotoxicity against KB human epidermoid carcinoma cells and NCI-H187 small cell lung cancer cells with IC_{50} values in the range from 2.9 to 9.8 μg/mL [32]. In 2012, Yan et al. investigated the cytotoxic activities of some *E. rubrum*-derived alkaloids and anthraquinones against seven tumor cell lines, including MCF-7, SW1990, SMMC-7721, Hela, HepG2, NCI-H460, and Du145. 9-dehydroxyeurotinone exhibited cytotoxic activity with IC_{50} values of 25 μg/mL against SW1990; variecolorin G exhibited cytotoxic activity with IC_{50} values of 20, 22, and 20 μg/mL against HepG2, NCI-H460, and Hela, respectiveiy; alkaloid E-7 **(64)** exhibited cytotoxic activity with IC_{50} values of 20, 20, 20, and 30 μg/mL against MCF-7, SW1990, SMMC-7721 and Hela cells, respectively; 12-demethyl-12-oxo-eurotechinulin B **(60)** exhibited slight cytotoxic activity with IC_{50} values of 30 μg/mL against SMMC-7721, and only emodin exhibited moderate cytotoxic activity with IC_{50} values of 15 μg/mL against Du145 [31]. Besides, cristatumin E showed cytotoxicity against K562 tumor cell line with an IC_{50} value of 8.3 mM [53].

Rubrumol **(25)** showed the relaxation activity for topoisomerase I, with the IC_{50} value of 23 μM [25]. In 2018, Zhong et al. found that (+)-variecolortin B **(94)** showed moderate cytotoxicities against SF-268 and HepG2 cell lines with IC_{50} values of 12.5 and 15.0 μM, while (+)-variecolortin C **(95)** had the values of 30.1 and 37.3 μM. Compounds (-)-variecolortin B and (-)-variecolortin C were inactive (>100 μM) for SF-268 and HepG2 cells [56]. In addition, compound (+)-dihydrocryptoechinulin D showed moderate cytotoxicities against SF-268 and HepG2 cell lines with IC_{50} values of 51.7 and 49.9 μM, and (-)-dihydrocryptoechinulin D had the values of 97.3 and 98.7 μM, respectively. Thus, (+)-enantiomers exhibited more valid activities than corresponding (-)-enantiomers [68]. Flavoglaucin displayed weak cytotoxic activity against HepG2 and HeLa with IC_{50} values of 41.48 and 33.60 μM, respectively [37]. (-)-Salicylaldehydium A **(127)** showed cytotoxic activity against SF-268 and HepG2 cells with IC_{50} values of 91.0 and 95.5 μM, respectively [61]. (±)-Euroticin F, (±)-euroticin I **(126)** and (±)-eurotirumin **(29)** exhibited moderate cytotoxic activities with IC_{50} values ranging from 12.74 to 55.5 μM [62]. Euroticin C exerted moderate cytotoxic activity against human SF-268, MCF-7, HepG-2, and A549 cells [60]. However, the compounds' relative toxicities are unknown; few literatures of target organ toxicities or even side effects exist in the report.

3.4. Insecticidal activity

Brine shrimp (*Artemia salina*), which is an aquatic species featuring with high sensitivity to toxic and easy culture to researchers, is usually used as a model organism to screen substances with insecticidal activity [54,55]. In 2012, Du et al. reported that cristatumin B **(67)**, isoechinulin A, and variecolorin G exhibited moderate lethal activity against brine shrimp with the median lethal dose (LD_{50}) values of 74.4, 16.9, and 42.6 μg/mL, respectively. The structure–activity relationships indicated that the number and substituted position of isoprenic chain is important for the insecticidal activities of these compounds [45]. As for the lethality against brine shrimp, eurorubrin exhibited moderate activity with the lethal rate 41.4% at a concentration of 10 μg/mL [30]. Rubrumazine B **(74)**, dehydroechinulin, and neoechinulin E exhibited potent activity against brine shrimp with the LD_{50} values of 2.43, 3.53, and 3.93 μM, respectively, which were lower than that of the positive control colchicine (LD_{50} 19.4 μM) [54]. In addition, Du et al. showed that isovariecolorin I **(85)**, neoechinulin C **(89)**, alkaloid E-7, and didehydroechinulin **(90)** displayed potent activity against brine shrimp with the LD_{50} values of 19.4, 70.1, 19.8, and 27.1 μg/mL, respectively [55].

Some *Eurotium*-derived compounds were evaluated for their antifouling activities against the larval settlement of barnacle *Balanus amphitrite*, which is one of the representative marine fouling

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organisms. Compounds (±)-eurotiumides A-D **(167-170)** inhibited the barnacle larval settlement with the EC_{50} values < 25.0 μg/mL, which was lower than the standard requirement established by the U.S. Navy. Specifically, (+)-eurotiumide B, (-)-eurotiumide B, (+)-eurotiumide D, and (-)-eurotiumide D with the cis configurations of H-3/H-4 exhibited better antifouling activities (EC_{50} values of 1.5, 0.7, 2.3, and 1.9 μg/mL) than corresponding (+)-eurotiumide A, (-)-eurotiumide A, (+)-eurotiumide C, and (-)-eurotiumide C (trans configurations of H-3/H-4; EC_{50} values of 19.4, 22.5, 20.2, and 23.2 μg/mL). This suggested that the relative configuration of H-3/H-4 might be an important factor affecting antifouling activity [20]. In addition, compounds neoechinulin A and echinulin inhibited the barnacle larval settlement with EC_{50} values of 15.0 and 17.5 μg/mL, respectively [76].

3.5. Antimalarial activity

In 2012, Gao et al. measured the antiprotozoal activity of secondary metabolites from the fungus *E. repens in vitro* against chloroquine-sensitive and chloroquine-resistant strains of *Plasmodium falciparum*. Compounds flavoglaucin, 2-(2',3-epoxy-1',3'-heptadienyl)-6-hydroxy-5-(3-methyl-2-butenyl)-benzaldehyde, auroglaucin, tetrahydroauroglaucin and (*E*)-2-(hept-1-enyl)-3-(hydroxymethyl)-5-(3-methylbut-2-enyl)-benzene-1,4-diol exhibited moderate antimalarial activities with IC_{50} values in the range of 1.1-3.0 μg/mL, among which compound **39** displayed the highest antimalarial activity. This suggested the three consecutive double bonds in compound **39** might contribute to the enhancement of antimalarial activity [18]. In addition, chevalone D, eurochevalierine, and CJ-12662 exhibited antimalarial activity against *Plasmodium falciparum* with IC_{50} values of 3.1, 3.4, and 6.5 μg/mL, respectively [32].

3.6. Anti-inflammatory activity

Kim et al. demonstrated that neoechinulin A had an anti-inflammatory effect on lipopolysaccharide-stimulated RAW264.7 macrophages. Further, compound **49** blocked the activation of nuclear factor-kappa B (NF-κB) by inhibiting the phosphorylation and degradation of inhibitor kappa B-α, and decreased p38 mitogen-activated protein kinase (MAPK) phosphorylation. The anti-inflammatory effect of compound **49** was thus attributed to the inhibition of NF-κB and p38 MAPK pathways [77]. In addition, compounds flavoglaucin, isotetrahydroauroglaucin **(33)**, and asperflavin were found to inhibit the production of pro-inflammatory mediators and cytokines, including tumor necrosis factor-α, interleukin-1β, interleukin-6, nitric oxide (NO), prostaglandin E2, nitric oxide synthase, and cyclooxygenase-2 [33,35,78]. Cristaldehyde A **(46)** and cristaquinone A **(176)** inhibited the NO production in lipopolysaccharide-induced RAW264.7 cells, with the IC_{50} values of 12.26 and 1.48 μM, when paclitaxel was used as a positive control with the IC_{50} value of 41.00 μM [37].

3.7. Other activities

Several isolated compounds have some unique biological activities, including a good binding affinity for human opioid or cannabinoid receptors activity, inhibiting the protein tyrosine phosphatase 1B activity, alleviating insulin resistance activity, inhibiting caspase-3 activity, inhibiting α-glucosidase activity, and antiviral activity.

Compounds flavoglaucin, auroglaucin, tetrahydroauroglaucin, (*E*)-2-(hept-1-enyl)-3-(hydroxymethyl)-5-(3-methylbut-2-enyl)-benzene-1,4-diol and (*E*)-4-(hept-1-enyl)-7-(3-methylbut-2-enyl)-2,3-dihydrobenzofuran-2,5-diol showed a good binding affinity for human opioid or cannabinoid receptors. This finding may contribute to the discovery of new selective ligands for opioid or cannabinoid receptors [39]. Fructigenine A **(57)**, viridicatol **(174)**, echinulin, flavoglaucin, and cyclopenol **(136)** were found to inhibit the protein tyrosine phosphatase 1B activity with the IC_{50} values of 10.7, 64.0, 29.4, 13.4, and 30.0 μM, respectively. This indicated that these compounds had potential for the treatment of type 2 diabetes and obesity [52]. In addition, eurocristatine **(58)** alleviated insulin resistance by increasing glucose consumption, glucose uptake, and glycogen content in high glucose-induced HepG2 cells in vitro. Further, compound **58** improved glucose

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metabolism and alleviated insulin resistance in db/db diabetic mice by activating the phosphatidylinositol 3-kinase/protein kinase B signaling pathway [79].

Compounds 7-*O*-methylvariecolortide A **(53)**, variecolortide B **(55)**, and variecolortide C **(56)** showed an inhibitory effect on caspase-3 in vitro, with the IC_{50} values of 1.7, 0.8, and 15.7 μM, respectively, when Ac-DEVD-CHO was used as a positive control (IC_{50} = 13.7 μM) [80]. Secondary metabolites isolated from the fungus *E. rubrum* SH-823 were examined for their α-glucosidase inhibitory activity. Eurothiocin A **(155)** and eurothiocin B **(156)** showed potent inhibitory potential (IC_{50} of 17.1 and 42.6 μM, respectively). Further, compounds **155** and **156** were competitive inhibitors of α-glucosidase [67]. In addition, compounds (±)-euroticin H **(125)** and (+)-euroticin G **(124)** exhibited significant inhibition against α-glucosidase with IC_{50} values of 16.31 and 38.04, which are even better than that of positive control acarbose (IC_{50} of 32.92 μM) [62]. It is worth mentioning that significant antiviral activity for physcion and dihydroauroglaucin was discovered against two important human viral pathogens (herpes simplex virus 1 and influenza A virus) [66] (Figure 5).

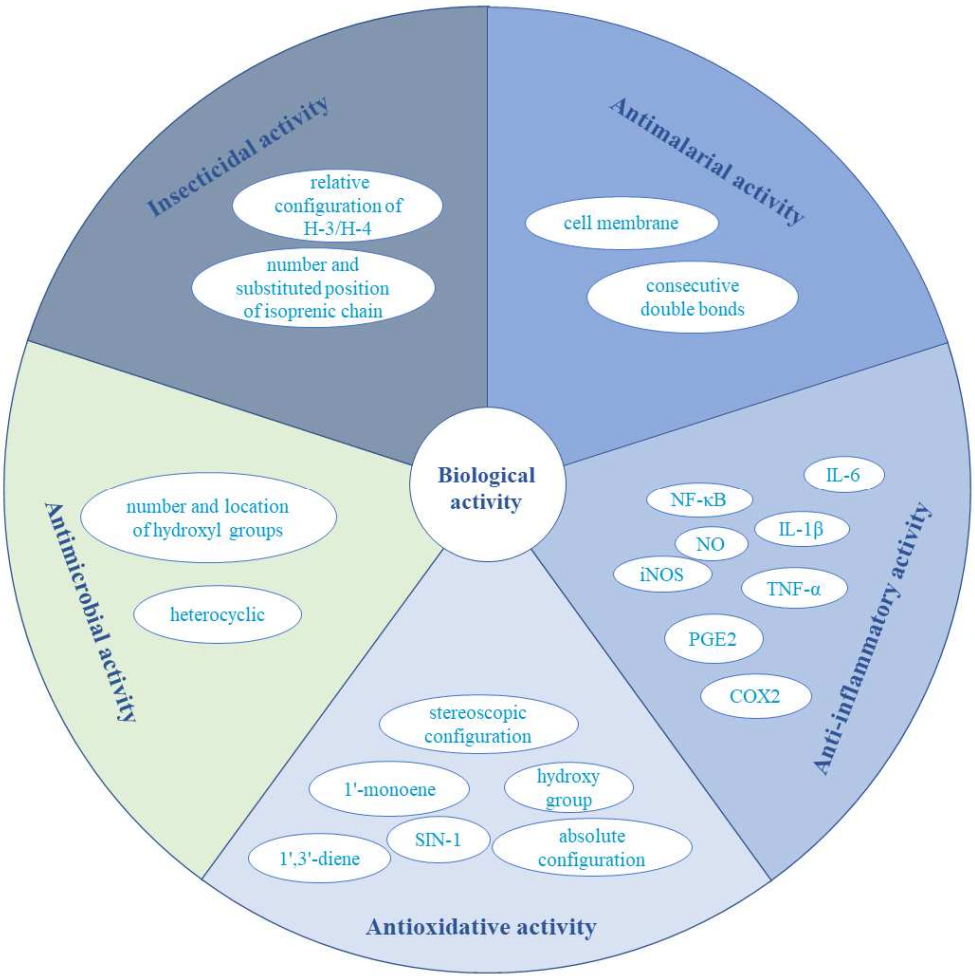

Figure 5. Overview of main biological activities.

4. Conclusion

Eurotium, which has been proven to be an important source of active compounds, is a crucial genus in the *Aspergillus* family. Several reasons contribute to importance of *Eurotium*'s: (1) an extensive distribution, (2) the key microorganism for the fermentation of traditional food and drink (e.g., Fuzhuan brick tea), and (3) an abundance of secondary metabolites with promising bioactivities. Nearly 180 chemical components have been isolated from *Eurotium* species, including anthraquinoes, benzaldehyde derivatives, indol diketopiperazine alkaloids, and some other compounds. Various pharmacological activities, including antioxidative, antimicrobial, cytotoxic, antitumor, insecticidal,

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antimalarial, and anti-inflammatory activities, have been demonstrated in *Eurotium* species through numerous test models. Nevertheless, the most of activity studies were carried out by using in vitro models, and in vivo models are needed in the further. The most of researches focused on three *Eurotium* species–*E. amstelodami*, *E. cristatum*, and *E. repens*. The other species in genus *Eurotium* should be further studied, and this study will also provide information on taxonomic relationships within *Eurotium* species. In addition, more attention should focus on the discovery of new secondary metabolites and their biological activities from fermented food/drink-derived and marine-derived *Eurotium* species (Table 1).

Table 1. Secondary metabolites from the genus Eurotium and their biological activities.

NO.	Compound class and name	Bioactivity	Source	Ref.
Anthraquinones				
1	questin	antimicrobial activity		[10]
			Eurotium sp. M30 XS-2012	
			E. herbariorum NU-2	[15]
			E. chevalieri KUFA 0006	[19]
			Eurotium	
			E. rubrum	[21]
		antioxidative activity		[29]
2	physcion		*E. herbariorum* NU-2	[15]
			E. chevalieri KUFA 0006	[19]
			E. repens	
		cytotoxic activity	*E. chevalieri* MUT 2316	[48]
		antiviral activity		[66]
3	erythroglaucin	antimicrobial activity	*Eurotium*	[21]
			E. cristatum KUFC 7356	[28]
4	emodin	antimicrobial activity		[19]
			E. chevalieri KUFA 0006	
			Eurotium	[21]
			E. rubrum	[25]
			E. cristatum KUFC 7356	[28]
			E. rubrum	
		cytotoxic activity		[31]
5	catenarin		*E. herbariorum* NU-2	[15]
			Eurotium	[21]
			E. rubrum	[25]
			E. cristatum KUFC 735	[28]
6	rubrocristin		*Eurotium*	[21]
			E. rubrum	[25]
7	rubrocristin-8-methylether		*Eurotium*	[21]
8	rubrocristin-6-acetate		*Eurotium*	[21]
9	querstin-6-methylether		*Eurotium*	[21]
10	2-*O*-methyleurotinone		*E. echinulatum*	[27]

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		antioxidative activity	*E. rubrum*	[29]
11	2,12-dimethyleurotinone		*E. echinulatum*	[27]
12	eurotinone		*E. echinulatum*	[27]
13	physcion-10,10'-bianthrone		*E. herbariorum* NU-2	[15]
14	questinol		*Eurotium sp.* M30 XS-2012	[10]
			E. herbariorum NU-2	[15]
			E. chevalieri KUFA 0006	[19]
			E. amstelodami	
		anti-inflammatory activity		[33]
15	asperflavin	antioxidative activity	*Eurotium sp.* M30 XS-2012	[10]
			E. herbariorum NU-2	[15]
			E. rubrum	[29]
		cytotoxic activity	*E. cristatum* EN-220	[30]
		antimicrobial activity	*E. repens*	[48]
		anti-inflammatory activity	*E. chevalieri* MUT 2316	[66]
			E. amstelodami	[78]
16	variecolorquinone A		*Eurotium sp.* M30 XS-2012	[28]
			E. cristatum EN-220	[30]
17	2-*O*-methyl-4-*O*-(*α*-D-ribofuranosyl)-9-dehydroxyeurotinone	antioxidative activity	*E. rubrum*	[29]
18	2-*O*-methyl-9-dehydroxyeurotinone	antioxidative activity	*E. rubrum*	[29]
19	eurorubrin	antioxidative activity	*E. rubrum*	[29]
		antimicrobial activity	*E. cristatum* EN-220	[30]
		insecticidal activity		
20	3-*O*-(*α*-D-ribofuranosyl)-questin	antioxidative activity	*E. rubrum*	[29]
			E. cristatum EN-220	[30]
21	3-*O*-(*α*-D-ribofuranosyl)-questinol	antimicrobial activity	*E. cristatum* EN-220	[30]
22	asperflavin ribofuranoside		*E. cristatum* EN-220	[30]
23	9-dehydroxyeurotinone	cytotoxic activity	*E. rubrum*	[31]
		antimicrobial activity		
24	acetylquestinol		*E.chevalieri* KUFA 0006	[19]
25	rubrumol	cytotoxic activity	*E. rubrum*	[25]
Benzaldehyde derivatives				

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26	2-(2',3-epoxy-1'-heptenyl)-6-hydroxy-5-(3''-methyl-2''-butenyl)-benzaldehyde		*E. rubrum*	[36]
27	(*E*)-6-hydroxy-7-(3-methyl-2-butenyl)-2-(3-oxobut-1-enyl)-chroman-5-carbaldehyd		*E. rubrum*	[36]
28	2-(1',5'-heptadienyl)-3,6-dihydroxy-5-(3''-methyl-2''-butenyl)-benzaldehyde		*E. rubrum*	[36]
29	eurotirumin	cytotoxic activity	*E. rubrum* *Eurotium sp.* SCSIO F452	[36] [62]
30	chaetopyranin		*E. rubrum*	[36]
31	flavoglaucin	antioxidative activity antimicrobial activity antimalarial activity anti-inflammatory activity cytotoxic activity	*Eurotium* *E. cristatum* *E. repens* *Eurotium sp.* SF-5989 *E. rubrum* *E. cristatum* *E. repens*	[11] [13] [18] [35] [36] [37] [39]
32	aspergin		*E. rubrum*	[36]
33	isotetrahydroauroglaucin	anti-inflammatory activity	*Eurotium sp.* SF-5989 *E. rubrum*	[35] [36]
34	isodihydroauroglaucin	antioxidative activity	*Eurotium* *E. cristatum* *E. rubrum* *E. repens*	[11] [13] [36] [39]
35	2-(2',3-epoxy-1',3'-heptadienyl)-6-hydroxy-5-(3-methyl-2-butenyl)-benzaldehyde	antimicrobial activity antimalarial activity	*E. cristatum* *E. repens* *E. rubrum* *E. repens*	[13] [18] [36] [39]
36	2-(2',3-epoxy-1',3',5'-heptatrienyl)-6-hydroxy-5-(3-methyl-2-butenyl)-benzaldehyde		*E. rubrum* *E. cristatum*	[36] [13]
37	eurotirubrin A		*E. rubrum*	[38]
38	eurotirubrin B		*E. rubrum*	[38]
39	auroglaucin	antioxidative activity antimicrobial activity	*Eurotium* *E. repens*	[11] [18]

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		antimalarial activity		
40	tetrahydroauroglaucin	antioxidative activity	*Eurotium*	[11]
			E. cristatum	[13]
		antimicrobial activity	*E. repens*	[18]
		antimalarial activity		
			E. repens	[39]
		cytotoxic activity	*E. repens*	[48]
41	dihydroauroglaucin	antioxidative activity	*Eurotium*	[11]
			E. cristatum	[13]
		antimicrobial activity	*E. repens*	[18]
			E. repens	[39]
		antiviral activity	*E. chevalieri* MUT 2316	[66]
42	(*E*)-2-(hept-1-enyl)-3-(hydroxymethyl)-5-(3-methylbut-2-enyl)-benzene-1,4-diol	antimicrobial activity	*E. repens*	[18]
		antimalarial activity	*E. repens*	[39]
43	(*E*)-4-(hept-1-enyl)-7-(3-methylbut-2-enyl)-2,3-dihydrobenzofuran-2,5-diol		*E. repens*	[39]
44	(3'S*,4'R*)-6-(3',5-epoxy-4'-hydroxy-1'-heptenyl)-2-hydroxy-3-(3''-methyl-2''-butenyl)-benzaldehyde		*Eurotium*	[34]
45	3'-OH-tetrahydroauroglaucin		*Eurotium*	[34]
46	cristaldehyde A	anti-inflammatory activity	*E. cristatum*	[37]
47	cristaldehyde B		*E. cristatum*	[37]
Indole diketopiperazine alkaloids				
48	echinulin	antimicrobial activity	*E. cristatum*	[28]
			E. cristatum EN-220	[45]
			E. cristatum	[46]
			E. repens	[47]
			E. repens	[48]
			E. amstelodami	[50]
			E. rubrum	
			E. herbariorum	
		antioxidative activity	*E. cristatum* EN-220	[55]
			Eurotium sp. SCSIO F452	[57]
		insecticidal activity	*Eurotium*	[76]
49	neoechinulin A	antimicrobial activity	*Eurotium sp.* M30 XS-2012	[10]

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				E. cristatum	
				E. cristatum EN-220	[28]
				E. cristatum	[45]
				E. rubrum Hiji 025	[46]
		antioxidative activity		*E. amstelodami*	[49]
				E. rubrum.	[50]
				E. herbariorum	
				E. rubrum MA-150	
		insecticidal activity		*Eurotium*	[54]
				Eurotium sp. SF-5989	[76]
		anti-inflammatory activity			[77]
50	neoechinulin B	antioxidative activity		*E. herbariorum* NU-2	[15]
				E. amstelodami	[50]
				E. rubrum.	
				E. herbariorum	
				E. cristatum EN-220	[55]
				Eurotium sp. SCSIO F452	[57]
51	preechinulin			*E. cristatum* EN-220	
				E. amstelodami	[45]
				E. rubrum	[50]
				E. herbariorum	
52	neoechinulin E			*E. cristatum*	[28]
				E. amstelodami	[50]
				E. herbariorum	
		insecticidal activity		*E. rubrum* MA-150	[54]
		antioxidative activity		*E. rubrum*	[72]
53	7-*O*-methylvariecolortide A	caspase-3 activity	inhibitory	*E. rubrum*	[51]
				Eurotium	[80]
54	variecolortide A			*E. rubrum*	[51]
55	variecolortide B	caspase-3 activity	inhibitory	*E. rubrum*	[51]
				E. rubrum MA-150	[54]
				Eurotium	[80]
56	variecolortide C	caspase-3 activity	inhibitory	*E. rubrum*	[51]
				E. rubrum MA-150	[54]
				Eurotium	[80]
57	fructigenine A			*Eurotium sp.* SF-5130	[52]
58	eurocristatine			*E. cristatum*	[28]

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59	variecolorin J		*E. cristatum* *E. rubrum*	[28] [31]
60	12-demethyl-12-oxo-eurotechinulin B	cytotoxic activity	*E. rubrum*	[31]
61	variecolorin G	cytotoxic activity insecticidal activity antioxidative activity	*E. rubrum* E. cristatum EN-220 E. rubrum MA-150 *Eurotium sp.* SCSIO F452	[31] [45] [54] [57]
62	eurotechinulin B		*E. rubrum*	[31]
63	cryptoechinuline G		*E. rubrum*	[31]
64	alkaloid E-7	cytotoxic activity insecticidal activity	*E. rubrum* *E. cristatum* EN-220	[31] [55]
65	isoechinulin B	antioxidative activity	*E. herbariorum* NU-2 *E. rubrum* *31*	[15] [31]
66	cristatumin A	antimicrobial activity	*E. cristatum* EN-220	[45]
67	cristatumin B	insecticidal activity	*E. cristatum* EN-220	[45]
68	cristatumin C		*E. cristatum* EN-220	[45]
69	cristatumin D	antimicrobial activity	*E. cristatum* EN-220	[45]
70	isoechinulin A	antioxidative activity insecticidal activity	*E. herbariorum* NU-2 *E. cristatum* EN-220 E. rubrum MA-150 *Eurotium sp.* SCSIO F452	[15] [45] [54] [57]
71	tardioxopiperazine A	antimicrobial activity	*E. cristatum* EN-220	[45]
72	cristatumin E	antimicrobial activity cytotoxic activity	*E. herbariorum* HT-2	[53]
73	rubrumazine A		*E. rubrum* MA-150	[54]
74	rubrumazine B	insecticidal activity	*E. rubrum* MA-150 *E. cristatum* EN-220	[54] [55]
75	rubrumazine C		*E. rubrum* MA-150	[54]
76	dehydroechinulin	insecticidal activity antioxidative activity	*E. cristatum* *E. rubrum* MA-150 *E. cristatum* EN-220 *Eurotium sp.* SCSIO F452	[46] [54] [55] [57]
77	variecolorin E		*E. rubrum* MA-150	[54]
78	dihydroxyisoechinulin A	antimicrobial activity	*Eurotium sp.* M30 XS-2012 *E. rubrum* MA-150	[10] [54]
79	variecolorin L		*E. rubrum* MA-150	[54]
80	tardioxopiperazine B		*E. rubrum* MA-150	[54]

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81	L-alanyl-L-tryptophan anhydride	antimicrobial activity	*Eurotium sp.* M30 XS-2012 *E. rubrum* MA-150	[10] [54]
82	cristatumin F		*E. cristatum*	[46]
83	variecolorin O	antioxidative activity	*E. herbariorum* NU-2 *E. cristatum* *Eurotium sp. SCSIO F452*	[15] [46] [57]
84	*N*-(4'-hydroxyprenyl)-cyclo(alanyltryptophyl)		*E. cristatum* EN-220	[55]
85	isovariecolorin I	insecticidal activity	*E. cristatum* EN-220	[55]
86	30-hydroxyechinulin		*E. cristatum* EN-220	[55]
87	29-hydroxyechinulin		*E. cristatum* EN-220	[55]
88	rubrumline M		*E. cristatum* EN-220	[55]
89	neoechinulin C	insecticidal activity	*E. cristatum* EN-220	[55]
90	didehydroechinulin	insecticidal activity	*E. cristatum* EN-220	[55]
91	variecolorin H		*E. cristatum* EN-220	[55]
92	(11*R*,14*S*)-3-(1*H*-indol-3ylmethyl)6-isopropyl-2,5-piperazinedione		*E. chevalieri* KUFA 0006	[19]
93	variecolortin A	antioxidative activity	*Eurotium sp.* SCSIO F452	[56]
94	variecolortin B	cytotoxic activity	*Eurotium sp.* SCSIO F452	[56]
95	variecolortin C	cytotoxic activity	*Eurotium sp.* SCSIO F452	[56]
96	eurotiumin A	antioxidative activity	*Eurotium sp.* SCSIO F452	[57]
97	eurotiumin B	antioxidative activity	*Eurotium sp.* SCSIO F452	[57]
98	eurotiumin C	antioxidative activity	*Eurotium sp.* SCSIO F452	[57]
99	fintiamin		*Eurotium*	[58]
Other compounds				
100	chevalone A		*E. chevalieri*	[32]
101	chevalone B	cytotoxic activity	*E. chevalieri*	[32]
102	chevalone C	antimicrobial activity cytotoxic activity	*E. chevalieri*	[32]
103	chevalone D	antimalarial activity cytotoxic activity	*E. chevalieri*	[32]
104	aszonapyrone A		*E. chevalieri*	[32]
105	aszonapyrone B		*E. chevalieri*	[32]
106	CJ-12662	antimalarial activity antimicrobial activity cytotoxic activity	*E. chevalieri*	[32]
107	3*β*,5*α*-dihydroxy-10*α*-methyl-6*β*-acetoxy-ergosta-7,22-diene		*E.rubrum*	[59]

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108	3β,5α-dihydroxy-6β-acetoxyergosta-7,22-diene		*E.rubrum*	[59]
109	(22*E*,24*R*)-ergosta-7,22-dien-3β-ol		*E.rubrum*	[59]
110	(22*E*,24*R*)-ergosta-7,22-dien-6β-methoxy-3β,5α-diol		*E.rubrum*	[59]
111	(22*E*,24*R*)-ergosta-7,22-dien-3β,5α,6β-triol		*E.rubrum*	[59]
112	(22*E*,24*R*)-ergosta-7,22-dien-3β,5α,6α-triol		*E.rubrum*	[59]
113	(22*E*,24*R*)-3β,5α,9α-trihydroxyergosta-7,22-dien-6-one		*E.rubrum*	[59]
114	(22*E*,24*R*)-3β,5α-dihydroxyergosta-7,22-dien-6-one		*E.rubrum*	[59]
115	(22*E*,24*R*)-5α,8α-epidioxyergosta-6,22-dien-3β-ol		*E.rubrum*	[59]
116	(22*E*,24*R*)-5α,8α-epidioxyergosta-6,22-dien-3β-acetate		*E.rubrum*	[59]
117	(22*E*,24*R*)-ergosta-4,6,8(14),22-tetraen-3-one		*E.rubrum*	[59]
118	euroticin A		*Eurotium sp.* SCSIO F452	[14]
119	euroticin B	antioxidative activity	*Eurotium sp.* SCSIO F452	[14]
120	euroticin C	antioxidative activity cytotoxic activity	*Eurotium sp.* SCSIO F452	[60]
121	euroticin D		*Eurotium sp.* SCSIO F452	[60]
122	euroticin E		*Eurotium sp.* SCSIO F452	[60]
123	euroticin F	cytotoxic activity antioxidative activity	*Eurotium sp.* SCSIO F452	[62]
124	euroticin G	antioxidative activity α-glucosidase inhibitory activity	*Eurotium sp.* SCSIO F452	[62]
125	euroticin H	cytotoxic activity α-glucosidase inhibitory activity	*Eurotium sp.* SCSIO F452	[62]
126	euroticin I	cytotoxic activity	*Eurotium sp.* SCSIO F452	[62]
127	salicylaldehydium A	cytotoxic activity	*Eurotium sp.* SCSIO F452	[61]
128	salicylaldehydium B		*Eurotium sp.* SCSIO F452	[61]

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129	asperglaucin A	antimicrobial activity	*Aspergillus chevalieri* SQ-8	[16]
130	asperglaucin B	antimicrobial activity	*Aspergillus chevalieri* SQ-8	[16]
131	citrinin		*Eurotium*	[63]
132	ochratoxin A		*Eurotium*	[63]
133	gliotoxin		*Eurotium*	[63]
134	aflatoxins		*Eurotium*	[63]
135	sterigmatocystin		*Eurotium*	[63]
136	cyclopenol		Eurotium sp. SF-5130	[52]
137	mycophenolic acid		*E. repens*	[64]
138	2-(2-methyl-3-en-2-yl)-1*H*-indole-3-carbaldehyde		*E. chevalieri* KUFA 0006	[19]
139	(2,2-dimethylcyclopropyl)-1*H*-indole-3-carbaldehyde		*E. chevalieri* KUFA 0006	[19]
140	2-(1,1-dimethyl-2-propen-1-yl)-1*H*-indole-3-carboxaldehyde		*Eurotium sp.*SCSIO F452	[65]
141	ergosterol		*E. chevalieri*	[32]
142	2[(2,2-dimethylbut-3-enoyl)amino]benzoic acid		*E. chevalieri* KUFA 0006	[19]
143	6,8-dihydroxy-3-(2-hydroxypropyl)-7-methyl-1*H*-isochromen-1-one		*E. chevalieri* KUFA 0006	[19]
144	ergosterol 5,8-endoperoxide		*E. chevalieri* KUFA 0006	[19]
145	(11*S*,14*R*)-cyclo(tryptophylvalyl)		*E. chevalieri* KUFA 0006	[19]
146	cinnalutein		*E. chevalieri* MUT 2316	[66]
147	*cyclo*-L-Trp-L-Ala		*E. chevalieri* MUT 2316	[66]
148	eurochevalierine	antimalarial activity antimicrobial activity cytotoxic activity	*E.* chevalieri	[32]
149	sequiterpene		*E.* chevalieri	[32]
150	zinniol		*E.rubrum* SH-823	[67]
151	butyrolactone I		*E.rubrum* SH-823	[67]
152	aspernolide D		*E.rubrum* SH-823	[67]
153	vermistatin		*E.rubrum* SH-823	[67]
154	methoxyvermistatin		*E.rubrum* SH-823	[67]
155	eurothiocin A	α-glucosidase inhibitory activity	*E.rubrum* SH-823	[67]
156	eurothiocin B	α-glucosidase inhibitory activity	*E.rubrum* SH-823	[67]

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157	7-isopentenylcryptoechinuline D		*E.rubrum*	[31]
158	methyl linoleate		*Eurotium sp.*SCSIO F452	[65]
159	*cyclo*-(L-Pro-L-Phe)		*Eurotium sp.* SCSIO F452	[57]
160	eurotinoid A	antioxidative activity	*Eurotium sp.* SCSIO F452	[68]
161	eurotinoid B	antioxidative activity	*Eurotium sp.* SCSIO F452	[68]
162	eurotinoid C	antioxidative activity	*Eurotium sp.* SCSIO F452	[68]
163	dihydrocryptoechinulin D	cytotoxic activity antioxidative activity	*Eurotium sp.* SCSIO F452	[68]
164	eurotone A		*Eurotium sp.* SCSIO F452	[69]
165	5,7-dihydroxy-4-methylphthalide	antimicrobial activity	*E. repens* *E. repens*	[18] [39]
166	cristatumside A		*E. cristatum* EN-220	[30]
167	eurotiumide A	insecticidal activity	*Eurotium sp.* XS-200900E6	[20]
168	eurotiumide B	insecticidal activity	*Eurotium sp.* XS-200900E6	[20]
169	eurotiumide C	insecticidal activity	*Eurotium sp.* XS-200900E6	[20]
170	eurotiumide D	insecticidal activity	*Eurotium sp.* XS-200900E6	[20]
171	eurotiumide E		*Eurotium sp.* XS-200900E6	[20]
172	eurotiumide F		*Eurotium sp.* XS-200900E6	[20]
173	eurotiumide G		*Eurotium sp.* XS-200900E6	[20]
174	viridicatol		*Eurotium sp.* SF-5130	[52]
175	monacolin K		*E. cristatum*	[70]
176	cristaquinone A	anti-inflammatory activity	*E. cristatum*	[37]
177	6-*O*-*α*-D–ribofuranoside		*E. cristatum* EN-220	[30]

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