Review

Chemical Diversity of Ketosteroids as Potential Therapeutic Agents

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Chemical Diversity of Ketosteroids as Potential Therapeutic Agents

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Abstract: This article presents a comprehensive overview of recent discoveries and advancements in the field of steroid chemistry, highlighting the isolation and characterization of various steroidal compounds from natural sources. The paper discusses a wide range of steroids, including pregnane steroids, steroidal alkaloids, ketosteroids, and novel triterpenoids, derived from marine organisms, fungi, and plants. Significant findings include the isolation of bioactive compounds such as the cytotoxic erectsterates from microorganisms, soft corals, the unusual tetracyclic steroid penicillitone from a fungal culture, and innovative steroidal derivatives with potential anti-inflammatory and anticancer activities. The synthesis of steroids from microorganisms as a tool for pharmaceutical development is also explored, showcasing the role of microbial biotransformation in generating steroidal drugs. Additionally, the paper emphasizes the ecological and medicinal relevance of these compounds, which are often used in traditional medicine and have potential therapeutic applications in treating diseases like cancer and microbial infections. This article serves as a vital resource for researchers interested in the chemical diversity of steroids and their applications in drug discovery and development.

Keywords: ketosteroids; microorganisms; fungal endophytes; invertebrates; plant; anticancer activity

Introduction

Ketosteroids are a subclass of steroids that contain a ketone group (a carbonyl group, C=O) at one or more positions in the steroid skeleton. The steroid skeleton, also known as the sterane core, is a tetracyclic structure consisting of three six-membered rings (A, B, and C) and one five-membered ring (D) [1–7]. The positions at which the ketone group can be located, 1, 2, 3, 4, 6, 7, 11, 12, 15, 16, 17, and 20 refer to specific carbon atoms in the steroid skeleton. The presence of a ketone group at these positions can significantly alter the biological activity of the steroid molecule [7–10]. Ketosteroids can be found in a variety of natural sources, including: various parts of plants, such as leaves, roots, seeds, and bark, can contain ketosteroids. These compounds are often involved in the plant's defense mechanisms against pests and diseases. Marine invertebrates, ketosteroids are commonly found in marine organisms such as soft corals, marine and freshwater sponges, starfish, and other invertebrates [1–3,11–16].

Ketosteroids are also present in animals, where they serve as hormones and signaling molecules. For example, cortisone and cortisol are keto-steroids that are involved in the stress response and metabolism regulation in mammals. Some ketosteroids are produced by fungi and other microorganisms as secondary metabolites [17–21].

Ketosteroids are of interest in various fields of research, including pharmacology, biochemistry, and ecology, due to their diverse biological activities and potential therapeutic applications. The biological activity of keto-steroids can depend significantly on the position of the ketone group within the steroid skeleton. The location of the ketone group can influence the molecule's shape, electronic distribution, and ability to interact with specific biological targets, such as receptors, enzymes, and other proteins [22–24].

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The keto group's impact on the steroid molecule is significant because it alters how the steroid interacts with enzymes and receptors. These interactions can change the steroid's solubility, its distribution within the body, its clearance rate, and its ability to enter target cells. In drug design, these properties are considered to maximize therapeutic effects and minimize unwanted side effects [25–27]. For example, the presence of a ketone group at the C-3 position (as in cortisone) or the C-11 position (as in cortisol) can greatly impact the anti-inflammatory and glucocorticoid activities of these steroids. Similarly, the presence of a ketone group at the C-17 position can influence the androgenic or estrogenic activity of a steroid. The specific configuration and substitution pattern of the steroid skeleton, including the presence and position of other functional groups, also contribute to the overall biological activity of the molecule. Therefore, even small changes in the structure of a keto-steroid can lead to significant differences in its biological effects.

This review focuses on ketosteroids, which are characterized by the presence of a ketone group at positions 1, 2, 3, 4, 6, 7, 11, 12, 15, 16, 17, and 20 in the steroid skeleton. These compounds are found in various natural sources, including plants, marine invertebrates, and are also produced by fungal endophytes and microorganisms. The review discusses questions related to their biological activity and the implications of the specific positioning of the ketone group within the steroid structure.

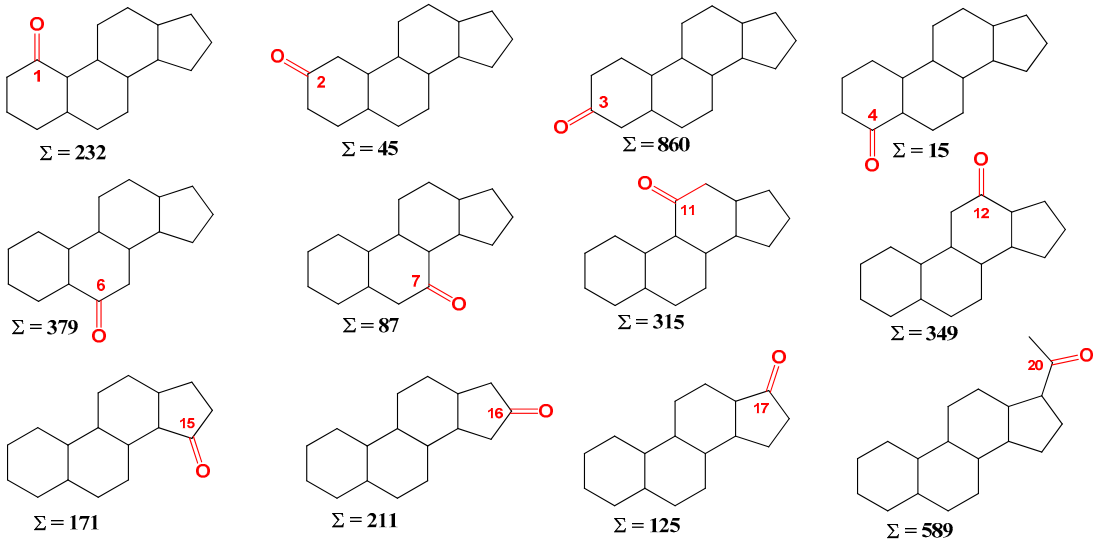

Figure 1. The structures of ketosteroids are discussed in this review. According to ChemNetBase (*Dictionary of Natural Products*) as of May 2024, the number of individual steroids (Σ = 100) containing a carbonyl group in various positions. By reviewing the scientific literature, the data presented by the *Dictionary of Natural Products* may be underestimated. This is apparently due to the fact that incomplete data were analyzed.

1-Ketosteroids

Steroids skeleton containing a carbonyl group at position 1 are found in nature in the amount of over 200 compounds, mainly in plants [28,29]. The carbonyl group at position 1 of steroids plays a crucial role in determining the chemical and biological properties of these compounds. The carbonyl group adds rigidity to the steroid structure, which can influence the overall shape and conformation of the molecule. This can have a significant impact on the interaction of the steroid with biological receptors and enzymes. The presence of a carbonyl group introduces a polar character to the steroid molecule, which can influence its solubility in water and other solvents. This can affect the distribution and transport of the steroid within biological systems. The carbonyl group is a reactive functional group that can undergo various chemical reactions, such as reduction, oxidation, and nucleophilic addition. These reactions can be utilized in the synthesis and modification of steroid compounds. The presence and position of the carbonyl group can have a significant impact on the biological activity of the steroid. The carbonyl group can engage in hydrogen bonding and other intermolecular interactions, which can influence the binding of the steroid to receptors, proteins, and

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other biological molecules. Overall, the carbonyl group at position 1 of steroids is an important structural and functional element that influences the chemical reactivity, physical properties, and biological activities of these compounds.

For example, withanolides and related steroids which has a carbonyl group at position 1, are acnistins, physalins, sativolides, spiranoid-δ-lactones, subtriflora-δ-lactones, trechonolides, withametelins, withajardins, withaphysalins, ring-D aromatic withanolides, and norbornane-type withanolides, which have been found in extracts of plants belonging to the families *Datura, Dunalia, Hyoscyamus, Iochroma, Jaborosa, Larnax, Lycium, Solanum, Withania*, and *Witheringia* [28–31]. As an example, we present steroids with different structures containing a carbonyl group in position 1 isolated from plants.

Steroids with a carbonyl group at position 1 of the steroid skeleton in marine invertebrates are found only in Coelenterata, Formosan soft coral *Clavularia viridis* and *C. violacea.* It appears that these steroids could be found in corals that feed on plant remains, marine mangrove plants, algae, or phytoplankton [32]. The following marine steroids, structurally akin to the steroids from the *Physalis genus*, have been identified. Yonarasterols A (**1**), B (**2**), C (**3**), D (**4**), E (**5**), and F (**6**, structures see in Figure 2), resembling witanolides, were extracted from the Okinawan soft coral *Clavularia viridis* in the Japan Sea [33]. Additionally, several marine steroids named stoloniferones A (**7**), B (**8**), C (**9**), and D (**10**) have been isolated from *Clavularia viridis*, as identified by Quoy and Gaimard in Okinawa, and steroids C and D demonstrated growth inhibitory effects on HeLa S3 cells and human diploid cells *in vitro* [34]. Moreover, cytotoxic steroids stoloniferone E-G (**11**-**13**) were obtained from the methylene chloride extract of the Formosan soft coral *Clavularia viridis* and *C. violacea* [35]. Notably, stoloniferone Q, D, J, S, yonarasterol C (**14**), F (**15**), and I (**16**) feature a carbonyl group at C-1 with a double bond between C-2 and C-3, except for stoloniferone S, which exhibits a double bond between C-3 and C-4. Additionally, stoloniferone Q includes an extra bond between C-4 and C-5 [32–37].

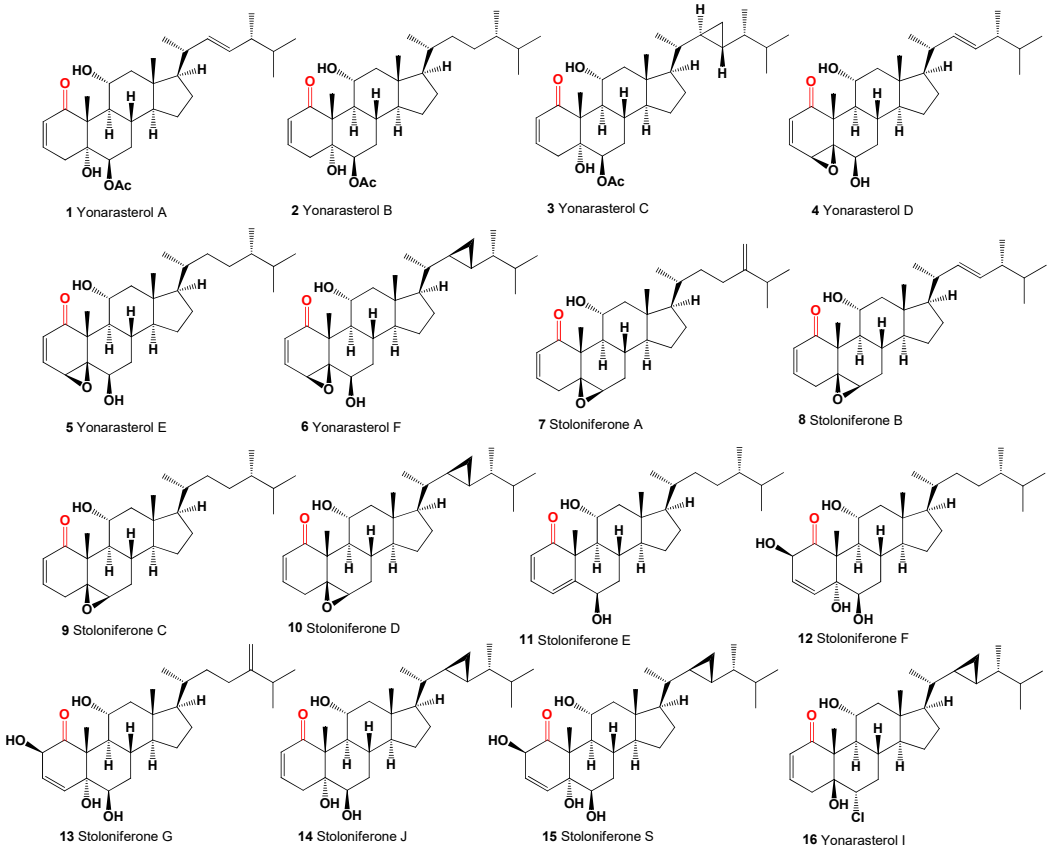

Figure 2. 1-Ketosteroids derived from some marine invertebrates and plants.

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The genus Physalis (Solanaceae), which includes over 100 species primarily found in North and South America, produces cytotoxic peruvianoxide (**17**), C28 steroidal lactones, and physalins (**18**-**27**) [38]. Notably, the cytotoxic peruvianoxide (**17**) was detected in extracts from *Physalis peruviana* [39].

The plant *Withania somnifera*, commonly known as ashwagandha or winter cherry, contains a steroid (**28**) [40] and an unusual variant, compound (**29**), featuring a 3α,6α-epoxy bridge. This was found in an extract from the same plant [41]. Chlorinated withanolide Z (**30**) [42], arising from *trans*-diaxial cleavage of the 6,7-epoxide, and compound (**31**) with a unique 5α,7α-epoxy bridge resulting from rearrangement of the 5α-hydroxy-6α,7α-epoxide, were identified in the leaves and roots of *Withania somnifera* [43]. Additionally, two 14α,20-epoxywithanolides, including the diol coagulin M (**32**) and coagulin I (**33**), were isolated from *W. coagulans* [44,45].

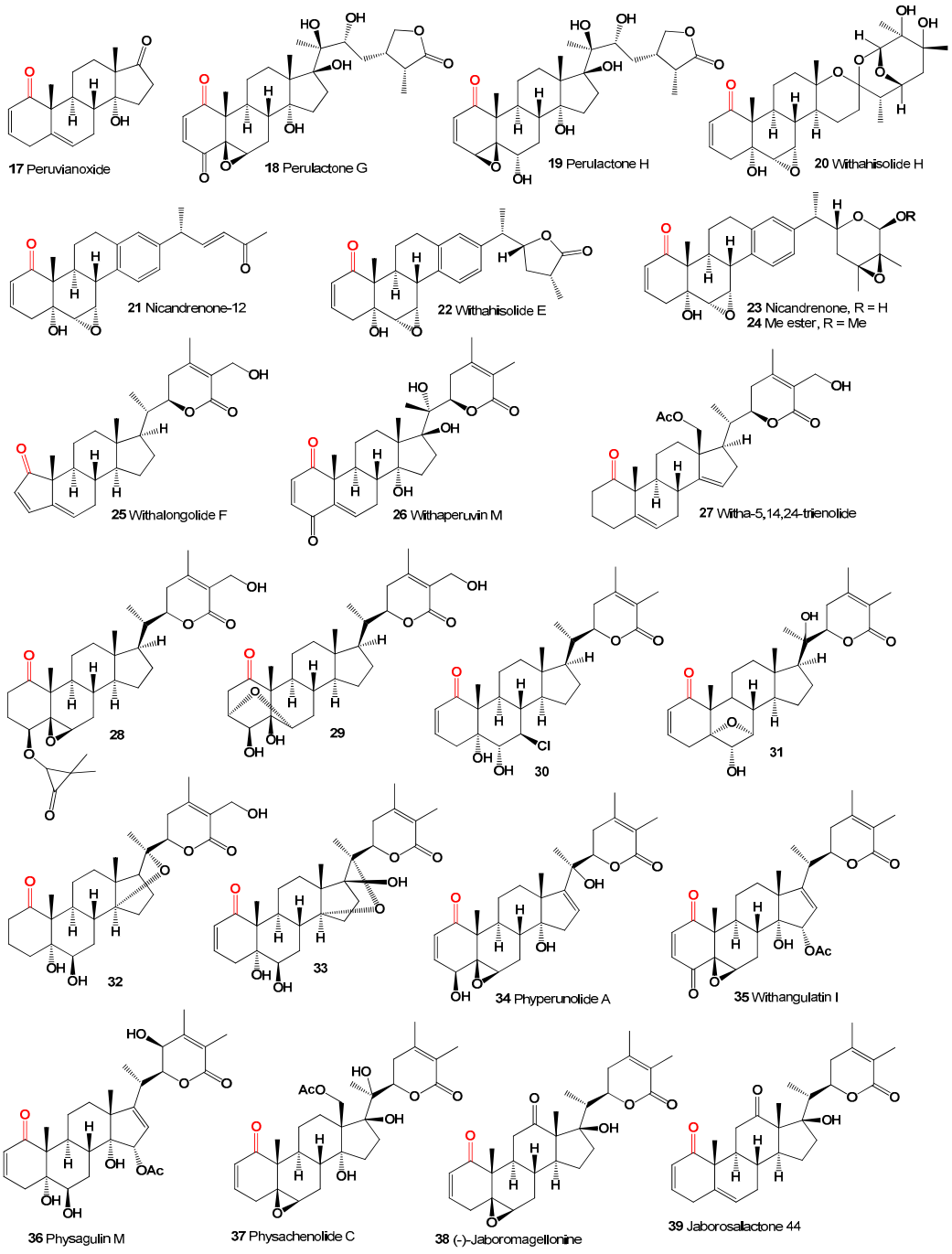

Figure 3. 1-Ketosteroids derived from microorganisms and plants.

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Several 14α-hydroxy withanolides have been reported from *Physalis* species, including phyperunolide A (**34**) [39] from *P. peruviana* and 15-acetyloxy withanolides from *P. angulata*, notably withangulatin I (**35**) [46] and physagulin M (**36**) featuring a free hydroxy group at C-23 [47]. A study on Mexican *Physalis* species revealed that physachenolide C (**37**) was isolated from the leaves, flowers, and stems of *Physalis chenopodifolia* [48]. Two withanolides with unmodified skeletons containing a free ketone at C-12 were reported from various plants, namely (-)-jaboromagellonine (**38**) from *Jaborosa magellanica* [49] and jaborosalactone 44 (**39**) from *J. kurtzii* [50]. A 12-oxygenated withanolide, daturalactone 7 (**40**), was isolated from *Datura ferox* collected in Argentina [51]. An intriguing example includes a C29 withanolide from the bark of *Eucalyptus globulus* (**41**) with an ethyl substituent at C-25 instead of the usual methyl group [52]. Daturacin (**42**), containing a 20,24 epoxide, was found in *D. inoxia* extract [53], and acnistins B (**43**), C (**44**), and D (**45**) were isolated from the leaves of *Dunalia solanacea* collected in Medellin, Colombia [54,55]. Withaphysalins K (**46**) and L (**47**) were isolated from *Eriolarynx lorentzii* (sub nom. *Vassobia lorentzii*) collected in Argentina [28].

The steroid Nic-1 (**48**) was obtained from *Nicandra physalodes* [30], and the minor component in *S. origanifolia* plants collected in Buenos Aires and Cordoba provinces, Argentina, was salpichrolide C (**49**) [56,57]. Salpichrolide H (**50**) was isolated from plants collected in Buenos Aires during the winter [58], and salpichrolide J (**51**) from plants collected in Salta province, Argentina, during the summer. Plants collected in Buenos Aires during the winter also contained two ergostane derivatives, salpichrolides E (**52**) and F (**53**), likely resulting from the degradation of the lactone side chain of salpichrolides A and C [59].

The 19-oxygenated trechonolide (**54**) was isolated from *Jaborosa laciniata*, with its 6,19-oxygen bridge being an unusual feature for a natural product [60]. Notably, synthetic steroids with this moiety exhibit significant biological properties as selective glucocorticoid receptor modulators [61], and jaborosalactone 15 (**55**) was found in plants collected in the summer [62]. Jaborosalactone 31 (**56**), isolated from *J. rotacea*, closely relates to the spiranoid withanolides isolated from *J. odonelliana, J. runcinata*, and *J. araucana*, where the C-12–C-23 bond remains intact, forming a dlactone between the C-26 carboxyl and the C-12 hydroxy group [63].

Subtrifloralactones D (**57**) and E (**58**) are similar to the classic withanolide structure but notably lack the C-18 [64]. The isolation of 13β-hydroxymethylsubtrifloralactone E (**59**) from *Deprea subtriflora* suggests an oxidative pathway leading to the loss of C-18, potentially resulting in a 16-formate group through the rearrangement of a 16,18-hemiketal [65]. Additionally, subtrifloralactones F (**60**) and G (**61**), which exhibit a *trans* fusion between rings C and D, resulting in an ixocarpalactone-type structure, were also detected in *Deprea subtriflora* [64].

Withanolides, specifically TH-6 (**62A**) and TH-12 (**62B**), are 17-methyl-18-nor-ergostanes that were isolated over 30 years ago by Shingu and co-workers [66] from the acid hydrolysate of a methanolic extract of *Tubocapsicum anomalum*. The researchers linked these compounds to a presumable precursor with a withanolide side chain that is thought to rearrange under acidic conditions.

Summarized on the biological activity of 1-ketosteroids is presented in Table 1, and details are described partially in the text or a full description of the activity is written in the original articles.

Table 1. Summarized biological activity of 1-ketosteroids.

No. Steroids	Reported Activity of 1-ketosteroids	Ref.
9,10	Growth inhibitory effects on HeLa S3 cells and human diploid cells	[34]
11-13	Cytotoxic activity	[35]
35	Cytotoxic activity	[46]
40	Cytotoxicity towards colon and pancreatic cancer cells	[51]
42	Antibacterial activity	[53]
54	Selective glucocorticoid receptor modulator	[61]
56	Quinone reductase inducer	[63]

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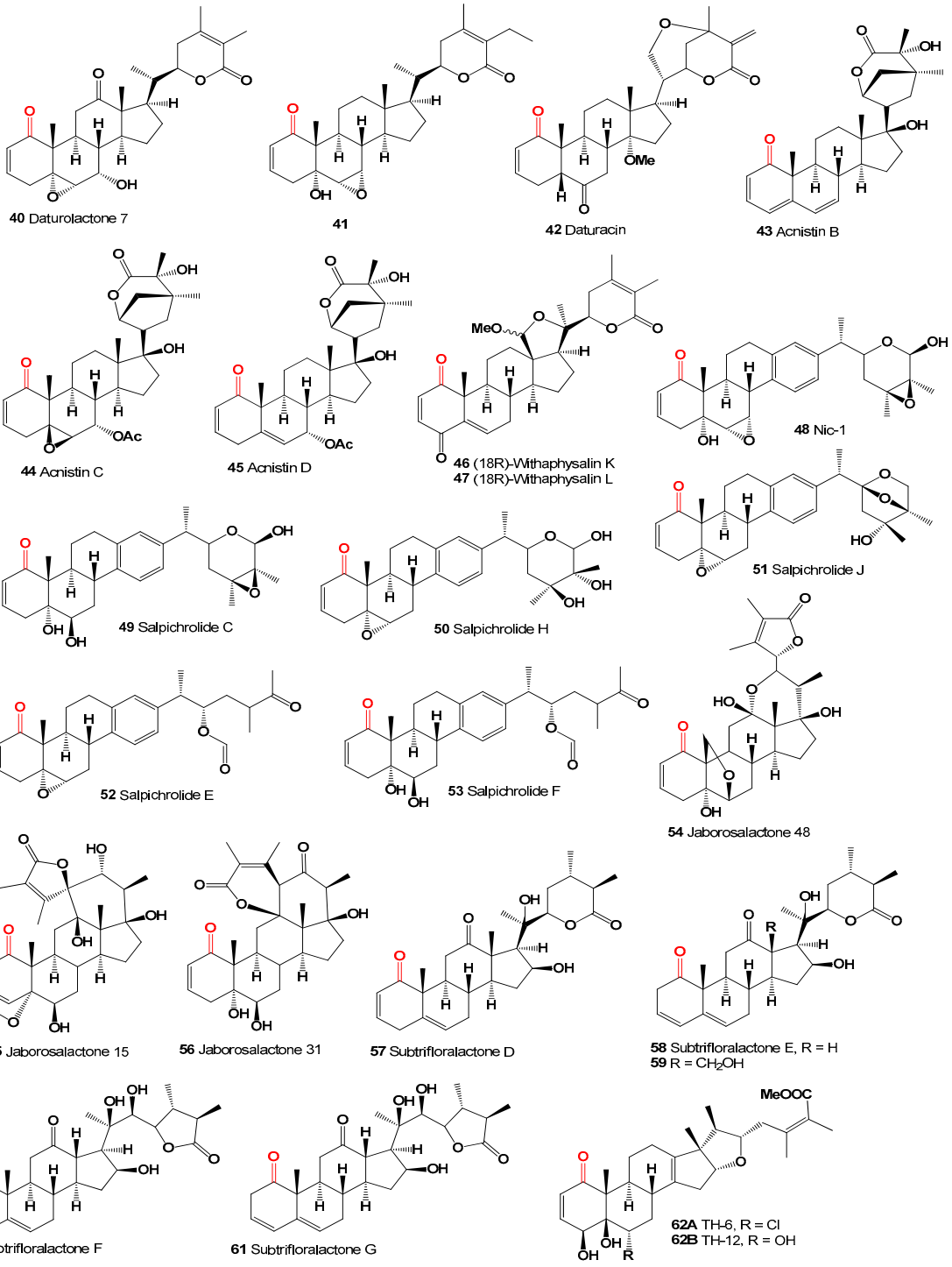

Figure 3. 1-Ketosteroids derived from microorganisms and plants.

2-Ketosteroids

2-Ketosteroids, also known as ketosteroids, are a group of steroid compounds that have a ketone group (C=O) at the second carbon atom in the steroid ring structure. This functional group distinguishes them from other steroids. These compounds are present in various biological systems and play important roles in metabolism and hormone regulation. 2-Ketosteroids can also be intermediate metabolites in the biosynthesis and metabolism of other steroids. For example, they can be precursors or breakdown products of hormones. 2-Ketosteroids are found in various tissues and

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organs, including the adrenal glands, gonads (ovaries and testes), and liver, depending on the specific function and type of steroid. They play crucial roles in maintaining homeostasis and regulating various physiological processes in the body [67–69].

3-Hydroxypregnane-2,16-dione (**63**) was isolated from ethanol extracts of the wood and bark of the Red cedar, *Trichilia hirta* [70]. The spirostane known as (25S)-3α-Hydroxy-5α-spirostane-2,12-dione, or nummularogenin (**64**), along with two other spirostanes (**65** and **66**), were discovered in the extract of the *Ziziphus nummularia* shrub, commonly referred to as wild jujube or jhahrberi in Hindi [71]. Monocarpine (**67**), a cycloartane derivative featuring an intriguing combination of oxygen functions in ring A and a unique C-17 side chain, was isolated from the trunk bark of *Monocarpia marginalis* [72], and monocarpinin (**68**) was detected in the same tree [73].

A series of 2-ketosteroids related to A-nor steroids have been identified in marine invertebrates and various plant species. Notably, crellasterones A (**69**) and B (**70**) were isolated from the sponge *Crella incrustans*, collected in New Caledonia [74]. These crellasterones structurally resemble the semi-synthetic steroid maltadiolone (**71**), which is medically used and exhibits calcium-binding activity comparable to cells not treated with calcium channel blockers [75]. This category also includes xidaosterol B (**72**), found in extracts from the South China Sea sponge *Neopetrosia chaliniformis* [76], and a compound from the brown alga *Sargassum carpophylum* (**73**), collected in the South China Sea [77]. Additionally, A-nor steroids (**74**-**77**) were detected in crude oil extracts, marine sediments, and other geological and environmental sources [67].

Viburnum dilatatum, known as linden viburnum, a deciduous shrub from the Adoxaceae family, is noted for producing clusters of red drupes when ripe. Introduced in the mid-Atlantic regions of the USA, from New York to Virginia, its berries, leaves, and stems are used in Traditional Chinese Medicine to treat snake bites, dysentery, and as an anti-helminthic. From this shrub, A-nor triterpenoids viburnols E (**78**) and G (**79**) have been isolated [78,79].

The fruits of *Citrullus colocynthis* contain a cucurbitane 3-nor-triterpenoid named norcolocynthenin B (**80**), with a unique 5/6/6/5-fused ring system, showing significant cytotoxic activity against human cancer cell lines HL-60 and PC-3 [80].

Dysoxylum hainanense, known for its twigs and leaves, produces triterpenoids such as dysoxyhainic acid A (**81**, structures see in Figure 4), with a novel 2-nor-1,3-cyclotirucallane skeleton, showing moderate antibacterial activity against Gram-positive bacteria [81].

Moreover, a phytochemical analysis of *Citrullus colocynthis* fruits revealed a variety of structurally diverse nonanorcucurbitane-type triterpenoids, including colocynins, among which colocynin A (**82**) displayed anti-acetylcholinesterase activity and notable cytotoxicity against various cancer cell lines [82,83].

In the study of *Dysoxylum hainanense*, a novel triterpenoid named dysoxyhainol (**83**) was identified from its twigs and leaves. This compound, with a modified ring A structure, exhibited moderate antibacterial activity against Gram-positive bacteria [81]. Additionally, malabanone B (**84**), featuring a unique tricyclo[4.3.1.01,6]decane unit, was isolated from the same plant parts [84].

Aphanamixis grandifolia stems produced aphanamgrandins E (**85**) and F (**86**), which are derivatives of 2,3-seco-tirucallane triterpenoids [85]. The rootwood of *Aglaia sylvestris* yielded dammarane-type triterpenoids, including silvaglin A (**87**), isosilvaglin A (**89**), and their 1H-β-epimers, silvaglin B (**88**) and isosilvaglin B (**90**), characterized by a $^{\Delta}$1(3)-bond [86]. *Viburnum dilatatum* leaves yielded dammarane triterpenoids viburnols E (**91**) and G (**92**) [87,88], and the cytotoxic steroid kiheisterone B (**93**) was discovered in a Maui sponge [89]. The minor steroid (**93**), isolated from the red alga *Laurencia obtusa* of the Lakshadweep islands, was identified through spectroscopic data and synthesis as 2α-oxa-2-oxo-5α-hydroxy-3,4-di-norcholestane, marking the first isolation of a ring A-dinorsteroid from a natural source. This compound, named 2α-oxa-2-oxo-5α-hydroxy-3,4-dinorcholestane (**94**), was also found in the Arabian Sea red alga *Laurencia obtuse* [90]. Additionally, three compounds (**95**, **96**, and **97**) were isolated from a Western Australian sponge, *Spongia* sp. [91].

Zeng and co-workers [92] reported the discovery of new compounds zimoclactone A (**98**) and zimoclactone B (**99**) from marine sponges. Furthermore, Parrish and co-workers isolated three new diterpenes: 18-nor-3,17-dihydroxy-spongia-3,13(16),14-trien-2-one (**100**), 18-nor-3,5,17-

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trihydroxyspongia-3,13(16),14-trien-2-one (**101**), and spongiapyridine (**102**) from an unidentified *Spongia* species collected in Sulawesi, Indonesia [93].

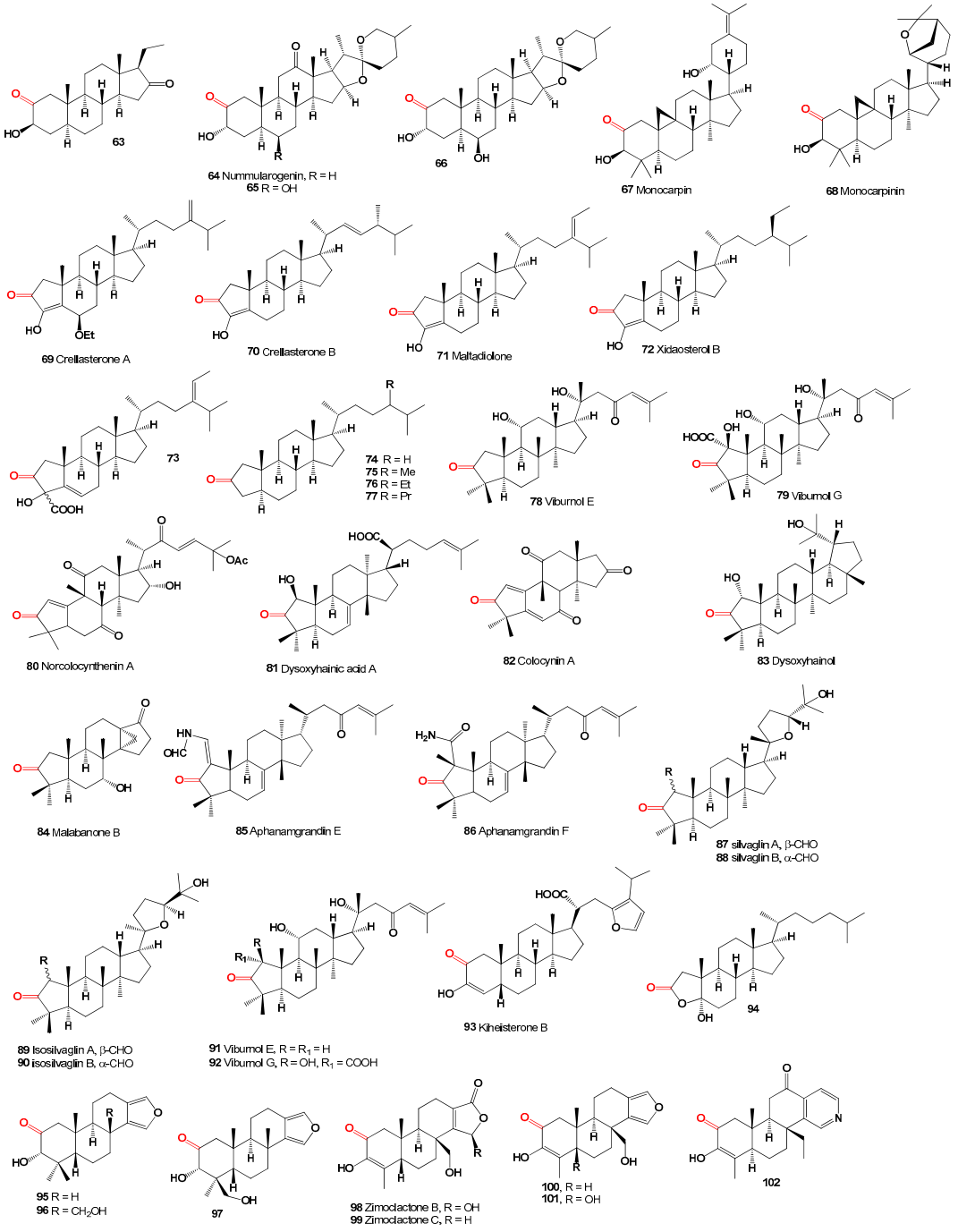

Figure 4. 2-Ketosteroids derived from algae, plants, and sponges.

Summarized on the biological activity of 2-ketosteroids is presented in Table 2, and details are described partially in the text or a full description of the activity is written in the original articles.

Table 2. Summarized biological activity of 2-ketosteroids.

No. Steroids	Reported Activity of 2-ketosteroids	Ref.
71	Calcium-binding activity	[75]
78,79	Anti-helminthic activity	[78,79]
81	Antibacterial activity against Gram-positive bacteria	[81]
82	Anti-acetylcholinesterase activity	[82,83]
83	Antibacterial activity against Gram-positive bacteria	[81]

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85,86	Anti-inflammatory activity	[85]
93	Cytotoxic activity	[89]
98.99	Cytotoxic activity against P388 cells	[93]

3-Ketosteroids

3. -Ketosteroids are interesting primarily because of their biological significance and their roles in various physiological processes. Many 3-ketosteroids are key hormones, including corticosteroids and sex hormones like testosterone and progesterone. These hormones play crucial roles in regulating metabolism, immune function, salt and water balance, development of sexual characteristics, and reproductive functions. Due to their hormonal activities, 3-ketosteroids are used in a variety of therapeutic applications. For example, corticosteroids are widely used to treat inflammation, allergies, and autoimmune diseases. Similarly, synthetic derivatives of sex hormones can be used in hormone replacement therapy, contraception, and treatment of hormone-sensitive cancers. 3-ketosteroids are involved in key biochemical pathways such as steroidogenesis, where they are intermediates in the synthesis of various other steroids. This makes them critical for maintaining the balance and production of hormones in the body [94–97].

In scientific research, 3-ketosteroids are studied for their role in metabolic pathways, their impact on various health conditions, and their potential as targets for new drugs. Understanding how these compounds interact with cellular receptors and enzymes can lead to the development of new treatments for a variety of diseases [94,98].

The 3-keto group in these steroids affects their chemical reactivity and interaction with biological molecules, influencing how they bind to receptors and other proteins. This structural aspect is crucial for their biological function and is a key area of study in biochemistry and pharmacology. Overall, the study of 3-ketosteroids blends aspects of biochemistry, medicine, and pharmacology, making them a fascinating and important area of scientific inquiry [98–101].

Wallenone (**103**, structures see in Figure 5), a C32 tirucallane-type triterpene, was isolated from the leaves of *Gyrinops wala*, a small tree from the Thymelaeaceae family grown in Ceylon [102]. More recently, this compound was also extracted from the ethyl acetate extract of the dried leaves of *Esenbeckia stephani* (Rutaceae) [103]. A neosteroid named 24ξ-methoxy-24,25-dimethyl-lanost-9(11)-en-3-one (**104**) was isolated from extracts of *Neolitsea pulchella*, a tree primarily found in the subtropical biome of Hong Kong, in the early 1970s [104,105]. Additionally, the triterpenoid 24,25-dimethyl-9(11),23-lanostadienol (**105**) was obtained from the stems of various *Quercus* species (*Q. bambusaefolia, Q. championi,* and *Q. myrsinaefolia*) [106].

An anticancer agent, *t*-Bu 7α,12α-dihydroxy-4,4,14α-trimethyl-3,11,15-trioxo-5α-chol-8-en-24-oate (**106**), known as *t*-butyl lucidenate B, was isolated from the fruiting bodies of the oriental fungus *Ganoderma lucidum* [107]. Cycloeucalenone (**107**) was isolated from an unidentified fungus collected in New Jersey [108]. Akihisa and co-workers [109] reported that the fungus *Glomerella fusarioides* transformed cycloartenol into cycloartane-3,24-dione (**108**), rare 4α,4β,14α-trimethyl-9β,19-cyclopregnane-3,20-dione (**109**), and 24,25-dihydroxy-cycloartan-3-one (**110**). An extract from *Parthenium argentatum*, commonly known as guayule, contained a cytotoxic steroid named argentatin A (**111**), which showed cytotoxic effects against human colon cancer cell lines and normal epidermal keratinocytes [110].

Unique steroids named malabanone A (**112**), which incorporate a unique tricyclo [4.3.1.01,6] decane unit, were isolated from the stem bark of *Ailanthus malabarica*. The biosynthesis of these steroids is suggested to originate from ailanthol, also found in this plant [111]. Three steroids with an incorporated cyclopropane unit at positions 14 and 18, named ailanthusins A (**113**), B (**114**), and D (**115**), were isolated from the CH_2Cl_2 extracts of the Thailand rainforest tree *Ailanthus triphysa* [112].

A $CHCl_3$-MeOH extract from the bark of *Aglaia crassinervia* collected in Indonesia led to the isolation of aglaiaglabretol A (**116**), found in the stems of *Spathelia excelsa* (Rutaceae), exhibiting larvicidal properties against the yellow fever mosquito, *Aedes aegypti*, with an LC_{50} of 4.8 μg/mL [113]. A series of antitumor triterpene glucosides, named cumingianosides M (**117**), containing a 14,18-

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cycloapotirucallane-type skeleton, were isolated from a cytotoxic fraction of the leaves of *Dysoxylum cumingianum*, displaying significant cytotoxicity against leukemia and melanoma cell lines [114,115].

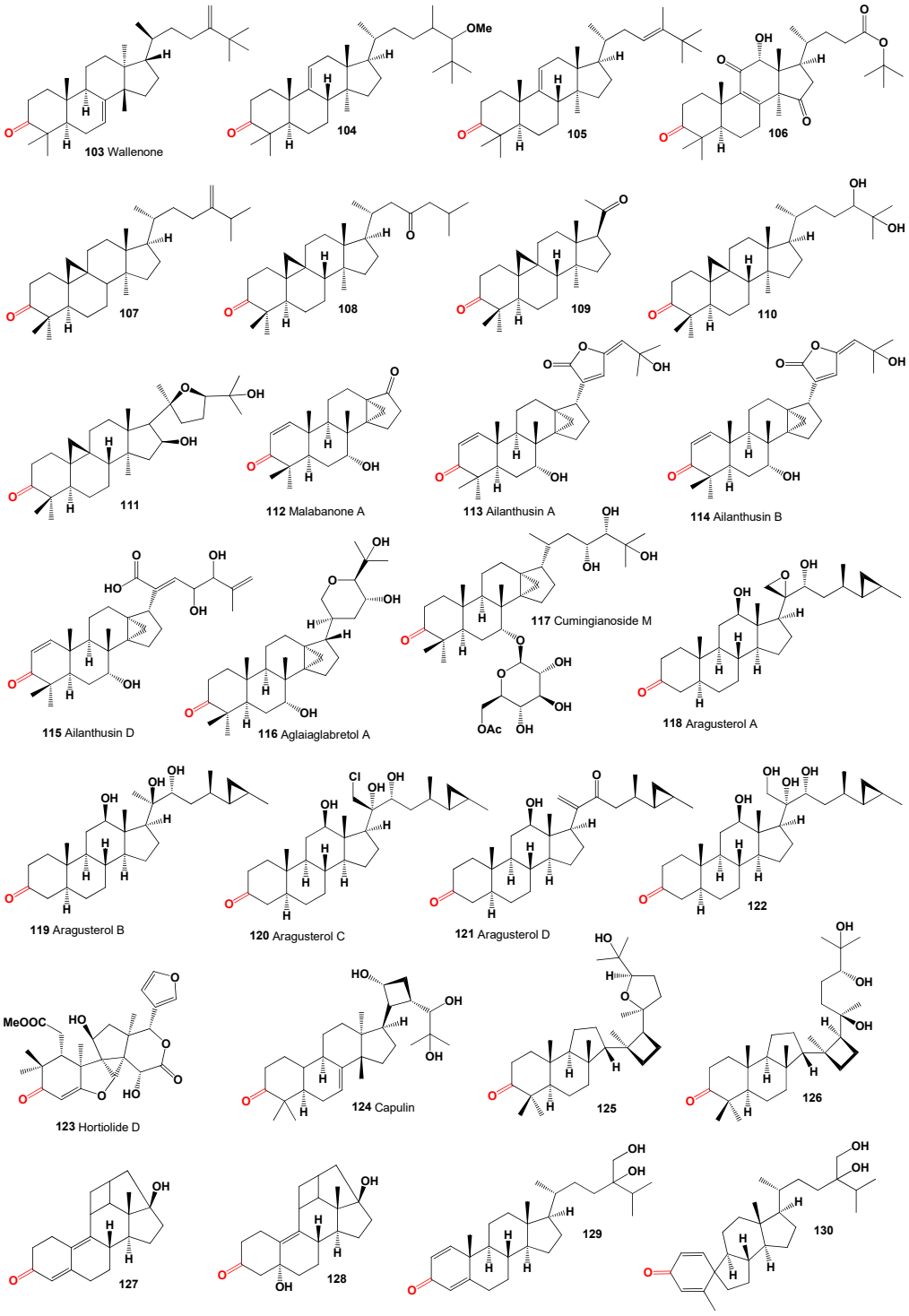

Figure 5. 3-Ketosteroids derived from fungal endophytes, sponges, and plants.

A cytotoxic steroid, aragusterol A (**118**), possessing potent antitumor activity, was isolated from an Okinawan sponge of the genus *Xestospongia*. The compound strongly inhibited cell proliferation in KB, HeLaS3, P388, and LoVo cells *in vitro* and demonstrated potent *in vivo* antitumor activity against P388 and L1210 in mice [116]. Additionally, 26,27-cyclosterols aragusterols B (**119**), C (**120**), and D (**121**) have been identified in the same Okinawan marine sponge [116,117]. A wide array of steroids, including aragusterol A (**118**) and another compound (**122**), were found in the marine sponge *Petrosia* (*Strongylophora*) sp. collected from the Similan Island, Thailand [118].

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A limonoid named hortiolide D (**123**) was found in CH_2Cl_2 and MeOH extracts from the stem of *Hortia oreadica* [119], and a protolimonoid named capulin (**124**), featuring a four-membered ring in its side chain, was isolated from the stem barks of *Capuronianthus mahafalensis*, a species endemic to Madagascar [120].

A limonoid named hortiolide D (**123**) was found in CH_2Cl_2 and MeOH extracts from the stem of *Hortia oreadica* [119], and a protolimonoid named capulin (**124**), featuring a four-membered ring in its side chain, was isolated from the stem barks of *Capuronianthus mahafalensis*, a species endemic to Madagascar [120].

Two unusual malabaricane-type triterpenes, (14S,17S,20S,24R)-25-hydroxy-14,17-cyclo-20,24-epoxy-malabarican-3-one (**125**) and (14S,17S,20S,24R)-20,24,25-trihydroxy-14,17-cyclo-malabarican-3-one (**126**), were isolated from the oleoresin of the wounded trunk of *Ailanthus malabarica* [121]. The steroid altrenogest, a progestin from the 19-nortestosterone group widely used in veterinary medicine to suppress or synchronize estrus in horses and pigs, produces two photoproducts (**127** and **128**) through photolysis experiments [122]. The steroid erectasteroid H (**129**) exhibited cytotoxic activity against P-388 (leukemia) and HT-29 cells [123], and a spirosteroid (**130**) was isolated from the Formosan soft coral *Nephthea erecta* [124,125].

Two steroids, theonellasterone (**131**) and conicasterone (**132**), featuring a keto group at C-3, were identified in marine sponges from the genus *Theonella* [126]. Additionally, two steroidal oximes (**133** and **134**) from the *Cinachyrella* sp. sponge were found to inhibit human placental aromatase competitively, suggesting their potential as inhibitors in hormone-dependent tumors [127]. Holland and colleagues described the synthesis of these compounds [128]. The cytotoxic kicheisterone A (**135**), distinguished by *cis*-fused rings A and B with carboxy groups at position 21 and furan fragments in the side chains, was isolated from an unidentified Hawaiian sponge of the *Poecilosclerida* sp. [129]. This steroid, along with kicheisterones C-E (**136**-**138**) which contain a chlorine atom and are part of a rare group of halogenated steroids, was also found in the sponge *Strongylacidon* sp. [130].

A series of 3-oxo-4,6,8(14)-triunsaturated steroids with cholestane (**139** and **140**), ergostane (**141**–**143** and **145**), and stigmastane skeletons (**144** and **146**–**148**) were discovered in the lipid extract of *Dysidea herbacea* [131]. Steroids **145** through **148** were isolated as C-24 epimeric mixtures. Compounds **139** through **148** represent the second instance of steroids from a marine source featuring a conjugated 3-oxo-4,6,8(14)-triene system; compound **140** had previously been isolated from *Dyctionella incisa* [132]. Cholest-4-ene-3,6-dione (**149**) and (24R)-24-ethylcholest-4-ene-3,6-dione (**150**) were isolated from the marine sponge *Cinachyra tarentina* [133]. Compound **149** was synthesized from cholesterol, while the structure of **150** was confirmed by synthesis from sitosterol, involving Jones oxidation to determine the R chirality at C-24.

The steroid mycalone (**151**), with a six-membered lactone side chain, was isolated from a *Mycale* species in southern Australia [134]. Ergosta-4,24(28)-dien-3-one (**152**) was identified in the subantarctic shallow-water sponge *Geodia cydonium* [135], and a similar compound, (25S)-26-Methyl-24-methylenecholest-4-en-3-one (**153**), was isolated from the marine fossil sponge *Neosiphonia supertes* [136].

Finally, a dimeric steroid, bistheonellasterone (**154**), likely biosynthesized *via* a Diels-Alder cycloaddition of theonellasterone, was discovered in the Okinawan marine sponge *Theonella swinhoei* [137].

A series of steroid hydroperoxides (**155**-**158**) isolated from the red alga *Galaxaura marginata* collected near the coasts of Taiwan demonstrated high cytotoxic activities against tumor cells P-388, KB, A-549, HT-29, with semi-inhibiting concentrations (IC_{50}) within the range of 0.2 μg/mL [138]. The steroidal 3,6-diketone **159**, oxygenated at C(16), was isolated from the alga *Jania rubens*, showing high toxicity against some tumor cells (IC_{50} = 0.5 μg/mL) [139]. Hydroperoxides (**160** and **161**) isolated from the brown alga *Turbinaria conoides* also exhibited cytotoxic properties [140].

Sterols and sterones were discovered in a sponge *Stelletta* sp., collected at a depth of 700 m in the deep Coral Sea, southeast of Noumea. These compounds, the first examples of stigmastane steroids with a $\Delta^{24,25}$ from a marine origin, were elucidated as stigmasta-4,24(25)-dien-3-one (**162**), stigmasta-

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4,6,24(25)-trien-3-one (**163**), stigmasta-4,24(25)-diene-3,6-dione (**164**), 6β-hydroxystigmasta-4,24(25)-dien-3-one (**165**), stigmasta-5,24(25)-dien-3β-ol (**166**), and compound **167** [141].

Guggulsterones (**168** and **169**), phytosteroids found in the resin of the guggul plant, *Commiphora mukul*, exist as two stereoisomers, (*E*)-guggulsterone and (*Z*)-guggulsterone [142,143]. In humans, they act as antagonists of the farnesoid X receptor, initially thought to decrease cholesterol synthesis in the liver, though studies indicate no overall reduction in total cholesterol, with levels of low-density lipoprotein increasing in many cases [143–147].

An ethyl acetate extract from the gorgonian *Leptogorgia* sp., collected from the South China Sea, contained a dihydroxy-ketosteroid (**170**) [148]. From the gorgonian coral *Euplexaura anastomosans*, collected off the shore of Keomun Island, South Sea Korea, steroidal hemiacetals named anastomosacetals A (**171**) and D (**172**) were obtained. Another gorgonian species, *Bebryce indica*, collected off the coast of Sanya (Hainan, China), was found to contain a steroidal glycoside named bebrycoside (**173**) [150]. Additionally, bebrycoside (**173**) and related compounds such as 27-O-[β-D-arabino-pyranosyloxy]-20β,22α-dihydroxy-cholest-4-ene-3-one, named muricellasteroid D (**174**), and the rare steroid 22α-O-acetyl-2β-O-methylene-[4β-hydroxy-phenyl]-cholest-4-ene-3-one, named muricellasteroid E (**175**), were isolated from the EtOH/CH_2Cl_2 extracts of the South China Sea gorgonian coral *Muricella flexuosa*. Both compounds **174** and **175** demonstrated moderate cytotoxicity against A375, K562, and A549 cancer cell lines [151].

An unusual hemiketal steroid, 23-keto-cladiellin A (**176**), was obtained from the monohydroxylated sterol fraction of the soft coral *Chromonephthea braziliensis* [152]. From the soft coral *Nephthea* sp., a unique pentacyclic hemiacetal sterol named nephthoacetal (**177**) and its acetyl derivative (**178**) were isolated. Compound (**177**) exhibited significant inhibitory effects with an EC_{50} value of 2.5 μg/mL, while maintaining low toxicity with an LC_{50} greater than 25.0 μg/mL. The *in vitro* cytotoxic activity of both compounds (**177** and **178**) showed moderate effects with IC_{50} values of 12 and 10 μg/mL, respectively [153].

Krempene A (**179**, structures in Figure 6), an unprecedented pregnane-type steroid with a highly unusual hexacyclic oxadithiino unit fused to the steroidal ring A, was isolated from the marine soft coral *Cladiella krempfi* [154]. Additionally, a rare steroidal hydroperoxide, 13,14-seco-22-norergosta-4,24(28)-dien-19-hydro-peroxide-3-one (**180**), has been found in the diethyl ether fraction of the Red Sea soft coral *Litophyton arboretum* [159]. Lastly, an unprecedented spinaceamine-bearing pregnane named scleronine (**181**) was produced by a Chinese soft coral *Scleronephthya* sp. [156].

Two steroids (**182** and **183**) along with pregna-1,4,20-trien-3-one (**184**) have been isolated from the Pacific octocoral *Carijoa multiflora*. Compound (**182**), featuring a spiropregnane-based steroidal skeleton, has demonstrated antibacterial activity [157]. Additional pregnane steroids (**185** and **186**), similar to compounds (**183** and **184**), were isolated from a gorgonian *Carijoa* sp. collected from the South China Sea. These compounds, particularly (**184**, **185**, and **186**), exhibited cytotoxicity against the human hepatoma cell line Bel-7402, with IC_{50} values of 9.3, 11.0, and 18.6 μM, respectively [158]. The Hainan soft coral *Scleronephthya gracillimum* has released a pregnane analogue (**187**) [159], and two unique chloro-pregnane steroids (**188** and **189**) have been isolated from the eastern Pacific octocoral *Carijoa multiflora* [160].

An unusual steroid thioester, parathiosteroid A (**190**), was isolated from the 2-propanol extract of the soft coral *Paragorgia* sp. collected in Madagascar. This compound displayed cytotoxicity against a panel of three human tumor cell lines at the micromolar level [161]. The reef soft coral *S. brassica*, which was cultured in an aquarium, yielded four steroids with methyl ester groups: sinubrasones A (**191**), B (**192**), D (**193**), and C (**194**). Compounds **191** and **192** showed significant cytotoxicity, while compounds **193** and **194** demonstrated notable anti-inflammatory activities [162]. Additionally, the ethyl acetate extract of a reef soft coral *S. brassica*, cultured in a tank, produced two steroids, sinubrasones A (**195**) and B (**196**), both of which exhibited significant cytotoxicity [163].

The soft coral *Umbellulifera petasites* produces steroid (**197**), while petasiterone B (**198**), and 5α-pregna-20-en-3-one (**199**) have been found in the soft coral *Alcyonium gracillimum* [162,164,167].

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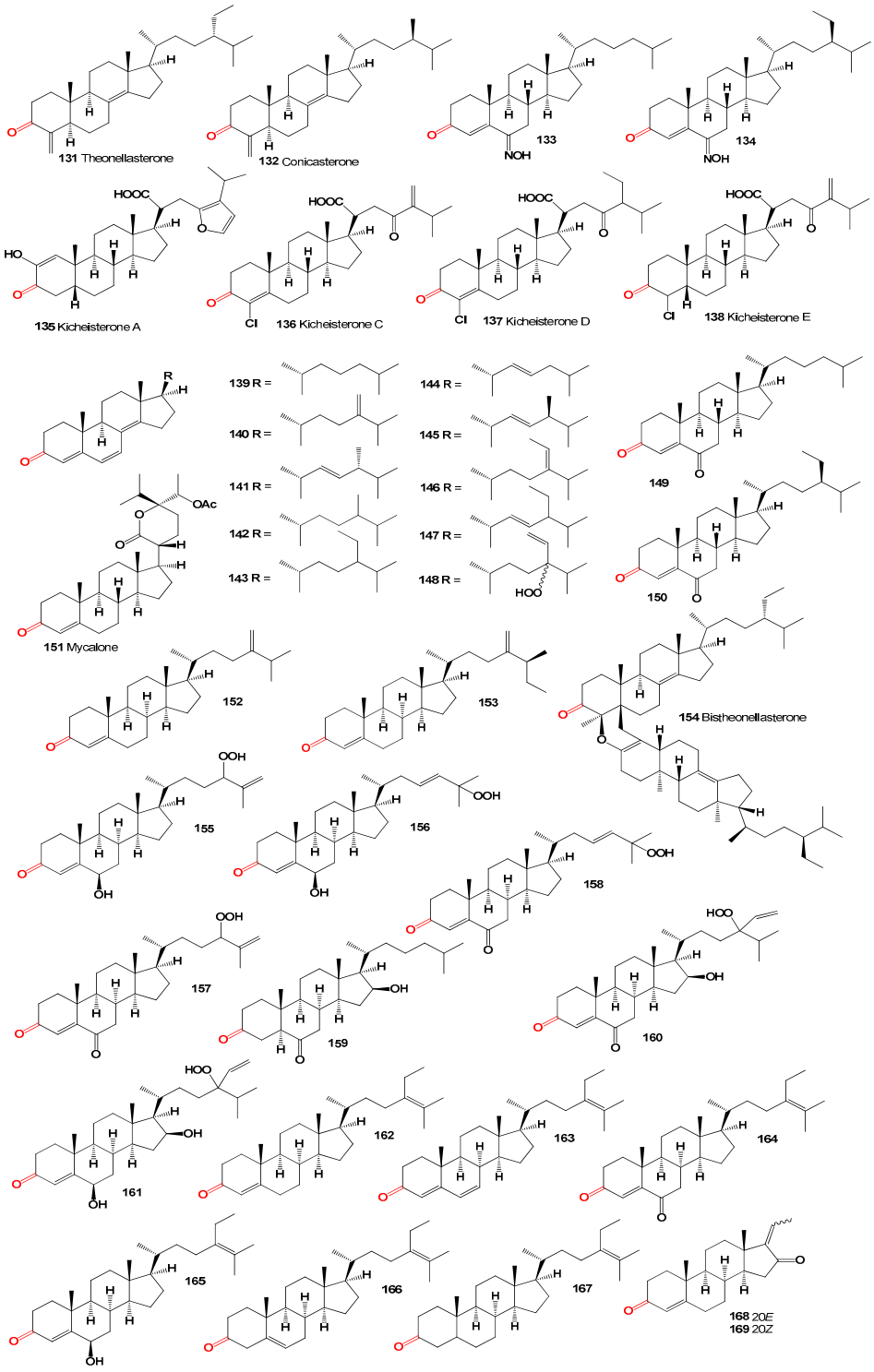

Figure 6. 3-Ketosperoids derived from algae, marine invertebretes and plants.

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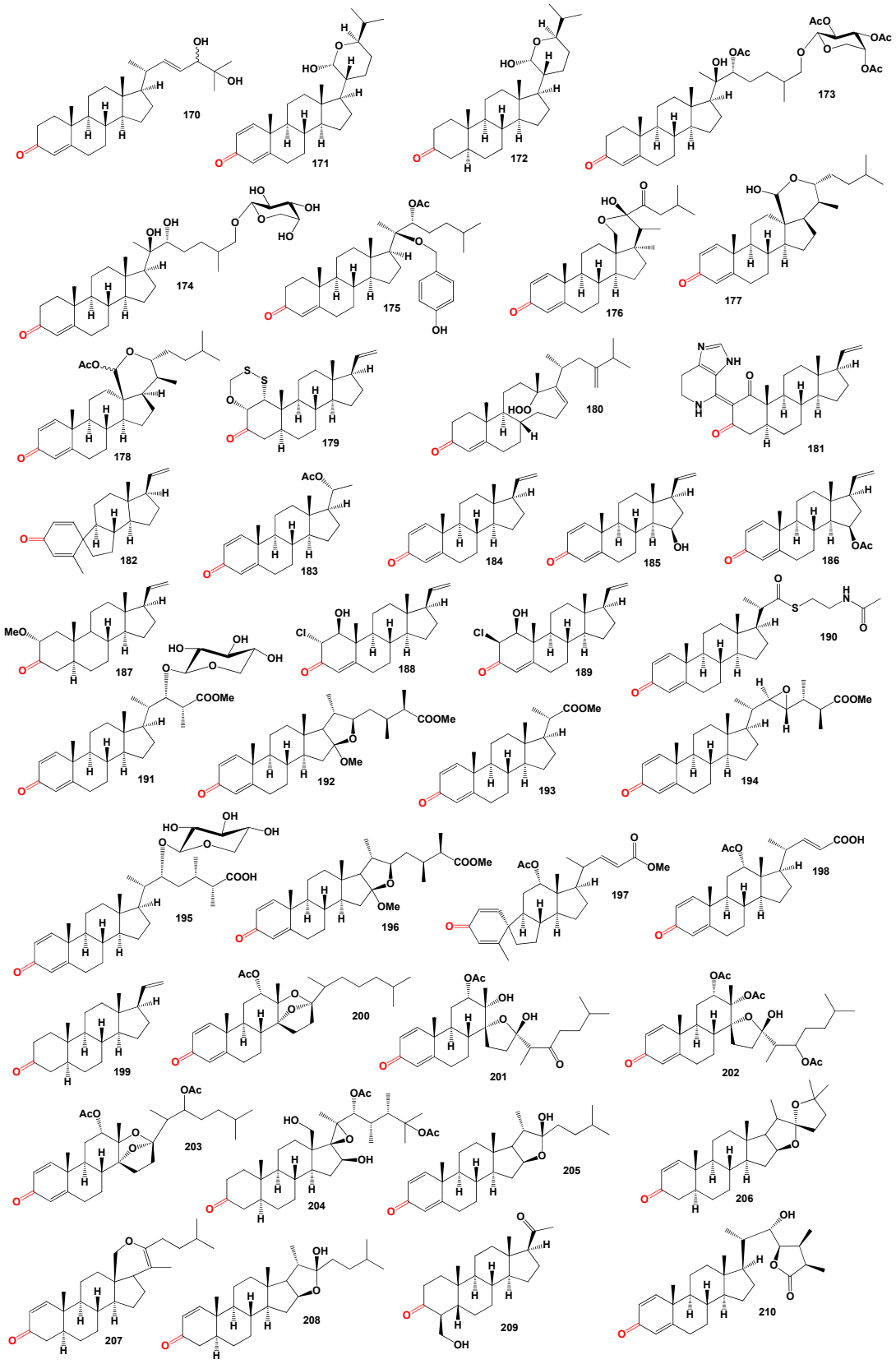

Figure 6. 3-Ketosteroids derived from marine invertebretes and plants.

Unique highly oxygenated 13,17-secosteroids with a split D ring, named isogosterones A–D (**200**–**203**), were obtained from extracts of a Japanese octocoral of the genus *Dendronephthya* collected off the Izu Peninsula. These steroids have demonstrated the ability to inhibit the settlement of *B. amphitrita* cyprid larvae [166]. A polyhydroxygenated steroid, hipposterone M (**204**), showing

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cytotoxicity against human cytomegalovirus (HCMV), was derived from extracts of the Taiwanese octocoral *Isis hippuris* collected at Orchid Island [167]. Additionally, steroids (**205–208**), isolated from the crude extract of *Alcyonium gracillimum*, exhibited moderate cytotoxicity (IC_{50} 22 μg/mL) and antiviral activity (IC_{50} 8 μg/mL) against P388 and HSV-I (human α-herpesvirus), respectively [168,169].

A pregnane derivative, 4-hydroxymethyl-5β-pregnan-3, 20-dione (**209**), was isolated from the South China Sea gorgonian *Subergorgia suberosa* [170]. From the lipid extracts of the Formosan soft coral *Paraminabea acronocephala*, a marine withanolide named paraminabeolide D (**210**) was obtained [171]. Summarized on the biological activity of 3-ketosteroids is presented in Table 3, and details are described partially in the text or a full description of the activity is written in the original articles.

Table 3. Summarized biological activity of 3-ketosteroids.

No. Steroids	Reported Activity of 3-ketosteroids	Ref.
111	Cytotoxic activity	[110]
116	Larvicidal properties against the yellow fever mosquito	[113]
117	Antitumor activity	[114,115]
118	Antitumor activity against P388 and L1210	[116]
129	Cytotoxic activity against P-388 (leukemia) and HT-29 cells	[123]
133,134	Human placental aromatase inhibitor	[127]
155-158	Strong cytotoxic activities against tumor cells P-388, KB, A-549, HT-29	[138]
159	Strong toxicity against some tumor cells	[139]
160,161	Cytotoxic properties	[140]
174,175	Cytotoxicity against A375, K562, and A549 cancer cell lines	[151]
177,178	Cytotoxic activity	[153]
182	Antibacterial activity	[157]
184-186	Cytotoxicity against the human hepatoma cell line Bel-7402	[158]
190	Cytotoxicity against a panel of three human tumor cell lines	[161]
191,192	Strong cytotoxicity	[162]
193,194	Anti-inflammatory activity	[162]
204	Cytotoxicity against human cytomegalovirus (HCMV)	[167]
205-208	Antiviral activity against P388 and HSV-I (human α-herpesvirus)	[168,169]

4-Ketosteroids

4-Ketosteroids are also a significant class of steroid compounds with a ketone group at the fourth carbon of the steroid backbone. While they are less commonly discussed compared to 3-ketosteroids, 4-ketosteroids also have important role. The presence of the ketone group at the fourth position affects the chemical behavior and biological interactions of these steroids. This ketone group can influence how the steroid interacts with various enzymes and receptors within the body. Some 4-ketosteroids are intermediates in the metabolism of more commonly known steroids. They can arise during the breakdown and transformation processes of hormones in the body. Understanding their metabolism helps in elucidating the pathways of steroid degradation and synthesis [172–175].

While 4-ketosteroids themselves may not be widely used therapeutically, understanding their structure and function can aid in the development of steroid-related treatments. They can serve as models or starting points for the synthesis of novel compounds with improved efficacy and reduced side effects. Although not as prominent as other steroids, some 4-ketosteroids may exhibit unique biological activities that could be of interest in hormone research or drug development. Exploring these activities might provide new insights into steroid hormone action and regulation [173,176].

An oxygenated steroid, named aspersteroid A (**211**, structures see in Figure 7), was isolated from the marine-derived fungus *Aspergillus flavus* collected from the Bohai Sea [177]. Solamaladine (**212**) was extracted from the green fruits of *Solanum hypomalacophyllum* [178]. Additionally, green berries of *S. hypomalacophyllum* provided the known alkaloid solaphyllidine (**213**, 16-acetoxy-3,23-dihydroxy-

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16,28-secosolanidan-4-one), its 16-deacetoxy analog (**214**), and the deacetoxy, 3-O-β-D-glucopyranoside derivative (**215**) [179]. A steroidal alkaloid named pachystermine A (**216**), extracted from *Pachysandra terminalis*, also known as Japanese pachysandra, exhibited an anti-ulcer effect [180].

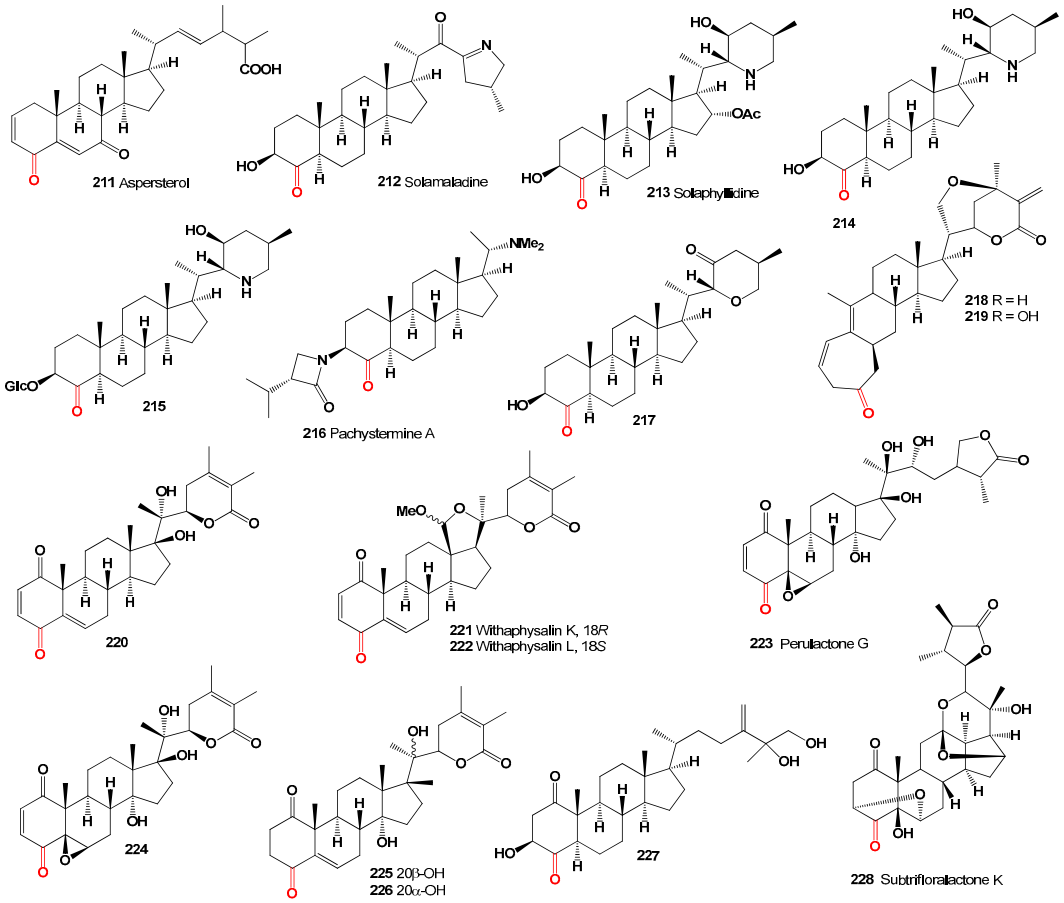

Figure 7. 4-Ketosteroids derived from fungi and plants.

Several 4-keto-withanolides and related steroids have been discovered in plants from the Solanaceae family. Specifically, 15-acetyloxy withanolide was isolated from *P. angulata*, along with withangulatin I (**35**) [46]. Compounds (**217**) and the secowithametelins **218** and **219**, as well as withaperuvin M (**220**), were obtained from the leaves and flowers of *Datura metel* [181]. Withaphysalins K (**221**) and L (**222**) were isolated from *Eriolarynx lorentzii* (sub nom. *Vassobia lorentzii*) collected in Argentina [28], and perulactone G (**223**) was found in *Physalis peruviana* [182]. Withaperuvin E (**224**), characterized by a special D2-1,4-dione system in ring A, was detected in *Physalis peruviana* [183]. Withanolides (**225**) and (**226**), showing nitric oxide inhibitory effects and affinities with iNOS, were also detected in *Physalis peruviana* [184]. Additionally, 3,25,26-trihydroxyergost-24(28)-ene-1,4-dione (**227**) was obtained from the leaves of the genus *Jaborosa* [185]. Subtrifloralactone K (**228**), a C-18 oxygenated withanolide, was isolated from the active fractions of the chloroform-soluble extract of *Deprea subtriflora* [186].

Summarized on the biological activity of 4-ketosteroids is presented in Table 4, and details are described partially in the text or a full description of the activity is written in the original articles.

Table 4. Summarized biological activity of 4-ketosteroids.

No. Steroids	Reported Activity of 4-ketosteroids	Ref.
216	Anti-ulcer effect	[180]
225,226	Nitric oxide inhibitory effects	[184]

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6-Ketosteroids

6-Ketosteroids are another interesting group within the steroid family, characterized by the presence of a ketone group at the sixth carbon of the steroid nucleus. Similar to other ketosteroids, 6-ketosteroids can be involved in specific metabolic pathways. They may serve as intermediates in the synthesis or breakdown of steroid hormones, although their presence and role in these pathways tend to be more specialized and less general than those of 3- or 4-ketosteroids. The specific activities of 6-ketosteroids can vary, but like other steroids, they might interact with certain receptors or enzymes, influencing various physiological processes. The exact functions and significance of these interactions can depend heavily on the particular structure and context of the 6-ketosteroid [187–191].

Due to their unique position of the ketone group, they may have distinct biochemical properties that could be exploited in drug development or in studies of steroid metabolism and function. The presence of a ketone group at the sixth position can significantly affect the steroid's ability to bind to and activate or inhibit various receptors. Structural studies, such as X-ray crystallography or NMR spectroscopy, can help elucidate how these changes impact receptor interaction and function. While not as directly utilized in therapy as some other ketosteroids, understanding the properties of 6-ketosteroids could lead to the development of new drugs, particularly if these steroids exhibit unique interactions with biological molecules that can be modulated for therapeutic benefit [191–193]. In general, 6-ketosteroids are a more niche area of study within the broader field of steroid research. Their unique characteristics can provide valuable insights into steroid chemistry and biology, contributing to our overall understanding of steroid functions and their implications in health and disease.

Antibiotic WF 15604A (**229**, structures see Figure 8), a bioactive secondary metabolite that inhibits cholesterol synthesis, has been found in the leaves of *Preussia minima* collected in the Iberian Peninsula [194]. Two steroids, chiograsterone (**230**) and isochiograsterone (**231**), have been isolated from *Chionographis japonica* [195].

Plant hormones such as 3,24-diepicastasterone (**232**) were detected in the seeds of *Phaseolus vulgaris*. Homoteasterone (**233**) was isolated from the EtOAc-hexane extract of rice from *Oryza sativa*, radish *Raphanus sativus*, and "Remo" seeds. Furthermore, 25-methylcastasterone (**234**) and another compound (**235**) were isolated from a methanol extract of ryegrass *Lolium perenne* pollen [196].

Polyoxygenated meroterpenoids named aperterpene N (**236**) and O (**237**) were isolated from the marine algal-derived fungus *Aspergillus terreus* EN-539 [197]. Compound (**236**) displayed neuraminidase inhibitory activity, with an IC_{50} value of 18.0 μM. Meroterpenoid terretonin D1 (**238**) was obtained from the marine sediment-derived fungus *Aspergillus ustus* KMM 4664 and from *Aspergillus terreus* EN-539, associated with the fresh gut of a Pacific oyster [198].

The 5α,9α-endoperoxide (**239**) was isolated from the fruiting bodies of *Stropharia rugosoannulata* and protected neuronal cells by attenuating endoplasmic reticulum stress caused by thapsigargin, an inhibitor of Ca2+-ATPase [199]. Additionally, two steroids containing an oxetane ring (**240** and **241**) have been isolated from the endophytic fungi *Chaetomium* sp. and *Colletotrichum* sp., respectively. Both compounds demonstrated activity in an AChE inhibitory assay [200,201].

A cytotoxic steroid (**242**) has been discovered in the filamentous fungus *Talaromyces stipitatus*, belonging to the family Trichocomaceae. It exhibited cytotoxic activity against Hep3B (IC_{50} 4.75 μM), HepG2 (IC_{50} 8.85 μM), and Huh-7 (IC_{50} 13.78 μM) [202]. A 4-ketosteroid (**243**) was identified in several fungal species, including *Fomes fomentarius* [203], *Grifola frondosa* [204], and *Phellinus linteus* [205], showing activities such as β-hexosaminidase inhibition, HNE inhibitory, and NO production inhibition. *Hericium erinaceus*, commonly known as the lion's mane mushroom, contained a steroid (**244**) that demonstrated inhibition of TNF-α secretion and NO production in lipopolysaccharide-induced RAW 264.7 cells [206].

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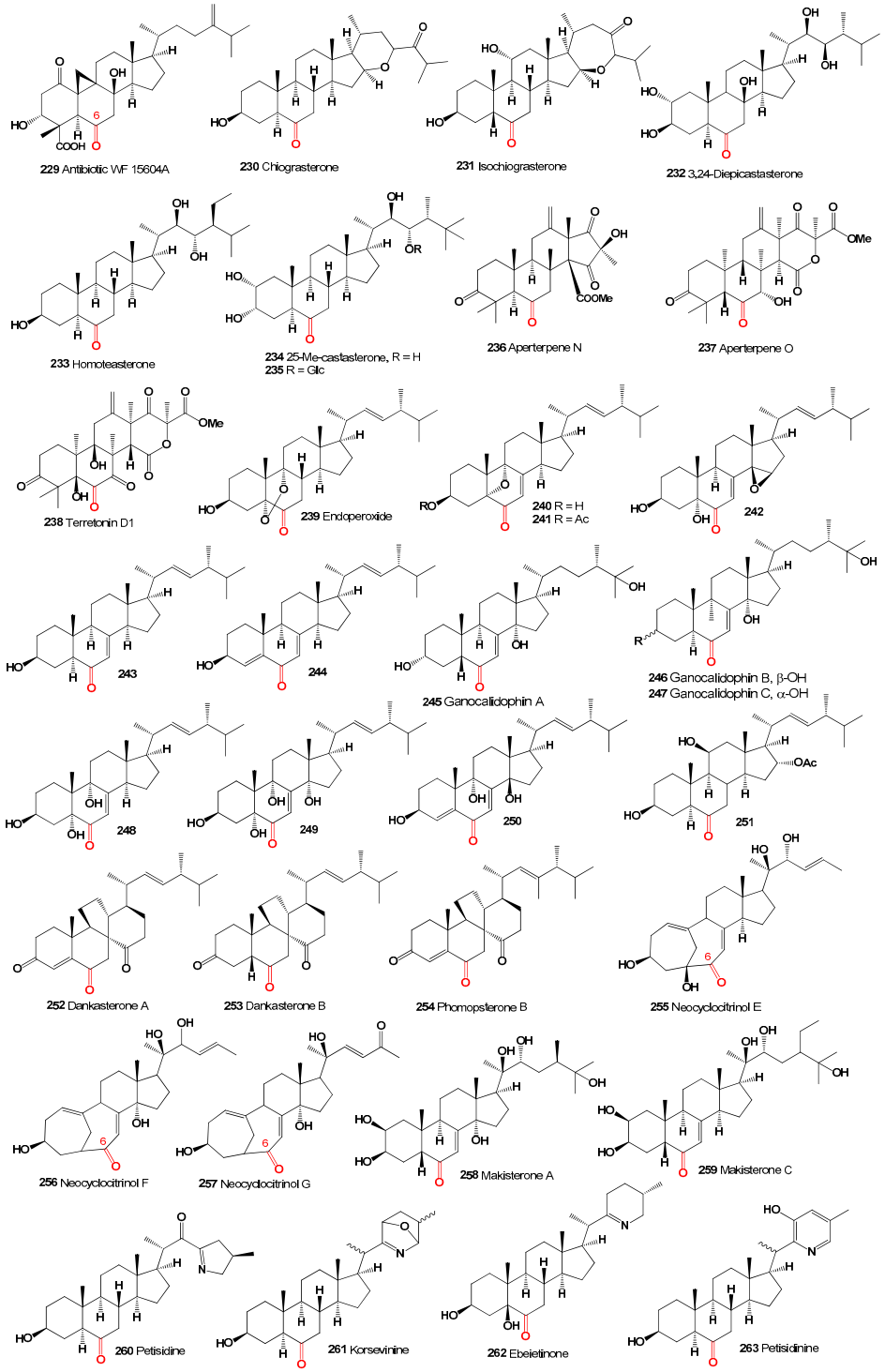

Figure 8. 6-Ketosteroids derived from fungal endophytes and plants.

Three ergosterols, ganocalidophins A–C (**245**–**247**), were isolated from the fruiting bodies of *Ganoderma sinense*. These compounds exhibited inhibitory activities against NO production with IC_{50} values of 17.7, 32.4, and 19.8 μM, respectively [207]. 4-Keto-ergosterol (**248**), produced by various fungi including *Colletotrichum* sp. [200], *Ganoderma sinense* [207], *Pleurotus eryngii* [208], *Psathyrella candolleana* [209], and *Volvariella volvacea* [210], demonstrated cytotoxic activity against HepG2 (IC_{50} 5.90 μM), SGC-7901 (IC_{50} 12.03 μM) [210], and minimal activity against A549, HL-60, MCF-7, SMMC-7721, SW480 (IC_{50} > 40 μM) [209], RAW264.7 (IC_{50} > 100 μM) [208]. This compound also inhibited NO production with varying efficacy (IC_{50} 28.5 μM and 100 μM) [208].

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Steroid (**249**), obtained from the fungus *Volvariella volvacea*, exhibited cytotoxic activity against HepG2 cells with an IC_{50} of 20.27 μM [210]. Another steroid (**250**) was isolated from the rare poroid fungus *Ganoderma resinaceum* and showed inhibition of NO production with an IC_{50} of 35.19 μM [211]. A 3,11-diol steroid (**251**), detected in the fungus *Gliomastix* sp. belonging to the family Bionectriaceae, displayed antiviral activity against the EV-71 virus with an IC_{50} of 17.8 μM and cytotoxic activity against several cancer cell lines including HL-60 (IC_{50} 1.75 μM), DU-145 (IC_{50} 7.37 μM), HeLa (IC_{50} 12.1 μM), and MOLT-4 (IC_{50} 6.53 μM) [212].

Dankasterone A (**252**) and B (**253**) were isolated from a fungal strain of *Gymnascella dankaliensis* derived from the sponge *Halichondria japonica* [213]. Dankasterone A demonstrated significant cytotoxicity against tumor cells in culture. Phomopsterone B (**254**), produced by the endophytic fungus *Phomopsis* sp., exhibited anti-inflammatory activity and showed promising results in iNOS inhibitory and NO production inhibition assays [214]. Three C25 steroids, neocyclocitrinols E-G (**255**–**257**), were isolated from the endophytic fungus *Chaetomium* sp. M453 [200].

Makisterone A (**258**), a 28-carbon ecdysteroid distinguished from the common C27 molting hormones like ecdysone and 20-hydroxy-ecdysone by an additional methyl group at the C-24 position, was isolated and characterized from the leaves of *Podocarpus macrophyllus* [215]. The steroidal alkaloid petisidine (**260**) was isolated from the leaves of *Petilium raddeanum* [216]. Another alkaloid, korsevinine (**261**), was detected in the total ether-soluble alkaloids of *Korolkowia sewerzowii* [217]. A unique steroidal alkaloid with a 5β-hydroxyl group, ebeietinone (**262**), was isolated from the bulbs of *Fritillaria ebeiensis* var. *purpurea* [218], and petisidinine (**263**) was detected in the essential oil of *Petilium raddeana* [219].

Summarized on the biological activity of 6-ketosteroids is presented in Table 5, and details are described partially in the text or a full description of the activity is written in the original articles.

Table 5. Summarized biological activity of 6-ketosteroids.

No. Steroids	Reported Activity of 6-ketosteroids	Ref.
229	Cholesterol synthesis inhibitor	[194]
236	Neuraminidase inhibitory activity	[198]
239	Inhibitor of Ca2+-ATPase	[199]
240,241	Cholinesterase inhibitor	[200,201]
242	Cytotoxic activity against Hep3B, HepG2, and Huh-7	[202]
243	β-hexosaminidase inhibitor	[205]
244	Inhibition of TNF-α secretion	[206]
245-247	NO production inhibitor	[207]
248	Cytotoxic activity against HepG2 and SGC-7901	[210]
249	Cytotoxic activity against HepG2 cells	[210]
251	Antiviral activity against the EV-71 virus	[211]
252,253	Strong cytotoxicity against tumor cells	[213]
254	NO production inhibitor	[214]

7-Ketosteroids

7-Ketosteroids represent another specialized class of steroid compounds characterized by the presence of a ketone group at the seventh carbon of the steroid skeleton. While not as prominently featured in basic biological processes as some other steroid classes, 7-ketosteroids are noteworthy. The ketone group at the seventh position can significantly influence the steroid's chemical reactivity and interaction with biological molecules, such as enzymes and receptors. This unique placement may alter the way these steroids are metabolized compared to their counterparts with ketone groups at other positions. 7-ketosteroids can occur as natural metabolites in the body, particularly as products of steroid hormone metabolism. They might play roles in various physiological processes, although these roles are often less direct than those of primary hormones like estrogens, androgens, or corticosteroids [220–223].

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One of the most well studied 7-ketosteroids is 7-keto-DHEA (7-ketodehydroepi-androsterone). This compound is known for its potential in enhancing metabolism and is researched for its use in weight loss and immune function. Unlike many other steroids, 7-keto-DHEA is not converted to steroid hormones such as testosterone or estrogen, which makes it a candidate for non-hormonal applications. Overall, while 7-ketosteroids are not as central to major physiological pathways as some other steroids, they offer interesting possibilities for health and wellness applications, particularly in the realm of non-hormonal interventions. Their unique chemical structure and effects continue to be a subject of research and discussion in the scientific community [224–228].

The compound 15α-hydroxy-(22E,24R)-ergosta-3,5,8(14),22-tetraen-7-one (**264**, structures see in Figure 9) was isolated from the endophytic fungus *Penicillium* sp. FJ-1 associated with *Acanthus ilicifolius*, commonly known as holly-leaved acanthus, sea holly, or holy mangrove. This compound demonstrated potent cytotoxicity against glioma cell lines, with IC_{50} values of 3.2 μM for U251, 4.1 μM for BT-325, and 2.3 μM for SHG-44 [229].

The apolar extract of the marine sponge *Theonella swinhoei* revealed a family of polyhydroxy steroids, including conicasterol G (**265**) which was isolated [230]. The compound (22E,24R)-3β-hydroxyergosta-5,8,22-trien-7-one (**266**) was identified from the culture extracts of *Aspergillus oryzae*, an endophytic fungus isolated from the marine red alga *Heterosiphonia japonica* [231]. Another compound, (22E)-25carboxy-8β,14β-epoxy-4α,5α-dihydroxyergosta-2,22-dien-7-one (**267**), exhibited cytotoxic activity towards the A-549 cell line and was isolated from the marine-derived fungus *Aspergillus flavus* collected from the Bohai Sea [177].

Three steroids with a rearranged ring B, including eringiacetal B (**268**), were isolated from the fruiting bodies of *Pleurotus eryngii* [232]. Eringiacetal B (**268**) demonstrated an IC_{50} of 13.0 μM and showed inhibitory effects on nitric oxide production, compared to 23.9 μM for the L-NMMA positive control.

Two sterols, gargalol B (**269**) and C (**270**), were isolated from the polypore fungus *Grifola gargal* from the family Meripilaceae. Both compounds showed potential in inhibiting osteoclast formation, which may be relevant for the prevention of osteoporosis [233].

A 5,6-epoxy steroid (**271**) was discovered in *Hericium erinaceum*, also known as the lion's mane mushroom, and demonstrated cytotoxic activity against HGC-27 with an IC_{50} of 29.34 μM [234]. This sterol was also found in the saprophytic and parasitic fungus *Omphalia lapidescens*, where it showed HNE inhibitory activity (IC_{50} 75 μM) and inhibited TNF-α secretion by 37% at 10 μM [235]. A polyoxygenated ergosteroid (**272**) was detected in an extract of the macrofungus *Omphalia lapidescens*, displaying a structure-cytotoxicity relationship with an IC_{50} of 23.41 μM against the human gastric cancer cell line HGC-27 [235]. Another epoxy sterol (**273**) was obtained from the fruiting bodies of the fungus *Amauroderma subresinosum* and demonstrated 20.9% inhibition of acetylcholinesterase at 100 μM [236].

In the family Tricholomataceae, the agaric fungus Tricholoma imbricatum contained two steroids (**274** and **275**), which exhibited cytotoxic activity against various cancer cell lines: A549 (IC_{50} 12.4 μM), HL-60 (IC50 12.2 μM), K562 (IC50 13.8 μM), MCF-7 (IC50 17.8 μM), SMMC-7721 (IC_{50} 27.6 μM), and SW480 (IC_{50} 19.7 μM) [237]. Additionally, steroid (**275**) was found in the fungus *Phomopsis* sp. [238] and *Chaetomium globosum* [239] and demonstrated α-glucosidase inhibition (IC_{50} > 100 μM). Steroid (**276**) from the fruiting bodies of *Tricholoma imbricatum* showed cytotoxicity against A549 (IC_{50} 22.8 μM) and SMMC-7721 (IC50 19.5 μM) [237].

Two steroids (**277** and **278**) were discovered in the *Ganoderma mushroom*. Specifically, **277**, isolated from *Ganoderma philippii*, exhibited acetylcholinesterase inhibition [240], while steroid (**278**), found in Ganoderma resinaceum, demonstrated inhibition of NO production [241].

The compound 22E-3β-hydroxy-5α,6α,8α,14α-diepoxy-ergosta-22-en-7-one (**279**) was isolated from the fungus *Aspergillus awamori*, which was obtained from soil surrounding the mangrove plant *Acrostichum speciosum* [242]. Compound **279** exhibited weak cytotoxic activity against A549 cancer cell lines. Two 7-keto-ergosterol derivatives, 3β,11α-dihydroxyergosta-8,24(28)-dien-7-one (**280**) and 3β-hydroxyergosta-8,24(28)-dien-7-one (**281**), were isolated from the fungus *Aspergillus ochraceus* EN-31 obtained from the marine brown alga *Sargassum kjellmanianum* [243].

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The marine-derived fungus *Rhizopus* sp., isolated from the bryozoan *Bugula* sp. collected in Jiaozhou Bay, China, yielded several ergosterols: 3β-hydroxy-(22E,24R)-ergosta-5,8,22-trien-7,15-dione (**282**), 3β-hydroxy-(22E,24R)-ergosta-5,8,14,22-tetraen-7-one (**283**), 3β,15β-dihydroxy-(22E,24R)-ergosta-5,8(14),22-trien-7-one (**284**), and 3β-hydroxyl-(22E,24R)-ergosta-5,8(14),22-trien-7,15-dione (**285**) [244]. All isolated compounds demonstrated cytotoxic activity to varying degrees against four different cancer cell lines.

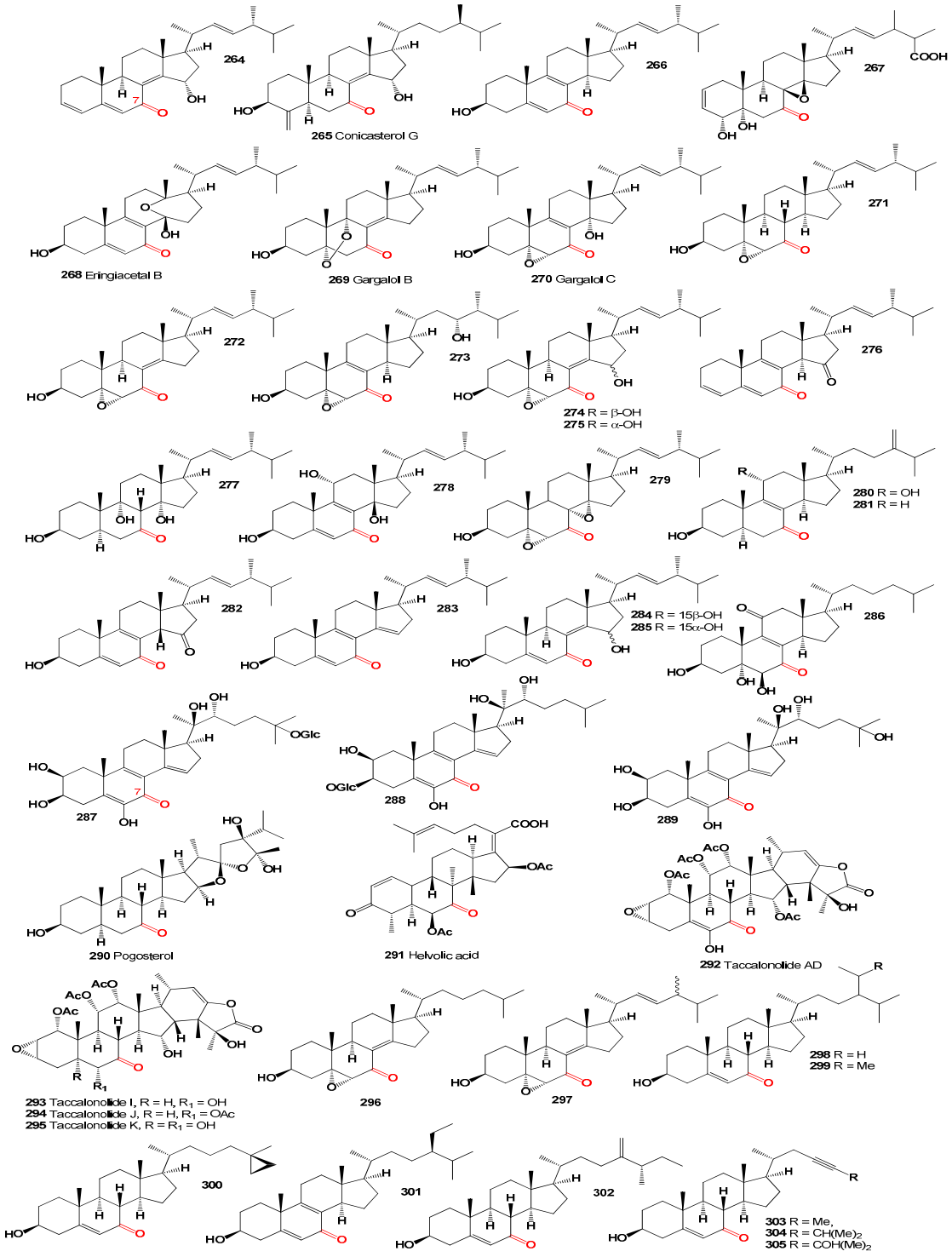

Figure 9. 7-Ketosteroids derived from fungi, fungal endophytes, plants.

Incrustasterol B (**286**), derived from the Mediterranean sponge *Dysidea incrustans*, is distinguished from other polar sponge steroids by the presence of $\Delta^{8(9)}$-7,9-diketo fragments, which are uncommon for marine steroids [245].

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Three 7-keto-phytoecdysteroids (**287**-**289**), cyclopentanoperhydrophenanthrene-ringed polyhydroxylated chemicals known for protecting plants from nematodes and insect pests, have been isolated from various plant extracts [246]. Two ecdysterone-type sterol glycosides, which also act as melanogenesis inhibitors, were isolated from different sources: pfaffiaglycosides E (**287**) from the roots of *Pfaffia glomerata* and brainesteroside C (**288**, 25-deoxycalonysterone-3-O-β-D-glucopyranoside) from the rhizomes of *Brainea insignis* [247]. A minor ecdysteroid named calonysterone (**289**) was detected in extracts of *Cyanotis arachnoidea* [248].

The steroidal sapogenin, pogosterol (**290**), isolated from the leaves of *Vernonia pogosperma*, was characterized for its structure and stereochemistry. Pogosterol exhibited weak cytotoxic activity against L-1210 cells in vitro, with an IC_{50} of 1.7 μg/mL [250]. Additionally, an antibiotic metabolite, helvolic acid (**291**), was isolated from the rice sheath rot pathogen fungus *Sarocladium oryzae* [251].

Taccalonolides are a unique class of microtubule-stabilizing agents isolated from plants of the genus *Tacca*, demonstrating effectiveness against drug-resistant tumors in cellular and animal models [252]. Taccalonolides AD (**292**), I (**293**), J (**294**), and K (**295**) are 7-keto steroids that exhibit cytotoxic effects. Taccalonolide AD (**292**) was isolated from *Tacca plantaginea*, increasing cellular microtubule density and microtubule bundling in HeLa cells at 17 μM, with anti-proliferative actions exhibiting an IC_{50} of 3.48 μM [253]. Taccalonolides I, J, and K, characterized by a shift of the ketone group from C6 to C7 on ring B, were detected in extracts of *T. plantaginea*, with taccalonolide K (**295**) also found in *T. paxiana* [254].

The methanol extract of the Mediterranean encrusting sponge Oscarella lobularis yielded small amounts of two polyoxygenated sterols (**296** and **297**) featuring a unique 5α,6α-epoxy-7-keto function [255]. The marine sponge *Polymastia sobustia* from the South China Sea contained 3β-hydroxystigmast-5-en-7-one (**298**) [256], and polysterol A (**299**) was obtained from a Japanese sponge, *Epipolasis* sp. [257]. A rare steroid with a cyclopropane ring at C-25 and C-26, named 7-oxopetrosterol, 26,27-cyclo-24,27-dimethyl-3β-hydroxycholest-5-en-7-one (**300**), was observed in the marine sponge *Strongylophora corticata* [258]. An oxygenated sterol (**301**), obtained from a collection of marine sponge *Polymastia tenax* from the Caribbean coast of Colombia, exhibited significant anti-proliferative activity toward A-549, HT-29, H-116, MS-1, and PC-3 tumor cells in the range of 0.5–10 μg/mL [259]. A specimen from the South China Sea of *Geodia japonica* yielded 26-methylergosta-5,24(28)-dien-3β-ol (**302**) [260].

Acetylenic sterols, gelliusterol B (**303**, 26,27-bisnorcholest-5-en-23-yn-3β-ol-7-one), gelliusterol C (**304**, cholest-5-en-23-yn-3β,7-one), and D (**305**, cholest-5-en-23-yn-3β,25-diol-7-one), were isolated from an unidentified species of sponge, *Gellius* sp. [261].

Summarized on the biological activity of 7-ketosteroids is presented in Table 6, and details are described partially in the text or a full description of the activity is written in the original articles.

Table 6. Summarized biological activity of 7-ketosteroids.

No. Steroids	Reported Activity of 7-ketosteroids	Ref.
264	Cytotoxicity against glioma cell lines	[229]
267	Cytotoxic activity towards the A-549 cell line	[177]
268	Nitric oxide production inhibitor	[232]
271	Cytotoxic activity against HGC-27	[234]
272	Cytotoxic activity against human gastric cancer cell line HGC-27	[235]
274,275	Cytotoxic activity against various cancer cell lines	[237]
276	Cytotoxicity against A549	[237]
278	NO production inhibitor	[241]
282-285	Cytotoxic activity against four different cancer cell lines	[244]
290	Cytotoxic activity against L-1210 cells	[250]
301	Anti-proliferative activity toward A-549, HT-29, H-116, MS-1, and PC-3 tumor cells	[259]

11-Ketosteroids

11-Ketosteroids are notable for their biological activities and their roles in human physiology. These steroids, characterized by a ketone group at the eleventh carbon of the steroid nucleus, include important physiological compounds such as 11-keto-testosterone and 11-dehydrocorticosterone. 11-

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Ketosteroids are biologically active and play crucial roles in the body. For example, 11-keto-testosterone is a potent androgen in fish, although it has lesser activity in mammals. However, its presence and effects in various species suggest a significant evolutionary and functional role [262–266].

Corticosteroid 11-ketosteroids, like 11-dehydrocorticosterone, are involved in the body's stress response and immune regulation. They help modulate inflammation and immune responses, acting through glucocorticoid receptors to exert their effects [267–269]. These steroids are part of the metabolism of more commonly known corticosteroids and androgens. They are metabolized by enzymes in the liver and other tissues, influencing both the production and degradation of steroid hormones. Levels of certain 11-ketosteroids can serve as biomarkers for diagnosing and monitoring diseases that involve steroid metabolism disorders or adrenal function anomalies.

In essence, 11-ketosteroids contribute to a variety of physiological processes, and their study helps in understanding both the endocrine system's complexity and the potential for targeted therapeutic strategies in medicine **[270–272]**.

An antifungal antibiotic, 18,22-cyclosterol, Mer-NF8054X (**306**), and its analog (**307**) have been isolated from *Aspergillus* sp. [273]. Additionally, Mer-NF8054X was isolated from a shaken culture of *Aspergillus ustus* and from the culture filtrate of *Emericella heterothallica* [274]. Three lanostanoid triterpenes, ganotropic acid (**308**), 3β,7β,15α,24-tetrahydroxy-11,23-dioxo-lanost-8-en-26-oic acid (**309**), and 3β,7β,15α,28-tetrahydroxy-11,23-dioxo-lanost-8,16-dien-26-oic acid (**310**, structures see in Figure 10), were isolated from the *n*-BuOH extract of the fruiting bodies of the mushroom *Ganoderma tropicum*. Ganotropic acid possessed a two-oxygenic five-membered ring system in the side chain of the lanostane skeleton [275]. Both compounds demonstrated cytotoxic activity against A549, HepG2, THP-1 (with an IC_{50} > 80 μM), as well as IL-6 immune-suppressive activity (with an IC_{50} of 21 μM) and TNF-secretion inhibition (with an IC_{50} of 28 μM) [275].

A polyhydroxy steroid, zahramycin B (**313**), has been isolated from the polar fraction of the extract of the coral *Sarcophyton trocheliophorum*. This steroid showed high antibacterial activity against *Staphylococcus aureus, Bacillus subtilis*, and the fungus *Pythium ultimum* [276].

Furthermore, 3β,7β-dihydroxy-5α-cholestan-11-one (**314**) was found in a mixture of chloroform and methanol (1:1) extracts of the red alga *Laurencia papillosa* [277].

The male African catfish (*Clarias gariepinus*) secretes 11-ketotestosterone (**315**), a potent androgen, in addition to testosterone. Research indicates that 11-ketotestosterone stimulates spermatogenesis, unlike testosterone, which promotes the development of pituitary gonadotrophs [278]. Additionally, 11-ketotestosterone (**315**) has been extracted from postspawned male sockeye salmon, *Oncorhynchus nerka* [279].

Three 11-ketosteroids, namely incrustasterol A (**316**), (**317**), and (**318**), were identified in the Mediterranean sponge *Dysidea incrustans* [280] and *Dysidea fragilis* from the Venice lagoon [281]. From the soft coral *Klyxum flaccidum*, two bioactive steroids, klyflaccisteroid C (**319**) and D (**320**), were isolated [282]. Furthermore, a sulfated polyhydroxy steroid (**321**) was isolated from three species of brittle stars collected near Noumea (New Caledonia): *Ophiocoma dentata*, *Ophiarthrum elegans*, and *Ophiarachna incrassata* [283].

Asperflotone (**322**), an 8(14-->15)-*abeo*-ergostane derived from the sponge-associated fungus *Aspergillus flocculosus* 16D-1, exhibited cytotoxic effects against A549, HepG2, and THP-1 cell lines with an IC_{50} exceeding 80 μM, along with notable IL-6 immune-suppressive activity (IC_{50} 22 μM) [284]. Additionally, the same fungal genus yielded three steroids featuring identical side chains, including asperflosterol (**323**) [285], compound (**324**), and asperfloroid (**325**) [285,286], both asperflosterol (**323**) and asperfloroid (**325**) exhibited anti-inflammatory properties. From the same fungus, an ochratoxin-ergosteroid heterodimer, ochrasperfloroid (**326**), was isolated and shown to significantly inhibit IL-6 and nitric oxide (NO) production in LPS-stimulated cells [284].

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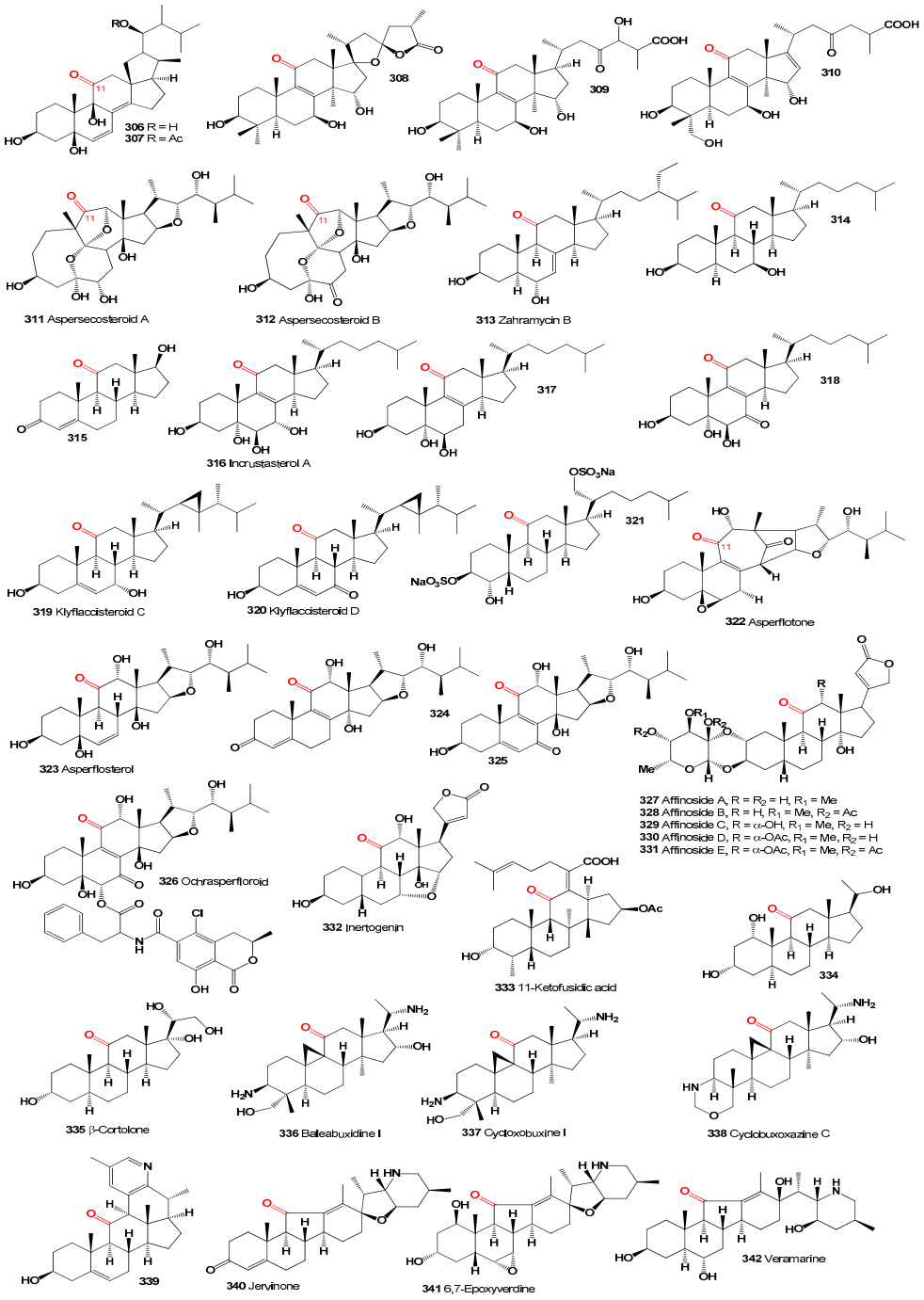

Figure 10. 11-Keto steroids and triterpenoids derived from diferent sources.

Major cardenolide glycosides, affinosides La-Le (**327**-**331**), featuring oxygen functionalities at C-11 of the aglycone, were isolated from the leaves of *Anodendron affine* [288]. The unique steroid inertogenin (**332**), characterized by a rare 7,15-tetrahydrofuran group, was found in the leaves of *Strophanthus amboensis*, a deciduous shrub used medicinally in Southwest Africa [289]. Furthermore, the fusidic acid-related antibiotics, including 11-keto-fusidic acid (**333**) produced by *Fusidium coccineum*, effectively inhibit protein synthesis both *in vivo* and *in vitro* in prokaryotic and eukaryotic cells [290–292].

The sex hormone 1,3,20-trihydroxypregnan-11-one (**334**) was identified in the urine of a patient diagnosed with 17α-hydroxylase deficiency syndrome [293]. Similarly, β-cortolone (3α,17α,20β,21-tetrahydroxypregnane-11-one, **335**), a consistent metabolite, was detected in the urine of 20 young and elderly individuals of both genders [294].

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Steroidal alkaloids (**336-342**), characterized by a basic steroidal structure with a nitrogen atom integrated into the rings or side chains, represent a significant group of natural compounds [295]. Among these, the rare 11-keto *Buxus* alkaloids (**336-338**), a type of triterpenoid alkaloids derived from the cycloartenol skeleton with a modified C-20 side chain and nitrogen-containing groups at C-3 and/or C-20, have shown diverse biological effects [296–298]. These alkaloids are notable secondary metabolites found in various plant families, including Solanaceae, Liliaceae, Apocynaceae, and Buxaceae [295]. Notably, steroidal alkaloids (**339-342**) featuring a carbonyl group at position 11 were extracted from *Veratrum album* and *V. taliense*, exhibiting antihypertensive properties [299–301].

Summarized on the biological activity of 11-ketosteroids is presented in Table 7, and details are described partially in the text or a full description of the activity is written in the original articles.

Table 7. Summarized biological activity of 11-ketosteroids.

No. Steroids	Reported Activity of 11-ketosteroids	Ref.
308-310	Cytotoxic activity against A549, HepG2, THP-1 IL-6 immune-suppressive activity and TNF-secretion inhibition	[275]
313	Antibacterial activity	[276]
332	Cytotoxic effects against A549, HepG2, and THP-1 cell lines	[284]
323,325	Anti-inflammatory properties	[285]
333	Protein synthesis inhibitor	[290–292]
339-342	Antihypertensive properties	[299–301]

12-Ketosteroids

12-Ketosteroids are indeed rare and interesting compounds, primarily found in plants and algae, as opposed to the more commonly studied animal-derived steroids. 12-ketosteroids are predominantly found in plants and algae. Their presence indicates specialized roles in the biochemistry of these organisms, potentially involved in plant and algal growth, development, or defense mechanisms against environmental stressors. Steroids in plants, including 12-ketosteroids, contribute to the chemical diversity found in the plant kingdom. These compounds can vary greatly in structure and function, reflecting the wide array of evolutionary adaptations plants have developed to thrive in diverse environments. In plants, steroids, including those with a ketone group at the 12th position, are thought to play roles in cell membrane integrity, signaling, and possibly as precursors to other important biochemicals. Their exact functions, however, can be quite specific to the species and the environmental context [302–304].

A halotolerant fungus, *Aspergillus flocculosus* PT05-1, was discovered in the sediment of the Putian saltern in Fujian Province, China, cultivated in a hypersaline medium. It produced (22R,23S)-epoxy-3β,11α,14β,16β-tetrahydroxyergosta-5,7-dien-12-one (**343**), which exhibited cytotoxic effects against HL-60 and BEL-7402 cells with IC_{50} values between 12-18 μM, and demonstrated antimicrobial activity against *Enterobacter aerogenes*, *Pseudomonas aeruginosa*, and *Candida albicans* with MIC values ranging from 1.6-15 μM [305].

The chloroform/methanol extract of the red alga *Laurencia papillosa*, sourced from the Red Sea in Saudi Arabia, was found to contain a cholestane derivative: 3α,6α-dihydroxy-5β-cholestan-12-one (**344**) [306].

From the organic extract of *Allium porrum*, sapogenins named 12-keto-porrigenin ((25R)-5α-spirostan-3β,6β-diol-12-one, **345** and **346**) were isolated and shown to possess antiproliferative activity against four tumor cell lines *in vitro* [307].

The toxic 12-keto-bufadienolide, daigremontianin (**347**), was isolated from the plant *Kalanchoe daigremontiana*, formerly known as *Bryophyllum daigremontianum* [308]. Additionally, two bufadienolide glycosides, orbicusides A (**348**) and C (**349**), were identified as toxic constituents in *Cotyledon orbiculata* var. *orbiculata* [309].

Bufadienolides and their more polar conjugates, bufotoxins, are present in toads from the genus *Bufo*. These compounds are found not only in their unconjugated forms but also as several C-3 conjugates [310]. Two bufodienolides, arenobufagin (3β,11α,14-trihydroxy-12-oxo-5β,14β-bufa-20,22-dienolide, **350**), and a second compound (**351**) were isolated from the Central Asian green toad,

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Bufo viridis [311]. Arenobufagin, a primary bufadienolide from *Bufo viridis* toad venom, has been shown to inhibit growth in various cancer cell lines [312].

Research into the defensive mechanisms of fireflies, specifically *Photinus pyralis, P. ignitus*, and *P.marginellus* (Coleoptera: Lampyridae), resulted in the isolation of certain compounds (**352**-**357**) that make the fireflies distasteful to birds [313].

Additionally, microbial transformation of 20(S)-protopanaxatriol by cell suspension cultures of *Aspergillus niger* AS3.1858 produced two steroids (**358** and **359**), which exhibited anticancer activity against multiple cancer cell lines including Du-145, Hela, K562, K562/ADR, SH-SY5Y, HepG2, and MCF-7 [314].

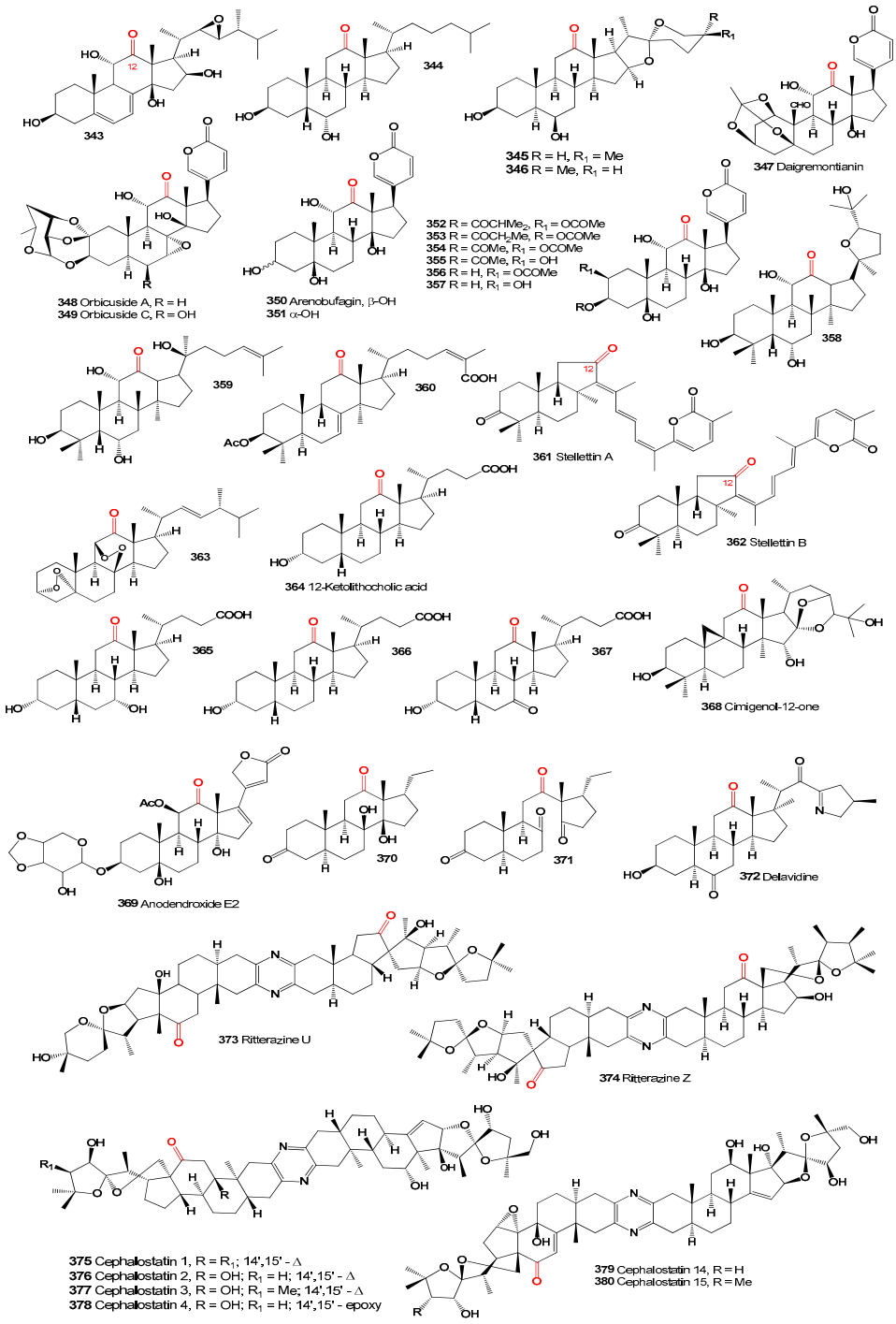

Figure 11. 12-Ketosteroids derived from algae, plants, and fungi.

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Hu and colleagues [315] identified a triterpenoid named kadcoccinone F (**360**) from the plant *Kadsura coccinea*. Additionally, a bioactive triterpenoid pigment, stellettin A (**361**), was detected in the marine sponge *Stelletta tenuis* [316], while the cytotoxic triterpenoid pigment stellettin B (**362**) was isolated from the marine sponge *Jaspis stellifera* [317]. Stellettin B demonstrated significant inhibitory effects on the growth of human glioblastoma cancer SF295 cells.

An unusual steroidal compound, (3α,5α),(8β,11β)-diepidioxy-ergost-22E-en-12-one (**363**), was isolated and characterized from the dried fruit bodies of *Trametes orientalis* [318].

Regarding bile acids, most naturally occurring varieties are part of the 5β-series, featuring hydroxyl groups in the A, B, and C rings of the steroid system, commonly located at positions C3, C6, C7, C12, and C23, and predominantly oriented in the α configuration. Typically, the A/B ring junction is *cis*, whereas both the B/C and C/D ring junctions are *trans* [319]. 12-Ketolithocholic acid (**364**) was first identified in cattle bile by Wieland and Kishi over 90 years ago [320] and has also been detected in the feces of some animal species [321]. Furthermore, 3α,7α-dihydroxy-12-keto-5β-cholanic acid (**365**) has been identified in human feces [322]. This acid and its esters are crucial intermediates in the synthesis of chenodeoxycholic acid from cholic acid. 3α-Hydroxy-12-keto-5β-cholanoic acid (**366**), 3α-hydroxy-7,12-diketo-5β-cholanoic acids (**367**), and **365** were found in the urine of male patients with liver cirrhosis [323].

A 9,19-cycloartane triterpene, cimigenol-12-one (**368**), was isolated from the aerial parts of *Cimicifuga foetida* [324], and anodendroxide E2 (**369**) was detected in the volatile oil from matured leaves of *Calotropis procera* [325]. Additionally, a steroidal sapogenin (**370**) and its oxidized analogue (**371**) were isolated from the roots of *Cynanchum otophyllum*, demonstrating cytotoxic activities [326]. An isosteroidal alkaloid, delavidine (**372**), was isolated from *Fritillaria delavayi* collected from Sichuan, China [327].

Ritterazines, a class of complex natural compounds, have been isolated from ascidians, commonly known as sea squirts [328]. These compounds were first discovered in the 1990s in the ascidian *Ritterella tokioka* [329]. Characterized by their unique and diverse structures, which include macrocyclic lactams and multiple fused rings, ritterazines have garnered attention for their potent biological activities, particularly their cytotoxic properties against various cancer cell lines. Notably, ritterazines U (**373**) and Z (**374**), which are 12-keto *bis*-steroidal pyrazine alkaloids produced by *Ritterella tokioka*, have demonstrated significant anticancer properties [328].

FABCephalostatins are a group of steroidal pyrazine alkaloids that were first isolated from the marine worm *Cephalodiscus gilchristi* [331,332]. They are known for their potent cytotoxicity and have been the subject of extensive research due to their potential as anticancer agents. The cephalostatins exhibit remarkable biological activity, with some compounds in the series showing nanomolar or even picomolar potency against various cancer cell lines. Their mechanism of action is believed to involve the inhibition of tubulin polymerization, which disrupts the formation of the mitotic spindle, leading to cell cycle arrest and apoptosis in cancer cells. The chemical structure of cephalostatins is characterized by a unique dimeric steroid framework, with two steroid units linked by a pyrazine bridge. This complex structure has made the total synthesis of cephalostatins a challenging and significant achievement in synthetic organic chemistry. Due to their potent biological activity and complex structure, cephalostatins continue to be a focus of research in the fields of natural products chemistry, medicinal chemistry, and cancer pharmacology [333]. Cephalostatins 1-4 (**375**-**378**), 14 (**379**) and 15 (**380**) containing unique dimeric 12-keto steroids were found, isolated and their biological activity was established [334,335].

12-Ketosteroids in plants and algae may exhibit unique biological activities, such as antifungal, antibacterial, or anti-inflammatory properties. The rarity and specific occurrence of 12-ketosteroids in plants and algae make them fascinating subjects for chemical ecology and natural product chemistry. Overall, while not as extensively studied as their animal-derived counterparts, 12-ketosteroids in plants and algae represent an intriguing area of natural product research, with potential implications for both ecological studies and biotechnological applications. Summarized on the biological activity of 12-ketosteroids is presented in Table 8, and details are described partially in the text or a full description of the activity is written in the original articles.

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Table 8. Summarized biological activity of 12-ketosteroids.

No. Steroids	Reported Activity of 12-ketosteroids	Ref.
343	Cytotoxic effects against HL-60 and BEL-7402 cells	[305]
345,346	Antiproliferative activity against four tumor cell lines	[307]
350,351	Inhibitors growth various cancer cell lines	[312]
358,359	Anticancer agents against Du-145, Hela, K562, K562/ADR, SH-SY5Y, HepG2, and MCF-7	[314]
362	Strong inhibitory effects againt human glioblastoma cancer SF295 cells	[317]
373,374	Strong anticancer properties	[328]

15-Ketosteroids

15-Ketosteroids are a class of steroids characterized by the presence of a ketone group at the 15th carbon atom of the steroid nucleus. These compounds are found across a diverse range of organisms, including fungi, sea sponges, and some plants, reflecting their broad biological importance and diversity. In fungi, 15-ketosteroids may play roles in their development, reproduction, and secondary metabolism. Fungi are known for their capability to produce a variety of bioactive secondary metabolites, and ketosteroids can be crucial components of these pathways.

In marine sponges, these steroids are part of a complex chemical arsenal used for defense against predators and microbial infection, as well as for communication. Sponges are known to house a rich array of chemical compounds that serve ecological functions, and steroids such as 15-ketosteroids contribute to these roles [336–338].

In plants, while less commonly reported, steroids including 15-ketosteroids can influence growth, development, and defense mechanisms. They are part of the broader group of plant steroids that regulate various physiological processes [339].

Additionally, the biochemical pathways leading to the synthesis of 15-ketosteroids involve modifications of standard steroidal structures, which can alter their biological activity significantly. These modifications can impact receptor binding and biological outcomes, influencing processes such as hormone signaling and cellular regulation. Research into 15-ketosteroids often focuses on their potential pharmacological applications, given their structural diversity and biological activity. These studies might look into anti-inflammatory, anti-cancer, or antimicrobial properties, which are common areas of interest in natural product drug discovery.

A 15-ketosteroid (**381**, structures see in Figure 12) discovered in the fruiting bodies of the fungus *Amauroderma subresinosum* exhibited cytotoxic activity against the HL-60 cell line with an IC_{50} of 32.1 μM and demonstrated less potency (IC_{50} > 40 μM) against SMMC-7721, A549, MCF-7, and SW480 cell lines [340]. This compound was also detected in the culture of the basidiomycete *Polyporus ellisii* [341]. Additionally, a cytotoxic steroid (**382**) isolated from extracts of the king trumpet mushroom, *Pleurotus eryngii*, showed anti-proliferative activity toward RAW264.7 cells with an IC_{50} over 30 μM and inhibited NO production with an IC_{50} of 13.2 μM [342].

The compound 5β,6β-epoxide (**383**) was found in *Polyporus ellisii* and a *Phomopsis* species, exhibiting antibacterial activity (MIC of 28.2 μM against *Micrococcus tenuis*) and cytotoxic activity against cancer cell lines HL-60, SMMC-7721, A549, MCF-7, and SW480 (IC50 > 40 μM) [17,342]. A similar steroid (**384**) detected in fungi *Ganoderma resinaceum*, *Polyporus ellisii*, and *Phomopsis* sp. also showed cytotoxic activity, particularly against HL-60 with an IC_{50} of 18.8 μM and other mentioned cell lines with IC_{50} values over 40 μM [342].

The fungus *Penicillium purpurogenum*, known as a steroid producer (**385**), has demonstrated cytotoxic activity against A549, HepG2, and MCF-7 cancer cell lines, with IC_{50} values exceeding 100 μM [343]. Furthermore, a fungus derived from the *Halichondria* sponge, *Gymnacella dankaliensis*, was cultured resulting in the isolation of gymnasterone C (**386**) from the original malt extract medium [344,345].

Marine sponge *Theonella swinhoei*, sourced from various locations in the Solomon Islands (Malaita and Vangunu Is.), has produced conicasterol J (**387**) [230], and theonellasterol C (**388**) was also detected in the same sponge [346]. Contignasterol (**389**), a highly oxygenated steroid with an unusual 14β-configuration, was obtained from the Papua New Guinea sponge *Petrosia contignata* [347]. Additionally, two unique pentacyclic steroids (**390** and **391**) with a cis C/D ring junction were

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isolated from *Xestospongia bergquistia* and have been noted as powerful inhibitors of histamine release [348].

Marine sponges from the genus *Oceanapia*, which includes over 50 species found in tropical and subtropical seas, contain tamasterone sulfates (**392**) and (**393**), a C-14 epimeric pair of polyhydroxylated sterols [349,350]. Similarly, 15-keto-haliclostanone sulfate (**394**) has been isolated from a *Haliclona* sponge [351].

Three saponins, pandaroside K–M (**395**–**397**), were identified from the marine sponge *Pandaros acanthifolium* (Martinique Is., Caribbean) and exhibited antiprotozoal activity [352]. Over 50 years ago, 14α-artebufogenin (**398**) and 14β-artebufogenin (**399**) were isolated from traditional Chinese medicine known as Chan Su [353].

Two structurally unusual steroids, compounds **400** and **401**, were metabolized by a marine strain of *Gymnasella dankaliensis* isolated from the sponge *Halichondria japonica* (Osaka Bay, Japan). These compounds exhibited significant and marginal growth inhibition against the lymphocytic leukemia P388 cell line with ED50 values of 0.9, and 2.5 μg/mL, respectively [344,345].

Three cycloartane triterpenoids, isodahurinol (**402**), 20,24-di-O-acetylisodahurinol-3-O-α-L-arabinopyranoside (**403**), and 24-O-acetylisodahurinol-3-O-α-L-arabinopyranoside (**404**) were isolated from the aerial parts of *Cimicifuga foetida* [324], and isodahurinol (**402**) was also detected in other *Cimicifuga* species [354]. Additionally, 15-oxo-cucurbitacin F (**405**) and 15-oxo-23,24-dihydrocucurbitacin F (**406**), isolated from *Cowania mexicana*, exhibited inhibitory activity against HIV-1 replication in H9 cells, with EC_{50} values of 0.3 and 2.5 μg/mL, respectively, and therapeutic index values of 17.0 and 15.2, respectively [355].

A cycloartane triterpene glycoside, 16α-hydroxyl-7(8)-en-dahurinol-3-O-[4′-O-acetyl]-α-L-arabinopyranoside, named cimiheraclein F (**407**), was isolated from the aerial parts of *Actaea heracleifolia* collected from Yichun County, Heilongjiang Province, China [356]. Dahurinol (**408**, (24R)-24,25-dihydroxy-15-oxoacta-(16R,23R)-16,23-monoxol) and acerionol (**409**, 3-deoxy-8,9-didehydro-(24S)-24,25-dihydroxy-(3S,10S)-3,10-epoxy-15-oxo-9,10-secoacta-(16R,23R)-16,23-monoxol) were found in extracts of *Actaea racemosa* [357].

Additionally, several 15-keto pregnane glycosides, namely stemmosides E, F, G, and H (**410**-**413**), were isolated from *Solenostemma argel*. These compounds, characterized by a unique 14 proton configuration, with stemmosides E and F additionally featuring a rare enolic function at C-16 and stemmosides G-J displaying an unusual C-17 side chain, effectively reduced cell proliferation in a dose-dependent manner [358].

The sponge *Melophlus sarasinorum*, belonging to the family Geodiidae and subfamily Erylinae, commonly found in the Indo-West Pacific tropical region, contains glycosides known as sarasinosides [359]. Dai and colleagues [360] isolated a glycoside, sarasinoside L (**414**), from specimens harvested near Sulawesi, Indonesia, while Santalova and coworkers [361] isolated a similar triterpene glycoside named sarasinoside A5 (**415**). Both steroids feature a keto group at position 15. Additionally, other steroidal oligoglycosides, mycalosides F (**416**) and H (**417**), were isolated from the polar extract of the Caribbean sponge *Mycale laxissima* [362].

From the Korean marine sponge *Clathria gombawuiensis*, a series of polyoxygenated steroids (**418** - **424**) were isolated. The structures of gombasterols A–F (**419**–**424**) were elucidated through combined spectroscopic analyses. These compounds are characterized as highly oxygenated steroids with a 3β,4α,6α,7β-tetrahydroxy substitution pattern or an equivalent structure (7β-sodium O-sulfonato for **421**) and a common structural motif of a C-15 keto group [363]. Summarized on the biological activity of 15-ketosteroids is presented in Table 9, and details are described partially in the text or a full description of the activity is written in the original articles.

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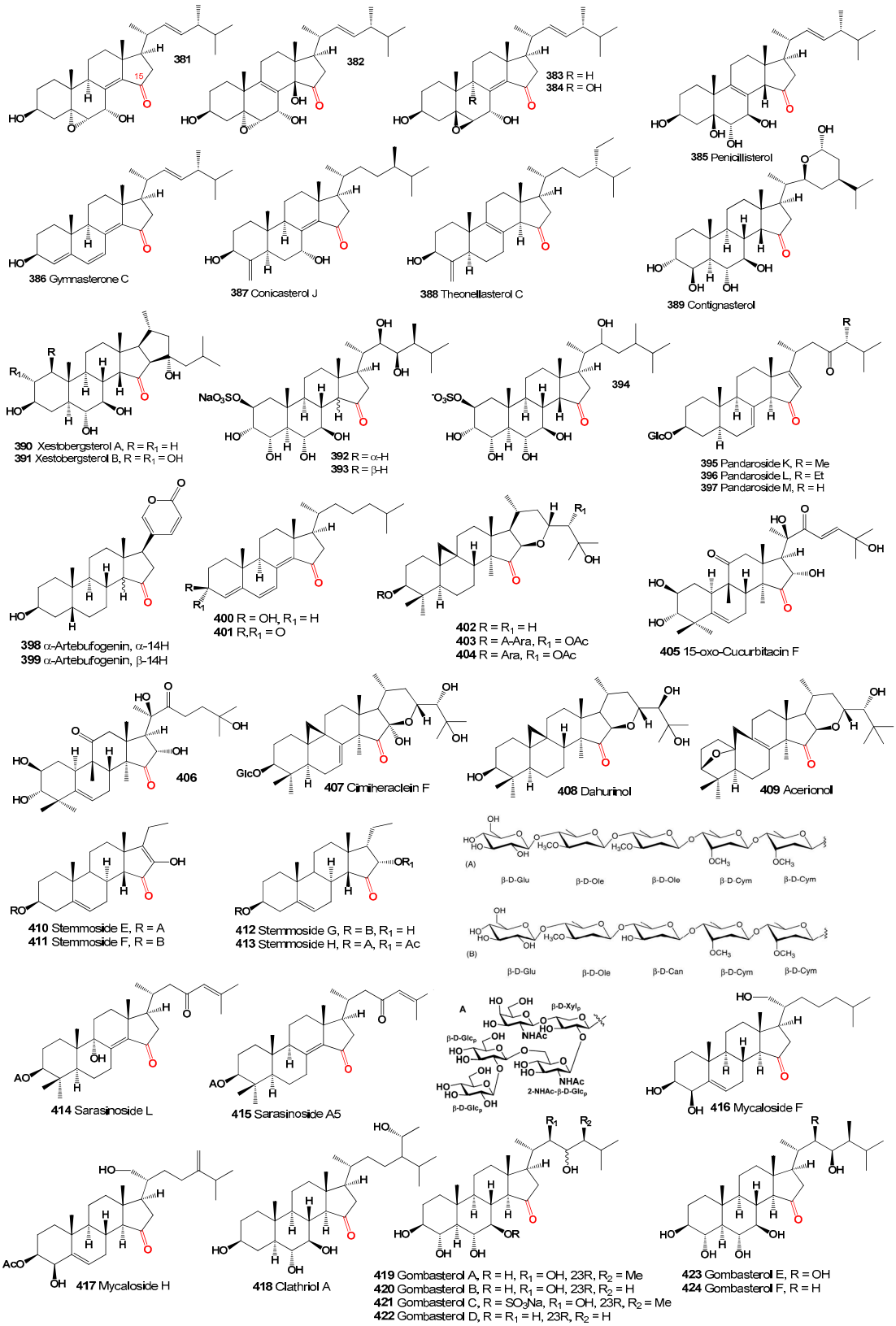

Figure 12. 15-Ketosteroids derived from fungi, marine invetevrates and plants.

Table 9. Summarized biological activity of 15-ketosteroids.

No. Steroids	Reported Activity of 15-ketosteroids	Ref.
381	Cytotoxic activity against the HL-60 cell line	[340]
382	Anti-proliferative activity toward RAW264.7 cells	[342]

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	NO production inhibitor	
383	Antibacterial activity; Cytotoxic activity against cancer cell lines HL-60, SMMC-7721, A549, MCF-7, and SW480	[17,342]
384	Cytotoxic activity against HL-60	[342]
400,401	Cytotoxic activity against P388 cell line	[344,345]
406	Strong antiviral activity against HIV-1 replication in H9 cells	[355]

16-Ketosteroids

16-Ketosteroids are another interesting class of steroid compounds, defined by the presence of a ketone group at the carbon-16 position in the steroid nucleus. These compounds are primarily known for their presence in various plant species but are also found in some marine organisms such as sea cucumbers and sponges.

In plants, 16-ketosteroids are typically found in the leaves, bark, roots, seeds, pollen, and fruits. Similar to other phytochemicals, ketosteroids can help protect plants from herbivores and pathogens. Their bitter taste or toxic properties can deter predators, while their antimicrobial properties can prevent fungal and bacterial infections. Steroids are crucial in plant growth and development, influencing cell division, elongation, and differentiation. The specific roles of 16-ketosteroids in these processes might be less well-defined but are likely important due to the widespread presence of related compounds in the plant kingdom. Plants produce certain steroids in response to environmental stresses such as drought, salinity, and extreme temperatures. These compounds can help the plant manage the stress by modulating biochemical pathways [364,365].

In marine organisms like sea cucumbers and sponges, the presence of 16-ketosteroids, though less common, suggests a potential role in similar biological functions such as defense against predators or infections. The rarity of these compounds in marine environments compared to plants might indicate specialized roles or specific ecological adaptations [15].

Pharmacologically, steroids including 16-ketosteroids are of interest for their potential anti-inflammatory, anticancer, and other bioactive properties. The modification at the 16th carbon could influence how these steroids interact with biological receptors, potentially leading to unique activities not seen in more common steroids [366].

Aglaia lawii, a species in the Meliaceae family, contains three 16-ketosteroids in its leaves: 3-*epi*-dyscusin C (**425**, structures see in Figure 13), 3-*epi*-lansisterone E (**426**), and (*Z*)-2α-hydroxyaglawone (**427**). These C-21 pregnane steroids feature a highly oxygenated ring A and have shown significant anti-inflammatory activities, with IC_{50} values for NO inhibition ranging from 4.47 to 7.67 μM [367].

From the wood of the Costa Rican tree *Trichilia hirta*, two steroids, trichiliasterone A (3β-hydroxypregnan-2,16-dione, **428**) and trichiliasterone B (2-hydroxyandrost-1,4-diene-3,16-dione, **429**), were isolated. Both compounds inhibited the growth of the European corn borer, *Ostrinia nubilalis*, and the variegated cutworm, *Peridroma saucia*. Steroid **428** was also isolated from *Trichilia americana* [368].

The fruits of *Artocarpus heterophyllus* led to the isolation of a steroid named artoheterophoid (**430**), which exhibited remarkable inhibitory effects on NO production with an IC_{50} value of 0.72 μM [369]. Additionally, three pregnanes (**431**-**433**) were isolated from the leaves of *Aglaia grandis* [370], and several pregnane-type steroids, including 2β,3β-dihydroxy-5α-pregn-17(20)-(*Z*)-en-16-one (**434**) and aglatomin A (**435**), were detected in the leaves of *Aglaia tomentosa* [371]. Lansisterone E (**436**) and 2β,3β,4β-trihydroxypregnan-16-one (**437**) were obtained from the branches of *A. perviridis* [372].

Ampelozizyphus amazonicus, a medicinal climbing shrub native to the Amazonian region, used traditionally to prevent malaria, contains aglycone structures of saponins in its crude extract, specifically 16-keto-tetrahydroxydammar-23-ene (**438**) and 16-keto-tetrahydroxy-dammar-24-methylene (**439**) [373].

Bacopa monnieri, known as brahmi in Ayurveda, is celebrated for enhancing intelligence, memory, and revitalizing sensory organs. Its nootropic activity has been extensively studied, with several researchers confirming that alcoholic/hydroalcoholic extracts of the whole plant exhibit varied activities. These extracts contain two steroids, bacoside A (**440**) and B (**441**), which contribute to its therapeutic properties [374].

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Several 9,10-seco-9,19-cyclolanostane arabinosides, named podocarpasides A–D (**442**-**445**), F (**447**), and G (**448**), were isolated from the roots of *Actaea podocarpa*, a species closely related to black cohosh, a well-known dietary supplement. Specifically, podocarpaside C (**444**) displayed modest complement activity inhibition with an IC_{50} value of 200 μM [375].

The structure of podocarpaside E (**446**), also from *Actaea podocarpa*, was revised to 3β,15α,25-trihydroxy-16,23-dioxo-6α,19α-epidioxy-9,10-seco-9,19-cyclolanost-5(10),9(11)-diene 3α-O-L-arabinopyranoside [375]. Another compound, podocarpaside (**449**), an arabinoside with a unique triterpene skeleton isolated from the same species, exhibited anticomplement activity [376].

A phytochemical study on the rhizomes of *Cimicifuga foetida* led to the isolation of two cycloartane triterpenoids (**450** and **451**), which are part of a seven-membered-ring variant of 9,10-seco-9,19-cycloartane triterpenoids. Additionally, compounds **452** and **453** were identified as 3-O-β-D-xylopyranosides [377]. Further, from the roots of *Actaea podocarpa*, three cycloartane-type triterpene arabinosides, podocarpasides H-J (**454**-**456**), were isolated, with podocarpaside I (**455**) showing moderate anticomplement activity with an IC_{50} value of 250 μM [375].

A glycoside named acanthifolioside A (**457**), a minor component, was isolated from the marine sponge *Pandarosa canthifolium*. Acanthifoliosides are distinct for having a rare oxidation pattern at C-15 and C-16 on the D ring [352].

From the Far Eastern sea cucumber *Psolus chitonoides*, collected near Bering Island (Commander Islands) at depths of 100–150 m, triterpene pentasides named chitonoidosides A (**458**) and A1 (**459**), which contain one or two sulfate groups, were isolated [378]. Additionally, from the sea cucumber *Actinopyga flammea*, 16-keto-holothurinogenin (**460**) was obtained through acid hydrolysis of the crude extract [379].

Steroidal alkaloids, cortistatins C (**461**) and D (**462**), featuring a 9(10−19)-abeo-androstane and isoquinoline skeleton, were isolated from the marine sponge *Corticium simplex*. These compounds demonstrated high selectivity in inhibiting the proliferation of human umbilical vein endothelial cells (HUVEC) [380].

Two toxic triterpenoid alkaloids, cyclobuxophylline O (**463**) and cyclobuxophylline M (**464**), have been discovered in the box tree moth *Cydalima perspectalis* [381]. Additionally, cyclobuxophylline M (**464**) and cyclobuxophylline K (**465**) were isolated from *Buxus* sp. and *Buxus sempervirens* [382,383]. An interesting feature of these alkaloids is the increase in the number of methyl groups on the amino group located at the 3rd position. Another alkaloid, sempervirone (**466**), was isolated from the leaves of *Buxus sempervirens* [384].

Pregnane alkaloids such as terminamine S (**467**), 3β-methylamino-16-oxo-5,17(20)-cis-pregnadiene (**468**) [385], (Z)-salignone (**469**) [386], terminamine H (**470**) [387], 3β-methylamino-16-oxo-5,17(20)-*trans*-pregnadiene (**471**) [385], and (*E*)-salignone (**472**) [386] were isolated from the whole herb of *Pachysandra terminalis* [388].

A phytochemical study on the stem of *Ecdysanthera rosea* resulted in the isolation of C-21 pregnane glycosides ecdysosides A–D (**473**–**476**). Notably, compound **473** exhibited moderate antibacterial activity against *Enterococcus faecalis* and *Providencia smartii* [389]. Summarized on the biological activity of 16-ketosteroids is presented in Table 10, and details are described partially in the text or a full description of the activity is written in the original articles.

Table 10. Summarized biological activity of 16-ketosteroids.

No. Steroids	Reported Activity of 16-ketosteroids	Ref.
425-427	Strong anti-inflammatory activity and NO inhibition inhibitor	[367]
430	NO production inhibitor	[369]
449	Anticomplement activity	[376]
454-456	Anticomplement activity	[375]
461,462	Proliferation of human umbilical vein endothelial cells (HUVEC)	[380]
473	Antibacterial activity	[389]

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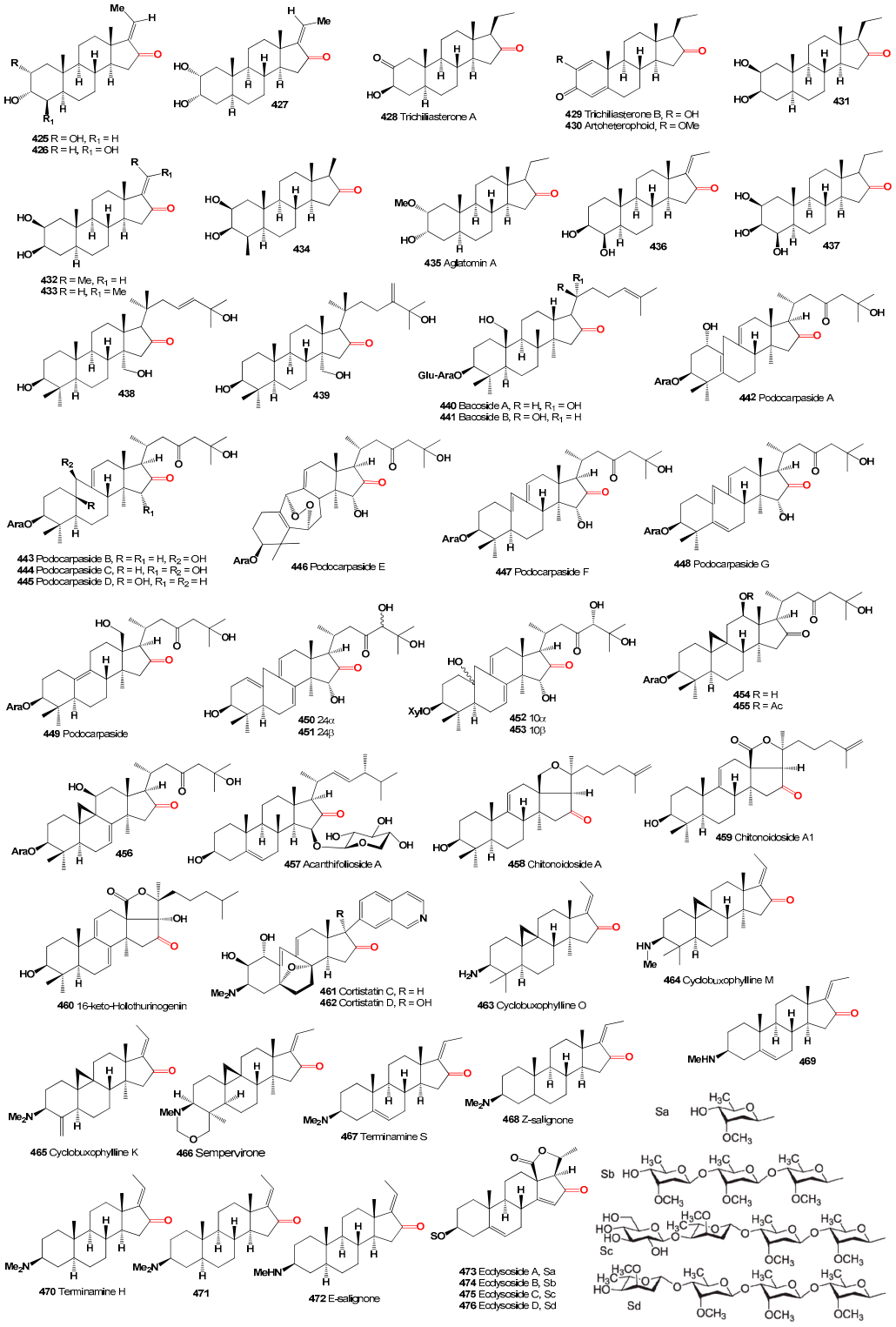

Figure 13. 16-Ketosteroids derived from marine invertebrates, and plants.

17-Ketosteroids

17-ketosteroids (17-KS) are metabolites derived primarily from the catabolism of androgens and, to a lesser extent, estrogens. These compounds are significant markers in the body, providing insights into adrenal and gonadal function. 17-KS are key byproducts found in the urine, originating from the metabolism of androgenic hormones like testosterone and dehydroepiandrosterone (DHEA). The presence and levels of these ketosteroids are indicators of androgenic activity in the body, reflecting the functioning of the adrenal cortex and gonads. The measurement of 17-KS in urine is a valuable

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diagnostic tool. It helps in assessing adrenal gland function and diagnosing disorders like adrenal hyperplasia, adrenal tumors, and conditions affecting the gonads. This is particularly useful in clinical settings to monitor and diagnose endocrine disorders [9,100,390,391].

Though 17-KS themselves are not hormonally active, their formation and excretion reflect the body's metabolic pathways in breaking down sex hormones. Thus, they indirectly influence the regulatory mechanisms associated with hormonal balance, impacting physiological processes such as growth, reproduction, and stress responses. In research, the levels of 17-KS can be studied to understand variations in hormonal activity due to various diseases, lifestyle factors, or environmental influences. This research helps in developing treatments for hormonal imbalances and related health issues [392,393]. In non-human animals, the specific functions of 17-KS can vary, but generally, they serve as markers of similar hormonal and metabolic processes. For example, in veterinary medicine, measuring these ketosteroids can assist in diagnosing health conditions in domestic and wild animals, particularly those related to reproductive and adrenal functions [393].

17-Ketosteroids are vital as both metabolic intermediates and diagnostic markers across various species, playing a significant role in understanding and managing health issues related to hormone regulation and adrenal gland function [393–397].

Holarrhena pubescens, an Indian medicinal tree indigenous to the tropical Himalaya and Assam, is known for its stem bark, commercially referred to as kurchi. This bark has astringent, antidysenteric, anthelmintic, stomachic, febrifugal, and tonic properties. A unique compound, puboestrene [3-acetoxy-17-oxo-1,3,5(10)-estratriene] (**474**, structures see in Figure 14), has been isolated from the bark of *Holarrhena pubescens* [398].

Estra-1,3,5(10)-triene-3-ol-17-one (**475**), commonly known as estrone, is a naturally occurring estrane steroid produced *in vivo* from androstenedione and/or testosterone via estradiol. This estrogen demonstrates estrogenic activity, with variations depending on its structure, some of which may also exhibit anticancer properties [399–401]. Butenandt and Jacobi [402] isolated estrone (**475**) from seeds and pollen of *Phoenix dactylifera, Punica granatus, Malus pumila, Hyphaene thebaica, Salix caprea*, and *Glossostemon bruguieri*. In 1926, Dohrn and co-workers first detected estrone (**475**), equilin (**476**), and hippulin (**477**) as female sex hormonal steroids in plants [403]. This discovery was followed by further identifications in the 1930s by Butenandt and Jacobi [402] and Skarzynski [404]. Additionally, extracts from the bark of the main wooden rod of ketapang *Terminalia catappa* (Combretaceae) contained estrone (**474**), equilin (**475**), and equilin sulfate (**478**) [405].

6,8-Didehydroestrone (**479**) and estra-1,3,5(10),6,8-pentaen-3-ol-17-one, known as equilenin, were first isolated from the urine of pregnant mares in 1936 by Desmond Beall [406]. Later, equilenin sulfate (**480**) was also extracted from the urine of pregnant mares by Schachter and Marrian in 1938, and subsequently synthesized by Bachmann and Wilds in 1939 [407,408]. Two naphthalene-containing steroids (**481** and **482**) have been found in the bark of *Terminalia catappa*, although it's speculated that these compounds are naphthalenic steroids produced by the tree itself [409]. *Terminalia catappa* and *Terminalia mantaly* (Combretaceae) are recognized medicinal plants used in Cameroon to treat various diseases.

In the lipophilic fractions of *Loranthus micranthus*, a medicinal plant known in eastern Nigeria as a species of the African mistletoe and commonly used in traditional medicine, two notable steroids were identified: 5α,16,16-dimethyl-androstan-17-one (**483**) and 6β-hydroxy-17-oxo-4,5-secoandrostan-4-oic acid (**484**) [410].

Additionally, 3β-Hydroxy-5α-androstan-17-one (epiandrosterone, **485**), 5α-androstan-3,17-dione (**486**), and 3α-hydroxy-5α-androstan-17-one (androsterone, **487**), have been identified in the solvent-soluble fraction of peat from Bolton Fell Moss (Cumbria, U.K.). The structures and $\delta^{13}C$ values of these androstane derivatives suggest a diagenetic origin from sterols also present in the peat, providing the first evidence that cleavage of the C-17 side-chain can occur during early diagenesis, likely through microbial oxidation [411].

Comamonas testosteroni is recognized as a key model in the study of bacterial aerobic steroid degradation, capable of degrading cholic acid. Three major steroids (**488**-**490**) have been identified as byproducts of cholic acid degradation [412].

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From the stem bark of *Ailanthus malabarica*, rare octanor- and nonanor-triterpenoids, malabanones A (**491**) and B (**492**), featuring a unique tricyclo[4.3.1.0.1,6]decane unit, were isolated [413]. Additionally, a strain of the fungus *Fusarium oxysporum* SC1301, isolated from soil samples, is known as a steroid producer (**493**) [414].

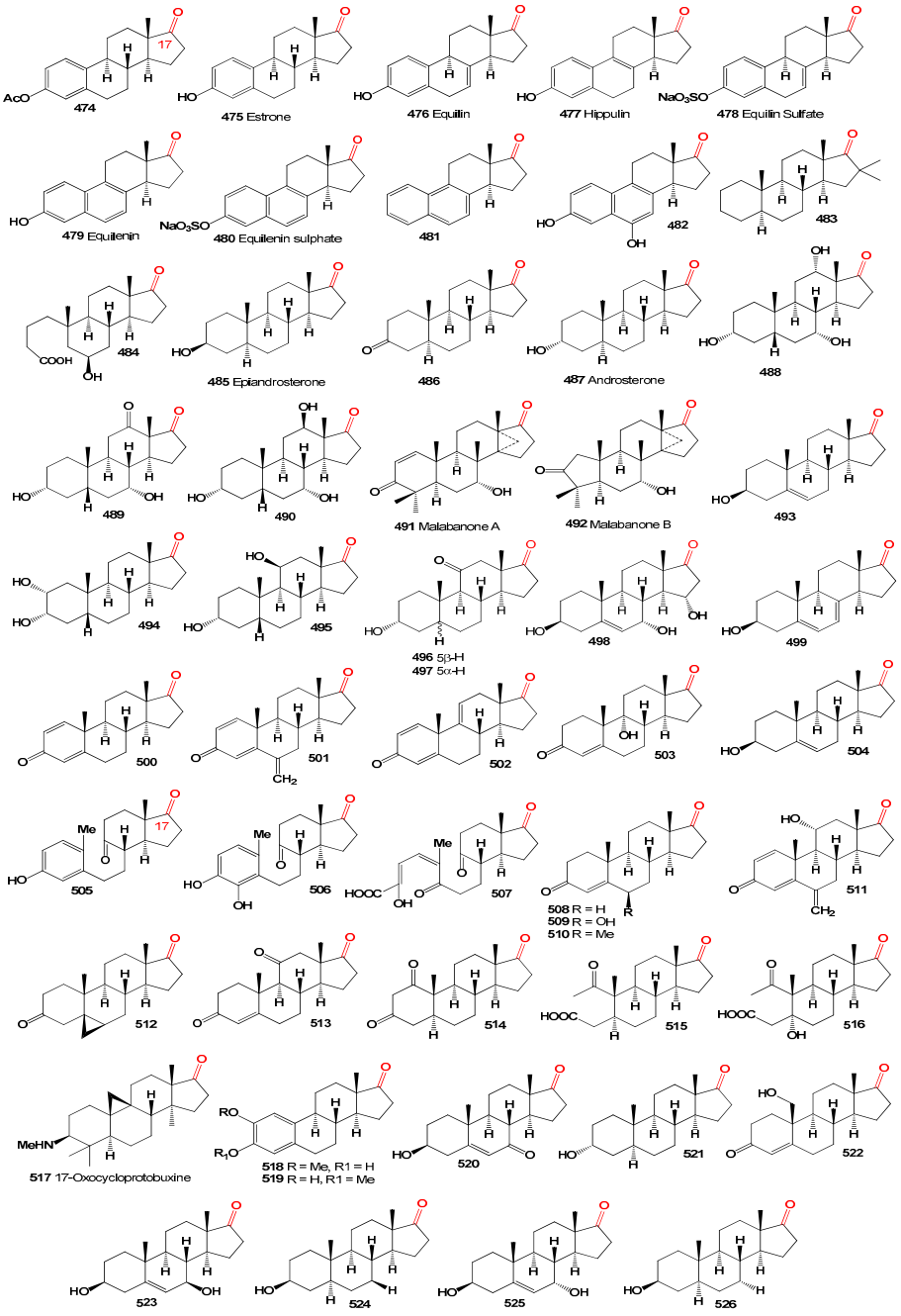

Figure 14. 17-Ketosteroids derived from animals, fungi, and plants.

Pinus nigra, also known as the Austrian pine or black pine, is found across Southern Europe from the Iberian Peninsula to the eastern Mediterranean, the Anatolian peninsula of Turkey, Corsica, Cyprus, and the high mountains of Northwest Africa. Various steroid hormones have been detected in the pollen of this pine species. These include epiandrosterone (**485**), androsterone (3α-hydroxy-5α-androstan-17-one, **487**), dehydroepiandrosterone (3β-hydroxyandrost-5-en-17-one, **493**), 2α,3α-dihydroxy-5β-androstan-17-one (**494**), 11β-hydroxy-etiocholanolone (3α,11β-dihydroxy-5β-androstan-17-one, **495**), 3α-hydroxy-5β-androstane-11,17-dione (**496**), and 3α-hydroxy-5α-

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androstane-11,17-dione (**497**) [415]. Additionally, androstane-3,17-dione (**486**) was identified in the sugar pine (*Pinus lambertiana*) [416].

Steroid modifications *via* selected wild and engineered microbial strains have become a crucial method for producing valuable steroid drugs and their precursors for the pharmaceutical industry. These microorganisms excel in sterol side chain degradation, oxyfunctionalization of the steroid core, and redox reactions at various positions of the steroid molecule. Over ten 17-ketosteroids (**498**-**516**) have been isolated and identified, demonstrating the diverse capabilities of these microorganisms [9,99,417–421].

Phytochemical studies on an ethanol-soluble extract of the roots of *Buxus sempervirens* of Turkish origin have led to the isolation of (+)-17-oxocycloprotobuxine (**517**) [422].

Urinary steroids, metabolites of steroid hormones excreted in urine, are pivotal in assessing an individual's metabolic state, endocrine function, and overall health [423]. The measurement of these steroids plays a critical role in diagnosing and monitoring various endocrine disorders. For example, elevated levels of certain urinary steroids may indicate adrenal gland disorders such as Cushing's syndrome or adrenal tumors [425].

Urinary steroid profiles are invaluable for understanding an individual's metabolic processes. The ratios of specific steroids can reveal the activity of enzymes involved in steroid metabolism. These steroids are end products of steroid hormone metabolism, formed in the liver and other tissues through various chemical modifications before being excreted in the urine [426].

Common urinary steroids include metabolites derived from steroid hormones such as cortisol, testosterone, estrogen (**475**), and progesterone. Notable among these are etiocholanolone (**485**), androsterone (**487**), and a range of 17-ketosteroids (**485**, **487**, **518**-**526**) [427].

Summarized on the biological activity of 17-ketosteroids is presented in Table 11, and details are described partially in the text or a full description of the activity is written in the original articles.

Table 11. Summarized biological activity of 17-ketosteroids.

No. Steroids	Reported Activity of 17-ketosteroids	Ref.
475	Estrogenic activity	[399–401]
485, **487**, **518**-**526**	Estrogenic activity, and adrenal antitumor agents	[425–427]

20-Ketosteroids

20-Ketosteroids are a category of steroid hormones characterized by the presence of a ketone group at the 20th carbon of the steroid structure. These compounds include important hormones such as cortisone, which is a significant glucocorticoid. The most well-known 20-ketosteroid, cortisone, plays a crucial role in the body's stress response. It is involved in regulating metabolism, immune response, and inflammatory processes. Cortisone is produced in the adrenal cortex, specifically in the zona fasciculata and zona reticularis [428–431].

As a glucocorticoid, cortisone helps in the regulation of glucose metabolism. It stimulates gluconeogenesis, the process by which the liver generates glucose from amino acids and other substrates, which is vital during periods of fasting or stress [432–434]. Cortisone and similar 20-ketosteroids have potent anti-inflammatory and immunosuppressive effects. They inhibit the activities of white blood cells and other components of the immune system, thus reducing inflammation and the immune response. This makes them useful in treating a variety of inflammatory and autoimmune conditions, such as asthma, allergies, and rheumatoid arthritis. Cortisone is also part of the body's response to stress. It is released in response to ACTH (adrenocorticotropic hormone) from the pituitary gland, which is stimulated by physical, emotional, or chemical stressors [435]. Due to their powerful anti-inflammatory and immunosuppressive actions, synthetic derivatives of 20-ketosteroids (such as prednisone) are commonly used in medical treatments. These are designed to mimic the effects of naturally occurring cortisone but may be more potent or have longer-lasting effects [435,436].

Overall, 20-ketosteroids like cortisone are crucial for maintaining homeostasis in the body, especially in response to stress. They play significant roles in metabolism, immune regulation, and

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inflammation control, making them vital both as natural hormones and as pharmacological agents [437,438].

The gorgonian *Menella spinifera*, collected off the South China Sea, was found to contain 3β-hydroxy-5α-pregnane-20-one (**527**) [439]. Additionally, several pregnane steroids—3α-hydroxy-5β-pregnan-20-one (**528**), 3β-hydroxy-pregnan-5-en-20-one (**529**), 5β-pregnan-3,20-dione (**530**), 5α-pregnan-3,20-dione (**531**), pregnan-4-en-3,20-dione (**532**), and pregnan-1,4-dien-3,20-dione (**533**) - were isolated from another species of the gorgonian *Menella*, collected off Meishan Island, Sanya Bay, Hainan province, China [440]. A strain of the fungus *Fusarium oxysporum* SC1301, isolated from soil samples, is known to produce pregnenolone (**534**) [414]. Moreover, extracts of *Rhodococcus* sp. cells have been shown to produce two oxygenated pregnane steroids (**535** and **536**) [441]. Phytochemical analysis of the methanolic extract of *Euonymus alatus* twigs led to the isolation of a sterol identified as (3,16)-3,16-dihydroxypregn-5-en-20-one (**537**) [442]. The sponge *Psammaplysilla purpurea* contains 3β-hydroxy-5α-pregnan-20-one (**528**) and 3β-hydroxy-pregn-5-en-20-one (**529**) as minor constituents in its free sterol mixture [443].

Recent findings highlight that only a few insect taxa are known to produce steroids essential for insects, including several chrysomelids (Chrysomelidae), carrion beetles (Silphidae, Staphylinidae), lampyrid beetles (Lampyridae), and giant aquatic bedbugs (Belostomatidae) [444–446]. The prothoracic protective glands of dytiscids are noted for producing a remarkable array of known vertebrate steroid hormones along with new and unusual steroids (**530**, **531**, **532**, **537–544**), found also in predaceous diving beetles and belostomatid bugs. Some of these molecules are believed to be synthesized from cholesterol acquired from their prey [445].

Brassinosteroid metabolites, known as plant hormones (**545**-**547**), have been detected in extracts of the flowering plant *Ornithopus sativus* from the family Fabaceae [447]. Several pregnane glycosides and their aglycones (**548**-**550**) were identified in the roots of *Asclepias tuberosa* [448]. Chemical investigations into the roots of *Dysoxylum densiflorum* identified two known steroids, (**527** and **528**) [449], and from the leaves of oleander (*Nerium indicum*), pregnane 3β,14-dihydroxy-5α,14β-pregnan-20-one (**551**) has been identified [450].

A bioactive steroid (**552**) was isolated from an alcohol extraction of *Solanum nigrum*, demonstrating significant cytotoxic activities against SW480 and Hep3B cells [451].

Steroidal alkaloids, which possess a basic steroidal skeleton with a nitrogen atom integrated into rings or side chains, showcase a broad range of biological activities. Some steroidal alkaloids, such as abiraterone acetate—a widely used treatment for prostate cancer—exemplify how these compounds can be developed into therapeutic drugs. The structural diversity of natural steroidal alkaloids presents a spectrum of biological activities, making them highly valuable to both natural product chemistry and medicinal chemistry communities [295]. Examples include two steroidal alkaloids, cyclobuxomicreinine (**553**) and cyclorolfeine (**554**), found in extracts of *Buxus hildebrandtii* [452], cyclobuxomicreinine (**555**) identified from *Buxus* species [453], and buxippine K (**556**) which would be isolated from the leaves of *Buxus hyrcana* [454]. An antiprotozoal nor-triterpene alkaloid, 16-α-hydroxybuxaminone (**557**), was isolated from *Buxus sempervirens* and *Buxus* sp. [455,456].

Several steroidal glycosides (**558**-**565**) were isolated from the aerial parts of Ceropegia fusca (Asclepiadaceae), a crassulacean acid metabolism plant endemic to the Canary Islands, traditionally used as a cicatrizant, vulnerary, and disinfectant. The dichloromethane extract exhibited significant cytostatic activity against HL-60, A-431, and SK-MEL-1 cells—models for human leukemic, epidermoid carcinoma, and melanoma cells respectively [457]. Summarized on the biological activity of 20-ketosteroids is presented in Table 12, and details are described partially in the text or a full description of the activity is written in the original articles.

Table 12. Summarized biological activity of 20-ketosteroids.

No. Steroids	Reported Activity of 20-ketosteroids	Ref.
552	Strong cytotoxic activities against SW480 and Hep3B cells	[451]
557	Strong antiprotozoal aqctivity	[455,456]
558-565	Strong cytostatic activity against HL-60, A-431, and SK-MEL-1 cells	[457]

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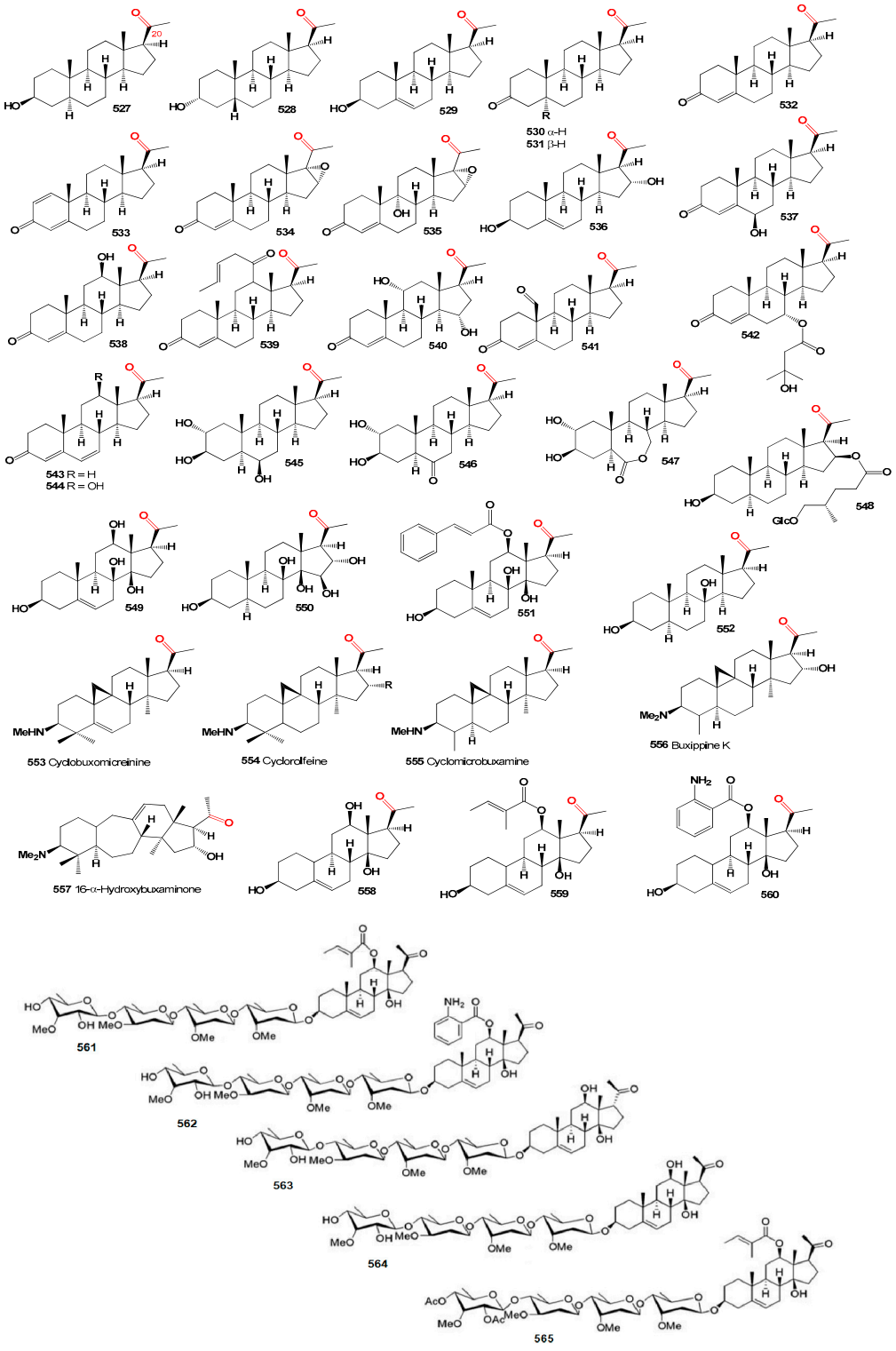

Figure 15. 20-Ketosteroids derived from insects, and plants.

Miscellaneous Ketosteroids Derived from Natural Sources

A rearranged sterol with an unusual tetracycle core skeleton, penicillitone (**566**), was obtained from the culture of the fungus *Penicillium purpurogenum* SC0070. This compound demonstrated potent inhibitory effects on tumor cell growth and key pro-inflammatory cytokine production in macrophages [458]. The mushroom *Stropharia rugosoannulata*, known as saketsubatake in Japanese and wine-cap stropharia in English, produces an unusual steroid, strophasterol A (**567**), which exhibited an inhibitory effect on TG toxicity in a dose-dependent manner [459].

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An unusual steroid-type compound, dankasterone A (**568**), is produced by the fungus *Gymnascella dankaliensis*, which was isolated from the Japanese sponge *Halichondria japonica* [344,345]. Citreoanthrasteroid A (**569**) was isolated from the mycelia of a hybrid strain, KO 0231, prepared by a cell fusion technique using *Penicillium citreo-viride* IFO 6200 and 4692 [460].

Ergosteroid, gloeophyllin J (**570**), has been isolated from the solid cultures of fungus *Gloeophyllum abietinum*. This compound represents the first ergosteroid featuring the cleavage of a C8−C14 bond [461]. Steroids (234R)-3β-hydroxy-24-methyl-4-methylene-8,14-secocholestane-8,14-dione (**571**) and swinhosterol A (**572**) were isolated from an Okinawan sponge *Theonella swinhoei*. An undescribed 9,11-secosteroid, cyclosecosteroid A (**573**), was isolated from the mangrove endophytic fungus *Talaromyces* sp. SCNU-F0041, and it showed moderate inhibitory activity against AChE, with an IC_{50} value of 46 μM [462].

An oxygenated 4-exo-methylene sterol, 28-homoswinhoeisterol (**574**), was discovered in the marine sponge of *Theonella swinhoei* collected from the Bohol province in the Philippines [463].

The 9,11-secosteroids, pinnigorgiols A (**575**) and E (**576**) with a rare carbon skeleton, a tricyclo[5,2,1]decane ring, were isolated from a gorgonian coral identified as *Pinnigorgia* sp. These compounds displayed inhibitory effects on the generation of superoxide anions and the release of elastase by human neutrophils [464,465]. Two secosteroids, 3β,11-dihydroxy-5β,6β-epoxy-9,11-secocholestan-9-one (**577**) and 3β,11-dihydroxy-5β,6β-epoxy-9,11-secogorgostan-9-one (**578**), have been identified from extracts of the Taiwanese soft coral *Cespitularia taeniata* [466–468].

Steroid, 8αH-3β,11-dihydroxy-5α,6α-epoxy-24-methylene-9,11-secocholestan-9-one (**579**) was obtained from *Sinularia granosa* and *S. crassa* soft coral extracts [469]. Two unusual steroidal derivatives, erectsterates A (**580**) and B (**581**), epimers at C-10, were isolated from the South China Sea soft coral *S. erecta*. These compounds are characterized by a high degree of degradation in ring B and an ester linkage between the A and C/D rings, similar to the compounds chaxines B and D from the edible mushroom *Agrocybe chaxingu* [470]. Compound (**581**) displayed cytotoxic activity against several cancer cell lines including A549 (human adenocarcinoma), HT-29 (human colorectal adenocarcinoma), SNU-398 (hepatocellular carcinoma), and Capan-1 (human pancreatic ductal adenocarcinoma) [471].

A series of cytotoxic steroids called stereonsteroids B (**582**) and F (**583**) were isolated from the methylene chloride extract of the Formosan soft coral *Stereonephthya crystalliana*. This coral extract showed significant cytotoxicity against A549, HT-29, and P-388 cancer cells *in vitro* [472].

Several neotecleanin-type limonoids, walrobsin C (**584**), I (**585**), Q (**586**), R (**587**), and U (**588**), were detected in methanol (MeOH) extracts of the root barks of *Walsura robusta* [473].

Belamchinanes A–D (**589**-**592**), four triterpenoids with a novel skeleton, were isolated from the seeds of *Belamcanda chinensis*. These structures feature a unique 4/6/6/6/5 polycyclic system where a four-membered carbocyclic ring bridges the C-1 and C-11 positions of a classical triterpenoid framework [474].

Strophasterols E and F (**594** and **595**) were isolated from *Pleurotus eryngii*, showing interesting structural properties [342], and tricholumin A (**595**), an ergosterol derivative from *Trichoderma asperellum*, exhibited antimicrobial activity [475].

In marine pharmacology, stellettins Q (**596**) from *Stelletta* sp. is a D-nor steroid with a cyclopentane unit linked to different positions of side chains [476,477], and stelliferins L (**597**) and M (**598**) from *Rhabdastrella* cf. *globostellata* exhibited antimicrobial activity [478].

Two C-nor-D-homo-estrones (**599** and **600**) were discovered in the Solanum family [479]. These compounds underscore the diverse potential of C-nor steroids in various therapeutic applications.

C-nor derivatives such as 14-hydroxy-7-methoxy-11,16-diketo-apian-8-en-(22,6)-olide (**601**) and 7-methoxy-11,16-diketo-apian-8,14-dien-(22,6)-olide (**602**) have been identified in *Salvia officinalis*, along with three other complex apianane terpenoids (**603**, **604**, and **605**) [480,481].

An unusual steroid-like metabolite, asterogynin B (**606**), with potential antimalarial properties, was produced by an endophytic fungus from the small palm *Asterogyne martiana* [482].

From the aerial parts of *Premna fulva*, a plant used in Zhuang medicine, a unique metabolite, premnafulvol A (**607**), was isolated. This compound features a distinct 6/5/7/3-fused tetracyclic

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carbon skeleton [483]. Spiroseoflosterol (**608**), an unusual ergostane steroid, was isolated from *Butyriboletus roseoflavus* and demonstrated cytotoxicity against liver cancer cell lines [484].

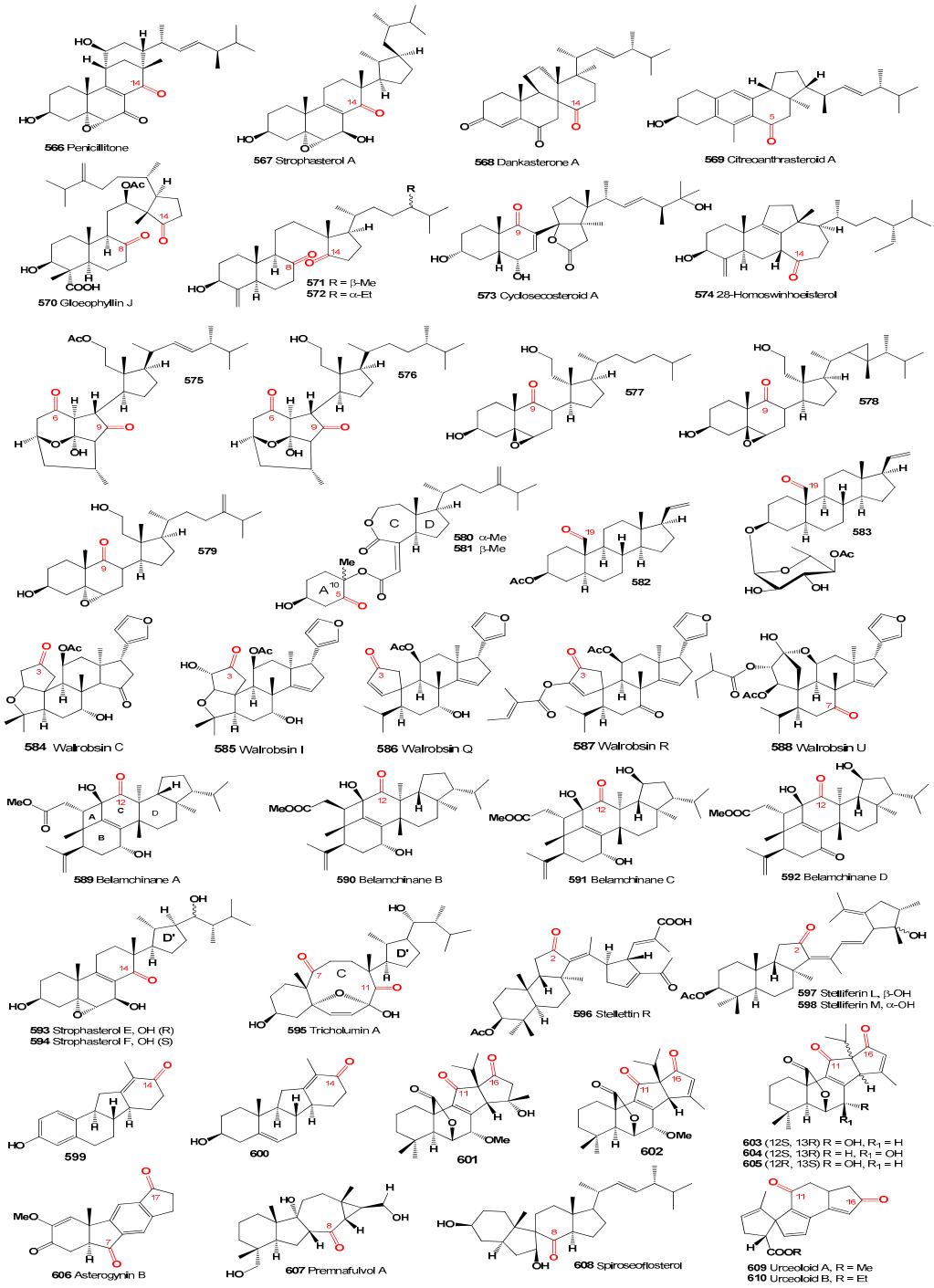

Figure 16. Miscellaneous ketosteroids derived from different speices.

Additionally, two steroids, urceoloids A (**609**) and B (**610**), characterized by a rearranged carbon skeleton with a unique spiro[4.4]nona-3,6,8-triene system, were identified. Both compounds exhibited immune-suppressive activities [485]. Summarized on the biological activity of 20-ketosteroids is presented in Table 12, and details are described partially in the text or a full description of the activity is written in the original articles.

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Table 12. Summarized biological activity of miscellaneous ketosteroids.

No. Steroids	Reported Activity of miscellaneous ketosteroids	Ref.
573	Inhibitory activity against cholinesterase	[462]
575,576	Inhibitors on the generation of superoxide anions and the release of elastase by human neutrophils	[464,465]
581	Cytotoxic activity against cancer cell lines, A549, HT-29, SNU-398, Capan-1 (human pancreatic ductal adenocarcinoma)	[471]
582,583	Strong cytotoxicity against A549, HT-29, and P-388 cancer cells	[472]
595	Strong antimicrobial activity	[475]
597,598	Strong antimicrobial activity	[478]
606	Strong antimalarial properties	[482]
608	Cytotoxicity against liver cancer cell lines	[484]
609,610	Immune-suppressive activities	[485]

Conclusions

The comprehensive review of steroidal compounds isolated from diverse natural sources such as marine organisms, fungi, plants, and through biotechnological processes reveals a profound complexity and immense pharmacological potential within the realm of natural steroids. This exploration has not only broadened our understanding of steroid chemistry but also highlighted the pivotal role these compounds play in both ecological systems and potential therapeutic applications.

The isolated steroids, ranging from pregnane steroids and steroidal alkaloids to ketosteroids and novel triterpenoids, exhibit a wide array of biological activities. Notably, many of these compounds have shown significant cytotoxic activities against various cancer cell lines, indicating their potential as anticancer agents. For instance, compounds like erectsterates A and B and penicillitone have demonstrated potent effects in inhibiting tumor growth and pro-inflammatory cytokine production. Such findings suggest that these natural steroids could be utilized as lead compounds for the development of new anticancer drugs.

The diverse mechanisms through which these steroids exert their effects are particularly intriguing. Many of these compounds interact with cellular pathways, influencing processes such as cell proliferation, inflammation, and immune response. The ability of these steroids to modulate these pathways at various levels underscores their potential utility in designing drugs with specific targets. This is particularly evident in the case of steroidal alkaloids like abiraterone acetate, which has been successfully developed into a therapeutic drug for prostate cancer by specifically inhibiting critical enzymes involved in steroid metabolism.

From an ecological perspective, the roles these steroids play in their native environments, such as defense mechanisms in marine sponges or regulatory functions in plant systems, provide insight into their natural functions and evolutionary significance. Understanding these roles not only enriches our ecological knowledge but also assists in bioprospecting, where ecological traits guide the search for pharmacologically active compounds.

Looking forward, the challenge lies in harnessing the full potential of these natural steroids. The complexity of their structures often makes synthesis challenging, and while microbial biotransformation offers a promising avenue, scaling these processes for industrial production requires further innovation. Additionally, the bioactivity of these compounds must be evaluated in more complex biological models to fully understand their potential adverse effects and therapeutic windows.

In conclusion, the study of natural steroids not only continues to push the boundaries of natural product chemistry but also offers promising leads for novel drug development. By advancing our understanding of their mechanisms, optimizing their synthesis, and investigating their ecological roles, we can better leverage the therapeutic potential of these diverse and potent molecules.

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