BIOACTIVE COMPOUNDS PROFILE OF GORGONIAN CORALS AND THEIR PHARMACOLOGICAL ACTIVITIES: A REVIEW

F. J. Kelutur¹, N. M. Saptarini^{1,✉}, R. Mustarichie¹ and D. Kurnia²

¹Department of Pharmaceutical Analysis and Medicinal Chemistry, Universitas Padjadjaran, Jatinangor-453631, (Jawa Barat) Indonesia

²Department of Chemistry, Universitas Padjadjaran, Jatinangor-453631, (Jawa Barat) Indonesia

✉Corresponding Author: nyi.mekar@unpad.ac.id

ABSTRACT

Soft corals and gorgonians live in an extreme and competitive area, giving them the ability to survive by utilizing chemical defense systems in the form of secondary metabolites. These secondary metabolites with various types can be used to develop a new drug substance. This review article summarizes the types of gorgonian corals, secondary metabolites' content, and pharmacological activities. It certainly provides the latest insights about the source of medicinal ingredients from the marine. Types of gorgonian corals include *Junceella fragilis*, *Heteroxenia fuscescens*, *Briareum violaceum*, *Briareum excavatum*, *Echinomuricea* sp., *Rumphella antipathies*, *Pseudopterogorgia acerosa*, *Eunicella singularis*, *Pseudopterogorgia elisabethae*, *Rumphella* sp., *Verrucella corona*, *Pseudopterogorgia americana*, *Pinnigorgia* sp., *Subergorgia suberosa*, *Subergorgia rubra*, *Dendronephthya griffini*, and *Paramuricea clavata*. All gorgonian corals contain terpenoids, steroids, and alkaloids (rare) with activities as an anti-inflammatory, anti-cancer, analgesic, gastroprotective, anti-viral, anti-bacterial, and anti-fouling agents. That is due to the structural relationship to the activity, which includes the stereochemical influence of the hydroxy group, the presence of an epoxide group, a methoxy group, the configuration of the methylenecyclohexane ring, and changes in the side chain on the carbonyl group.

Keywords: Marine, Gorgonian, Secondary Metabolites, Pharmacological Activities.

RASĀYAN J. Chem., Vol. 14, No.3, 2021

INTRODUCTION

Gorgonians are a type of coral found in shallow to deep-sea waters.¹ In the last ten years, it has been reporting that soft coral and gorgonian octacorallia derived from marine natural resources can become novel bioactive natural products as lead compounds in drug development.² Soft corals and gorgonians live in very extreme and competitive ecosystems but can defend themselves very well from predators. It is due to a chemical defense system, namely secondary metabolites.^{2,3} These metabolites become weapons to attack or fight other organisms, not to grow or die if they are in the same place.⁴

Each type of gorgonian has various secondary metabolites and has medicinal potencies, including anti-inflammatory, analgesic, gastroprotective, anti-bacterial, and anti-fouling agents.^{2,5} Many studies have reported that gorgonian corals contain a wide variety of cyclic terpenes, namely sesquiterpenes, steroids, prostanoids, and very rare alkaloids.⁶ The terpenes' highly variable structure provides various biological activities, namely anti-cancer⁷, anti-inflammatory, immunomodulators, and anti-diabetic.⁸ This review was conducted to determine each type of gorgonian coral's secondary metabolites, thus providing various pharmacological activities.

Gorgonian Coral's Secondary Metabolites

Terpenoids

Junceella fragilis

This gorgonian (Fig.-1)⁹ has been investigating to contain the secondary metabolite of two 11,20-epoxibriaranes, namely juncenolide K (1) and fragilide X (2) (Fig.-2). The secondary metabolite has

extracted with a mixture of methanol–dichloromethane, a ratio of 1:1, to obtain crude extract. Then the partition was carried out with ethyl acetate and water.¹⁰

Fig.-1: *J. fragilis*⁹

Fig.-2: The Structure of juncenolide K (1) and fragilide X (2)¹⁰

Heteroxenia fuscescens

This gorgonian (Fig.-3)¹¹ contains a new hydroperoxy sesquiterpene, heterofusceterpene A (**3**) (Fig.-4), extracted using 90% methanol. The extract has separated by Diaion HP-20 chromatography and eluted using 100% distilled water and 100% methanol to obtain distilled water and methanol fractions.¹²

Fig.-3: *H. fuscescens*¹¹

Fig.-4: The Structure of Heterofusceterpene A (**3**)¹²

Briareum violaceum

Research conducted by Xu *et al.* on the gorgonian coral *B. violaceum* (Fig.-5) contains a new secondary metabolite briarane diterpenoid, namely briaviolides K–N (**4–7**) (Fig.-6) extracted using a mixture of methanol–dichloromethane solvents (1:1). Then, to elucidate secondary metabolites' structure with IR, ¹H, ¹³C-NMR, ESIMS, and HRESIMS.¹³

Fig.-5: *B. violaceum*¹³ Fig.-6: The structure of briaviolide K–N (4–7)¹³***Briareum excavatum***

This type of coral (Fig.-7)¹⁴ has extracted with methanol–dichloromethane (1:1) solvent, then partitioned with distilled water and ethyl acetate. Furthermore, re-purification has been carrying out with normal phase silica gel eluted using *n*-hexane–ethyl acetate (80:1) to obtain a pure isolate, namely excavatolide B (8) (Fig.-8).¹⁵

Fig.-7: *B. excavatum*¹⁴ Fig.-8: The Structure of excavatolide B (8)¹⁵***Echinomuricea* sp.**

This gorgonian (Fig.-9)¹⁶ contains a new labdane type diterpenoid, namely echinolabdane A (9) (Fig.-10), which has extracted using methanol–dichloromethane (1:1) solvent and fractionated with silica gel using eluent in the form of *n*-hexane–ethanol–methanol.¹⁷

Rumphella antipathies

Chung *et al.* reported that this gorgonian (Fig.-11) contains two new caryophyllene derivatives of the sesquiterpenoid type, namely rumphellol A (10) and B (11) (Fig.-12), which were extracted using a

combination of solvents from methanol–dichloromethane and analyzed by IR, 1D and 2D NMR spectroscopy, and HR–ESIMS.¹⁸

Fig.-9: *Echinomuricea* sp.¹⁶

Fig.-10: The Structure of echinolabdanone A (9)¹⁷

Fig.-11: *R. Antipathies*¹⁸

Fig.-12: The Structure of rumphellol A (10) dan B (11)¹⁸

***Pseudopterogorgia acerosa*.**

The *P. acerosa* (Fig.-13)¹⁹ contains pseudopterane diterpenes, pseudopterolides (**12**) (Fig.-14), which have extracted using methanol and dichloromethane.²⁰

Fig.-13: *P. acerosa*¹⁹

12

Fig.-14: The Structure of pseudopterolide (12)²⁰***Eunicella singularis.***

This gorgonian (Fig.-15)²¹ contains a diterpenoid type eunicellin, palmonine F (**13**) (Fig.-16), which is extracted by maceration using methanol–dichloromethane (1:1) for 48 hours and repeated three times. The extract has then fractionated with C18 cartridges subjected to gradient elution with 10, 50, and 80% methanol to obtain three fractions.⁵ The same research was carried out with gradient elution using organic solvents in ethanol, acetone, and methanol–dichloromethane (1:1) to obtain three semi-purified fractions, namely ethanol, acetone, and methanol–dichloromethane.²²

Fig.-15: *E. singularis*²¹

13

Fig.-16: The structure of palmonine F (13)⁵***Pseudopterogorgia elisabethae.***

The *P. elisabethae* extract (Fig.-17)²³ was fractionated with silica gel to produce F-1 [pseudopterogens PsQ (**14**), PsS (**15**), and PsU (**16**)], F-2 [amphilectosins A (**17**) and B (**18**), PsG (**19**), PsK (**20**), PsP (**21**), and PsT (**22**)] as well as *seco*-pseudopterogens *seco*-PsJ (**23**) and *seco*-PsK (**24**)], and F-3 [elisabethatrienol (**25**), 10-acetoxy-9-hydroxy- (**26**) and 9-acetoxy-10-hydroxy-amphilecta-8,10,12,14-tetraenes (**27**) and amphilecta-8(13)-11,14- triene-9,10-dione (**28**)] (Fig.-18).²⁴

Fig.-17: *P. elisabethae*²³

Fig.-18: The Structure of pseudopterosins PsQ (14), PsS (15), PsU(16), amphilectosins A (17) and B (18), PsG (19), PsK (20), PsP (21), PsT (22), *seco*-pseudopterosins *seco*-PsJ (23) and *seco*-PsK (24), elisabethatrienol (25), 10-acetoxy-9-hydroxy- (26) and 9-acetoxy-10-hydroxy-amphilecta-8,10,12,14-tetraenes (27), as well as amphilecta-8(13)-11,14-triene-9,10-dione (28)²⁴

Steroids

Heteroxenia fuscescens.

This gorgonian contains secondary metabolites of new sterol types, heterofuscesterols A (29) and B (30), and 3 β ,5 α ,6 β -trihydroxyandrosta-17-one (31) (Fig.-19).¹²

Fig.-19: The Structure of heterofuscesterols A (29) and B (30) as well as 3 β ,5 α ,6 β -trihydroxyandrosta-17-one (31)¹²

Rumphella sp.

Yin *et al.* reported that the gorgonian coral *Rumphella* sp.²⁵ (Fig.-20)^{15,26} extracted using acetone as a solvent containing new hydroperoxy steroids called xidaosteroids A (32) and B (33) 5 α ,8 α -epidioxyergosta-6,9(11)-diene-3 β -ol (34), 5 α ,8 α -epidioxyergosta-6,9(11)-diene-3 β -ol (35), 3 β -hydroxy-5 α ,6 α -epoxy-7-megastigmen-9-one (36), grasshopper 3 ketone (37), (3*R*)-4-[(2*R*,4*S*)-4-acetoxy-2-hydroxy-2,6,6-trimethylcyclohexylidene] but-3-en-2-one (38) (Fig.-21).²⁵

Fig.-20: *Rumphella* sp.^{15,26}

Fig.-21: The structure of xidaosteroid (32 and 33), 5 α ,8 α -epidioxyergosta-6,9(11)-diene-3 β -ol (34), 5 α ,8 α -epidioxyergosta-6,9(11)-diene-3 β -ol (35), 3 β -hydroxy-5 α ,6 α -epoxy-7-megastigmen-9-one (36), grasshopper 3-ketone (37), (3*R*)-4-[(2*R*,4*S*)-4-acetoxy-2-hydroxy-2,6,6-trimethylcyclohexylidene] but-3-en-2-one (38)²⁵

Verrucella corona.

The type of gorgonian coral *V. corona* (Fig.-22)²⁷ studied by Nam *et al.* contains secondary metabolites of steroids, namely verrucorosteroid A–F (41–46), verrucorosteron (47), 3 β -acetyl-20*R*-hydroxycholest-5,22-dien-24-oic acid γ -lactone (48), 3 β ,20*R*-dihydroxycholest-5,22-dien-24-oic acid γ -lactone (49), suberoretisteroids A–C (50–52), (22*E*)-3 β ,25-dihydroxycholest-5,22-dien-24-one (53), 5,6 α -epoxy-3 β -hydroxy-(22*E*)-ergosta-8,22-dien-7-one (54), 5,6 α -epoxy-3 β -hydroxy-(22*E*)-ergosta-8(14),22-dien-7-one (55), (22*E*,24*S*)-24-methyl-5 α -cholesta-7,22-diene-3 β ,5,6 β ,9-tetraol (56), and (22*E*,24*S*)-24-methyl-5 α -cholesta-7,22-diene-3 β ,5,6 β -triol (57) (Fig.-23).²⁸

Fig.-22: *V. corona*²⁷

Fig.-23: The structure of verrucorosteroid A–F (41–46), verrucorosteron (47), 3 β -acetyl-20 R -hydroxycholest-5,22-dien-24-oic acid γ -lactone (48), 3 β ,20 R -dihydroxycholest-5,22-dien-24-oic acid γ -lactone (49), suberoretisteroids A–C (50–52), (22 E)-3 β ,25-dihydroxycholest-5,22-dien-24-one (53), 5,6 α -epoxy-3 β -hydroxy-(22 E)-ergosta-8,22-dien-7-one (54), 5,6 α -epoxy-3 β -hydroxy-(22 E)-ergosta-8(14),22-dien-7-one (55), (22 E ,24 S)-24-methyl-5 α -cholesta-7,22-diene-3 β ,5,6 β ,9-tetraol (56), and (22 E ,24 S)-24-methyl-5 α -cholesta-7,22-diene-3 β ,5,6 β -triol (57)²⁸

Pseudopterogorgia americana.

The *P. americana* (Fig.-24)²⁹ has extracted using methanol, which produced two types of sterols that have rarely found, namely ameristerenol A (**58**) and B (**59**), both 9,11-secosterol, which have a cyclic enol-ether with seven members on the ring C, and **58** are natural examples of 9,11-secosterol containing gorgosterol side chains with a C-24 double bond. **58** is converted to a sterol derivative of **61–63**, while the structure of compounds **58–63** with three analogs is **64–66** (Fig.-25).³⁰

Fig.-24: *P. americana*²⁹

Fig.-25: The Structure of ameristerenol A (58), sterols derived from 61–63, and 3 analogs (64–66)³⁰

Pinnigorgia sp.

This gorgonian (Fig.-26)³¹ was extracted with ethyl acetate, then partitioned with *n*-hexane and methanol. The methanol layer was separated using a Sephadex LH-20 column and eluted with a mixture of dichloromethane–methanol (1:1). Each fraction was separated by silica gel column chromatography and purified with NP (*Normal Phase*) and RP (*Reverse Phase*)–HPLC, then elucidated using ¹H-NMR and ¹³C-NMR spectroscopy and HR-ESIMS to obtain 11-acetoxy-9,11-secoesterol, pinnisterol D–J (67–73), sterol (74), and pinnisterol A (75) (Fig.-27).³²

Fig.-26: *Pinnigorgia* sp.³¹

Fig.-27: The structure of pinnisterol D–J (67–73), sterol (74), and pinnisterol A (75)³²

***Subergorgia suberosa*.**

This coral (Fig.-28)³³, based on research by Cheng *et al.* has reported containing five new pregnan steroid types called subergol T-X (76–80) and three others known as analogs (81–83) (Fig.-29).³⁴

Fig.-28: *S. suberosa*³³ Fig.-29: The Structure of Subergorgol T-X (76–80) and three analogs (81–83)³⁴***Subergorgia rubra*.**

The *S. rubra* (Fig.-30)³⁵ was extracted by an ultrasonic technique using ethanol solvent. The extract was partitioned with ethyl acetate and distilled water, then fractionated by column chromatography using a mixture of petroleum ether–ethyl acetate to produce four fractions. The second fraction was purified by column chromatography using a combination of petroleum ether–ethyl acetate, 90:10, and re-purified by semi-preparative HPLC (methanol–H₂O, 90:10). Characterization of isolates using IR, ¹H and ¹³C-NMR spectrometry, and HR-ESI-MS. This gorgonian has reported containing a new 3 Δ^1 -3-ketosteroid characterized by 9-OH, subergosteron A–C (84–86) together with five steroids, namely 9 α -hydroxycholest-1-en-3-one (87), pregna-1,4,20-trien-3-one (88), cholesta-1,4-dien-3-one (89), dendronesterone C (90), and ergosta-1,4-dien-3-one (91) (Fig.-31) determined using comprehensive spectroscopic methods and ECD (Electronic Circular Dichroism).³⁶

Fig.-30: *S. rubra*³⁵ Fig.-31: The structure of subergosteron A–C (84–86), 9 α -hydroxycholest-1-en-3-one (87), pregna-1,4,20-trien-3-one (88), cholesta-1,4-dien-3-one (89), dendronesterone C (90), and ergosta-1,4-dien-3-one (91)³⁶

***Eunicella singularis*.**

The *E. singularis* has been studied to contain sterols, namely cholest-5-ene-3 β ,7 α -diol (**92**); (22*E*)-cholesta-5,22-diene-3 β ,7 α -diol (**93**); ergosta-5,24(28) diene-3 β ,7 α -diol (**94**); and cholesta-5, 22-diene-3 β -ol (**95**) (Fig.-32).²²

Fig.-32: The structure of cholest-5-ene-3 β ,7 α -diol (**92**), (22*E*)-cholesta-5,22-diene-3 β ,7 α -diol (**93**), ergosta-5,24(28) diene-3 β ,7 α -diol (**94**), and cholesta-5, 22-diene-3 β -ol (**95**)²²

***Echinomuricea* sp.**

This gorgonian contains a new sterol, namely 6-*epi*-yonarasterol B (**96**) (Fig.-33), which has extracted using methanol–dichloromethane (1:1).¹⁷

Fig.-33: The structure of 6-*epi*-yonarasterol B (**96**)¹⁷

***Dendronephthya griffini*.**

The *D. griffini* (Fig.-34)³⁷ was extracted with ethanol, then partitioned with ethyl acetate and distilled water. The ethyl acetate fraction was fractionating by column chromatography on silica gel, a mixture of n-hexane–ethyl acetate and ethyl acetate–methanol, so that 10 fractions were obtained. The fraction has purified by HPLC (CH₃CN–H₂O, 82:18) YMC Pack Pro C18 reverse-phase Dynamax variant, namely Si-60 with normal phase column, 250 × 21,4 mm, 100 Å, 5 μ m. The purification results contained two new sterol compounds, namely griffiniteron F–I (**97–100**) and griffinipregnon (**101**) (Fig.-35), whose structures were analyzed using IR, ¹H- and ¹³C-NMR spectroscopy, ESIMS, and HR-ESIMS.³⁸

Fig.-34: *D. griffini*³⁷

Fig.-35: The structure of griffiniteron F–I (**97–100**) and griffinipregnon (**101**)³⁸

Alkaloids

Paramuricea clavata.

Research conducted by Pérez *et al.* on this gorgonian coral (Fig.-36) and reported that it contains two new alkaloids, namely 2-bromo-*N*-methyltryptamine (**102**), 3-bromo-*N*-methyltyramine (**103**), and eight other components (**104–111**) (Fig.-37) obtained by extraction using a mixture of dichloromethane-methanol (1:1,3), while purification using semi-preparative HPLC with a flow rate of 3 mL/minute.⁶

Fig.-36: *P. clavata*⁶

Fig.-37: The structure of 2-bromo-*N*-methyltryptamine (**102**), 3-bromo-*N*-methyltyramine (**103**), and nine known components (**104–111**)⁶

Pharmacological Activities

Anti-inflammatory

11,20 terpenoids epoxibriarane, juncenolide K (**1**) and fragilide X (**2**) (Fig.-2) with anti-inflammatory activity. *In-vitro* testing of anti-inflammatory activity targets COX-2 and iNOS from lipopolysaccharide (LPS) stimulated by RAW 264.7 macrophage cells. The results showed that fragilide X had an LPS expression value of 113.65% on COX-2 and iNOS targets 122.87%, which indicated that the compound was not active in reducing the two's expression pro-inflammatory enzymes, in contrast to juncenolide K obtained COX-2 89.59% and iNOS 94.81%. It is due to the hydroxy group's stereochemical effect on the C-8 of the secondary metabolite fragilide X compared to juncenolide K, which only has an epoxide group on the C-11 and -20.¹⁰

Terpenoid briarane

Briaviolide K–N (**4–7**) (Fig.-6) contained in gorgonian *B. violaceum* was helpful as a pro-inflammatory inhibitor in iNOS targets with values 118.02±10.81; 46.68±4.56; 92.49±14.67; 71.49±3.78% LPS as well as COX-2, 112.77±20.69; 61.81±12.14; 101.95±8.22; 104.51±4.22% LPS when stimulated using RAW 264.7 macrophage cells. Briaviolide L effectively reduced iNOS and COX-2 with values of 46.68 and 61.81%, respectively. However, it is different from briaviolide K, which is inactive in reducing the two pro-inflammatory enzymes' expression due to the hydroxy groups' stereochemistry on the C-11.¹³ Even though the hydroxy group is very crucial because it plays an important role in providing biological activity.³⁹

Excavatolide B.

This metabolite (Fig.-8) was isolated from *B. excavatum* gorgonian coral, which has significant activity in inhibiting iNOS protein expression at doses of 1, 10, 25, and 50 µM. These secondary metabolites are

also administered via subcutaneous injection at a 15 or 60 mg/kg dose, significantly eliminating hind limb weight distribution changes after 2–24 hours.¹⁵

Echinolabdane A and 6-*epi*-yonarasterol B.

Echinolabdane A (**9**) secondary metabolite (Fig.-10) have found in *Echinomuricea* sp. which can inhibit superoxide anion derivatives with IC₅₀ values >10 µg/mL and 2.98±0.29 µg/mL with inhibition values of 2.52±3.02% and 89.76±5.63% and the release of elastase by neutrophils in humans with inhibition values of 1.83±3.46% and 95.54±6.17%, so that the IC₅₀ values >10 µg/mL and 1.13±0.55 µg/mL have obtained. The secondary metabolite 6-*epi*-yonarasterol B (**96**) (Fig.-33) exhibits a significant inhibitory effect on the superoxide anion derivative and elastase release by human neutrophils.¹⁷

Caryophyllene sesquiterpenoids.

The gorgonian coral of *R. antipathies* showed that the caryophyllene derivatives of the sesquiterpenoid type, rumphellol A (**10**) and B (**11**) (Fig.-12), had anti-inflammatory effects when tested *in-vitro*. These secondary metabolites showed inhibitory activity on superoxide anions of 31.95 and 42.22%. Also, it inhibits the release of 51.64 and 42.10% elastase by human neutrophils with concentrations of 42.4 and 37.6 µM (10 µg/mL for each of these secondary metabolites).¹⁸

Pseudopterane diterpene.

Pseudopterolide (**12**) (Fig.-14) can inhibit the production of inflammatory mediators NO, TNF-α, IL-6, IL-1β, and IP-10 induced by LPS with IC₅₀ values from 2.75±0.68 µM to 12.25±0.40 µM. It is due to a methoxy functional group at C-9.²⁰

Diterpenoid type cunicellin.

Secondary metabolite palmonine F (**13**) (Fig.-16) sourced from gorgonian *E. singularis* has anti-inflammatory activity when tested using the carrageenan-induced rat paw edema model and acetic acid writhing test mice. Organic extracts have a very high edema reduction for 3 hours with 45, 60, and 65% inhibition given at an average dose of 50, 100, and 200 mg/kg, with ED₅₀ of 63.34 mg/kg. Polar fractions (F2 and F3), where F3 activity at a dose of 25 and 50 mg/kg i.p at the 3rd time after carrageenan injection showed inhibition of 54.5 and 66% reduction in paw volume with ED₅₀ of 19.2 mg/kg whereas, in F2, the edema inhibition was 59% at time three at a dose of 50 mg/kg.⁵

Pseudopterins PsQ, PsS, PsU, amphilectosins A and B, PsG, PsK, PsP, PsT, *seco*-pseudopterins *seco*-PsJ and *seco*-PsK, elisabethatrienol, 10-acetoxy-9-hydroxy- and 9-acetoxy-10-hydroxy-amphilecta-8,10,12,14-tetraenes, and amphilecta-8(13)-11,14-triene-9,10-dione.

This metabolite (Fig.-18) has anti-inflammatory activity by *in-vivo* assay extracts and fractions using the 12-O-tetradecanoyl-phorbol-acetate (TPA)-inducing rat ear edema model. Anti-inflammatory activity was also carried out *in-vitro* from isolates using *in-vitro* myeloperoxidase (MPO) assay by human polymorphonuclear neutrophils (PMNs) inhibition of 62±3, 65±4, and 40±3%. These secondary metabolites also inhibit NO, 52–58% or 10 µM, and 38–50% or 1 µM. Secondary metabolite activity in NO scavengers also provides inhibition with a percentage of 42±3, 31±6, and 38±4%.²⁴

Secosterol consists of pinnisterol D–J (**67–73**), sterol (**74**), and pinnisterol A (**75**) (Fig.-27). These secondary metabolites, when carried out by anti-inflammatory tests, showed that secosterol E, H, and J had an inhibitory effect on elastase release with IC₅₀ values of 2.33; 2.59; and 3.89 µM while for secosterol F, H, and J showed an inhibitory effect on human neutrophils in superoxide anion with IC₅₀ of 5.52; 3.26; and 3.71 µM.³¹

Sterol. Cholest-5-ene-3β,7α-diol (**92**), (22*E*)-cholesta-5,22-diene-3β,7α-diol (**93**), ergosta-5,24(28) diene-3β,7α-diol (**94**), and cholesta-5, 22-diene-3β-ol (**95**) (Fig.-32) have anti-inflammatory activity on the ethanol fraction. The organic extract at a 200 mg/kg dose effectively inhibited edema of 64.75%. In comparison, the ethanol fraction had a very high activity at a dose of 50 mg/kg, which effectively

inhibited edema by 66.9%. Simultaneously, the acetone and methanol/dichloromethane fractions at a dose of 50 mg/kg can eliminate edema with an average of 49 and 54%.²²

Sterol. The secondary metabolites griffiniteron F-I (**97–100**) and griffinipregnon (**101**) (Fig.-35) have anti-inflammatory activity. Griffiniteron F–I significantly inhibited the accumulation of the pro-inflammatory protein iNOS LPS-stimulated RAW 264.7 macrophage cells of 10 μ M. Whereas the griffiniteron G inhibited the proliferation of pro-inflammatory COX-2 protein, which was analyzed using Westren's blot analysis, Lowry's method, and SDS-PAGE.³⁸

Anti-cancer

Hydroperoxy Sesquiterpene.

Secondary metabolites *H. fuscescens* have cytotoxic activity in colorimetric MTT assay [3-(4,5-dimethylazol-2-il)-2,5-diphenyltetrazolium bromide] with cancer cell lines MCF-7 (human breast adenocarcinoma) and OVK-18 (endometrioid ovarian carcinoma). Heterofusceterpene A (**3**) (Fig.-4) shows cytotoxic activity on MCF-7 and OVK-18 with IC₅₀ values of 23.2 $\pm$ 3.22 and 38.01 $\pm$ 2.63 μ g/mL.¹²

Sterol. Heterofuscesterols A (**29**) showed excellent activity on cancer cell lines with IC₅₀ values of 35.9 $\pm$ 5.98 μ g/mL (MCF-7) and 46.9 $\pm$ 3.93 μ g/mL (OVK-18). While the heterofuscesterols B (**30**) and 3 β ,5 α ,6 β -trihydroxyandrosta-17-one (**31**) did not show any cytotoxic activity on cancer cell lines with concentrations >100 μ g/mL. It can be seen from the relationship between the sterol activity structure of the isolated compounds (Fig.-19), which shows a decrease in polyhydroxylation cytotoxic activity due to the replacement of side chains with carbonyl groups.¹²

Diterpene Pseudopterane.

This secondary metabolite pseudopterolide (**12**) (Fig.-14) did not affect cell viability cytotoxicity when tested using the MTT assay method with concentrations of 12.5 and 25 μ M.²⁰

Hydroperoxy Steroids.

Secondary metabolites of xidaosteroid A (**32**) and B (**33**) and five other types of compounds (Fig.-21) have screened using cancer cell lines, namely A-549 (lung adenocarcinoma), HT-29 (colonic carcinoma), SNU-398 (hepatocellular carcinoma), and Capan-1 (pancreatic carcinoma) showed component 5 α ,8 α -epidioxyergosta-6,9(11)-diene-3 β -ol (**34**) inhibits SNU-398 and Capan-1 cells with IC₅₀ values of 35.93–37.18 μ M.²⁵

Steroid. Secondary metabolites of the steroid class, namely verrucorosteroid A–F (**41–46**), verrucorosteron (**47**), 3 β -acetyl-20 R -hydroxycholest-5,22-dien-24-oic acid α -lactone (**48**), 3 β ,20 R -dihydroxycholest-5,22-dien-24-oic acid α -lactone (**49**), suberoretisteroids A–C (**50–52**), (22 E)-3 β ,25-dihydroxycholest-5,22-dien-24-one (**53**), 5,6 α -epoxy-3 β -hydroxy-(22 E)-ergosta-8,22-dien-7-one (**54**), 5,6 α -epoxy-3 β -hydroxy-(22 E)-ergosta-8(14),22-dien-7-one (**55**), (22 E ,24 S)-24-methyl-5 α -cholesta-7,22-diene-3 β ,5,6 β ,9-tetraol (**56**), and (22 E ,24 S)-24-methyl-5 α -cholesta-7,22-diene-3 β ,5,6 β -triol (**57**) (Fig.-23) has cytotoxic activity against 8 cancer cell lines (LNCaP, HepG2, KB, MCF-7, SK-Mel2, HL-60, LU-1, and SW480). The results showed that secondary metabolites verrucorosteron (**47**), 5,6 α -epoxy-3 β -hydroxy-(22 E)-ergosta-8,22-dien-7-one (**54**), and 5,6 α -epoxy-3 β -hydroxy-(22 E)-ergosta-8(14),22-dien-7-one (**55**) were significant for all cancer cell lines (IC₅₀ from a value of 12.32 $\pm$ 1.47–33.77 $\pm$ 1.28 μ M) as well as component 13 on the HepG2 cell lines (IC₅₀ of 35.13 $\pm$ 3.84 μ M), SK-Mel2 (IC₅₀ of 32.56 $\pm$ 4.88 μ M), and HL-60 (IC₅₀ of 28.66 $\pm$ 2.40 μ M).²⁸

Ameristerenol A and Derivatives.

Component ameristerenol A (**58**) has converted into sterol derivatives (**61–63**) and three analogs (**64–66**) (Fig.-25), with the results showing component **63** has anti-cancer activity in inhibiting the growth of breast cancer cell lines in humans (MDA-MB-231).³⁰

Secosterol, namely pinnisterol D–J (**67–73**) (Fig.-27), has a cytotoxic effect on HSC-T6 (Hepatic stellate cell line) cells with IC₅₀ of 3.93 μ M.³¹

Analgesic

Diterpenoid Type eunicellin.

The secondary metabolite palmonine F (**13**) (Fig.-16) has reported having analgesic activity administered subcutaneously at doses of 100, 200, and 400 mg/kg resulting in a significant reduction in abdominal narrowing with a value of 16.57; 40.44; and 64.35% in the acetic acid writhing test in mice (ED₅₀ of 295.66 mg/kg).⁵ Also, it has reported that writhes of inhibition in the methanol–dichloromethane fraction of 31.42 (63.46%) and ethanol fraction of 32.56 (62%) at a dose of 100 mg/kg had a very high analgesic activity when compared to the acetone fraction of 57.53 (56.36%).²²

Gastroprotective

Diterpenoid type eunicellin.

Palmonine F (**13**) (Fig.-16) is also useful as a gastroprotective. Polar fraction (F2 and F3), were at a dose of 100 mg/kg, effectively inhibited gastric lesions for F2 (75 and 80.46%) and F3 (87.5%), the same as the percentage of the drug omeprazole which has been using as a drug reference.⁵ Meanwhile, research from Deghrigue *et al.* reported that organic extracts could inhibit gastric lesions (46.7 and 68.8%) at doses of 25 and 100 mg/kg, ethanol fraction (45, 53, 70, 78, and 80%) at doses of 5, 10, 25, 50, and 100 mg/kg, and methanol/dichloromethane fraction (65, 68, and 73%) at doses of 25, 50, and 100 mg/kg. Meanwhile, the acetone fraction was unable to eliminate ethanol/HCl-induced gastric lesions.²²

Anti-viral

Steroid type pregnan.

Subergorgol T–X (**76–80**) and three analogs (**81–83**) (Fig.-29) have potential as inhibitors in the influenza A/WSN/33 (H1N1) virus strain by propagating them on MCDK cells through cytopathic effect reduction (CPE) and CellTiter-Glo, where the IC₅₀ is 35.64–50.95 μ M.³⁴

Anti-bacterial

3 Δ^1 -3-ketosteroid.

Subergosterone A–C (**84–86**) and the steroid group, namely 9 α -hydroxycholest-1-en-3-one (**87**), pregna-1,4,20-trien-3-one (**88**), cholesta-1,4-dien-3-one (**89**), dendronesterone C (**90**), and ergosta-1,4-dien-3-one (**91**) (Fig.-31), have antibacterial activity against *Staphylococcus aureus*, *Staphylococcus albus*, *Bacillus cereus*, *Escherichia coli*, *Tetragenococcus halophilus*, *Pseudomonas putida*, *Vibrio parahaemolyticus*, and *Nocardia brasiliensis* with a MIC value of 1.56–12.5 μ M.³⁶

Alkaloid.

2-bromo-*N*-methyltryptamine (**102**), 3-bromo-*N*-methyltyramine (**103**), and eight other components (**104–111**) (Fig.-37) to have anti-bacterial activity. All Components have 70% inhibitory activity of bacterial adhesion for one strain, but at 2-bromo-*N*-methyltryptamine (**102**) shows the highest activity.⁶

Anti-fouling

Alkaloid. The components **106** and **111** give EC₅₀ are 95 and 90 μ M, while the toxicity effect is EC₅₀ of >1000 mg/L or 5000 μ M (**106**) and 55 mg/L or 284 μ M (**111**).⁶

CONCLUSION

Gorgonian corals contain secondary metabolites of terpenoids, steroids, and alkaloids with pharmacological activities including anti-inflammatory, anti-cancer, analgesic, gastroprotective, anti-viral, anti-bacterial, and anti-fouling agents. That is due to the structural relationship to activity, including the stereochemical effect of hydroxy groups, epoxide groups, methoxy groups, methylenecyclohexane ring configuration, and the effect of side-chain replacement on carbonyl groups.

ACKNOWLEDGEMENT

The author would like to thank the Education Fund Management Institution, Indonesia, for providing opportunities and support in education and research.

REFERENCES

1. C. S. Mcfadden, S. C. France, J. A. Sánchez and P. Alderslade, *Molecular Phylogenetics and Evolution*, **41**, 513(2006), <https://doi.org/10.1016/j.ympev.2006.06.010>
2. W. Changyun, L. Haiyan, S. Changlun, W. Yanan, L. Liang and G. Huashi, *Acta Ecologica Sinica*, **28(5)**, 2320(2008), [https://doi.org/10.1016/S1872-2032\(08\)60048-7](https://doi.org/10.1016/S1872-2032(08)60048-7)
3. A. R. Reo, S. Berhimon and R. Montolalu, *Jurnal Ilmiah Platax*, **5(1)**, 42(2017).
4. J. Bao, Y. L. Sun, X. Y. Zhang, Z. Han, H. C. Gao, F. He, P. Y. Qian and S. H. Qi, *The Journal of Antibiotics*, **66(4)**, 219(2013), <https://doi.org/10.1038/ja.2012.110>
5. M. Deghrigue, S. Lajili, M. Turki, N. Eltaief and A. Bouraoui, *Journal of Annals of Medical ad Biomedical Sciences*, **1(1)**, 23(2015).
6. N. Pérez, G. Culioli, T. Pérez, J. F. Briand, O. P. Thomas and Y. Blache, *Journal of Natural Products*, **74(10)**, 2304(2011), <https://doi.org/10.1021/np200537v>
7. L. Anwar, A. Santoni, D. P. Putra, and M. Efdi, *Rasayan Journal of Chemistry*, **12(3)**, 1641(2019), <https://doi.org/10.31788/RJC.2019.1235025>
8. K. Budipramana, K. R. Wirasutisna, M. W. Wartono, Y. B. Pramana, S. Sukrasno and T. A. Yuniarta, *Rasayan Journal of Chemistry*, **14(1)**, 149(2021), <https://doi.org/10.31788/RJC.2021.1415813>
9. [https://commons.wikimedia.org/wiki/File:Junceella fragilis.jpeg](https://commons.wikimedia.org/wiki/File:Junceella_fragilis.jpeg)
10. T. Su, T. Kuo, S. Yang, G. Lee, Y. Lee, Y. Wang, J. Chen, Z. Wen, T. Hwang and P. Sung, *Marine Drugs*, **18**, 3(2020).
11. <https://commons.wikimedia.org/w/index.php?search=Heteroxenia+fuscescens&title=Special:MediaSearch&go=Go&type=image>
12. F. M. Abdelkarem, E. E. K. Desoky, A. M. Nafady, A. E. Allam, A. Mahdy, M. Nagata, T. Miyamoto and K. Shimizu, *Phytochemistry Letters*, **36**, 156(2020), <https://doi.org/10.1016/j.phytol.2020.02.006>
13. J. H. Xu, K. H. Lai, Y. D. Su, Y. C. Chang, B. R. Peng, A. Backlund, Z. H. Wen and P. J. Sung, *Marine Drugs*, **16(3)**, 1(2018), <https://doi.org/10.3390/md16030075>
14. N. F. Chen, Y. D. Su, T. L. Hwang, Z. J. Liao, K. H. Tsui, Z. H. Wen, Y. C. Wu, P. J. Sung and T. J. Schmidt, *Molecules*, **22(3)**, 1(2017), <https://doi.org/10.3390/molecules22030475>
15. Y. Lin, S. Lin, C. Feng, P. Chen, Y. Su, C. Li, S. Yang, Y. Jean, P. Sung, C. Duh and Z. Wen, *Marine Drugs*, **13**, 2559(2015), <https://doi.org/10.3390/md13052559>
16. https://www.marinethemes.com/gen-gallery-search/?tag=Echinomuricea_sp
17. H. M. Chung, P. H. Hong, J. H. Su, T. L. Hwang, M. C. Lu, L. S. Fang, Y. C. Wu, J. J. Li, J. J. Chen, W. H. Wang and P. J. Sung, *Marine Drugs*, **10**, 1169(2012), <https://doi.org/10.3390/md10051169>
18. H. M. Chung, W. H. Wang, T. L. Hwang, J. J. Chen, L. S. Fang, Z. H. Wen, Y. B. Wang, Y. C. Wu, and P. J. Sung, *International Journal of Molecular Sciences*, **15(9)**, 15679(2014), <https://doi.org/10.3390/ijms150915679>
19. https://coralpedia.bio.warwick.ac.uk/en/octocorals/pseudopterogorgia_acerosa
20. Y. González, D. Doens, R. Santamaría, M. Ramos, C. M. Restrepo, B. D. Arruda, R. Leonart, M. Gutiérrez and P. L. Fernández, *PLOS ONE*, **8(12)**, 1(2013), <https://doi.org/10.1371/journal.pone.0084107>
21. https://commons.wikimedia.org/wiki/File:Eunicella_singularis_2.JPG
22. M. Deghrigue, C. Festa, L. Ghribi, M. V. D. Auria, S. De, H. B. Jannet and A. Bouraoui, *Asian Pacific Journal of Tropical Medicine*, **8(8)**, 606(2015), <https://doi.org/10.1016/j.apjtm.2015.07.019>
23. <https://www.reef2reef.com/threads/pseudopterogorgia-elisabethae-any-experience.581461/>
24. H. Correa, A. L. Valenzuela, L. F. Ospina and C. Duque, *Journal of Inflammation*, **6(1)**, 1(2009), <https://doi.org/10.1186/1476-9255-6-5>
25. F. Z. Yin, M. Yang, S. W. Li, M. J. Wu, X. J. Huan, Z. H. Miu, H. Wang and Y. W. Guo, *Steroids*, **155**, 108558(2020), <https://doi.org/10.1016/j.steroids.2019.108558>

26. Y. H. Teffu, R. Suwandi and N. Nurjanah, *Jurnal Pengolahan Hasil Perikanan Indonesia*, **18(1)**, 83(2015), <https://doi.org/10.17844/jphpi.2015.18.1.83>
27. J. S. Y. Kumar, C. Raghunathan and K. Venkataraman, *Marine Faunal Diversity in India*, **2015**,15(2015), <https://doi.org/10.1016/b978-0-12-801948-1.00002-1>
28. N. H. Nam, N. T. Ngoc, T. T. H. Hanh, N. X. Cuong, N. V. Thanh, D. T. Thao, D. C. Thung, P. V. Kiem and C. V. Minh, *Steroids*, **138**, 57(2018), <https://doi.org/10.1016/j.steroids.2018.06.006>
29. https://coralpedia.bio.warwick.ac.uk/en/octocorals/pseudopterogorgia_americanana
30. Y. He, S. L. Caplan, P. Scesa and L. M. West, *Steroids*, **125**, 47(2017), <https://doi.org/10.1016/j.steroids.2017.06.008>
31. W. Cheng, M. Ji, X. Li, J. Ren, F. Yin, L. V. Ofwegen, S. Yu, X. Chen and W. Lin, *Tetrahedron*, **73(17)**, 2518(2017), <https://doi.org/10.1016/j.tet.2017.03.037>
32. Y. C. Chang, T. L. Hwang, L. M. Kuo and P. J. Sung, *Marine Drugs*, **15(11)**, 1(2017), <https://doi.org/10.3390/md15010011>
33. <http://museum.wa.gov.au/online-collections/names/subergorgia-suberosa>
34. W. Cheng, J. Ren, Q. Huang, H. Long, H. Jin, L. Zhang and H. Liu, *Steroids*, **108**, 99(2016), <https://doi.org/10.1016/j.steroids.2016.02.003>
35. https://www.123rf.com/photo_71447568_detail-of-sea-fan-subergorgia-rubra-showing-open-polyps-macro-image-sanganeb-sudan-red-sea-.html
36. F. Cao, C. Shao, M. Wang, X. Zhang and C. Wang, **12**, 1068(2015).
37. <https://es.wikipedia.org/wiki/Dendronephthya>
38. C. H. Chao, Z. H. Wen, J. H. Su, I. M. Chen, H. C. Huang, C. F. Dai and J. H. Sheu, *Steroids*, **73(14)**, 1353(2008), <https://doi.org/10.1016/j.steroids.2008.06.008>
39. S. D. Siva, N. Vijayakumar, R. Jayaprakash and N. M. Reddi, *Rasayan Journal of Chemistry*, **13(3)**, 1580(2020), <https://doi.org/10.31788/RJC.2020.1335793>

[RJC-6406/2021]